

https://dspace.org/

Transition metal catalysed reactions for the synthesis of heteroaromatic compounds

Pelly, Stephen Christopher

2008-12-22T08:11:20Z
http://hdl.handle.net/10539/5900

Downloaded from a DSpace repository. https://dspace.org/

Transition Metal Catalysed Reactions for the Synthesis of Heteroaromatic Compounds

Stephen Christopher Pelly

A thesis submitted to the Faculty of Science,

University of the Witwatersrand,
Johannesburg

In fulfilment of the requirements for the Degree of Doctor of Philosophy

January 2007

DECLARATION

I declare that the work presented in this thesis was carried out exclusively by myself under the supervision of Professor C.B. de Koning. It is being submitted for the degree of Doctor of Philosophy in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination in any other University.

_____

27th day of January, 2007

ABSTRACT

The carbazole and 2-isopropenyl-2,3-dihydrobenzofuran structures are widely found in many naturally occurring compounds. For example, the naturally occurring anti-cancer compound, rebeccamycin, contains an indolocarbazole core. Rotenone, which contains an *(R)*-2-isopropenyl-2,3-dihydrobenzofuran moiety, is widely used today as an effective naturally occurring pesticide.

In the carbazole section of this thesis, the synthesis of the naturally occurring furanocarbazole, furostifoline is described. As key steps in this sequence, a Suzuki coupling reaction is utilised to couple appropriately functionalised indole and furan moieties. After further functional group transformations, a metathesis reaction is employed to construct the carbazole system, leading to furostifoline. The synthesis of the unnatural thio-analogue of furostifoline was similarly conducted and is described. Finally, in a somewhat different approach, the synthesis of the indolocarbazole core is described, utilising a Madelung approach initially to form the *bis*-indole system, 2,2'-biindolyl. After several functional group transformations, a metathesis reaction was once again successfully employed to form the carbazole system, thereby synthesising di(*tert*-butyl) indolo[2,3-*a*]carbazole-11,12-dicarboxylate.

In the benzofuran section of this thesis, the successful chiral synthesis of two 2-isopropenyl-2,3-dihydrobenzofuran systems is described. As a precursor to rotenone, the synthesis of *(R)*-2-isopropenyl-2,3-dihydrobenzofuran-4-ol is described starting from resorcinol. The key step in this synthesis is a stereoselective intramolecular Pd π-allyl mediated cyclisation utilising the *R,R'*-Trost ligand, thereby forming *(R)*-2-isopropenyl-2,3-dihydrobenzofuran-4-ol in excellent yield and enantiomeric excess. The alternative enantiomer, *(S)*-2-isopropenyl-2,3-dihydrobenzofuran-4-ol, was similarly synthesised. Finally, a similar approach was utilised to synthesise both *(S)*- and *(R)*-2-isopropenyl-2,3-dihydrobenzofuran, starting from 2-allyl-phenol, and thereby completing a formal synthesis of the naturally occurring compounds, *(S)*-fomannoxin and *(R)*-trematone, respectively.

ACKNOWLEDGMENTS

Personal acknowledgments

First and foremost, to my supervisor, Professor Charles de Koning, for his guidance and wisdom in this project, but so much more so for his guidance and wisdom for life. You were, and continue to be an inspiration to me, both in and out of chemistry.

Professor J.P. Michael, with whom many valuable discussions led to interesting and valuable results – more importantly, these humbling discussions made me realise just how little I really know.

Thank you to Dr W.A.L. van Otterlo, Dr C.J. Parkinson and Dr A. Dinsmore for many helpful discussions.

To my family – My mother, and my sisters Tina and Lynne, whose support and encouragement was just wonderful. Without you, this PhD would not have been possible. Family truly is everything.

Mr Richard Mampa for the seemingly endless amount of NMR spectra – without you, all we would have is a yellow splodge at the bottom of a flask. I also express my gratitude to Mr Tommy van der Merwe for the similarly numerous mass spectral analyses. For the crystallographic analyses, I'd like to thank Dr Manuel Fernandes and Andreas Lemmerer.

To all the guys and girls in the lab – specifically (and in no particular order), Sameshnee, Darren, Jenny, Eddie, Simon, Phil, Angie and Garreth. And let's not forget Theo, whom by now I hope has finally come to realisation that when you spray water on the girls three floors below and they run away screaming, it's probably NOT because they like it. I'm going to miss you weirdo's.

A special mention to Joni who is so pure in heart, and kind in every thought and deed. You are constantly in my thoughts, and how I hope the sun will always shine warmly upon you.

To Dr Mandy Rousseau who so kindly edited large parts of this thesis when I just couldn't bear to look at it any more – and promptly kicked me in the foot if I didn't keep those chapters coming.

And finally, to my closest friend and lifelong partner, Sameshnee Govender. Who would have thought that we could come from such different worlds and yet we think so alike, and dream such similar dreams. How I look forward to a wonderful journey with you. Moreover, this thesis would probably never have been written were it not for you giving me numerous scoldings, forcing me to sit in front of my computer and threatening to take away my motorbike. It's all about the right motivation.

Actually, if I may squeeze in one more – to Samesh's mother Mrs G (otherwise known as Mom-in-law, or battle-axe), who, besides having a heart of gold could never quite grasp the fact that although I am studying at University I don't actually write exams to complete this degree. May I just say, yes, I have finished studying now (er, I've written the exams), but no, this does not mean that babies are forthcoming – well, not as far as I know anyhow.

Acknowledgements for funding

Without the funding I received, this PhD would not have been possible and I would like to express my sincere appreciation to the following organisations:

To the CSIR, for their generous bursary, as well as for the opportunity to continue working in this field I love upon completing my PhD.

The University of the Witwatersrand for several scholarships and awards, including the Post Graduate Merit Award, the Backeberg Scholarship and the University Council Award.

Declaration i
Abstract ii
Acknowledgments iii
Personal acknowledgments iii
Acknowledgements for funding iv
PREFACE XII
A note to the reader xii
Regarding the thesis layout xii
Interpretation of ^{1}H NMR spectra and ^{13}C NMR spectra xii
CHAPTER 1 - ABOUT CARBAZOLE ALKALOIDS 1
1.1 An introduction to carbazole based natural products 1
1.1.1 The isolation of interesting carbazoles and associated biological activity 1
1.1.2 Indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles, and the cell cycle 10
1.1.3 A new generation of potent Ru containing carbazoles 13
1.2 Selected syntheses of carbazole compounds 16
1.2.1 Total syntheses of furostifoline 16
1.2.1.1 The first total synthesis of furostifoline – An iron mediated synthesis 16
1.2.1.2 An improved iron mediated synthesis 18
1.2.1.3 A Stille coupling and oxidative photocyclisation method 19
1.2.1.4 Thermal electrocyclisation of a 2,3-disubstituted indole 21
1.2.1.5 Cyclisation using a nitrene 23
1.2.1.6 Synthesis of furostifoline by a tetrabutylammonium fluoride promoted ring formation 24
1.2.2 Selected syntheses of indolo[2,3-*a*]carbazoles and ruthenium carbazole complexes 26
1.2.2.1 Synthesis of the indolo[2,3-*a*]carbazole core 27
1.2.2.2 Total synthesis of staurosporinone 30
1.2.2.3 First total synthesis of staurosporine and its enantiomer *ent*-staurosporine 33
1.2.2.4 Synthesis of a ruthenium carbazole complex – a highly selective and potent GSK-3 inhibitor 39
CHAPTER 2 – BENZOFURAN CONTAINING NATURAL PRODUCTS 42
2.1 Rotenone, and related structures 42
2.1.1 Not all that is natural is good for you – about rotenone 42
2.1.2 Other interesting natural products containing the 2-isopropenyl-2,3-dihydrobenzofuran functionality 47
2.1.3 Syntheses of trematone and related structures 49
2.1.3.1 First synthesis of trematone 49
2.1.3.2 A chiral synthesis of trematone employing a chiral resolution step 50
2.1.3.3 Synthesis of racemic fomannoxin, and friends 52
2.1.3.4 Chiral synthesis of fomannoxin, and friends 54
2.1.4 The role of palladium in the synthesis of trematone and related structures 56

2.1.4.1 Early Pd(II) mediated reactions 56
2.1.4.2 Early stereoselective Pd(II) mediated reactions - the Wacker approach 57
2.1.5 Sharpless asymmetric dihydroxylation as a chiral resolution approach to 2-isopropenyl-2,3-dihydrobenzofuran derivatives 61
2.1.6 Asymmetrical Pd(0)-catalysed intramolecular cyclisations 63

CHAPTER 3 - PLANNED APPROACHES 73

3.1 Towards carbazole compounds of interest 73
3.1.1 An introduction to methodology previously developed in our laboratories 73
3.1.2 An envisaged approach for the total synthesis of furostifoline 75
3.1.3 An envisaged approach to synthesise the indolocarbazole core 77
3.2 Towards the rotenone precursor 80
3.2.1 An envisaged chiral approach to synthesise 2-isopropenyl-2,3-dihydrobenzofuran-4-ol 80

CHAPTER 4 - AN ENVISAGED LIGHT MEDIATED APPROACH 84

4.1 Towards Furostifoline 84
4.1.1 A planned model study to investigate the feasibility of the light mediated cyclisation 84
4.1.1.1 Synthesis of 2-acetyl-3-bromofuran – 82 86
4.1.1.2 Synthesis of 2-bromo-1,3-dimethyl-1*H*-indole – 263 87
4.1.1.3 Synthesis of *N*-methyl 2-(2-acetylfuran-3-yl)-3-methylindole by utilisation of the Suzuki reaction – 265 89
4.1.1.4 Attempted synthesis of *N*-methyl furostifoline using a light mediated cyclisation reaction 93
4.2 Towards the indolocarbazole core 93
4.2.1 A planned model study to investigate the feasibility of the light mediated cyclisation 93
4.2.1.1 Synthesis of 2-bromo-1-methyl-1*H*-indole-3-carbaldehyde using a modification of the Vilsmeier reaction – 279 95
4.2.1.2 Suzuki coupling to form the *bis*-indole system – 277 97
4.2.1.3 Attempted synthesis of *N,N'*-dimethyl[2,3-*a*]indolocarbazole using a light mediated cyclisation reaction 99
4.3 Concluding remarks for the light mediated route 99

CHAPTER 5 – A METATHESIS APPROACH 101

5.1 Ring closing metathesis as a key step to synthesise furostifoline and the indolocarbazole core 101
5.1.1 The olefin metathesis reaction – background and mechanism 102
5.1.2 Total synthesis of furostifoline employing metathesis as a key step 104
5.1.2.1 Outline of the synthetic strategy 104
5.1.2.2 Synthesis of 1-(*tert*-butoxycarbonyl)-1*H*-indol-2-yl-2-boronic acid – 305 108
5.1.2.3 Synthesis of *tert*-butyl 2-(2-acetylfuran-3-yl)-1*H*-indole-1-carboxylate – 306 109
5.1.2.4 Synthesis of 2-(2-acetylfuran-3-yl)-1*H*-indole – 307 112
5.1.2.5 Synthesis of 2-(2-acetylfuran-3-yl)-1*H*-indole-3-carbaldehyde – 308 115
5.1.2.6 Synthesis of *tert*-butyl 2-(2-acetylfuran-3-yl)-3-formyl-1*H*-indole-1-carboxylate - 309 117

5.1.2.7 Unexpected synthesis of *tert*-butyl 2*a*-methyl-1,2,2*a*,10*c*-tetrahydro-6*H*-cyclobuta[*c*]furo[3,2-*a*]carbazole-6-carboxylate – 312 118
5.1.2.8 Synthesis of furostifoline – 18 123
5.1.3 Total synthesis of a thio-analogue of furostifoline employing metathesis as a key step 127
5.1.3.1 Outline of the synthetic strategy 128
5.1.3.2 Synthesis of 2-acetyl-3-bromothiophene –318 129
5.1.3.3 Synthesis of *tert*-butyl 2-(2-acetylthiophen-3-yl)-1*H*-indole-1-carboxylate by Suzuki coupling – 321 130
5.1.3.4 Removal of the Boc protecting group to synthesise 1-(3-(1*H*-indol-2-yl)thiophen-2-yl)ethanone – 322 133
5.1.3.5 Vilsmeier formylation to synthesise *tert*-butyl 2-(2-acetylthiophen-3-yl)-3-formyl-1*H*-indole-1-carboxylate – 317 134
5.1.3.6 Wittig reaction, followed immediately by RCM to synthesise *tert*-butyl 4-methyl-10*H*-thieno[3,2-*a*]carbazole-10-carboxylate – 315 138
5.1.3.7 Boc deprotection affording thiofurostifoline - 314 141
5.1.4 Synthesis of the indolocarbazole core – a metathesis approach 143
5.1.4.1 Outline of the strategy 143
5.1.4.2 Synthesis of oxalyl-*o*-toluidide – 336 146
5.1.4.3 2,2'-Biindolyl using a Madelung-type reaction – 337 147
5.1.4.4 2,2'-Biindolyl-3,3'-dicarboxaldehyde – 338 149
5.1.4.5 *N,N'*-Di-*tert*-butylcarboxylate-2,2'-biindolyl-3,3'-dicarboxaldehyde – 339 150
5.1.4.6 *N,N'*-Di-*tert*-butylcarboxylate-2,2'-biindolyl-3,3'-divinyl – 340 151
5.1.4.7 Di(*tert*-butyl) indolo[2,3-*a*]carbazole-11,12-dicarboxylate – 341 152
5.2 Off the beaten track – reactions conducted out of interest or reactions not leading anywhere 155
5.2.1 *En route* to furostifoline and thiofurostifoline 155
5.2.1.1 Attempted coupling of the carbonyl moieties by means of a samarium diiodide mediated reaction 155
5.2.1.2 Attempted McMurry coupling of the indolo-furan dicarbonyl compound 156
5.2.1.3 Carbazole formation by metathesis from inadvertently prepared *tert*-butyl 2-(2-(1-(*tert*-butoxycarbonyloxy)vinyl)thiophen-3-yl)-3-formyl-1*H*-indole-1-carboxylate 157
5.2.2 The indolo-carbazole series of compounds 160
5.2.2.1 Attempted coupling of the carbonyl moieties utilising a samarium diiodide mediated reaction 160
5.3 Concluding remarks pertaining to the synthesis of various carbazoles 161

CHAPTER 6 – BENZOFURAN BASED NATURAL PRODUCTS 165

6.1 Asymmetric syntheses of two benzofuran compounds as valuable routes towards the synthesis of several natural products 165
6.1.2 Towards the synthesis of rotenone – a collaborative study 165
6.1.3 Asymmetric synthesis of the required chiral benzofuran - a rotenone precursor 166
6.1.3.1 Outline of the synthetic strategy 166
6.1.3.2 A planned synthesis of *(R)*-2-isopropenyl-2,3-dihydrobenzofuran-4-ol – a disconnection approach 168
6.1.3.3 Synthesis of *tert*-butyl(3-methoxyphenoxy)dimethylsilane – 460 172

6.1.3.4 Attempted synthesis of (2-allyl-3-methoxyphenoxy)(*tert*-butyl)dimethylsilane 173
6.1.3.5 A change of plan regarding the protecting group strategy 174
6.1.3.6 Synthesis of 1,3-*bis*(methoxymethoxy)benzene – 462 175
6.1.3.7 Synthesis of 2-allyl-1,3-*bis*(methoxymethoxy)benzene – 463 176
6.1.3.8 MOM deprotection, forming 2-allylbenzene-1,3-diol –464 177
6.1.3.9 Protection of the diol as the *bis*-silyl ether, 2-allyl-1,3-*bis*(*tert*-butyldimethylsilyloxy)-benzene – 465 179
6.1.3.10 Ozonolysis to form 2-(2,6-*bis*(*tert*-butyldimethylsilyloxy)-phenyl)acetaldehyde – 466 180
6.1.3.11 Horner-Wadsworth-Emmons reaction to synthesise *(E)*-ethyl-4-(2,6-*bis*(*tert*-butyl-dimethylsilyloxy)phenyl)-2-methylbut-2-enoate – 467 181
6.1.3.12 Synthesis of *(E)*-4-(2,6-*bis*(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-en-1-ol – 468 184
6.1.3.13 Synthesis of *(E)*-4-(2,6-*bis*(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-enyl acetate - 469 185
6.1.3.14 Synthesis of *(E)*-4-(2,6-dihydroxyphenyl)-2-methylbut-2-enyl acetate – 470 188
6.1.3.15 Synthesis of racemic (±)-2-isopropenyl-2,3-dihydrobenzofuran-4-ol by Pd π-allyl chemistry – *rac*-247 189
6.1.3.16 Synthesis of *(E)*-4-(2,6-*bis*(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-enyl methyl carbonate – 478 192
6.1.3.17 Removal of the silyl protecting groups affording *(E)*-4-(2,6-dihydroxyphenyl)-2-methylbut-2-enyl methyl carbonate – 479 193
6.1.3.18 Synthesis of racemic 2-isopropenyl-2,3-dihydrobenzofuran-4-ol from the carbonate, by Pd π-allyl mediated chemistry - *rac*-247 194
6.1.3.19 Investigations into various chiral Pd π-allyl mediated cyclisations, leading to the synthesis of (+)-2-isopropenyl-2,3-dihydrobenzofuran-4-ol – (+)-*(S)*-247 196
6.1.3.20 Synthesis of racemic and (+)-2-isopropenyl-2,3-dihydrobenzofuran-4-yl acetate - 482 200
6.1.3.21 Derivatisation of the (+)-dihydrobenzofuran enantiomer to 2-isopropenyl-2,3-dihydrobenzofuran-4-yl-(7,7-dimethyl-2-oxobicyclo-[2.2.1]-heptan-1-yl)-methanesulfonate – 483 203
6.1.3.22 Derivatisation of the (+)-dihydrobenzofuran enantiomer to 2-isopropenyl-2,3-dihydrobenzofuran-4-yl 4-bromobenzenesulfonate – 484 204
6.1.3.23 Further derivatisation of 2-isopropenyl-2,3-dihydrobenzofuran-4-yl 4-bromobenzenesulfonate to – 484b 206
6.1.3.24 Yet further derivatisation, forming 2-isopropenyl-2,3-dihydrobenzofuran-4-yl 4-(1*H*-indol-2-yl)benzenesulfonate – 484c 207
6.1.3.25 Derivatisation of the (+)-dihydrobenzofuran enantiomer to (+)-*(S)*-2-isopropenyl-2,3-dihydrobenzofuran-4-yl-2-nitrobenzenesulfonate – 485 209
6.1.3.26 Synthesis of (-)-*(R)*-2-isopropenyl-2,3-dihydrobenzofuran-4-ol using the *R,R'*-Trost ligand – (-)-*(R)*-247 210
6.1.3.27 Conversion of (-)-*(R)*-2-isopropenyl-2,3-dihydrobenzofuran-4-ol to the corresponding acetate in order to determine the enantiomeric excess by HPLC – (-)-*(R)*-482 211
6.1.3.28 Attachment of a suitable *ortho* director to (±)-2-isopropenyl-2,3-dihydrobenzofuran-4-ol – 486 212
6.1.4 A formal synthesis of trematone and fomannoxin 213

6.1.5 Asymmetric synthesis of the required chiral dihydrobenzofuran - precursors to trematone and fomannoxin 214
6.1.5.1 Outline of the synthetic strategy 214
6.1.5.2 A planned synthesis of both the *(R)*- and *(S)*-2-isopropenyl-2,3-dihydrobenzofurans 217
6.1.5.3 Synthesis of (2-allylphenoxy)(*tert*-butyl)dimethylsilane – 490 218
6.1.5.4 Ozonolysis to synthesise 2-(2-(*tert*-butyldimethylsilyloxy)-phenyl)acetaldehyde – 491 219
6.1.5.5 A Horner-Wadsworth-Emmons reaction to synthesise *(E)*-ethyl 4-(2-(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-enoate – 492 221
6.1.5.6 Reduction to synthesise *(E)*-4-(2-(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-en-1-ol – 493 227
6.1.5.7 Synthesis of *(E)*-4-(2-(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-enyl methyl carbonate – 494 229
6.1.5.8 Silyl deprotection affording *(E)*-4-(2-hydroxyphenyl)-2-methylbut-2-enyl methyl carbonate – 489 230
6.1.5.9 Synthesis of racemic 2-isopropenyl-2,3-dihydrobenzofuran by π-allyl Pd chemistry using achiral triphenylphosphine as a ligand source – *rac*-167 231
6.1.5.10 Synthesis of *(R)*- and *(S)*-2-isopropenyl-2,3-dihydrobenzofuran by π-allyl Pd chemistry using chiral Trost ligands – (+)-*(R)*-167 and (-)-*(S)*-167 233
6.2 Concluding remarks pertaining to the enantioselective syntheses of the benzofuran compounds 238
6.2.1 For both benzofuran precursors - interesting observations noted 238
6.2.2 Concluding remarks pertaining to the formal syntheses of trematone and fomannoxin 241
6.2.3 Future work to utilise *(R)*-2-isopropenyl-2,3-dihydrobenzofuran-4-ol in the synthesis of rotenone 243

CHAPTER 7 - EXPERIMENTAL 247

7.1 General procedures 247
7.1.1 Purification of solvents and reagents 247
7.1.2 Chromatography 247
7.1.3 Spectroscopic and physical data 247
7.1.4 High pressure liquid chromatography 248
7.1.5 Other general procedures 248
7.2 Experimental work pertaining to Chapter 4 249
7.2.1 Towards furostifoline - 18 249
7.2.1.1 2-Acetyl-3-bromofuran – 82 249
7.2.1.2 2-Bromo-1,3-dimethyl-1*H*-indole – 263 250
7.2.1.3 *N*-Methyl 2-(2-acetylfuran-3-yl)-3-methylindole – 265 251
7.2.2 Towards the indolocarbazole core 252
7.2.2.1 2-(1,3-Dimethyl-1*H*-indol-2-yl)-1-methyl-1*H*-indole-3-carbaldehyde – 277 252
7.3 Experimental work pertaining to Chapter 5 254
7.3.1 Synthesis of furostifoline - 18 254
7.3.1.1 1-(*tert*-Butoxycarbonyl)-1*H*-indol-2-yl-2-boronic acid – 305 254

7.3.1.2 *tert*-Butyl 2-(2-acetylfuran-3-yl)-1*H*-indole-1-carboxylate – 306 255
7.3.1.3 2-(2-Acetylfuran-3-yl)-1*H*-indole – 307 256
7.3.1.4 Synthesis of 2-(2-acetylfuran-3-yl)-1*H*-indole-3-carbaldehyde – 308 257
7.3.1.5 *tert*-Butyl 2-(2-acetylfuran-3-yl)-3-formyl-1*H*-indole-1-carboxylate – 309 258
7.3.1.6 *tert*-Butyl 2*a*-methyl-1,2,2*a*,10*c*-tetrahydro-6*H*-cyclobuta[*c*]furo[3,2-*a*]carbazole-6-carboxylate – 312 259
7.3.1.7 Furostifoline – 18 261
7.3.2 Synthesis of thiofurostifoline 314 261
7.3.2.1 2-Acetyl-3-bromothiophene – 318 261
7.3.2.2 *tert*-Butyl 2-(2-acetylthiophen-3-yl)-1*H*-indole-1-carboxylate – 321 262
7.3.2.3 2-(2-Acetyl-3-thienyl)-1*H*-indole – 322 263
7.3.2.4 *tert*-Butyl 2-(2-acetylthiophen-3-yl)-3-formyl-1*H*-indole-1-carboxylate – 317, as well as *tert*-butyl 2-(2-(1-(*tert*-butoxycarbonyloxy)vinyl)-thiophen-3-yl)-3-formyl-1*H*-indole-1-carboxylate - 324. 265
7.3.2.5 *tert*-Butyl 4-methyl-10*H*-thieno[3,2-*a*]carbazole-10-carboxylate – 315 267
7.3.2.6 Thiofurostifoline – 314 268
7.3.3 Synthesis of the indolocarbazole core - 341 269
7.3.3.1 Oxalyl-*o*-toluidide – 336 269
7.3.3.2 2,2'-Biindolyl-3,3'-dicarboxaldehyde – 338 269
7.3.3.3 *N,N'*-Di-*tert*-butylcarboxylate-2,2'-biindolyl-3,3'-dicarboxaldehyde – 339 270
7.3.3.5 *N,N'*-Di-*tert*-butylcarboxylate-2,2'-biindolyl-3,3'-divinyl – 340 270
7.3.3.6 Di(*tert*-butyl) indolo[2,3-*a*]carbazole-11,12-dicarboxylate – 341 271
7.3.4 Off the beaten track 272
7.3.4.1 *tert*-Butyl 4-(*tert*-butoxycarbonyloxy)-10*H*-thieno[3,2-*a*]carbazole-10-carboxylate - 326 272
7.4 Experimental work pertaining to Chapter 6 275
7.4.1 Towards the rotenone precursor 275
7.4.1.1 *tert*-Butyl(3-methoxyphenoxy)dimethylsilane – 460 275
7.4.1.2 Attempted synthesis of (2-allyl-3-methoxyphenoxy)(*tert*-butyl)dimethylsilane, resulting in the synthesis of 2-(*tert*-butyldimethylsilyl)-3-methoxyphenol - 461 275
7.4.1.3 2-Allyl-1,3-*bis*(methoxymethoxy)benzene – 463 276
7.4.1.4 2-Allylbenzene-1,3-diol – 464 277
7.4.1.5 2-Allyl-1,3-*bis*(*tert*-butyldimethylsilyloxy)-benzene – 465 278
7.4.1.6 2-(2,6-*bis*(*tert*-butyldimethylsilyloxy)-phenyl)acetaldehyde – 466 278
7.4.1.7 *(E)*-Ethyl-4-(2,6-*bis*(*tert*-butyl-dimethylsilyloxy)phenyl)-2-methylbut-2-enoate – 467 279
7.4.1.8 *(E)*-4-(2,6-*Bis*(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-en-1-ol – 468 280
7.4.1.9 *(E)*-4-(2,6-*Bis*(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-enyl acetate – 469 281
7.4.1.10 *(E)*-4-(2,6-Dihydroxyphenyl)-2-methylbut-2-enyl acetate – 470 282
7.4.1.11 *(E)*-4-(2,6-*bis*(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-enyl methyl carbonate – 478 283
7.4.1.12 *(E)*-4-(2,6-Dihydroxyphenyl)-2-methylbut-2-enyl methyl carbonate – 479 283
7.4.1.13 Racemic 2-isopropenyl-2,3-dihydrobenzofuran-4-ol – *rac*-247 284
7.4.1.14 (+)-*(S)*-2-isopropenyl-2,3-dihydrobenzofuran-4-ol – (+)-*(S)*-247 285
7.4.1.15 (-)-*(R)*-2-isopropenyl-2,3-dihydrobenzofuran-4-ol – *(R)*-247 286
7.4.1.16 (+)-*(S)*-2-isopropenyl-2,3-dihydrobenzofuran-4-yl acetate – (+)-*(S)*-482 287

7.4.1.17 (-)-*(R)*-2-isopropenyl-2,3-dihydrobenzofuran-4-yl acetate – (-)-*(R)*-482 288
7.4.1.18 *(S)*-2-Isopropenyl-2,3-dihydrobenzofuran-4-yl ((1*S*,4*R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonate – 483 289
7.1.4.19 *(S)*-2-isopropenyl-2,3-dihydrobenzofuran-4-yl 4-bromobenzene-sulfonate – (484) 290
7.4.1.20 *tert*-Butyl 2-(4-(2-isopropenyl-2,3-dihydrobenzofuran-4-yloxysulfonyl)phenyl)-1*H*-indole-1-carboxylate – 484b 290
7.4.1.21 (±)-2-Isopropenyl-2,3-dihydrobenzofuran-4-yl 4-(1*H*-indol-2-yl)benzenesulfonate – 484c 291
7.4.1.22 (+)-*(S)*-2-isopropenyl-2,3-dihydrobenzofuran-4-yl-2-nitrobenzenesulfonate – 485 292
7.4.1.23 (±)-4-(methoxymethoxy)-2-isopropenyl-2,3-dihydrobenzofuran – 486 293
7.4.2 Formal syntheses of fomannoxin and trematone 295
7.4.2.1 (2-Allylphenoxy)(*tert*-butyl)dimethylsilane – 490 295
7.4.2.2 2-(2-(*tert*-Butyldimethylsilyloxy)phenyl)acetaldehyde – 491 295
7.4.2.3 *(E)*-Ethyl 4-(2-(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-enoate – 492 297
7.4.2.4 *(E)*-4-(2-(*tert*-Butyldimethylsilyloxy)phenyl)-2-methylbut-2-en-1-ol – 493 298
7.4.2.5 *(E)*-4-(2-(*tert*-Butyldimethylsilyloxy)phenyl)-2-methylbut-2-enyl methyl carbonate – 494 299
7.4.2.6 *(E)*-4-(2-Hydroxyphenyl)-2-methylbut-2-enyl methyl carbonate – 489 300
7.4.2.7 Racemic 2-isopropenyl-2,3-dihydrobenzofuran from a mixture of 489 and 496 – *rac*-167 and recovery of 496 300
7.4.2.8 (-)-*(S)*-2-isopropenyl-2,3-dihydrobenzofuran – (-)-*(S)*-167 302
7.4.2.9 (+)-*(R)*-2-isopropenyl-2,3-dihydrobenzofuran – (+)-*(R)*-167 303

CHAPTER 8 – APPENDICES 304

8.1 Appendix I – X-Ray crystallographical data 304
8.1.1 X-Ray crystallographical data for 2-(2-acetylfuran-3-yl)-1*H*-indole – 307 304
8.1.2 X-Ray crystallographical data for d(*tert*-butyl) indolo[2,3-*a*]carbazole-11,12-dicarboxylate – 341 312
8.1.3 X-Ray crystallographical data for 2-isopropenyl-2,3-dihydrobenzofuran-4-yl 4-(1*H*-indol-2-yl)benzenesulfonate – 484c 318
8.1.4 X-Ray crystallographical data for (+)-*(S)*-2-isopropylidene-2,3-dihydrobenzofuran-4-yl-2-nitrobenzenesulfonate - 485 325
8.2 Appendix II – Papers published 331
8.2.1 Paper 1 - Metathesis reactions for the synthesis of ring-fused carbazoles 331
8.2.2 Paper 2 - Stereoselective syntheses of the 2-isopropenyl-2,3-dihydrobenzofuran nucleus. Potential chiral building blocks for the syntheses of tremetone, 4-hydroxytremetone and rotenone 331

CHAPTER 9 –REFERENCES 332

PREFACE

A NOTE TO THE READER

Regarding the thesis layout

This thesis consists of work relating to two major topics, namely: The synthesis of carbazole based compounds and the synthesis of benzofuran based compounds. In an effort to allow the thesis to flow as smoothly as possible, these two topics have not been completely separated. Rather, the introductory sections for each component follow one after the other, and similarly for the sections relating to the discussion of synthetic work and the experimental sections.

Interpretation of ^{1}H NMR spectra and ^{13}C NMR spectra

In an effort to allow for ease of reading in terms of the spectral analyses, an unconventional labelling system has been employed in this thesis. To this end, the atoms of the various molecules have been labelled using an alphabetical system rather than the conventional numbering system. Therefore, within a particular synthetic sequence of molecules, once an atom has acquired a label it retains this label throughout the synthetic sequence. This hopefully makes for very easy comparison of spectral changes relating to a particular proton or carbon within the synthetic sequence.

However, for the reader who wishes to peruse a more conventional labelling notation, the two papers that were published in this thesis are to be found in *Appendix II – Papers published*. These two papers, which separately cover the topics of Carbazoles and Benzofurans, contain the full experimental data for almost all of the compounds discussed in this thesis.

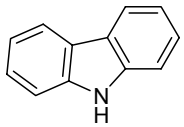
CHAPTER 1 - ABOUT CARBAZOLE ALKALOIDS

1.1 AN INTRODUCTION TO CARBAZOLE BASED NATURAL PRODUCTS

1.1.1 The isolation of interesting carbazoles and associated biological activity

Carbazoles form a small part of a very large group of natural organic compounds known as alkaloids. Alkaloids themselves are basic nitrogen containing compounds occurring mostly, but not exclusively, in the plant kingdom.[1] Carbazoles certainly fall into this group of compounds as they are tricyclic organic compounds containing a nitrogen in the indole moiety.

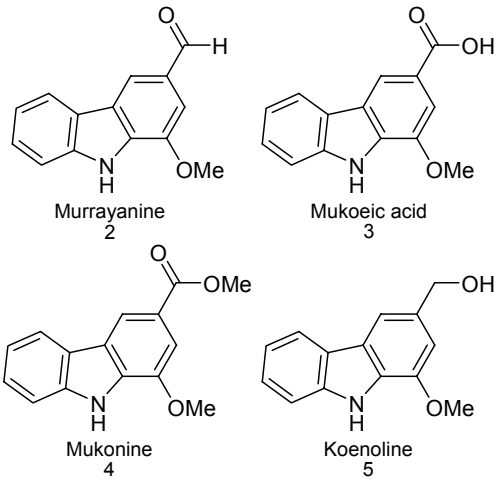
Figure 1



Carbazole
1

Carbazole itself **1** (Figure 1) is the simplest in this class of compounds and was first isolated from coal tar in 1872.[2] In 1965, the first carbazole isolated from a biological source was reported by Chakraborty from *Murraya koenigii*.[3] This 1-methoxy carbazole, subsequently called murrayanine **2** (Figure 2), was isolated from the stem bark. In India, *Murraya koenigii* is more commonly known as the 'curry-patta' and the leaves are used as a spice in curry dishes. Moreover, the plant is also used medicinally as it exhibits antibiotic properties.[4] This particular trait is not surprising as it was later discovered that the plant contained an abundance of various interesting and biologically active carbazoles. In fact, the genus *Murraya* is now known to be the richest source of naturally occurring carbazoles.[5] Other interesting carbazoles oxygenated in the 1-position which have also been isolated from *Murraya koenigii* include mukoeic acid **3** and its ester analogue, mukonine **4**, isolated from the stem bark. Koenoline **5**, isolated from the root of *Murraya koenigii* was found to be cytotoxic.[6]

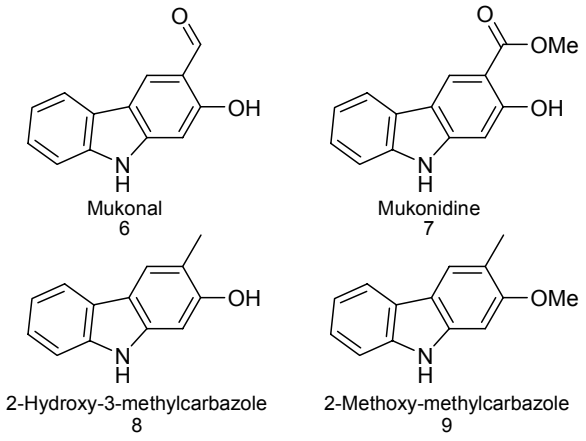
Figure 2



1-Oxygenated carbazoles from *Murraya Koenigii*

Carbazoles oxygenated in the 2-position, isolated from *Murraya koenigii* include mukonal **6** (Figure 3), mukonidine **7**, 2-hydroxy-3-methylcarbazole **8** and 2-methoxy-3-methylcarbazole **9**.[4] However, it might be interesting at this time to point out that most carbazoles isolated from *Murraya koenigii* contain a carbon in the 3-position, found in various states of oxidation.

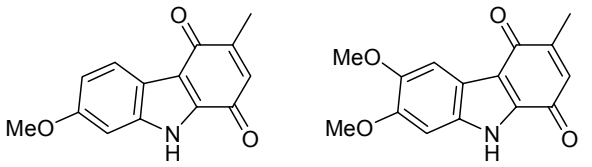
Figure 3



2-Oxygenated carbazoles from *Murraya Koenigii*

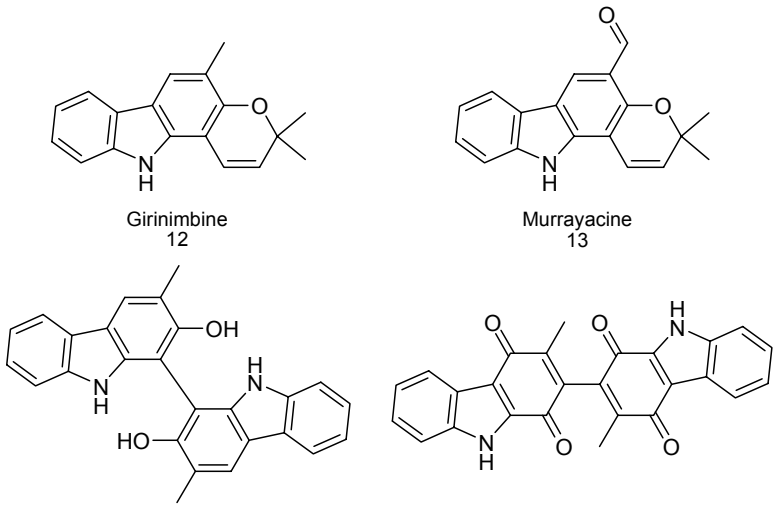
Structurally different quinone derivatives of carbazoles found in *Murraya koenigii* include koeniginequinone A **10** and B **11** (Figure 4), isolated by Chowdhury from the stem bark of the plant.[7]

Figure 4



Slightly more complicated carbazole alkaloids isolated from *Murraya koenigii* (Figure 5) include pyranocarbazoles such as girinimbine **12** and murrayacine **13**.[4] *Bis*-carbazoles such as 1,1′-*bis*-(2-hydroxy-3-methylcarbazole) **14** and *bis*-murrayaquinone-A **15** were isolated by Furukawa *et al*. from *Murraya koenigii* and in fact *bis*-murrayaquinone-A was the first dimeric carbazolequinone alkaloid to be isolated in nature.[8]

Figure 5



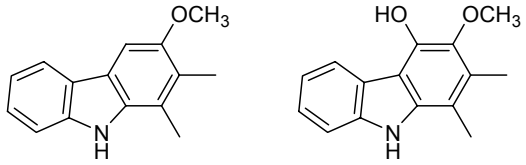
All of the carbazoles mentioned thus far have been extracted from various parts of *Murraya koenigii*, however, some of these are also found in other plants. Girinimbine **12**, for example was first isolated from *Murraya koenigii*,[9] then subsequently Joshi and co-workers isolated this compound from *Clausena heptaphylla*.[10]

Without a doubt the plant genus *Murraya* contains the richest source of carbazole alkaloids. Plants of the genera *Glycosmis* and *Clausena* contain a somewhat more limited variety of carbazole alkaloids. Interesting alkaloids have also been isolated from the lower

mould genus *Streptomyces*, as well as other natural sources such as from the blue-green algae *Hyella caespitosa*, *Aspergillus* species.[5]

As mentioned previously, many of the carbazole alkaloids exhibit interesting and potentially useful biological activity. Some of the more interesting carbazoles include deoxycarbazomycin-B **16** (Figure 6) which is derived from natural carbazomycin-B **17**. Deoxycarbazomycin-B exhibits significant inhibitory activity against Gram-positive and Gram-negative bacteria.[11]

Figure 6

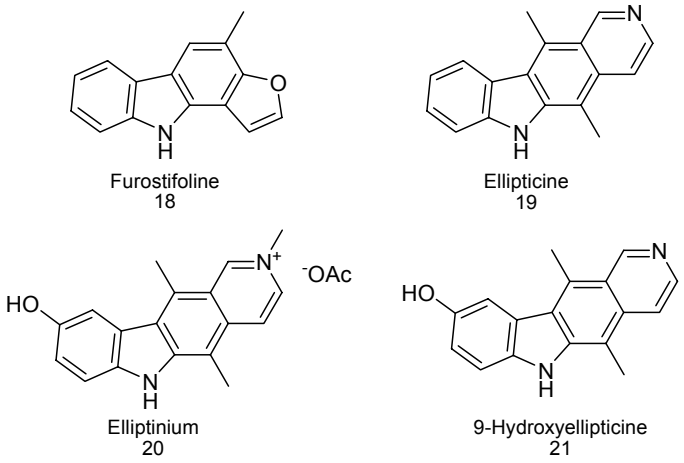


4-Deoxycarbazomycin B
16

Carbazomycin B
17

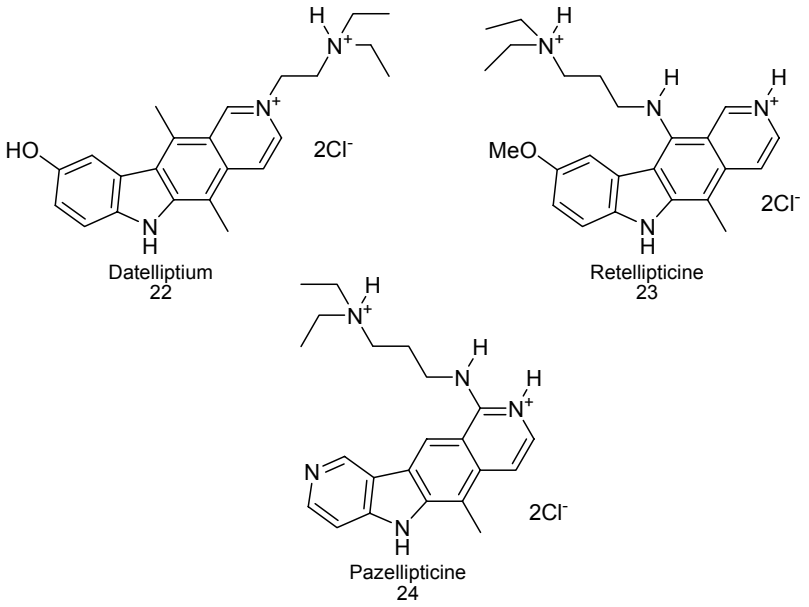
Carbazole alkaloids exhibiting somewhat more interesting biological activity include the heteroaryl annulated alkaloids (Figure 7).[4] For example, furostifoline **18**, a furo[3,2-*a*]carbazole alkaloid was first isolated by Furukawa and co-workers from *Murraya euchrestifolia* in 1990.[12] Although the pharmacological potential of furostifoline has not yet been fully established, interest in the compound exists in light of the fact that it is structurally similar to some indolo-isoquinolines and indolo-quinolines which possess antiretroviral activity.[13,14] Pyrido[4,3-*b*]carbazole alkaloids came under the spotlight in the 1970's and 1980's as it was discovered that they generally exhibit antitumour activity.[15] This stemmed from the isolation of ellipticine **19** from *Ochrosia elliptica* in 1959 by Goodwin[16] and the subsequent observations by Dalton and co-workers that the compound exhibited significant anti-tumour activity.[17] Subsequently, synthetic methodology towards these types of compounds grew and this resulted in the synthesis of *N*-2-methyl-9-hydroxy ellipticinium acetate (elliptinium) **20**, an analogue of 9-hydroxyellipticine **21**. This compound showed significant anti-tumour activity and was commercialised for the treatment of several types of cancer.[18]

Figure 7



The synthesis of a number of other compounds in this class led to the development of a second generation of pyrido-carbazole based anti-cancer agents (Figure 8). Datelliptium **22**, retellipticine (BD-84) **23** and pazellipticine (PZE or BD-40) **24** were all developed as clinical candidates.[5]

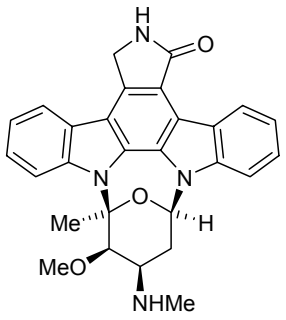
Figure 8



In continuation with our discussion on heteroaryl-annulated carbazoles perhaps the most significant structure class would be the indolocarbazole alkaloids. Without a doubt, this class of compounds is the most extensively studied and this is due to their interesting and

useful biological properties. Staurosporine **25** (Figure 9) was the first indolocarbazole to be discovered in nature from *Streptomyces staurosporeus* by Omura and co workers in 1977.[19] However, the absolute configuration of the compound remained unknown until 1994, when X-ray crystallographic data on the 4′-*N*-methylstaurosporine methiodide revealed the true structure.[20] In the meantime, studies on the potential usefulness of **25** had led to some promising results. Perhaps the most significant finding was the compound's tendency to inhibit protein kinase C (PKC), making it a potential candidate as an anti-cancer drug. This particular property was later discovered to be a common feature in other compounds of this class. Staurosporine was also found to possess antimicrobial properties, inhibited platelet aggregation and was found to be cytotoxic.[5]

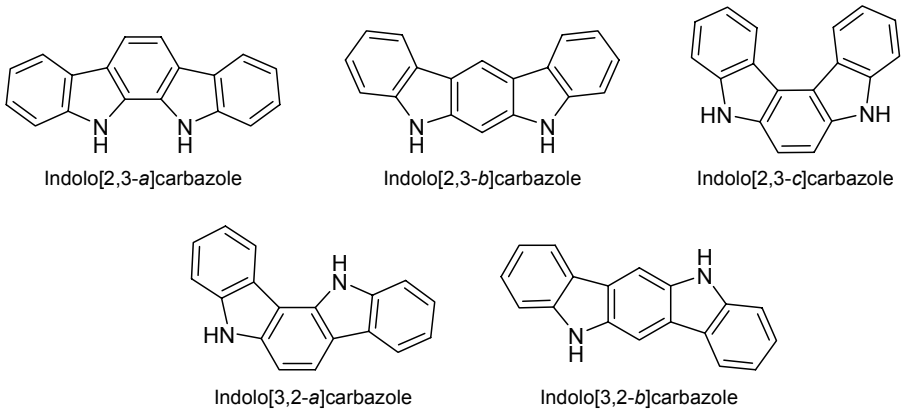
Figure 9



(+)-Staurosporine
25

When one considers the indolocarbazole framework there are in fact five different isomeric ring systems which are possible (Figure 10): The indolo[2,3-*a*]carbazoles, indolo[2,3-*b*]carbazoles, indolo[2,3-*c*]carbazoles, indolo[3,2-*a*]carbazoles and indolo[3,2-*b*]carbazoles.

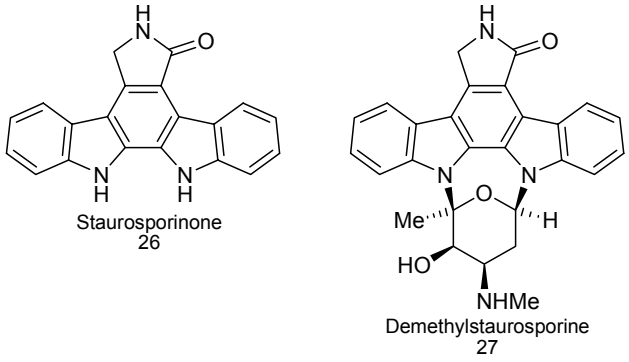
Figure 10



However, nearly all the research focus has been concentrated on the indolo[2,3-*a*]carbazoles and this is not surprising as this is the only isomeric form which is found naturally. Although synthetic versions of the other isomers have appeared in the literature they have shown little to no interesting or useful biological activity, with perhaps the indolo[3,2-*a*]carbazoles as a slight exception. Several aza analogues of this particular isomer were shown to be powerful benzodiazepine receptor ligands.[21,22]

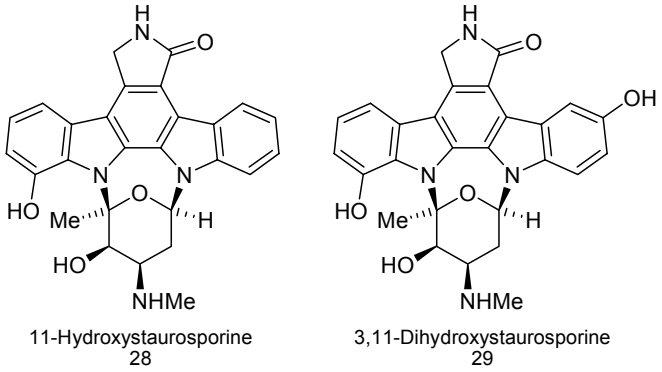
Most of the indolocarbazoles isolated from nature contain a pyrrole-based ring on the *c*-face of the carbazole moiety. For instance, staurosporine **25** contains a lactam in this position. Subsequent to the isolation of staurosporine in 1977, a very similar alkaloid was isolated from *Nocardiopsis* strain K-290, in 1986. The only difference between this compound and staurosporine was the lack of the sugar moiety and it was thus named staurosporinone **26** (Figure 11).[23,24] Demethylstaurosporine **27**, a staurosporine analogue, was then isolated from a modified strain of *Streptomyces longisporoflavus*.[25] Although this alkaloid was found to be less potent than staurosporine it did show a more selective inhibitory activity toward PKC isotypes α, β-2, and γ.[5]

Figure 11



The indolocarbazoles discussed thus far have all been isolated from various slime moulds and soil organisms, however, in 1992 Scheuer isolated 11-hydroxystaurosporine **28** and 3,11-dihydroxystaurosporine **29** (Figure 12) from the Pohnpei tunicate *Eudistoma sp.*[26] These were the first examples of carbazoles in this structural class isolated from an animal source.[5]

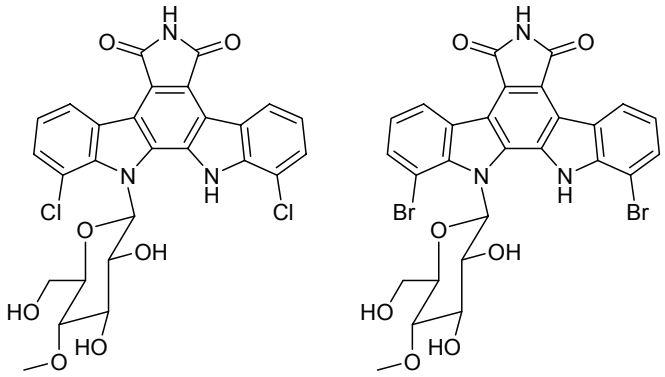
Figure 12



Indolocarbazoles of this structural type have also been isolated with a single *N*-glycosidic bond (Figure 13). Perhaps the most famous of these would be rebeccamycin **30**, isolated from *Saccharothrix aerocolonigenes* in 1985 by Nettleton and co-workers.[27] Rebeccamycin is a potent anti-tumour agent and is currently in the final stages of clinical trials as an anti-cancer agent. The mechanism by which this compound exhibits this activity is by topoisomerase I mediated DNA cleavage.[28] Shortly after this discovery, a bromo-analogue of this compound was obtained by culturing *S. aerocolonigenes* in the presence of bromide ions – the intention being to create a more water soluble compound

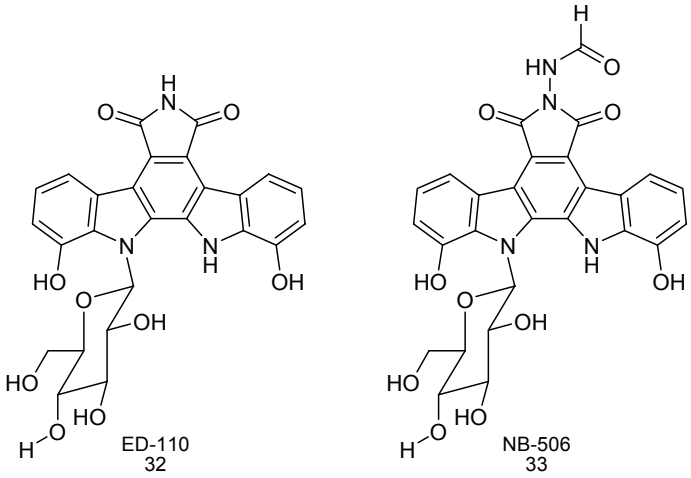
with increased anti-tumour activity.[5] This so-called 'bromo-rebeccamycin' **31** is also in the process of undergoing clinical trials as a possible anti-cancer drug.[29]

Figure 13



Two semi-synthetic derivatives of rebeccamycin, ED-110 **32** and NB-506 **33** (Figure 14) have been prepared as possible anti-cancer agents.[30,31] In comparison to rebeccamycin, an increase in water solubility was observed for ED-110 and this compound was found to be cytotoxic (*in vitro*) against a number of cancer cell lines. ED-110 also exhibited *in vivo* anti-tumour activity in xenotransplanted mice.[5] NB-506 showed *in vivo* anti-tumour activity in that a phase I clinical trial utilising this compound resulted in a reduction in tumour specific markers in ovarian and breast cancer patients clinically resistant to taxol therapy.[5]

Figure 14



1.1.2 Indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles, and the cell cycle

Although it has not been discussed in detail up to this point, the presence of the *N*-heterocycle on the carbazole nucleus of all of the biologically active indolocarbazoles discussed is of vital importance to the activity of these compounds. Perhaps at this point it would be pertinent to discuss the biochemical aspects of these compounds, and the mechanism by which they inhibit certain kinases resulting in their efficacy as anti-cancer agents.

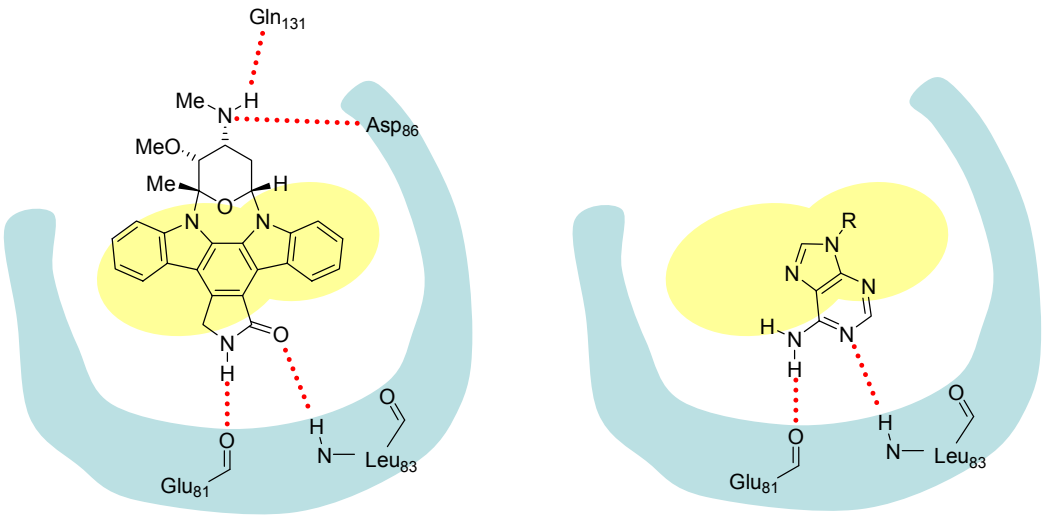
Cell proliferation, or the cell cycle can be divided into four phases.[32] The first phase is known as the G1 phase and is the onset of events. At this point cell proliferation is initiated by extracellular growth factors, however, the process can be halted by anti-proliferation agents. Late in the G1 phase there exists a restriction whereupon cell proliferation is either terminated or set to continue, without the need of intervention from external influences. Beyond this, the cell begins to make preparations for the process. Enzymes and proteins required for DNA replication are synthesised. Once DNA synthesis starts, the cell enters the S-phase and the chromosomes are duplicated. Following this, the G2 phase begins and at this time the new DNA is verified and repaired. Finally, during the M-phase the duplicated DNA is separated and the cell splits into daughter cells where the process may begin again. A successful cell division requires that these processes start and end precisely. There are control mechanisms that permit the transition from phase to phase across these checkpoints provided certain critical events are fulfilled.[32] Cyclin-dependent kinases (CDKs) are vitally important in the regulation of the crossing of these checkpoints.

There are ten known CDKs currently although it is believed that only the first 6 are directly involved in the cell cycle.[32] The other kinases are involved indirectly. Activation of the CDKs themselves occurs once they bind to their corresponding cyclin. In fact, the CDKs are always present in the cell, essentially at constant concentration levels, and it is the cyclins which are synthesised and degraded at appropriate times. Therefore, it is the cyclins which act as switches, activating their corresponding cyclin-dependent kinase.[32] Although the CDKs 1-6 are involved in various parts of the cell cycle, we'll focus our attention on the function of CDK4, which is critical in the process of moving from the G1 phase to the S phase of the cell cycle. If CDK4 is inhibited then the cell cycle is arrested at the G1 phase. Just as the cyclins are activators for their various CDKs, there are

proteinogenous inhibitors which also help to regulate the activity of the CDKs. These inhibitors can be broken up into two families, namely the CIP/KIP and INK4 families. Although the specific activity of these inhibitors will not be discussed in detail here, what is important is that the INK4 family of CDK inhibitors (CKIs) act specifically against CDK4 and 6. Interestingly, over 60% of human tumours show defects in the INK CKIs (specifically $p16^{INK4a}$).[32] In essence, one of the major causes of uncontrolled cell proliferation (tumour growth) is the failure of control mechanisms to switch off CDK4. It is for this reason that there is an interest in molecules such as staurosporine which act as CDK inhibitors.

Staurosporine was found to be a potent ATP-competitive CDK inhibitor. That is, staurosporine competes for the same binding site in the CDK protein pocket as ATP would. Unfortunately, staurosporine shows poor selectivity in its inhibition and it is capable of inhibiting other kinases by competing for the ATP pocket in the protein's active site. The reason for this is that staurosporine is simply 'too good' at mimicking ATP. The lactam ring of staurosporine is the binding point to the active site and the hydrogen bond donor and acceptor points on this lactam ring are very similarly arranged to that of the adenyl group of ATP* (Figure 15). The hydrogen bond donor and acceptor points on the lactam ring of staurosporine are structurally very similarly arranged to the donor and acceptor points of ATP.[32]

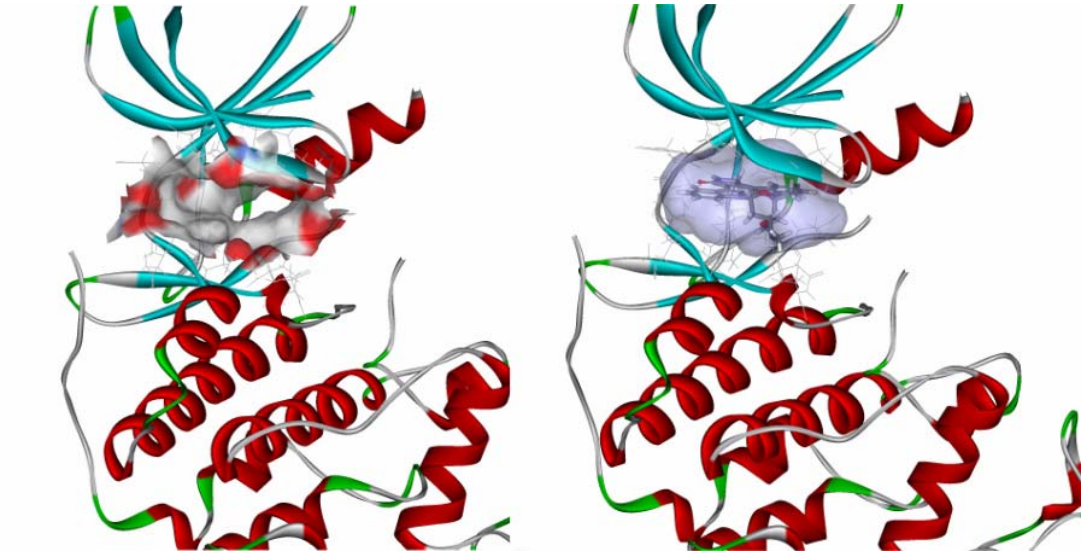
Figure 15



* The adenyl group is the binding point for ATP in the same pocket.

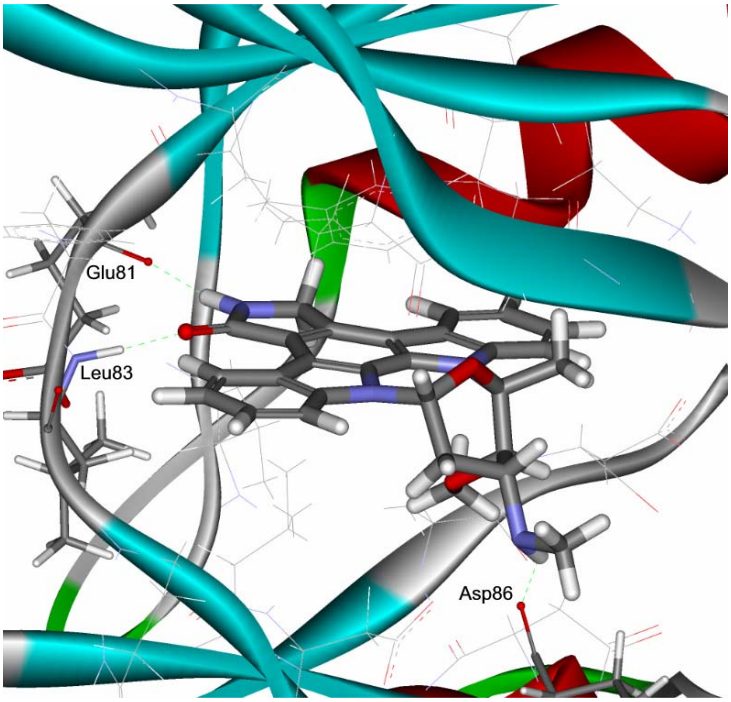
An X-ray crystal structure of human CDK2 containing staurosporine reveals the binding mode of these types of compounds within the active site.[33] The illustrations below show a graphically rendered protein and a Connolly surface (Figure 16 - left) has been generated to highlight the binding pocket. Staurosporine fits perfectly into this binding region (Figure 16 - right) preventing ATP from binding.

Figure 16



The staurosporine molecule is bound in the ATP binding site with the NH from the carbazole lactam forming a hydrogen bond with the backbone of the carbonyl of Glu81 (Figure 17). The carbonyl from the staurosporine lactam forms a hydrogen bond acceptor point, bonding with the backbone amide NH of Leu83, thus mimicking the binding mode of ATP. Moreover, there is another hydrogen bonding interaction somewhat out of the docking pocket formed by the secondary amine hydrogen of the glycal moiety on staurosporine interacting with Asp86 (hydrogen bonding interactions are illustrated as dashed yellow lines).

Figure 17



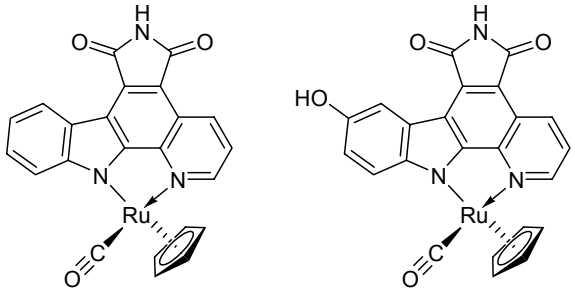
1.1.3 A new generation of potent Ru containing carbazoles

The issue of staurosporine-type compounds being unselective in their potent inhibition of various kinases is a topic that is being addressed by various groups. An intriguing approach is currently being adopted by Meggers and co-workers. Their area of interest is the use of metal centres as templates to more rigidly define the shape of their staurosporine-type kinase inhibitors, and this is being achieved with a significant amount of success.[34-37] The use of various metal complexes for medicinal purposes is by no means a novel idea. For instance, a platinum based drug is widely used for the treatment of cancer.[38] However, in these particular drugs, it is usually the metal itself that is the reactive centre of the molecule. Unfortunately, this also means that these drugs are associated undesirably toxic side effects. However, the ruthenium that is incorporated into the carbazole complexes being developed by Meggers serves no more than to act as a scaffold, imparting the correct geometry for the molecule so that it is more specific in binding to the associated active site of a particular protein. It is the shape of the molecule that determines its specificity in binding to the corresponding 'pocket' in the active site of the protein. The metal is essentially inert in the complex. The inactivation of the specific kinase is still due to the competitive binding of the carbazole complex to the ATP site, analogous to staurosporine.

Moreover, the presence of the ruthenium does not alter the binding mode of the compound. The key docking hydrogen bonds are still associated with the lactam ring of the carbazole.

The Ru compounds below, synthesised by Meggers *et al.* (Figure 18) were found to be potent glycogen synthase kinase (GSK) inhibitors. Compound-A **34** was found to have an IC_{50} inhibition of the protein kinase GSK-3 at just 3 nM. Hydroxylation of this compound (compound-B **35**) increased its activity, the IC_{50} inhibition of the same kinase was found to be just 30 pM.[34] In addition, as opposed to staurosporine-like compounds which are relatively unselective in their kinase inhibition, **35** does not inhibit any of the other kinases, even though the binding sites for these proteins are all quite similar.[35]

Figure 18

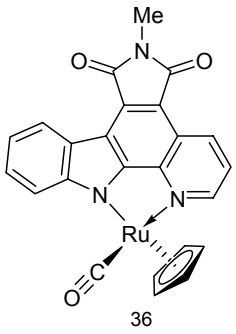


Compound-A
34

Compound-B
35

In order to confirm that this was indeed the binding pattern, in other words, that it was the lactam moiety which binds to the same site as would ATP, and competition for this binding site infers the observed biological activity on this compound, the imide hydrogen was replaced by a methyl group, forming **36** (Figure 19). This would of course eliminate the key hydrogen bonding interaction between the imide hydrogen and the carbonyl of Asp133, which is the relevant hydrogen bonding acceptor on the protein, GSK-3. This modification to the compound abolishes its ability to inhibit this kinase. To achieve the same measure of inhibition, thirty times the concentration of **34** was required, (a change in the IC_{50} from 10nM to 300 nM was observed).[35]

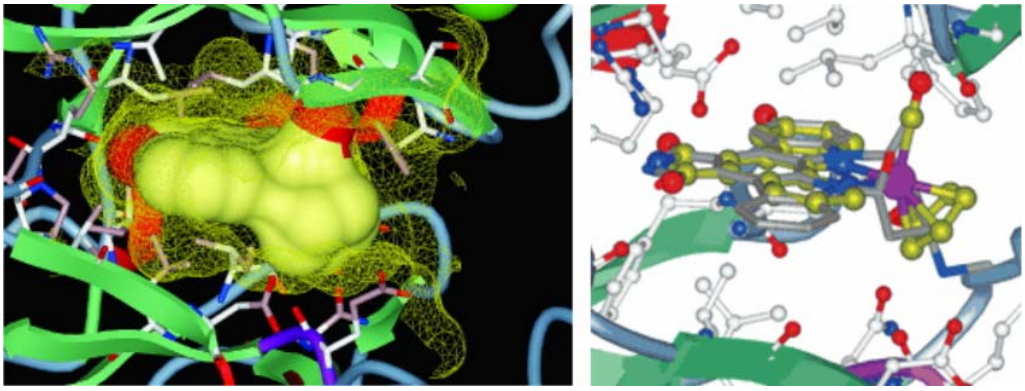
Figure 19



36

The molecular modelled interaction of compound-A bound to GSK3β illustrates how the molecule binds in the ATP site of the protein, and an overlay with staurosporine illustrates the similarity in spatial structure of these two compounds (Figure 20).[35]

Figure 20



This discussion of various natural and unnatural carbazoles highlights the isolation of the first and most simple of carbazoles, covers briefly a range of interesting heteroaryl fused carbazoles possessing some useful biological properties and finally progresses on to the indolo[2,3-*a*]carbazoles and it is clear that these carbazoles are by far the most biologically active against a range of kinases, provided the pyrrole ring is present on the *c*-face of the carbazole to facilitate binding to the ATP site in the kinase protein. Finally, a new generation of carbazole kinase inhibitors which contain a ruthenium metal atom to serve as a structural scaffold were discussed, and these compounds were found to be exceptionally active against various kinases. More importantly, some of these compounds were very specific in their inhibition, rendering them potentially more useful as potential drug candidates than the traditional staurosporine-type compounds. There have been many

excellent reviews covering these topics over the past few years and these have been referenced in this discussion. Perhaps at this point, a discussion on some of the present syntheses of several of the carbazoles that were of interest to us would be pertinent.

1.2 SELECTED SYNTHESES OF CARBAZOLE COMPOUNDS

For this particular research project we were interested in two main areas: The synthesis of furostifoline and its analogues, and the development of a new synthetic route to access the most important carbazole structural type in terms of biological activity, namely, the indolocarbazoles. The syntheses of these compounds are discussed in this next section.

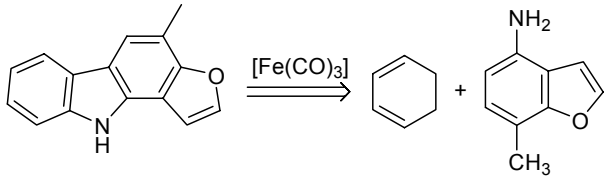
1.2.1 Total syntheses of furostifoline

Over the past eight years there have been six total syntheses of furostifoline reported in the literature. These syntheses will be covered briefly here.

1.2.1.1 The first total synthesis of furostifoline – An iron mediated synthesis

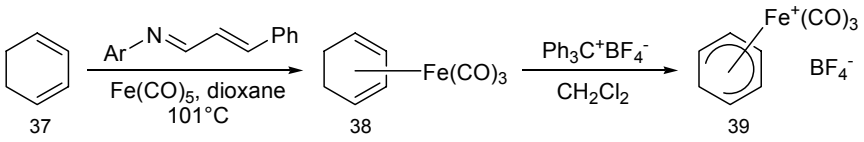
In 1996, Knölker and co-workers reported the first total synthesis of furostifoline, employing an iron mediated cyclisation to generate the carbazole framework as the key step in the synthesis (Scheme 1).[39]

Scheme 1



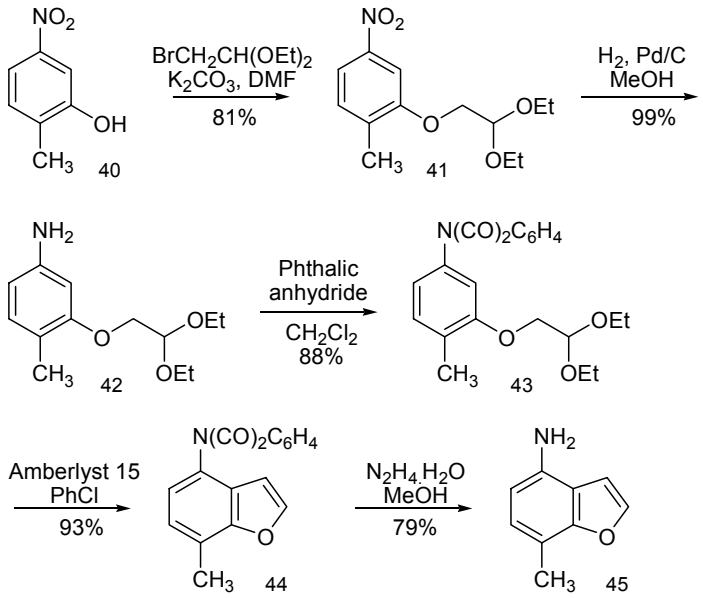
Generation of the iron complex salt **39** (Scheme 2) required for the reaction was achieved by azabuta-1,3-diene catalyzed complexation of cyclohexa-1,3-diene **37** in the presence of pentacarbonyl-iron affording **38**. This was followed by hydride abstraction using triphenylcarbenium tetrafluoroborate. In this way, it was possible to generate the iron complex **39** in multi-gram scale.

Scheme 2



The synthesis of the other key precursor **45** started from nitrophenol **40** (Scheme 3). This compound was easily derived from the corresponding aniline and had been synthesised before by this group as a precursor in the synthesis of dihydroxygirinimbime.[39] Alkylation of the phenol **40** using bromoacetaldehyde diethylacetal afforded **41** in good yield. Reduction over Pd/C produced amine **42**, which was then protected as the phthalic imide **43**. Under acid catalysed conditions, **43** was cyclised to the benzofuran **44** in excellent yield. Finally, cleavage of the imide **44** using hydrazine hydrate afforded the required key precursor **45** in 52% overall yield from the nitrophenol. In this way, **45** could be prepared on a multi-gram scale.[39]

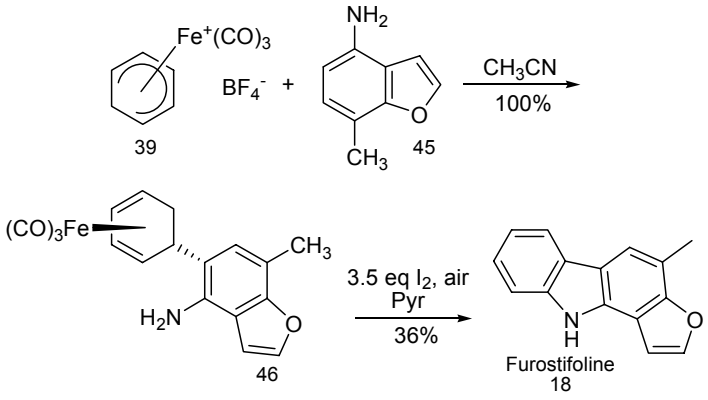
Scheme 3



Combining the two key precursors by means of an electrophilic aromatic substitution reaction afforded exclusively the desired regioisomer **46** in quantitative yield (Scheme 4). The final oxidative cyclisation was initially attempted using MnO_2 but this resulted in complete decomposition of the iron complex **46**. A modified procedure, involving cyclisation of **46** with concomitant aromatisation was finally achieved in air using iodine

and pyridine. The natural product, furostifoline **18**, was thus obtained in nine steps and 19% overall yield.[39]

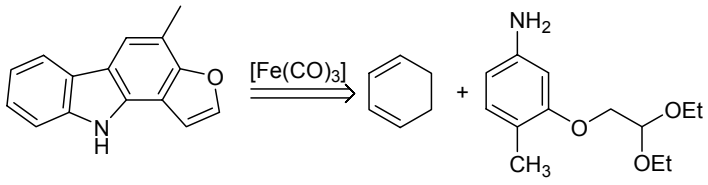
Scheme 4



1.2.1.2 An improved iron mediated synthesis

Four years after publishing the first total synthesis of furostifoline, Knölker and Fröhner published an improvement on their iron mediated synthesis.[40] By conducting the iron mediated aryl amine cyclisation to synthesise the carbazole before generating the furan ring, the need for protection of the amine was obviated, thus shortening the synthesis by two steps. The key disconnection is therefore subtly different (Scheme 5).

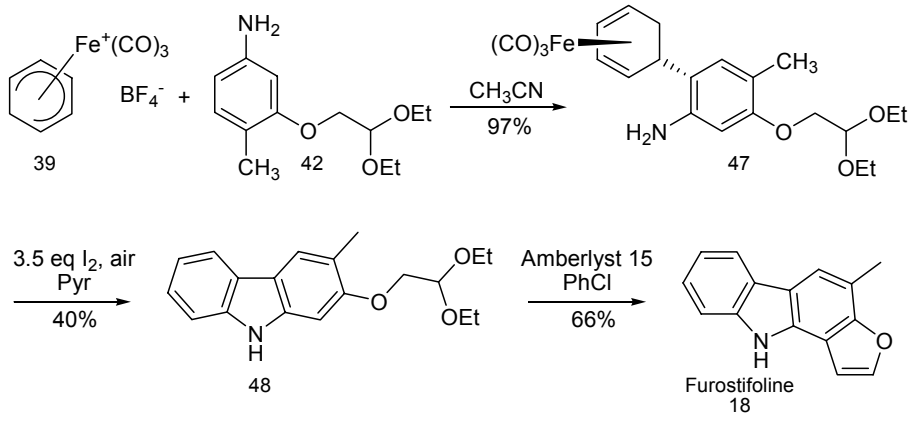
Scheme 5



The syntheses of the Fe complex salt 39 **and the amine** 42 **were carried out as per the initial synthesis (**

Scheme 6).[39] However, instead of first generating the furan, these two compounds were reacted generating the complex **47** in good yield. As before, the carbazole was generated by cyclisation of **47** with concomitant aromatisation affording **48** in a modest yield. Annulation of the furan ring by acid catalysis (Amberlyst 15) afforded furostifoline **18** directly, shortening the original synthesis to only seven steps and an overall yield of 21%, a slight improvement on the 19% obtained in the original synthesis.[15]

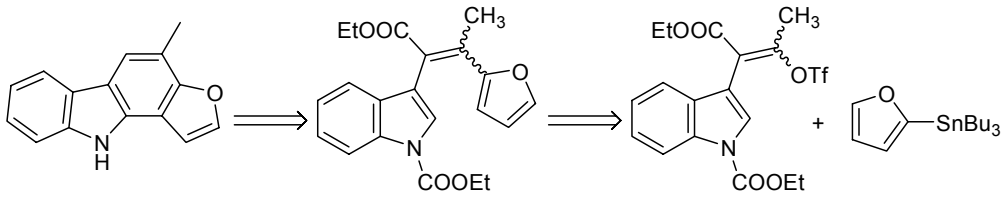
Scheme 6



1.2.1.3 A Stille coupling and oxidative photocyclisation method

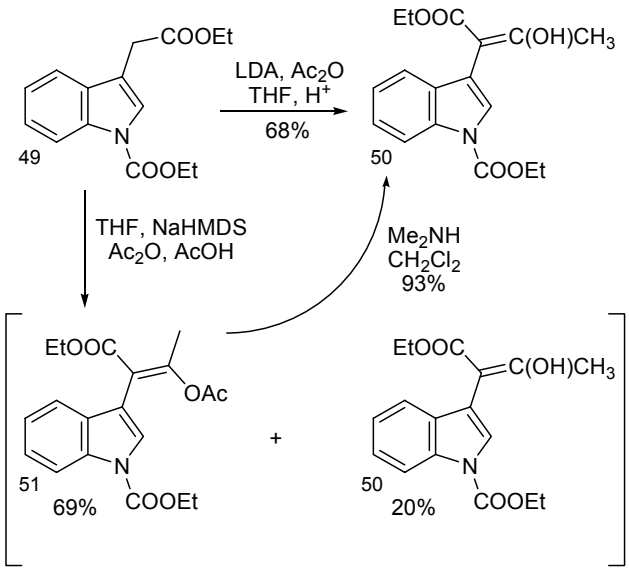
Two years after Knölker's original synthesis of furostifoline, Beccalli and co-workers published a synthesis which started with the indole ring already intact, and employed a Stille coupling and photocyclisation as key steps (Scheme 7).[41]

Scheme 7



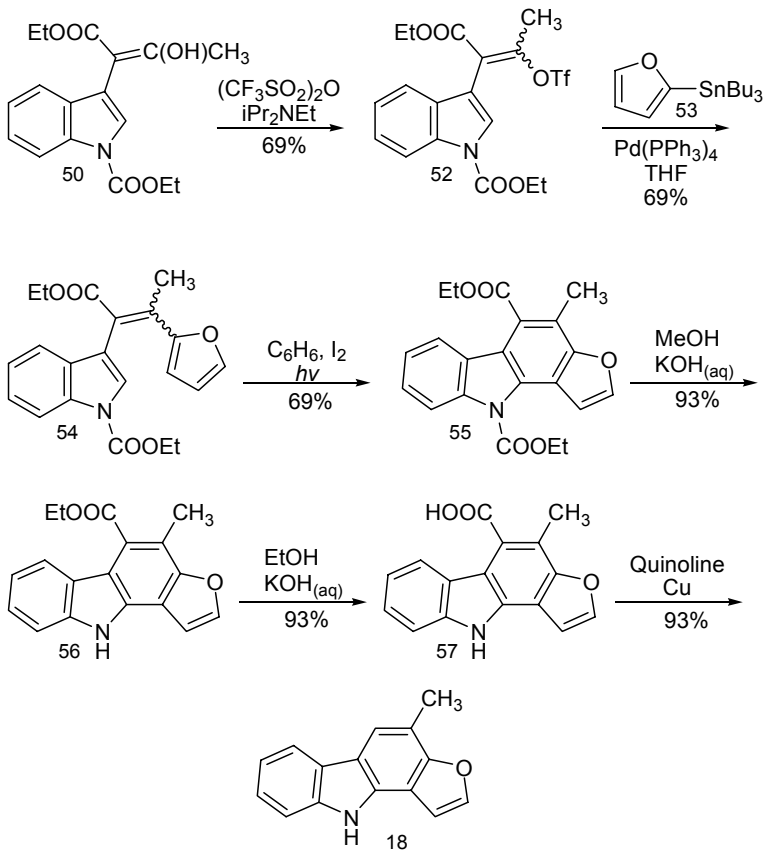
Starting from 3-ethoxycarbonylmethyl-indole-carboxylic acid ethyl ester **49 (**Scheme 8**)**, **50** could be synthesised directly using LDA and acetic anhydride at -20 °C in 68% yield. In an effort to improve the yield, an alternative procedure was employed whereupon **49** was treated with NaHMDS and acetic anhydride at -70°C but this afforded only 20% of **50** and 69% of **51**. Fortunately, **51** could easily be converted to **50** by treatment with dimethylamine in good yield. Thus, **50** was subsequently synthesised using this two step route in an improved overall yield of 84% over the two steps.[41]

Scheme 8



Treatment of **50** (Scheme 9) with trifluoromethanesulfonic anhydride produced a 1:1 mixture of the geometric isomers **52** which were not separable.[41] This did not pose a problem, and the furan **53** was coupled to the mixture by means of a Stille coupling affording a 1:1 mixture of the inseparable diastereomers **54**. This vinyl-furan regio-isomeric mixture was then subjected to photocyclisation in the presence of iodine affording the carbazole **55** in an acceptable yield. Alkaline hydrolysis of the carbamate affording **56**, was followed by similar alkaline hydrolysis of the aryl ester, affording **57**, which was subsequently decarboxylated finally affording furostifoline **18** in 30% overall yield based on **49**.

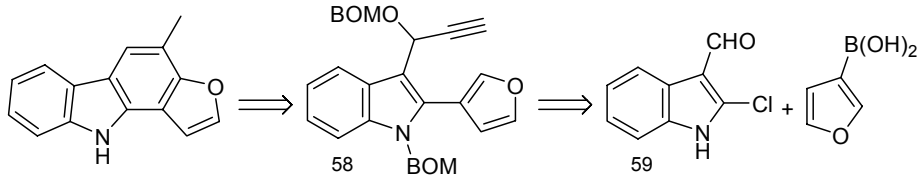
Scheme 9



1.2.1.4 Thermal electrocyclisation of a 2,3-disubstituted indole

In the same year, Hibino and co-workers developed an interesting synthesis of furostifoline employing a new type of thermal electrocyclisation reaction.[42,43] The key intermediate required for this reaction was the 2-(fur-3-yl)-3-propargylindole **58**, derived from the indole-carbaldehyde **59** (Scheme 10).

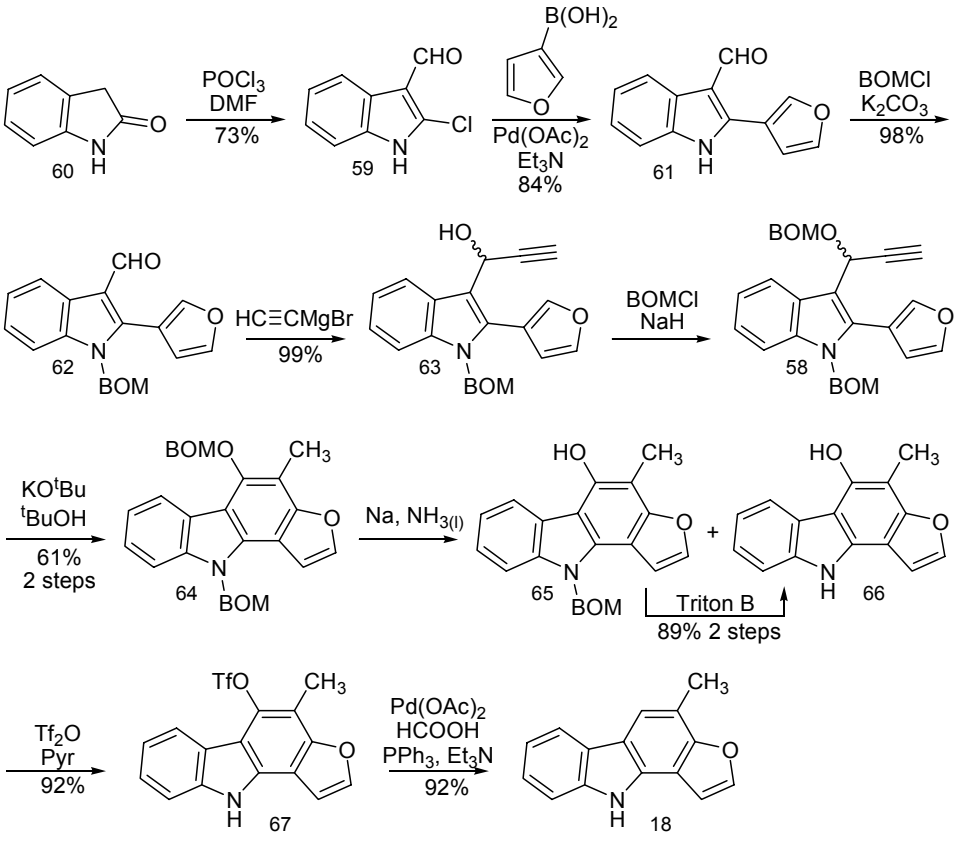
Scheme 10



Starting with commercially available oxindole **60** (Scheme 11), a Vilsmeier reaction afforded the 2-chloroindole-carbaldehyde **59**. A Suzuki coupling of this compound with furan-3-boronic acid followed by BOM protection of the indole nitrogen afforded **62**, with

excellent yields being obtained over both steps. Introduction of the alkyne by means of a Grignard reaction forming **63**, followed by BOM protection of the resulting alcohol proceeded in an acceptable yield over the two steps forming **58**. With this key intermediate in hand, generation of the carbazole **64** was achieved by thermal electrocyclisation in the presence of KO^{t}Bu at 90 °C. Simultaneous removal of the BOM protecting groups did not proceed as planned and a mixture of the desired completely deprotected compound **66** as well as a significant amount of **65** was obtained. Fortunately, **65** was easily converted to the desired deprotected compound **66** with Triton B in almost quantitative yields. Finally, removal of the hydroxyl functionality was achieved by initially converting the phenolic hydroxyl to the corresponding triflate **67** and then elimination of this functionality utilising palladium to afford furostifoline **18** in an impressive 29% overall yield over ten steps, starting from the oxindole **60**.[44]

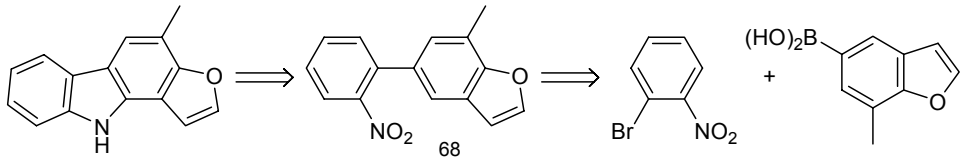
Scheme 11



1.2.1.5 Cyclisation using a nitrene

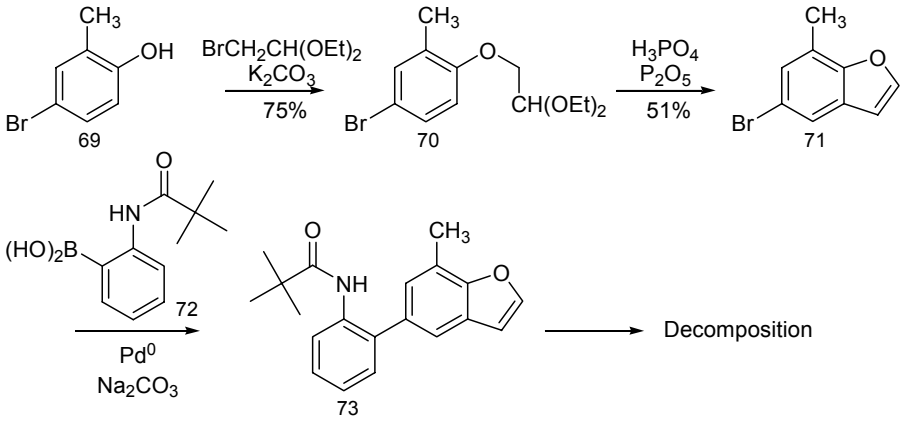
In the following year (1999), Timári and co-workers published a very short synthesis of furostifoline, obtaining the natural product in just six steps by employing a nitrene-based cyclisation. The key intermediate for the nitrene cyclisation involved synthesising the nitro-biaryl **68** (Scheme 12).

Scheme 12



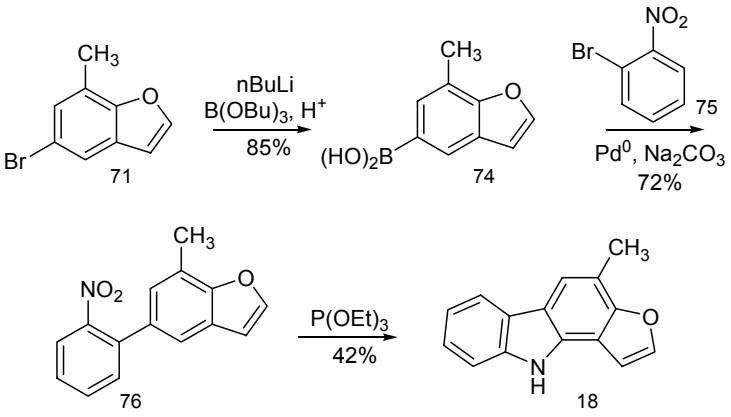
In their initial approach towards the synthesis of furostifoline (Scheme 13), Timári and co-workers synthesised the amide **73**. This was accomplished by brominating *o*-cresol to form the bromo *o*-cresol **69**. Alkylation of **69** was achieved in an acceptable yield forming **70** and this put Timári and co-workers in a position to form the furan **71** by acid catalysed annulation in a manner not too dissimilar to the method used by Knölker in 1996.[39] However, the somewhat harsher conditions employed in this synthesis resulted in the formation of the furan ring in only a modest yield. Coupling of the benzofuran derivative **71** to the boronic acid **72** proceeded in an acceptable yield but unfortunately at this point the synthesis drew to a halt as all attempts to hydrolyse the amide **73** to the corresponding amine resulted only in decomposition, most likely due to the sensitivity of the furan ring to the acidic conditions.[44]

Scheme 13



Thus a slight change in strategy was required (Scheme 14) and to this end the bromo-benzofuran **71** was converted to the corresponding boronic acid **74** and coupled with bromonitrobenzene **75**. Utilising conditions well known in the literature, the biaryl nitro compound **76** was reductively cyclised via the nitrene to afford furostifoline **18**.[44] The best yield was obtained in refluxing triethylphosphite (42%) however, furostifoline was also similarly obtained using ferrous oxalate in a poorer yield (26%). In summary, this synthesis affords furostifoline in six steps and 8% overall yield.

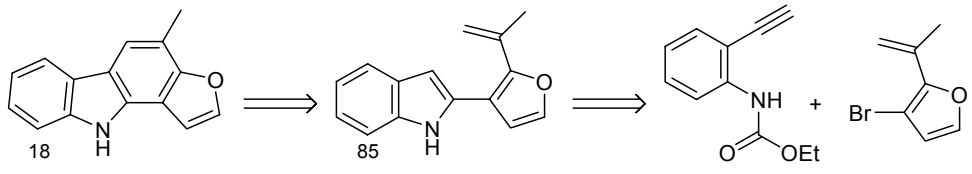
Scheme 14



1.2.1.6 Synthesis of furostifoline by a tetrabutylammonium fluoride promoted ring formation

In 2002 Yasuhara and co-workers described a synthesis of furostifoline involving initially a tetrabutylammonium-fluoride promoted cyclisation to form the indole moiety **85**, followed by a light mediated electrocyclisation to form the carbazole structure, and furostifoline **18** itself (Scheme 15).

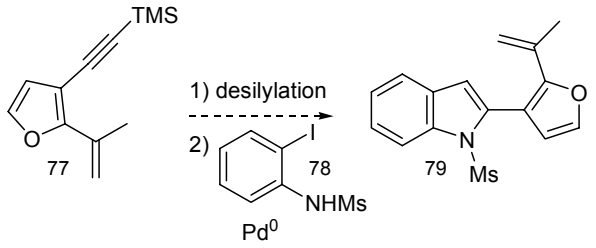
Scheme 15



In their initial approach toward the synthesis of furostifoline, Yasuhara and co-workers hoped to capitalise on methodology they had developed previously whereupon they observed that palladium catalysed cross coupling of *N*-(2-iodophenyl)methanesulfonamide

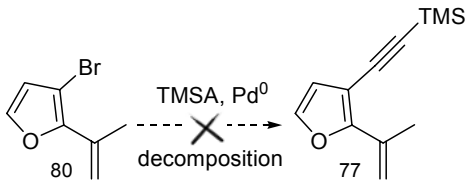
with terminal alkynes afforded 2-substituted indoles.[45] In order to utilise this methodology for the synthesis of furostifoline, Yasuhara and co-workers envisaged that they would need to prepare 3-trimethylsilylethenyl-2-(isopropenyl)furan **77** (Scheme 16). Reaction of this compound with *N*-(2-iodophenyl)methanesulfonamide **78** should lead to the desired indole precursor **79**, setting the stage for a light mediated cyclisation which should afford the *N*-mesylated analogue of furostifoline.[46]

Scheme 16



Unfortunately, synthesis of the required 3-trimethylsilylethenyl-2-(isopropenyl)furan **77** by Sonogashira coupling of trimethylsilylacetylene with isopropenyl-2-(3-bromo)furan **80** (Scheme 17) was unsuccessful and another approach had to be adopted.[46]

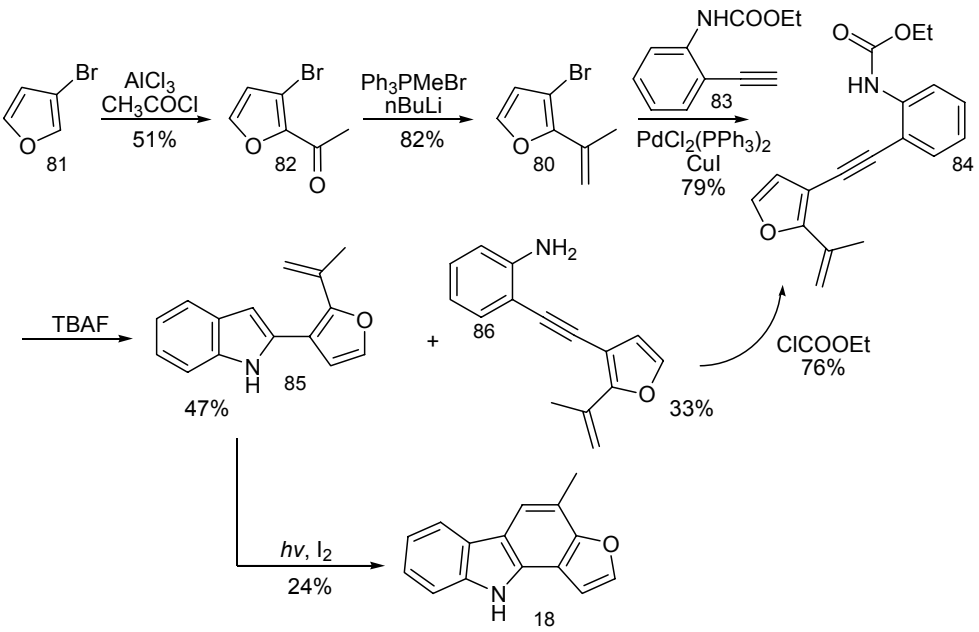
Scheme 17



To this end (Scheme 18), a Friedel Crafts acylation of 3-bromofuran **81** afforded 2-acetyl-3-bromofuran **82** as the only regioisomer, however, in a rather disappointing yield. Conversion of the ketone to the alkene using traditional Wittig conditions afforded isopropenyl-2-(3-bromo)furan **80** in good yield. A Sonogashira coupling of **80** with ethyl ethynylphenylcarbamate **83** afforded the alkyne **84** in good yield, setting the stage for a TBAF promoted cyclisation to form the indole **85**. Unfortunately, the TBAF cyclisation also lead to a significant amount of the deprotected aniline derivative **86**. Fortunately, **86** could be reprotected and recycled back into the cyclisation reaction. Finally, a second cyclisation, this time light mediated in the presence of iodine constructed the carbazole

ring system in a disappointing yield and thus produced furostifoline **18** in five steps and 6% overall yield starting from 3-bromofuran **81**.[46]

Scheme 18



This concludes all of the reported syntheses of furostifoline to date. In continuation with our discussion on the synthesis of various carbazoles we shall move onto the next structural type that was of interest to us in this PhD, namely the indolo[2,3-*a*]carbazoles.

1.2.2 Selected syntheses of indolo[2,3-*a*]carbazoles and ruthenium carbazole complexes

Due to their interesting biological activity, there have been numerous reported syntheses of indolo[2,3-*a*]carbazole compounds. Unfortunately, a discussion covering all these syntheses is not possible in this thesis. However, the interested reader is requested to consult several excellent reviews covering the literature pertaining to these compounds.[4,5]

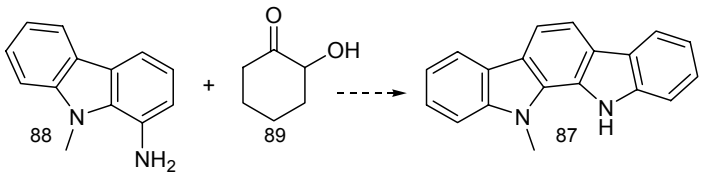
As we were specifically interested in the syntheses of the core indolo[2,3-*a*]carbazole skeleton, previous syntheses of this compound will be discussed. Moreover, our interest in this particular skeleton would have been unfounded if it could not be developed into the synthesis of more interesting biologically active indolo[2,3-*a*]carbazoles and so selected syntheses of staurosporine, and rebeccamycin will be discussed. Finally, inspired by

staurosporine, a synthesis of the recently developed Ru-carbazole complex **35** will be discussed.

1.2.2.1 Synthesis of the indolo[2,3-*a*]carbazole core

The initial attempts at the synthesis of the parent indolo[2,3-*a*]carbazole date back to the 1950's. In 1956 Tomlinson and co-workers reported the first synthesis of the indolo[2,3-*a*]carbazole ring system as its *N*-methyl derivative **87** (Scheme 19). In this approach, 8-amino-1,2,3,4-tetrahydro-9-methyl-9*H*-carbazole **88** was condensed with 2-hydroxy-cyclohexanone **89**. Unfortunately, all attempts to convert this structure to indolo[2,3-*a*]carbazole itself were unsuccessful.[47]

Scheme 19

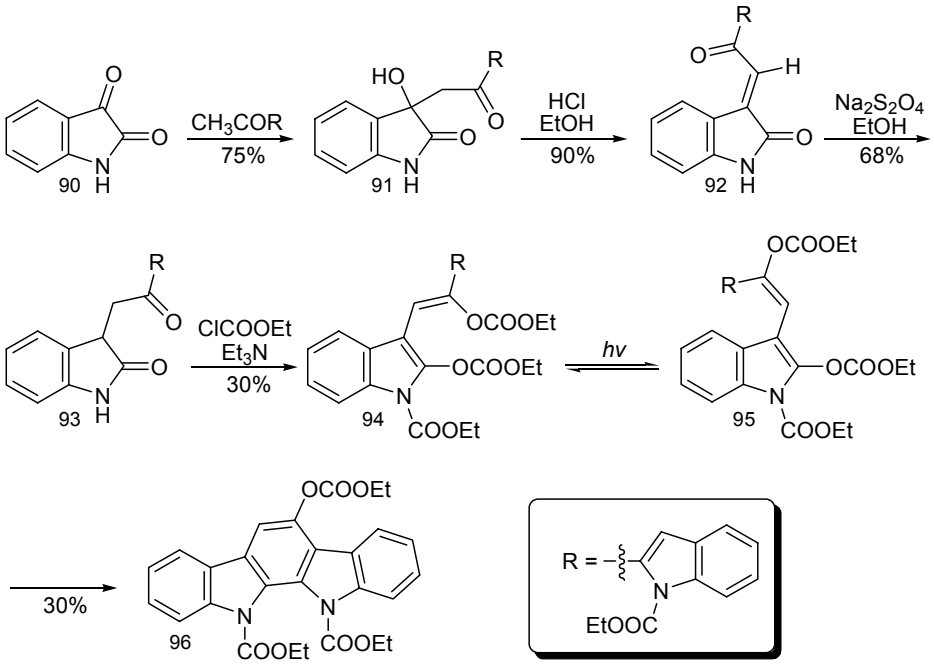


In the following year, Bhide and co-workers managed to synthesise the parent indolo[2,3-*a*]carbazole. In an approach similar to the attempted synthesis above, Bhide started with the carbazole framework already intact and built onto it utilising a Fischer indolisation[48] in order to construct the second indole moiety.[5] Following this, there were several reported syntheses of substituted indolo[2,3-*a*]carbazole systems including an interesting synthesis by Beccalli and co-workers utilising a 6π-electrocyclisation reaction, followed by aromatisation to synthesise substituted indolo[2,3-*a*]carabzoles.[49]

In this interesting synthesis (Scheme 20), Beccalli and co-workers condensed isatin **90** and 1-carbethoxy-2-acetylindolyl as the starting point for their synthesis producing the alcohol **91**. This was dehydrated under acid catalysed conditions affording **92**. It was necessary to use 1-carbethoxy-2-acetylindolyl as opposed to just 2-acetylindole as the unprotected acetylindole was found to be unreactive to isatin.[49] Fortunately, the attachment of a suitable electron withdrawing protecting group to the nitrogen of the indole solved this problem. The double bond of the dehydrated derivative **92** was then reduced using sodium hydrosulfite forming **93**. This compound was treated with an excess of ethyl chloroformate

in the hope of trapping both carbonyls in their enol form as carbonates, as well as protection of the indole nitrogen as the carbamate **94**. Unfortunately, this reaction resulted in a mixture of products including incomplete protection as well as –OCOOEt migration products. The desired compound **94** was only obtained in 30% yield. Nevertheless, this key precursor was then irradiated (HPK-125 W high pressure Hg lamp) forming the indolocarbazole **96** via a 6π-electrocyclisation followed by aromatisation with concomitant elimination of ethanol and carbon dioxide. The yield for this reaction was rather poor and some of the starting material **94** was recovered as well as its *(Z)*- isomer **95**, an indication that isomerisation of the alkene was also occurring prior to the electrocyclisation reaction.[49]

Scheme 20

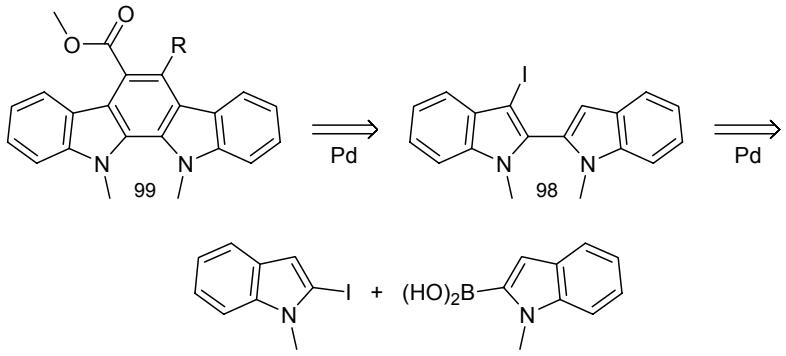


Tomlinson and co-workers synthesised a range of substituted carbazoles in this manner by starting with various arylmethylketones.[47]

Several years later, Merlic and McInnes prepared several indolo[2,3-*a*]carbazole derivatives using palladium catalysed cross coupling reactions.[50] With subsequent iodination (Scheme 21), an appropriately halogenated *bis*-indole **98** would provide a useful

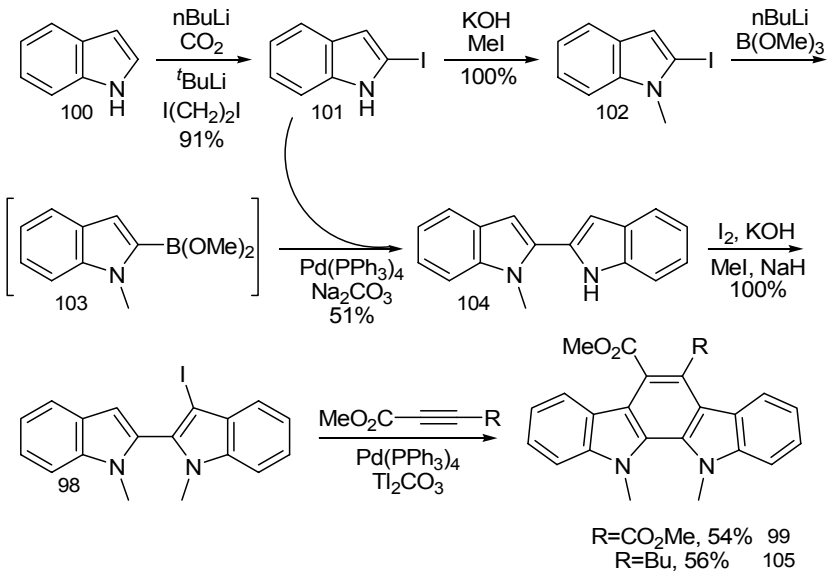
precursor to a Pd mediated alkyl insertion followed by arylation, thus generating the carbazole system **99**.

Scheme 21



Starting from indole **100** (Scheme 22), iodination at the 2-position afforded 2-iodoindole **101** in excellent yield as per the procedure outlined by Bergman and Venemalm.[51] It should be mentioned that direct halogenation of indoles at the 2-position is not easily accomplished if the 3-position is not blocked since the 3-position is the more reactive position. Activation of the 2-position can be achieved by carbonylation of the indole nitrogen, rendering the proton at the 2-positon susceptible to abstraction by a strong base such as *tert*-butyllithium.[51] The 2-iodoindole is a useful intermediate in this sequence as some of the material can be set aside for the coupling reaction to follow later whilst the rest of the material is suitably protected and converted to the corresponding borate ester. In the sequence outlined below, some of the 2-iodoindole was protected as the *N*-methyl derivative **102**, then treated with *n*BuLi and trimethyl borate thus affording the borate ester **103**. Due to the instability of the borate ester it was not characterised but rather subjected immediately to Suzuki cross-coupling conditions with the remaining 2-iodoindole **101** affording the desired *N*-methyl-*bis*-indole **104**. The strategy of leaving one indole moiety unprotected rendered the 3-position of this moiety far more nucleophilic than the protected moiety and so mono-iodination to form **98** proceeded smoothly and set the stage for a palladium catalysed benzannulation reaction. Thus, treatment of the iodo *bis*-indole **98** with dimethyl but-2-ynedioate in the presence of Pd^0 and thallium carbonate afforded the symmetrical indolocarbazole **99** in a modest yield. The use of the unsymmetrical alkyne, methyl hept-2-ynoate, resulted in the formation of the unsymmetrical indolocarbazole **105** in similarly modest yields.[50]

Scheme 22



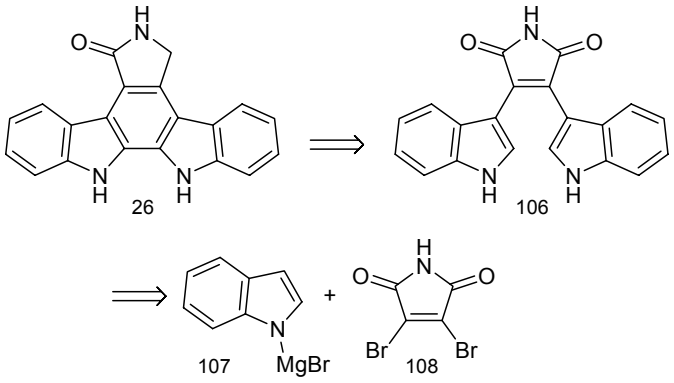
1.2.2.2 Total synthesis of staurosporinone

The lactam moiety located on the *c*-face is common to most of the indolocarbazole structures that possess interesting biological activity. As was discussed previously, it is this part of the indolocarbazole that binds to the ATP site in the relevant kinase, imparting its inhibitory activity. The most simple compound of this structural type is the naturally occurring compound known as staurosporinone **26**. Staurosporinone is essentially staurosporine **25** without the carbohydrate moiety.[5] Although several different groups have synthesised this compound, we'll focus our attention on transition metal mediated syntheses, since transition metal mediated transformations will form the key reactions in our envisaged syntheses.

Hill and co-workers reported an efficient synthesis of staurosporinone **26** in 1993 wherein they utilised a Pd mediated oxidative cyclisation.[52] Their intention for developing this methodology was to be able to synthesise a range of staurosporine-like compounds with minimal functionality initially, and then to develop this methodology to synthesise more complex compounds. These compounds could then be tested as potential protein kinase C inhibitors in the hope of ascertaining which structural features are important in various indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles resulting in their interesting biological activity.[52]

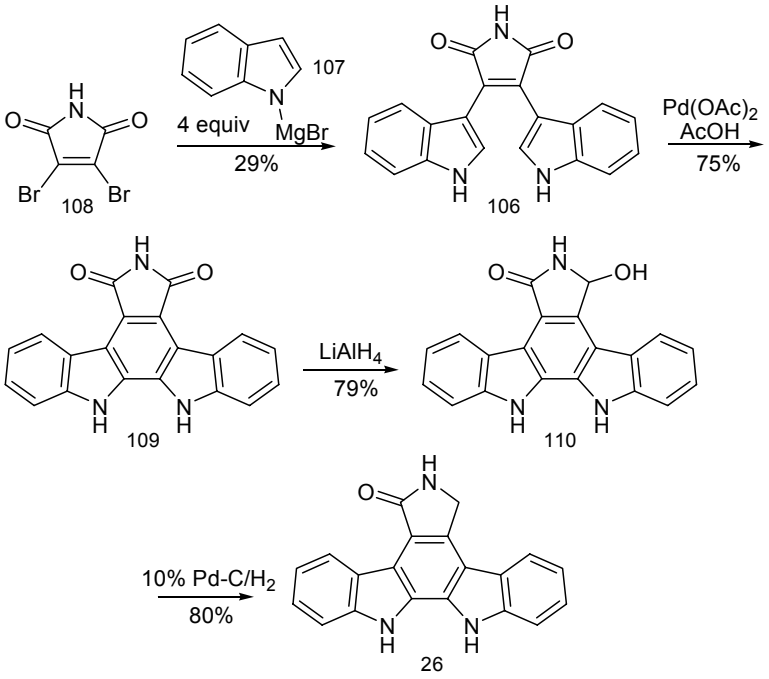
Hill *et al.* envisaged that an attractive approach would be via the *bis*-indolemaleimide **106**, utilising a Pd mediated oxidative cyclisation and subsequent reduction to form staurosporinone **26** (Scheme 23). The *bis*-indolemaleimide itself could be synthesised from indole magnesium bromide **107** and dibromomaleimide **108**.[52]

Scheme 23



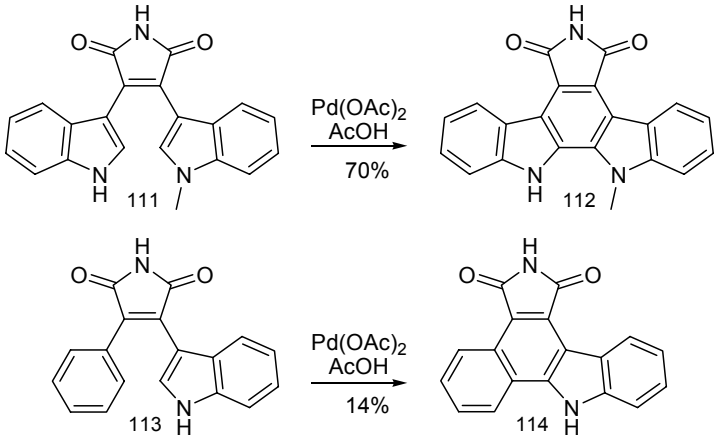
Treatment of dibromomaleimide **108** (Figure 24) with four equivalents of indole magnesium bromide **107** afforded the *bis*-indolemaleimide **106** in a somewhat poor yield of just 29%. Treatment of this compound with palladium acetate in acetic acid afforded the desired indolocarbazole **109** in an acceptable 75% yield. Since staurosporinone contains a lactam moiety on the carbazole *c*-face and not an imide, a reduction of one of the carbonyls was necessary. This was smoothly facilitated by treatment of **109** with lithium aluminium hydride producing the alcohol **110**. Cleavage of the unwanted hydroxyl functionality was facilitated by Pd mediated hydrogenolysis producing staurosporinone **26** in 14% overall yield from dibromomaleimide **108**.[52]

Scheme 24



With this methodology in hand, Hill investigated the synthesis of several other aryl-fused indolomaleimides (Scheme 25). To this end, imides **111** and **113** were cyclised to their corresponding carbazoles, **112** and **114**, respectively. The poor yield for **114** was attributed to the lack of nucleophilicity of the benzene ring as compared with the indole moiety.[52]

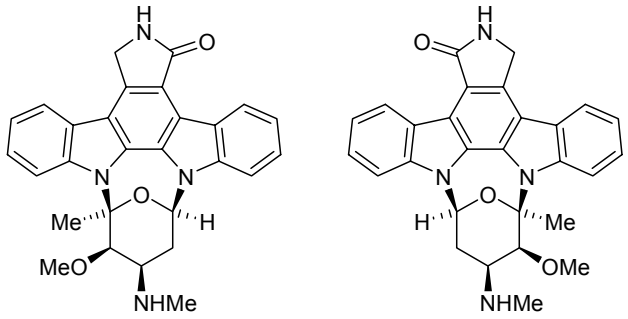
Scheme 25



1.2.2.3 First total synthesis of staurosporine and its enantiomer *ent*-staurosporine

In 1995 Danishefsky and co-workers published the first synthesis of staurosporine **25** and its enantiomer, *ent*-staurosporine **115** (Figure 21).[53] In fact, when they began the synthetic project the structure for staurosporine had been erroneously assigned as the *ent*-isomer and it was only during the latter part of their synthesis when Funato and co-workers revealed the correct structure, determined using X-ray crystallography.[20]

Figure 21



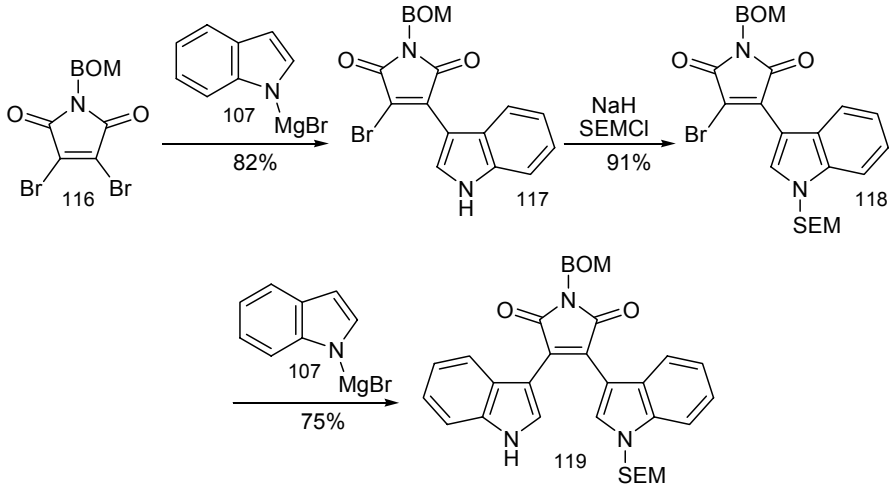
In the planning of the total synthesis of this molecule, Danishefsky and co-workers considered several items of importance: Fashioning of the glycosidic bonds to each of the indolic nitrogens was considered to be the most challenging. Moreover, reduction of the appropriate carbonyl in the planned imide precursor to form the desired lactam was foreseen to be problematic, as staurosporine is a nearly symmetrical molecule.

The first half of the synthesis was planned as a convergent approach. The group identified the *bis*-(indolyl)maleimide **119** (Scheme 26) and the oxazolidinone **126** (Scheme 27) as key intermediates which could be coupled and ultimately used to synthesise staurosporine.

Synthesis of the *bis*-(indolyl)maleimide moiety (Scheme 26) started with the addition of one equivalent of indolemagnesium bromide **107** to BOM protected dibromomaleimide **116** forming **117**. The indole moiety of **117** was then silyl protected affording **118** and then the addition of the second indole was performed in a similar manner, forming the first key intermediate **119**. At this point, although cyclisation to form the corresponding carbazole

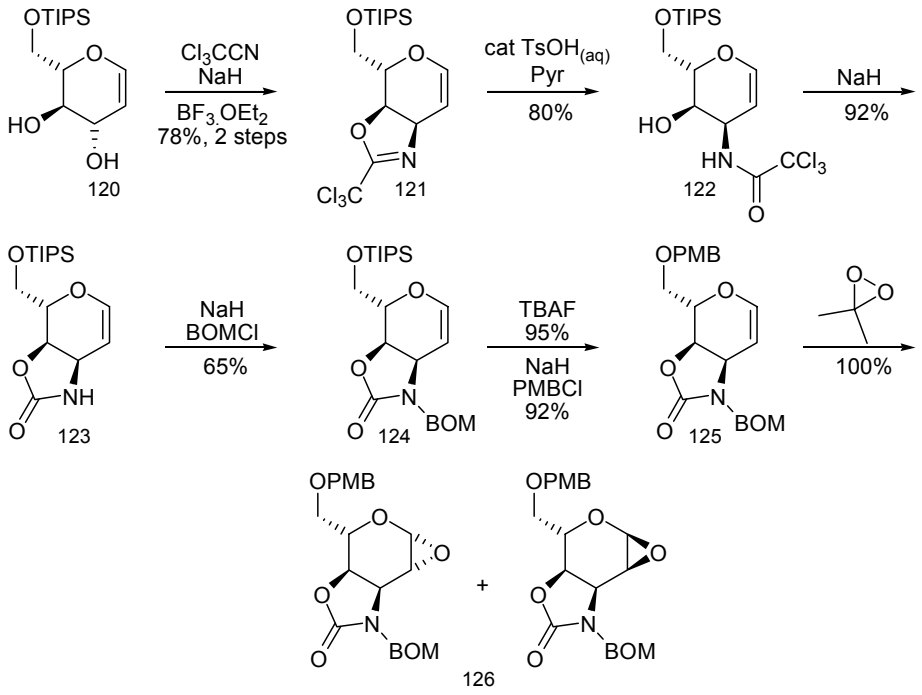
was possible, it was decided to first couple the envisaged glycosyl unit as the already cyclised carbazole unit is a poorer glycosyl acceptor.[53]

Scheme 26



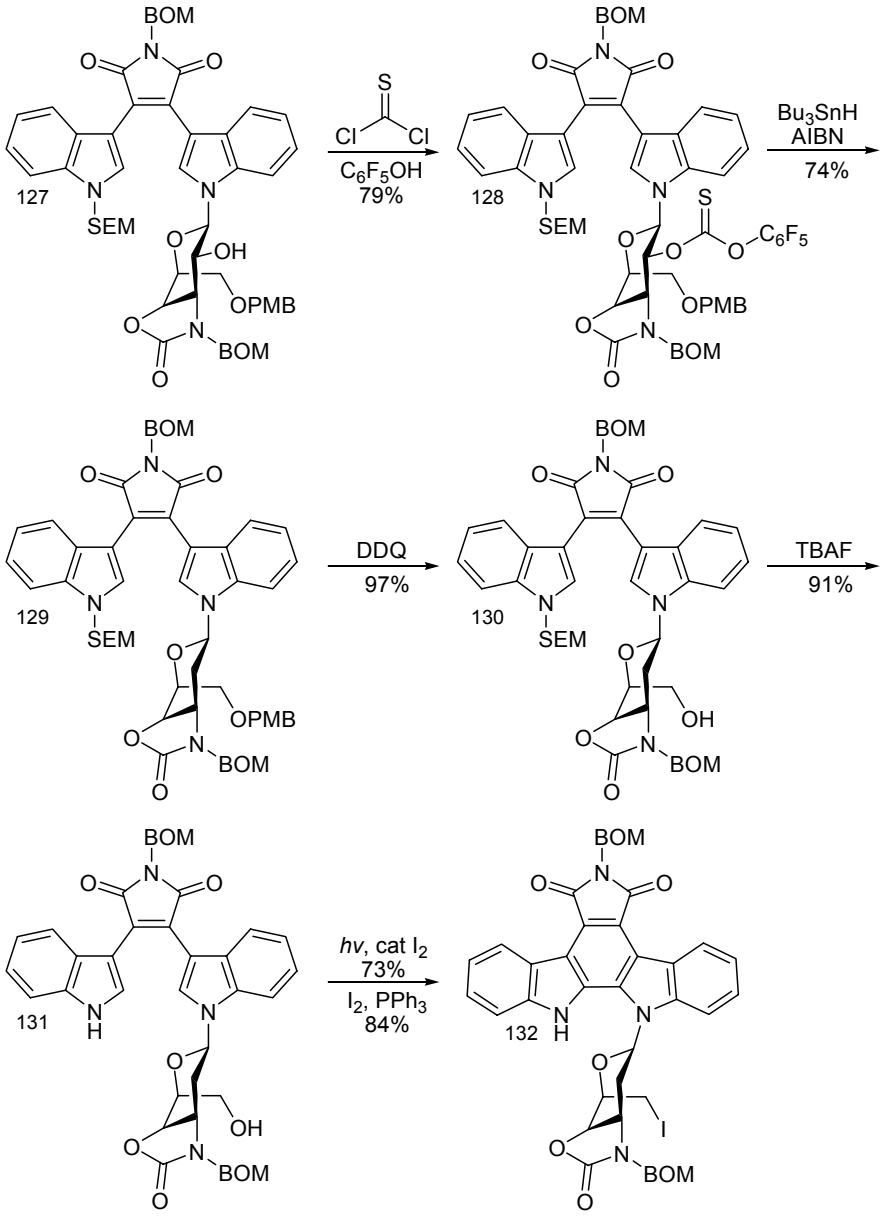
In the synthesis of the required glycosyl unit (Scheme 27), TIPS-L-glucal **120** was chosen as a suitable starting material. This material was initially converted to the *bis*-(trichloracetimidate) and then to oxazoline **121** by a vinylogous Schmidt glycosylation.[53] Ring opening of **121** by treatment with catalytic acid forming **122**, followed by NaH mediated ring closing formed the oxazolidinone **123** and this was subsequently protected as the BOM derivative **124**. At this point, it was decided to cleave the TIPS protecting group using TBAF and to install the PMB protecting group forming **125**. The final requirement for setting up the envisaged key intermediate was the epoxidation of the alkene and this was achieved using 2,2-dimethyldioxirane. Clearly, epoxidation could occur on either face and this was indeed the case - a mixture of inseparable epoxides **126** was formed in a ratio of ∝-epoxide to β-epoxide of 2.5:1, as determined by NMR spectroscopy.

Scheme 27



With these two key intermediates in hand (**119** and **126**), the mixture of epoxides **126** was treated with the sodium salt of *bis*-(indolyl)maleimide **119** forming the desired indole glycoside **127** in a modest 47% yield (Scheme 28).[53] Although the epoxidation of the glycosyl unit **125** had been disappointingly unselective, it was fortuitous that the undesired epoxide turned out to be far less reactive and this increased the selectivity of the desired indole glycoside **127** to 5.5:1. The resulting free hydroxyl functional group was removed using Barton methodology, initially forming the xanthate **128**, followed by its removal using Bu_3SnH and AIBN, yielding **129**. At this point, removal of the C_6' PMB protecting group using DDQ proceeded smoothly affording **130**, followed by liberation of the silyl protected indole using TBAF, affording **131**. Formation of the carbazole ring system was performed by treatment of the *bis*-indole compound **131** with catalytic I_2 under photolytic conditions. In preparation for the formation of the second critical *N*-glycosidic bond, the C_6' unit was iodated using a classical iodination method forming **132**.

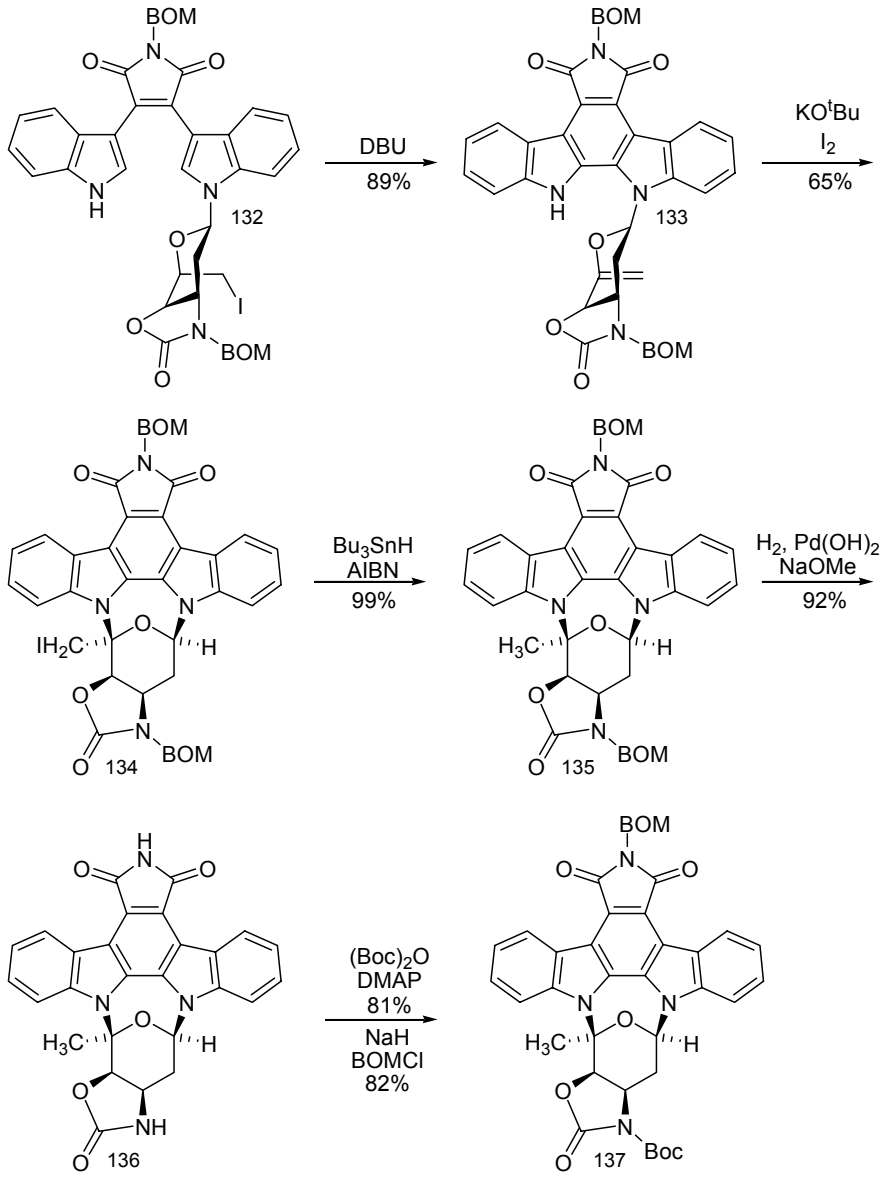
Scheme 28



Elimination of the iodine functionality (Scheme 29) afforded the olefin **133** and treatment of this olefin with KO^{t}Bu and iodine fashioned the second *N*-glycosidic bond in an acceptable 65% yield, forming **134**. This reaction unfortunately resulted in the formation of an unwanted iodine functionality in **134** and this was removed using tributyltin hydride affording **135**. At this point, deprotection of the glycosyl BOM was required, however this could not be achieved without also removing the imide BOM protecting group. Thus, the completely deprotected compound **136** was selectively Boc protected at the oxazolidinone

ring and the imide was re-protected using BOM, forming **137**. The reason for installing the Boc protecting group on the oxazolidinone ring was necessary, as it would play a crucial role in facilitating disconnection of the oxazolidinone by guarding against dimethylation of the amine once opening had occurred.[53]

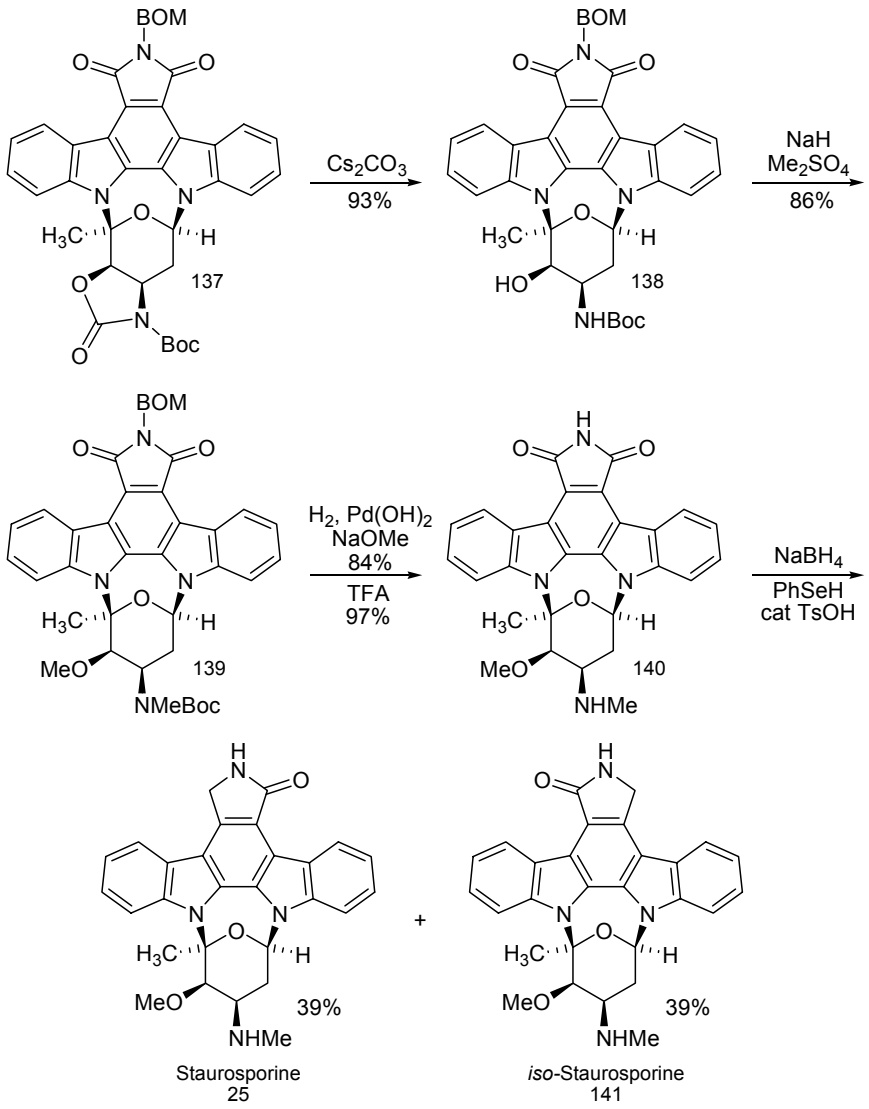
Scheme 29



Thus, treatment of **137** (Scheme 30) with caesium carbonate in methanol facilitated ring opening of the oxazolidinone ring and the amide **138**. The hydroxyl and amide functional groups of **138** were simultaneously methylated affording **139**. Removal of both protecting groups by means of Pd for the BOM, and TFA for the Boc afforded the crucial final

intermediate imide **140**, also known as 7-oxostaurosporine. Unfortunately, reduction of the imide to the lactam was not selective and a 1:1 mixture of staurosporine **25** and *iso*-staurosporine **141** was obtained.

Scheme 30

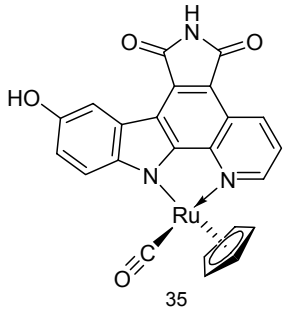


The synthesis of *ent*-staurosporine **115** was achieved in an analogous manner starting with D-glycal as opposed to L-glycal. In fact, owing to a misconception at the start of Danishefsky's synthesis that staurosporine was in fact *ent*-staurosporine, Danishefsky and co-workers initially embarked upon their synthesis using D-glycal, and therefore first synthesised the wrong isomer.[53]

1.2.2.4 Synthesis of a ruthenium carbazole complex – a highly selective and potent GSK-3 inhibitor

Perhaps the most novel class of carbazole kinase inhibitors are those recently synthesised by Meggers and co-workers. The ruthenium complex below **35** (Figure 22) has an IC_{50} value for GSK-3 in the region of 300 pM. Moreover, unlike the staurosporine-like kinase inhibitors which show poor selectivity and generally inhibit all kinases to a greater or lesser extent, this particular ruthenium complex is very selective for GSK-3.[34]

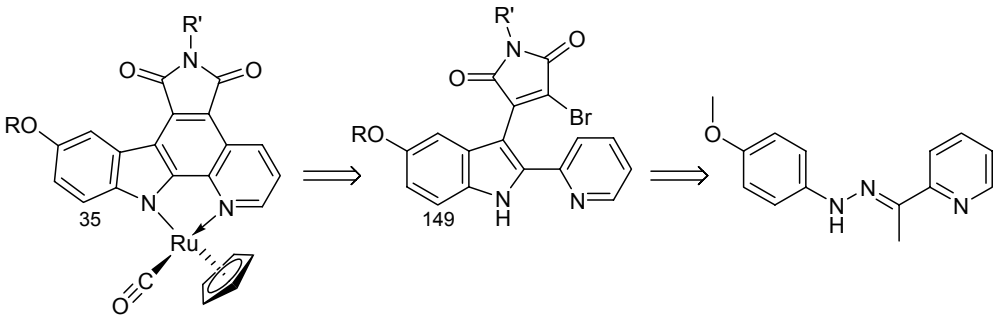
Figure 22



35

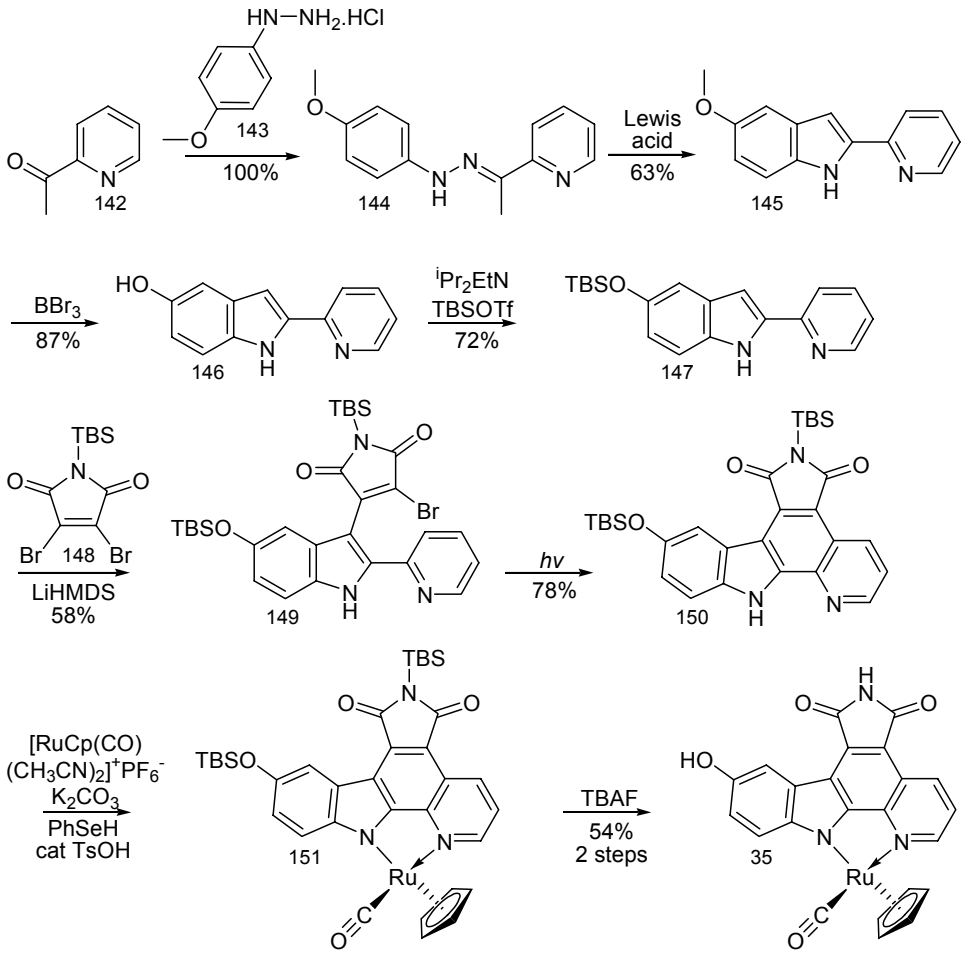
In their approach to the synthesis of this novel compound and analogues thereof (Scheme 31), Meggers and co-workers initially based their methodology on work done by Faul and Anderson,[54-56] with some adaptations as their own methodology developed, resulting in shorter syntheses.[34] Thus, in the construction of the novel compound **35**, Meggers *et al*. made use of a Fischer indolisation[48] to construct the indole system and then attachment of a suitably substituted maleimide provided the key intermediate **149**, which could be photolytically cyclised to form the desired carbazole ring system, ready for complexation with Ru. Interestingly, although many syntheses of staurosporine-like compounds (i.e. aryl[2,3-*a*]pyrrolo[3,4-*c*]carbazoles) make use of photolytic conditions to form the carbazole system, such as in the synthesis of staurosporine **25** previously described, normally this is done by first attaching the lactam unit across the aryl and indole moieties and then the light mediated cyclisation facilitates bond formation across the indolo-C_2 position and the aryl unit. However, Meggers *et al*. initially constructed the indolo-C_2-aryl bond and then made use of photolytic conditions to form the carbazole across the bridging lactam unit.

Scheme 31



Treatment of 2-acetylpyridine **142** (Scheme 32) with 4-methoxyphenylhydrazine HCl **143** afforded the hydrazone **144** in quantitative yields. This was then subjected to a Fischer indolisation[48] forming the 5-methoxypyridoindole **145**. It was found that the best yields were obtained when trimethylsilyl polyphosphate was used as a Lewis acid.[34] Demethylation of the aryl methoxy was achieved using BBr_3 and the resulting phenol **146** was protected as the TBS ether **147**. Dibromomaleimide **148** was then attached to the 3-position of the indole moiety and with the key compound **149** in hand, photolysis under Ar afforded pyridocarbazole **150** in good yield. Although at this point it is feasible to deprotect the molecule and then proceed with the cyclometallation, Meggers and co-workers found that these deprotected compounds were stubbornly insoluble in most organic solvents and this caused problems with the cyclometallation reactions. So, the protected carbazole **150** was treated with $[Ru(Cp^*)(CO)(MeCN)_2]^+PF_6^-$ in the presence of one equivalent of potassium carbonate forming **151**, followed by TBAF induced TBS deprotection, smoothly affording the racemic ruthenium complex **35**. It was found that these Ru complexes were quite stable to air and water.[34]

Scheme 32


HN—NH2.HCl
143
100%
142
144
Lewis acid
63%
145
BBr3
87%
146
iPr2EtN
TBSOTf
72%
147
TBS
148
LiHMDS
58%
149
hv
78%
150
[RuCp(CO)(CH3CN)2]+PF6-
K2CO3
PhSeH
cat TsOH
151
TBAF
54%
2 steps
35

CHAPTER 2 – BENZOFURAN CONTAINING NATURAL PRODUCTS

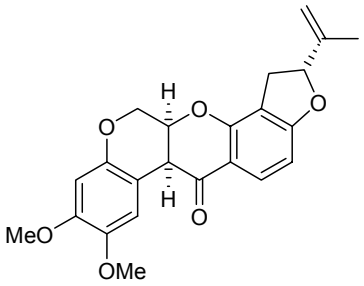
2.1 ROTENONE, AND RELATED STRUCTURES

In continuation with our interest in transition metal mediated reactions as key steps in the synthesis of interesting natural products, a collaboration was set up with The University of Köln, in Germany, as they were interested in using Pd mediated transformations in several key steps in their proposed synthesis of the interesting naturally occurring insecticide, rotenone.

2.1.1 Not all that is natural is good for you – about rotenone

Rotenone **152** (Figure 23) is a naturally occurring compound isolated from several plant species belonging to the genera *Lonchocarpus* or *Derris* of the tropical and subtropical family *Leguminosae*. The compound possesses significant insecticidal and piscicidal properties and these properties have been exploited for centuries. It is recorded that as early as 1649 in South America, the crushed root of the *Derris* plant was used to stun fish in lakes and ponds. The fish would swim to the surface where they could be harpooned and caught. The Chinese were using crushed *Derris* root pulp to prepare insecticides long before formal preparations of the root extract were patented for commercial use in 1912.[57] However, it was not until 1932 that the structure of rotenone was established which is not surprising, given the complexity of the structure and the lack of modern structure elucidation tools at the time.[58] The absolute stereochemistry of rotenone remained unknown for almost another thirty years when finally Büchi *et al*. revealed the structure using X-ray crystallography.[59]

Figure 23



Rotenone
152

Owing to the fact that rotenone is rather insoluble in water but very soluble in most organic solvents, it is not extremely toxic to mammals but is very efficient at eradicating fish and insects. Even at low concentrations, rotenone is readily absorbed into the gills of fish since the gills contain a relatively high lipid content. Once absorbed, the compound inhibits oxidative phosphorylation in cellular respiration. This is achieved by blocking electron transport in the mitochondrial enzyme NADH ubiquinone reductase.[60] The result is that oxygen in the blood cannot be utilised for cellular respiration. The fish, feeling a lack of oxygen swim to the surface and begin gasping for air and eventually succumb to the unavailability of oxygen in their system and die. If they are removed from the poisoned environment at the first signs of oxygen starvation and placed into fresh water the effects wear off and the fish recover. The trachea of insects are similarly lipophilic and therefore efficiently absorb rotenone from the surroundings. However, the gastrointestinal tract of mammals is somewhat more hydrophilic and absorption of rotenone is not particularly efficient. In contrast to this, the lungs in mammals are relatively lipophilic and so rotenone in the form of an airborne powder is hazardous to mammals.

Rotenone is still used in pest control today. Due to its complex structure, the synthesis of the compound on an industrial scale is not feasible and so preparations of the compound are obtained by extraction predominantly from the *Derris* root.[61] Rotenone is an efficient pesticide and the fact that it is of 'natural' origin means that it is especially used on crops regarded as 'organically grown'. Moreover, rotenone has a relatively short half life once it has been sprayed onto crops and so it is broken down within several days.[62] This installs a sense of confidence that the poison will not pervade the crop produce for any significant amount of time and thus it is regarded as safe to use. This is not to say that rotenone is non-toxic to humans and mammals in general. To date, there have been two documented cases of accidental rotenone ingestion leading to death.[62,63] Moreover, the natives of Papua New Guinea ingested the roots of rotenone containing plants in order to commit suicide, though these incidents have never been properly documented.[64]

Although rotenone has been used as a pesticide possibly for centuries, its safety has recently come under the spotlight. This is mainly due to a study conducted at Emory University by Greenamyre and co-workers. In this study, rats were infused with rotenone in small doses over a period of several weeks and a degeneration of dopamine neurons was

observed, accompanied by an onset of behavioural characteristics analogous to those of Parkinson's disease.[65] In fact, the mechanism by which Parkinson's disease manifests itself has only recently been established by pure chance. In the 1980's, a small group of drug addict teenagers were utilising a designer drug as a substitute for heroin. These teenagers rapidly developed irreversible symptoms analogous to that of severe Parkinson's disease. It was discovered that a contaminant in the drug known as MPTP* was a pro-toxin and was being metabolised to the mitochondrial poison MPP+†. This substance was found to inhibit mitochondrial respiration at complex I of the electron transport chain, resulting in a significant decrease in the amount of dopamine neurons. The selectivity of MPP+ for the dopaminergetic neurons can be attributed to the fact that it is an excellent substrate for the dopamine transporter and therefore accumulates in the cells that transport dopamine.[65] It is now known, that Parkinson's disease is also caused by degeneration of dopamine neurons leading to decreased levels of dopamine and this results in improper signal transduction within the neurons. The concern regarding pesticides, especially rotenone, is that it is known that the mechanism by which these chemicals operate is also by inhibition of the function of mitochondrial complex I.

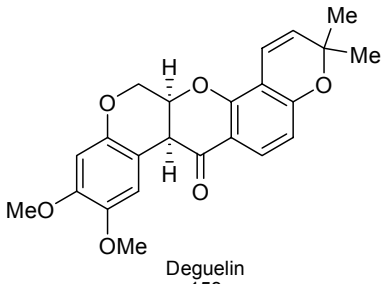
Although the Emory University study is causing concern worldwide regarding the safety of rotenone as a pesticide, there are other organisations that are disputing the study. Some believe that the study model was 'unrealistic', and that infusion of pesticide into the jugular vein of the rats in no way mimics the way in which people would normally ingest rotenone. This again illustrates the point that rotenone is hydrophobic and is only very poorly absorbed in the mammalian gastro-intestinal tract. Nevertheless, the fact that the insecticide seems to cause Parkinson's disease if it can get into your system is concern enough for most people, and the insecticide has been withdrawn in many parts of the USA pending further investigations. The irony of this is that up until now rotenone has been used on so-called 'organically grown' produce – which of course is free of all those 'nasty' synthetic pesticides and fertilizers!

* *N*-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine

† 1-Methyl-4-pyridinium

Although rotenone is currently receiving negative publicity as a pesticide one needs to bear in mind that the compound has been extremely useful for centuries. As a synthetic target, it poses some interesting and tempting challenges for the organic chemist. Moreover, the closely related rotenoid, deguelin **153** (Figure 24), has recently become a molecule of considerable interest due to its anti-cancer properties. It has been shown to be an efficient chemo-preventative agent for both *in vitro* and *in vivo* models.[66] Deguelin is very similar to rotenone in that structurally, the only difference between the two compounds lies in the fact that deguelin contains a benzopyran moiety rather than the benzofuran moiety of rotenone. In fact, rotenone has been successfully used as a synthetic precursor for a short synthesis of deguelin.[67]

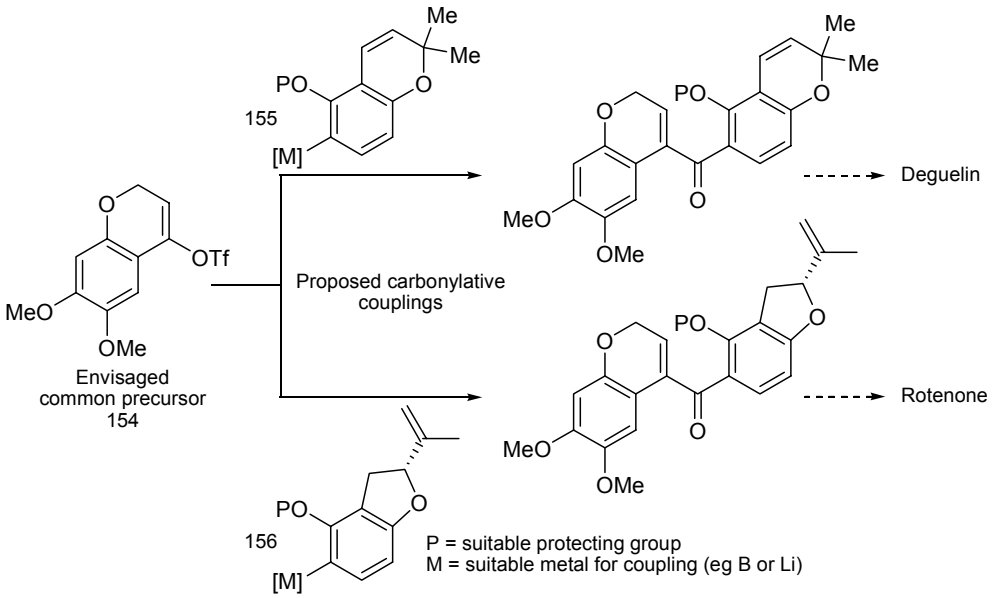
Figure 24



Deguelin
153

As mentioned previously, our interest in a synthetic strategy towards the assembly of rotenone involved a collaboration with Prof H.G. Schmalz of Köln University, Germany, as Schmalz *et al*. were working on the synthesis of deguelin. Due to the similarity between deguelin and rotenone, a common precursor **154** (Scheme 33) was proposed from which either deguelin or rotenone could be synthesised. Thus from this point, attachment of a suitable benzopyran moiety **155** using a carbonylative coupling would set the stage for a deguelin synthesis or, similar attachment of a chiral benzofuran moiety **156** could subsequently lead to rotenone.

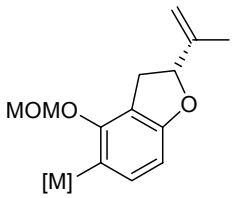
Scheme 33



A proposed route for deguelin and rotenone, employing a common precursor

Since investigations into the construction of the initial common moiety were well underway in Germany, we would need to focus our attention on a synthetic strategy towards the synthesis of the chiral 2-isopropenyl-2,3-dihydrobenzofuran unit **156**.

Figure 25

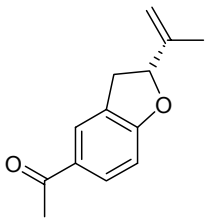


Rotenone precursor
156

2.1.2 Other interesting natural products containing the 2-isopropenyl-2,3-dihydrobenzofuran functionality

Interestingly, this potential benzofuran building block for the synthesis of rotenone is actually very similar in structure to a toxin known as trematone **157** (Figure 26), found in certain plants such as the white snakeroot (*Eupatorium rugosum*), which is well known to be toxic to grazing animals. It produces symptoms known as 'trembles' and for this reason the toxin contained in the plant was appropriately named trematone (also spelled tremetone). The compound is toxic to all mammals including man, and consumption of milk containing this toxin leads to a severe nervous disorder known as 'milk sickness'. The toxin is cumulative in animals and its effects become noticeable within 1 to 3 weeks if the animal consumes approximately 0.5 to 1.5 percent of its own body weight daily in plant material. Death will result if the animal is not removed from the source of the toxin immediately. Consumption of other species of *Eupatorium* including *E. wrightii* (crofton weed, found in Texas, Arizona and Mexico) has reportedly caused sudden death in cattle, also due to trematone poisoning.

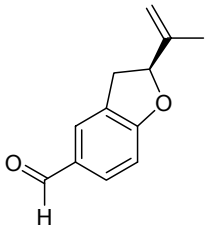
Figure 26



Trematone
157

Several other compounds very similar to trematone have been isolated in Nature and perhaps the most closely related would be fomannoxin **158** (Figure 27), possessing a formyl moiety on the benzene ring instead of a ketone as in trematone. Fomannoxin is isolated as a toxic metabolite of the Basidiomycete fungi, *Fomes annosus*, one of the few fungi that cause the death of the host cells in living trees. Interestingly, although fomannoxin is structurally very similar to trematone, the stereochemistry at the 2-position is opposite to that found in rotenone and trematone.[68]

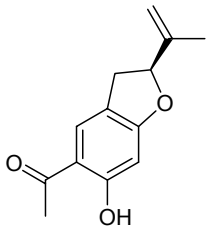
Figure 27



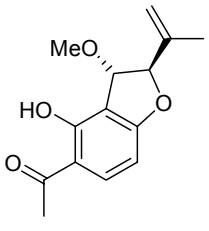
Fomannoxin
158

The hydroxyl-trematone derivatives below (**159** and **160** - Figure 28) have been isolated from *Lasiolaena morii*.[69] It is interesting to note that although these compounds are all very similar in structure, they do not all possess the same stereochemistry on the furan, an indication that these compounds are made utilising differing biological pathways. Trematone for instance has the opposite stereochemistry to the compounds shown below.[70]

Figure 28



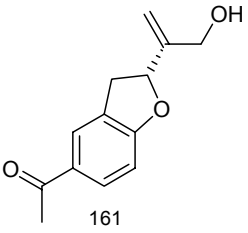
159



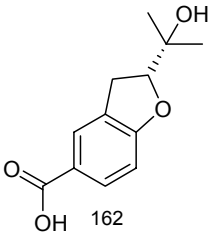
160

Two other dihydrobenzofurans isolated from natural sources and possessing the same stereochemistry as trematone are (-)-5-acetyl-2-(1-hydroxymethylvinyl)-2,3-dihydrobenzofuran **161** and anodendroic acid **162**, isolated from *Anodendron affine* (Figure 29).[71]

Figure 29



161



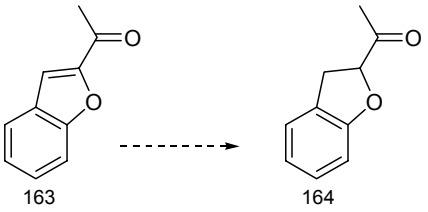
162

2.1.3 Syntheses of trematone and related structures

2.1.3.1 First synthesis of trematone

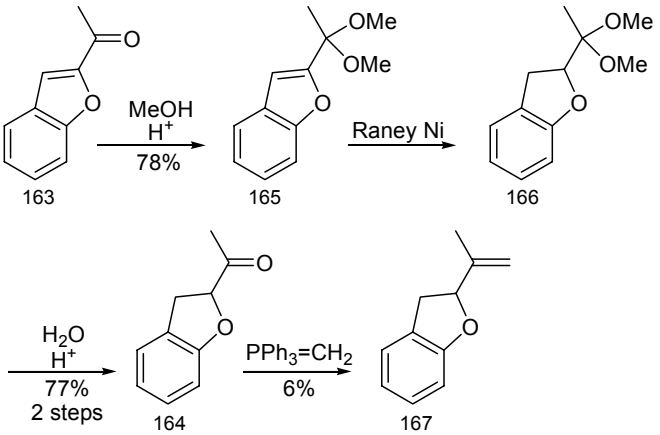
The racemic synthesis of trematone was first reported by DeGraw *et al*. in 1963.[72] In their approach, DeGraw *et al*. initially wished to obtain 2-acetyl-2,3-dihydrobenzofuran **164**. This compound had in fact been previously synthesised by two other groups by direct sodium amalgam reduction of 2-acetylbenzofuran **163** (Scheme 34).[73,74] Unfortunately, this procedure required a vast excess of sodium amalgam and also produced a number of by-products which were impossible to separate from the desired dihydrobenzofuran **164**.

Scheme 34



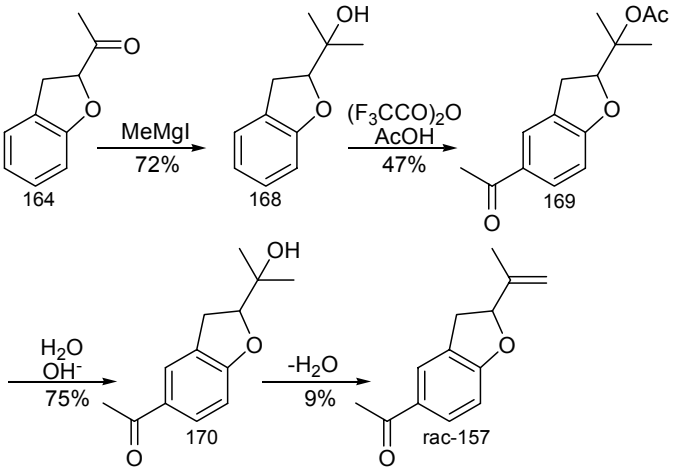
DeGraw *et al*. decided to modify this procedure (Scheme 35) by initially converting the ketone **163** to the corresponding diacetal **165**. Although this greatly improved the subsequent reduction step which could now be carried out using Raney nickel to afford **166**, conversion of the diacetal back to the ketone **164** was performed to explore the feasibility of the Wittig reaction and this afforded the alkene **167** in only 6% yield, and so this approach was abandoned.[72]

Scheme 35



In yet another modified approach (Scheme 36), DeGraw *et al*. decided to employ their Raney nickel reduction procedure to synthesise **164**, then the extra carbon required was introduced by treatment of the ketone **164** with methyl magnesium iodide, affording the alcohol **168**. Unfortunately, acetylation of the benzene ring could only be accomplished using trifluoroacetic anhydride, which resulted in simultaneous acetylation of the alcohol functionality, affording **169**. Fortunately, subsequent hydrolysis of the *O*-acetate **169** was easily accomplished by base hydrolysis, affording the alcohol **170**. Dehydration of **170** to afford trematone proved to be remarkably difficult using a variety of conditions. In the end, DeGraw *et al*. found that this could only be accomplished using phosphoryl chloride and pyridine at 75 °C, thereby affording racemic trematone **157** in a disappointingly low yield for this final step.[72]

Scheme 36

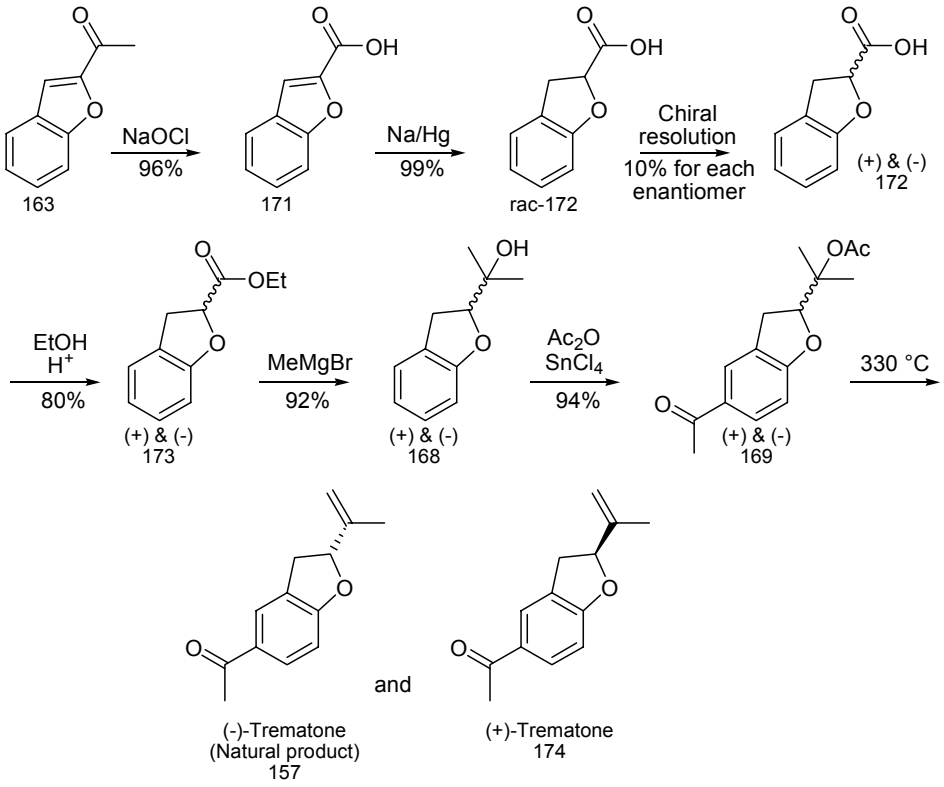


2.1.3.2 A chiral synthesis of trematone employing a chiral resolution step

In the same year, Bowen *et al*. embarked upon the synthesis both enantiomers of trematone, employing a chiral resolution step to separate the enantiomers early on in their synthesis.[75] Thus, starting from 2-acetylbenzofuran **163** (Scheme 37), an oxidative cleavage reaction using sodium hypochlorite afforded the carboxylic acid **171** in good yield. This was reduced to racemic coumarilic acid **172** using sodium amalgam and then the enantiomers were resolved by means of the enantiomers of amphetamine, affording

separated (+)- and (-)-coumarilic acid, albeit in poor yields.*[75] Each enantiomer was subsequently converted to the ethyl ester **173** and a Grignard reaction afforded the (+) and (-) alcohols **168**. At this point, a Friedel Crafts reaction of **168** both acetylated the benzene ring and formed the acetate on the alcohol moiety, in good yield. With the (+) and (-) acetates in hand, conversion to the final desired olefins was achieved by pyrolysis at 280-330 °C leading to the separate enantiomers of trematone **157** and **174**. Unfortunately however, this pyrolysis step led to a mixture of several compounds which needed to be separated and the amount of actual trematone recovered during this purification process is not mentioned in the publication. Nevertheless, the correct stereochemistry for natural trematone could now be assigned based on the specific rotation of each enantiomer.[75]

Scheme 37

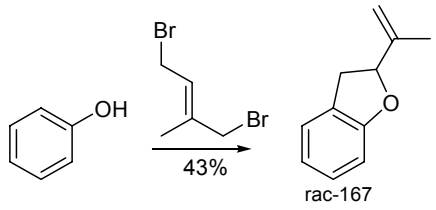


* In order to obtain sufficiently enantiomerically pure isomers of coumarilic acid, several recrystallisations were required resulting in significant loss in material. For example, after 2 recrystallisations, only 0.22 g of pure (+)-coumarilic acid was obtained from 4.30 g of (±)-coumarilic acid.

2.1.3.3 Synthesis of racemic fomannoxin, and friends

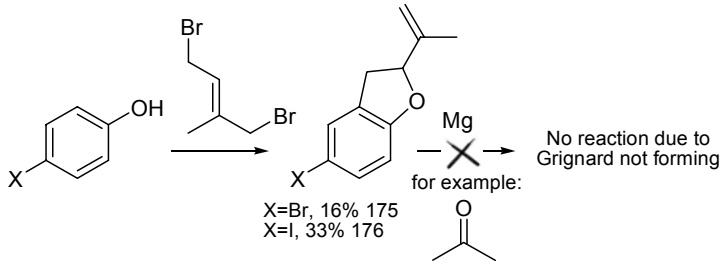
Seeking a better method for the synthesis of these dihydrobenzofuran compounds, Kawase and Yamaguchi applied methodology previously developed by Nickl,[76] thereby forming racemic isopropenyl dihydrofuran **167** in 43% yield in one step, by reacting phenol and 1,4-dibromo-2-methyl-2-butene (Scheme 38).[77]

Scheme 38



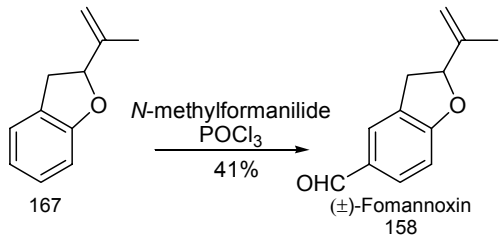
With this methodology in hand, Kawase *et al*. set about the synthesis of fomannoxin **158**, as well as (-)-5-acetyl-2-(1-hydroxymethylvinyl)-2,3-dihydrobenzofuran **161** and anodendroic acid **162**. Starting from para-iodo or para-bromo phenol (Scheme 39), Kawase *et al*. hoped that the benzofuran ring could be generated according to the methodology developed by Nickl and then the halogenated benzene ring could be appropriately substituted to access any one of the three natural products mentioned above. The bromo **175** and iodo **176** benzofurans were therefore synthesised as planned but unfortunately these could not be converted into the desired products by the envisaged Grignard reaction, due to the inactivity of the halogenated benzofuran to magnesium metal.[77]

Scheme 39



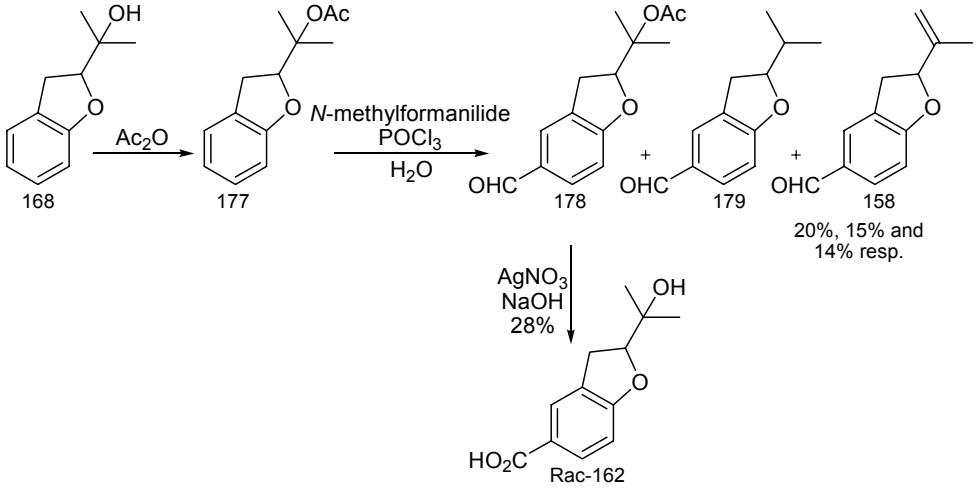
As an alternative approach (Scheme 40), the unsubstituted isopropenyl-dihydrobenzofuran **167** was formylated forming the aldehyde **158** in 41% yield, thus completing the synthesis of racemic fomannoxin.[77]

Scheme 40



In their preparation of racemic anodendroic acid **162** (Scheme 41), Kawase *et al*. started with hydroxyl derivative **168**. Acetylation of **168** provided the key precursor **177** but unfortunately, similar formylation of this compound resulted in a mixture of products, including fomannoxin **158**. Fortunately, these compounds were readily separable by column chromatography.[77] The desired aldehyde **178** was produced only in a minor excess as compared to **179** and **158** but was nevertheless oxidised to the carboxylic acid **162**, thus completing the synthesis of anodendroic acid.

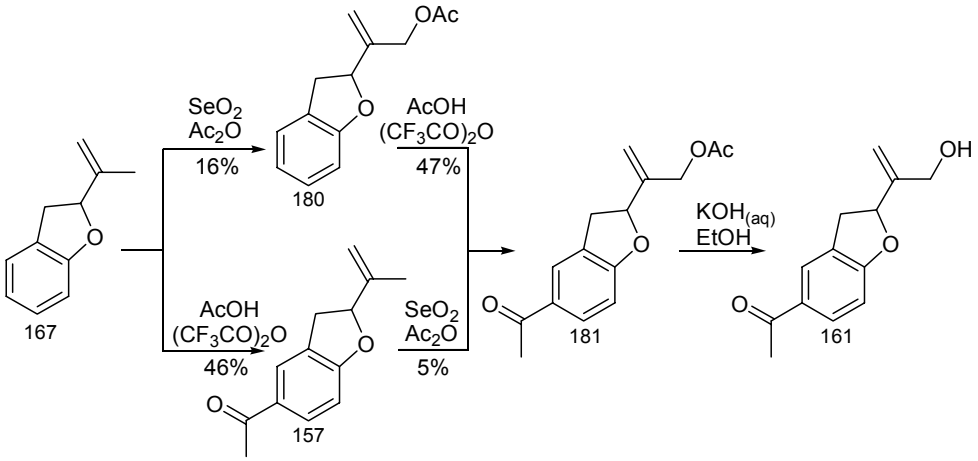
Scheme 41



In their synthesis of the natural product, (-)-5-acetyl-2-(1-hydroxymethylvinyl)-2,3-dihydrobenzofuran **161**, Kawase *et al*. envisaged two routes (Scheme 42), both starting with unsubstituted 2-isopropenyl-2,3-dihydrobenzofuran **167**.[78] As one option, acetylation the benzene ring of **167** should produce racemic trematone **157** and then a selenium mediated allylic oxidation should afford the keto acetate **181**. Conversely, the keto acetate **180** could be achieved by initially performing the allylic oxidation step and then

acetylation of the benzene ring should afford **181**. Finally, the keto acetate **181** could then be hydrolysed affording the natural product **161**.

Scheme 42

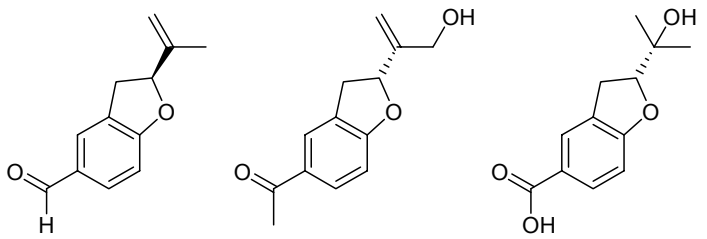


Although both routes were investigated and ultimately afforded the natural product it was the second route that provided the better overall yield. Thus, **167** was converted to the acetate derivative **180** utilising a selenium mediated allylic oxidation, which unfortunately afforded **180** in only 16% yield. Friedel Crafts acetylation of **180** afforded the keto acetate **181** in 47% yield and finally base induced hydrolysis of the acetate provided racemic **161** in a yield not mentioned in the publication.

2.1.3.4 Chiral synthesis of fomannoxin, and friends

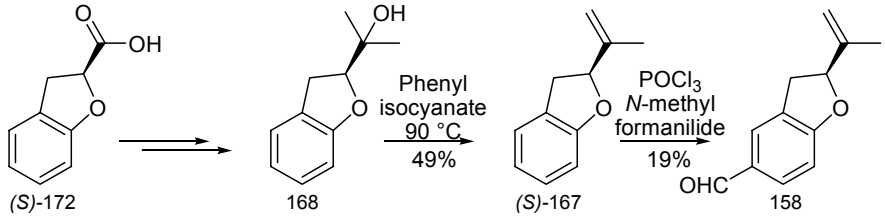
Two years after completing the racemic syntheses of these three compounds, Kawase *et al*. published the chiral syntheses of the same three compounds (Figure 30), starting from either the *(S)*- or *(R)*-2,3-dihydrobenzofuran-2-carboxylic acids **172**, which were once again obtained by chiral resolution of the racemic acid according to the procedure utilised by DeGraw *et al*., discussed previously.[72]

Figure 30



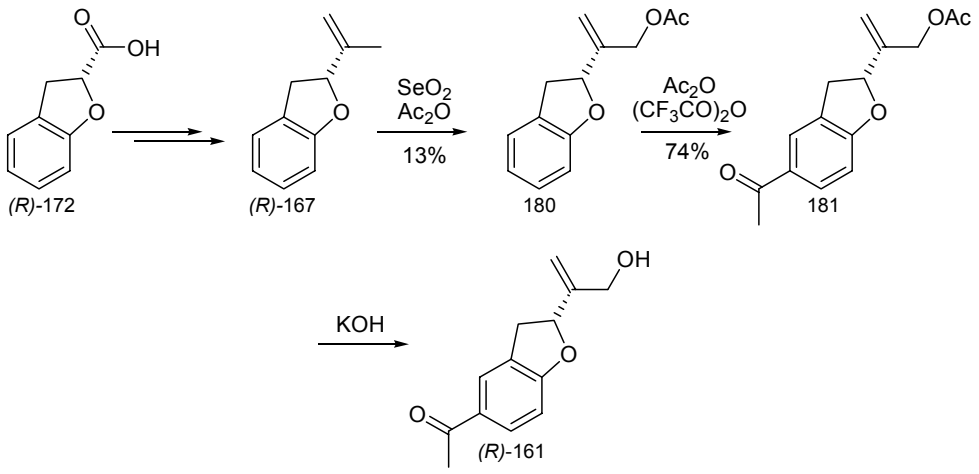
The preparation of fomannoxin **158** required the (-)-optically active acid **(-)-172** for the correct stereochemistry of the final product (Scheme 43). Using the methodology developed by DeGraw,[72] this was converted to the alcohol **168** and subsequent dehydration using methodology previously developed by Kawase *et al*.,[77] afforded the chiral isopropenyl dihydrobenzofuran ***(S)*-167** in a modest yield. Finally, formylation using *N*-methylformanilide afforded *(S)*-fomannoxin **158** in a disappointing yield.

Scheme 43



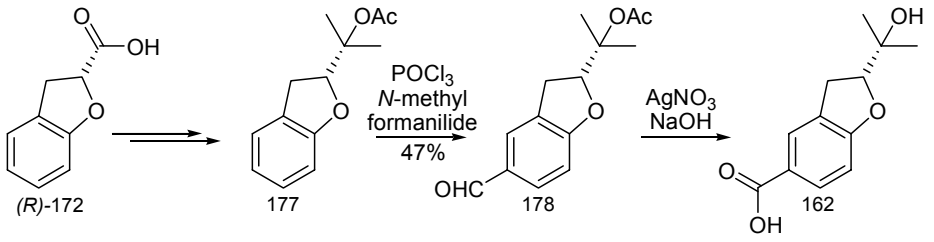
The syntheses of the other two natural products required starting with the (+)-optically active acid, **(+)-172**. The opposite chiral isopropenyl dihydrobenzofuran ***(R)*-167** (Scheme 44) was thereby synthesised analogously to ***(S)*-167**, which was required for fomannoxin **158**, and then a selenium mediated allylic oxidation afforded the acetate **180** in a poor yield. Friedel Crafts acetylation afforded **181** as the precursor to the natural product and finally, the *O*-acetate was cleaved by alkaline hydrolysis affording the natural product ***(R)*-161**, however the yield for this reaction was not reported.[71]

Scheme 44



Finally, anodendroic acid ***(R)*-162** was synthesised using a similar route (Scheme 45). To this end, the (+)-optically active acid, **(+)-172** was converted to the acetate **177** using the same methodology as for fomannoxin and then formylation afforded **178** in a modest yield. Simultaneous oxidation of the aldehyde and deprotection of the *O*-acetate gave anodendroic acid **162** in a yield once again not mentioned in the paper.[71]

Scheme 45



2.1.4 The role of palladium in the synthesis of trematone and related structures

In the 1970's and 1980's there was a surge in the number of organic transformations utilising transition metal mediated chemistry. It was soon realised that this type of chemistry would be extremely useful for intramolecular reactions, specifically cyclisation reactions.

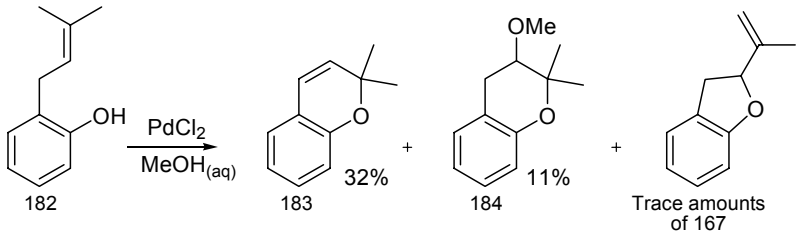
2.1.4.1 Early Pd(II) mediated reactions

In 1973, Hosokawa *et al*. published a paper describing the synthesis of 2-substituted benzofuran derivatives utilising a Pd^{II} mediated intramolecular cyclisation.[79] Thereafter,

Hosokawa expanded on this work investigating the regioselectivity of this reaction in order to better understand the underlying factors responsible for the formation of either a 6-membered heterocycle or a 5-membered heterocycle, depending on the regioselectivity of the Pd^{II} mediated cyclisation.[80]

During the course of these investigations Hosokawa discovered that the reaction of 2-allyl phenols (Scheme 46) involved attack by the phenoxyl oxygen atom on predominantly either the 2- or 3-position of the allylic side chain, depending on the conditions used. Thus treatment of **182** with $PdCl_2$ in aqueous methanol afforded a 43% yield of the 6-membered heterocycles **183** and **184**. The 5-membered heterocycle **167** which would have resulted from attack at the 2-position was only formed in trace amounts.[80]

Scheme 46



Interestingly, modification of the reaction conditions by the addition of NaOAc to the reaction mixture, or by using $Pd(OAc)_2$ instead of $PdCl_2$ afforded an increased amount of the 5-membered heterocycle. It should be noted that in these reactions, the amount Pd being used was typically 1 to 30 mole equivalents.

2.1.4.2 Early stereoselective Pd(II) mediated reactions - the Wacker approach

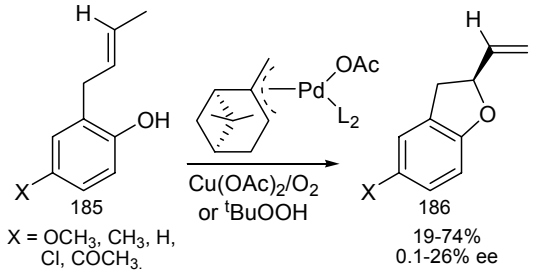
It was soon realised that the use of chiral ligands in association with transition metals* afforded optically active products. In 1981, Hosokawa and Murahashi published a paper describing the preparation of optically active benzofuran derivatives using a modified Wacker process to effect the cyclisation. In this process, it was well known that the palladium is reduced from Pd^{II} to Pd^0 and so the reaction is not catalytic, unless an oxidant is present. In this study, Cu(II) and oxygen were added stoichiometrically and this served

* In particular – Pd-mediated reactions

to reoxidise the Pd, thereby allowing for catalytic usage of the precious metal. The chiral ligand, (-)-β-pinene was employed in order to enhance the enantioselectivity of the reaction. This new process was the first example of an asymmetric Wacker-type oxidation for the preparation of asymmetric olefins.[81] A short while later, Hosokawa and Murahashi published another paper describing similar transformations, however, using ^{t}BuOOH as the co-catalyst, or oxidant.[82]

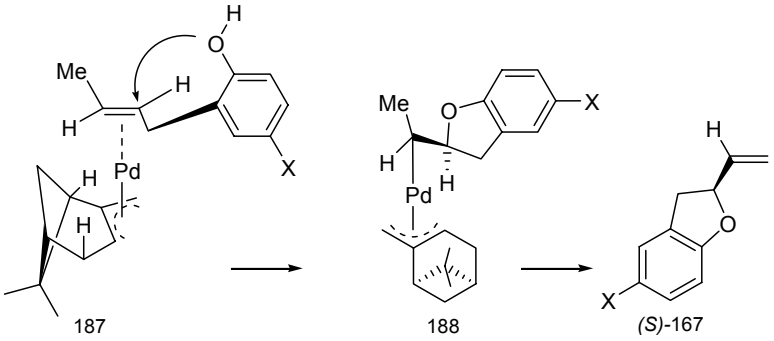
In these particular reactions (Scheme 47), several 2-(2-butenyl)-phenols **185** were reacted in the presence of a chiral (η^3-pinene)palladium(II) complex, molecular oxygen and copper(II) acetate, or ^{t}BuOOH, producing the corresponding 2-vinyl-2,3-dihydrobenzofurans **186** with very poor to moderate enantioselectivity, depending on the aromatic ring substituent.

Scheme 47



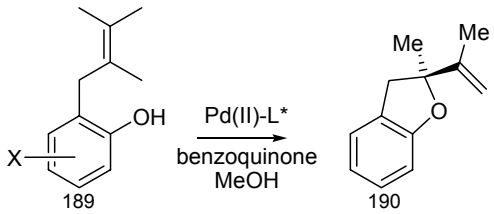
Hosokawa rationalised this stereoselectivity based upon a stereochemical model involving the π- complex (Scheme 48). An arrangement as depicted in **187** would provide the least steric hindrance between the reacting olefin and the chiral ligand. *Trans*-oxypalladation forming **188** followed by Pd-H elimination would afford the enantiomer ***(S)*-167** .[81]

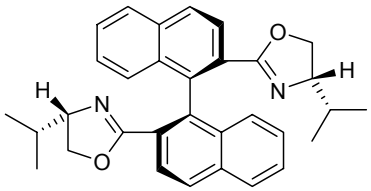
Scheme 48



Some years later, Uozumi and Hayashi improved upon this Wacker type synthesis by employing slightly different reaction conditions as well as a different chiral ligand (Scheme 49). They found that by using (*S,S*)-2,2′-*bis*-[4-(alkyl)oxazolyl]-1,1′-binaphthyl (or *S,S*-boxax) **191** as a chiral ligand along with palladium *bis*-(trifluoroacetate) and *p*-benzoquinone as a reoxidant, several 2-(2,3-dimethyl-2-butenyl)phenols **189** were readily cyclised with good enantioselectivity forming 2-methyl-isopropenyl-2,3-dihydrobenzofurans of the type **190**.[83]

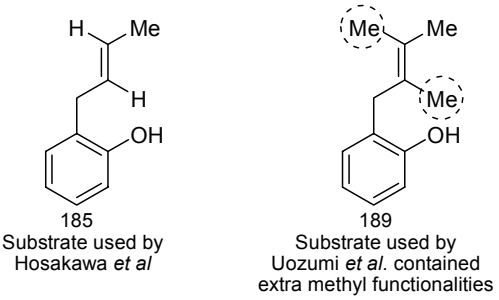
Scheme 49





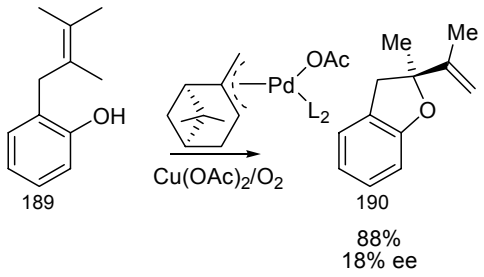
In light of the fact that this substrate **189** is slightly different compared to the 2-(2-butenyl)-phenols **185** previously used by Hosokawa and Murahashi (Scheme 47),[81] Uozumi *et al*. applied the conditions used previously by Hosakawa *et al*. to their system in order to ensure that the extra methyls in their substrate were not the sole reason for the vastly improved enantioselectivity (Figure 31).

Figure 31



To this end, treatment of their 2-(2,3-dimethyl-2-butenyl)phenol substrate **189** using the older conditions of (η^3-pinene)palladium(II) catalyst (Scheme 50), molecular oxygen and copper(II) acetate afforded (-)-*(S)*-2-methyl-2-isopropenyl-2,3-dihydrobenzofuran **190** in 88% yield, but only 18% ee.[83]

Scheme 50

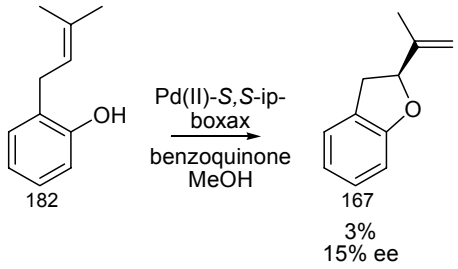


Moreover, it was found that the use of chiral phosphine based ligands were not suitable as the phosphines were readily oxidised to the phosphine oxides under these reaction conditions leading to the formation of racemic products.[83] (At this time, chiral phosphine ligands were being extensively utilised in Pd^0 catalysed asymmetric cyclisations).[84]

Inspired by the recent successful chiral cyclisations developed Uozumi and Hayashi (Scheme 49), Yamaguchi *et al*. revisited their attempted syntheses of chiral 2-isopropenyl-2,3-dihydrobenzofuran derivatives. Unfortunately, attempted application of Uozumi's improved Wacker process to their own substrate **182** did not prove to be successful (Scheme 51). Although the boxax ligand had worked very well for converting 2-(2,3-dimethyl-2-butenyl)phenol derivatives **189** into the corresponding chiral benzofurans **190** (Scheme 49), this was not the case when 2-prenylphenol derivatives were used as substrates. In fact, treatment of just plain 2-prenylphenol **182** with (*S,S*)-boxax **191**,

palladium *bis*-(trifluoroacetate) and *p*-benzoquinone afforded 2-isopropenyl-2,3-dihydrobenzofuran **167** in only 3% yield and 15% ee.[70]

Scheme 51

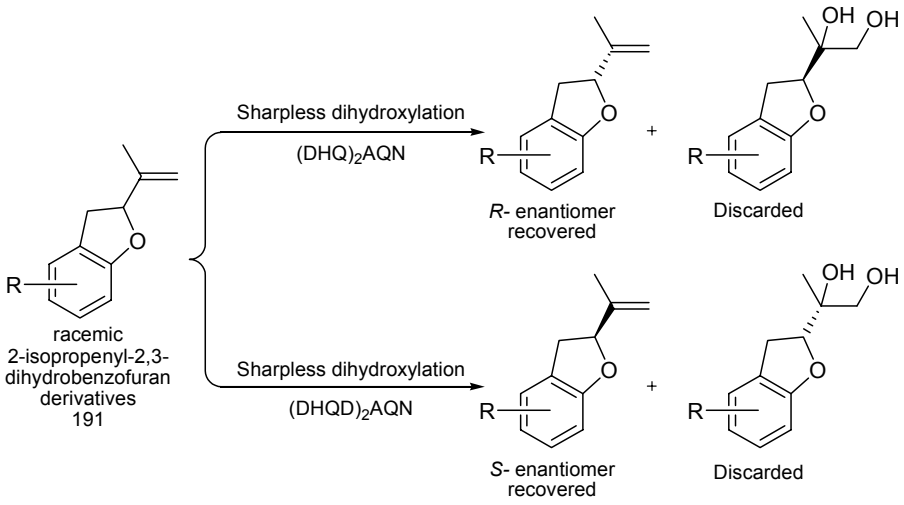


2.1.5 Sharpless asymmetric dihydroxylation as a chiral resolution approach to 2-isopropenyl-2,3-dihydrobenzofuran derivatives

At this point, in order to synthesise their envisaged target molecules, Yamaguchi *et al*. abandoned the idea of asymmetrically generating the 2-isopropenyl-2,3-dihydrobenzofuran derivatives **167** and opted for a chiral resolution procedure.[70] In the work that followed, several 2-isopropenyl-2,3-dihydrobenzofuran derivatives were prepared racemically according to previously developed methodology.[77] Then, by utilising a Sharpless asymmetrical dihydroxylation procedure,[85] the resulting diastereomers were separated affording the optically active precursors to their desired target molecules. In this type of procedure, kinetic resolution of the enantiomers is made possible by the fact that the chiral Sharpless ligands used in the dihydroxylation procedure result in a faster reaction with one enantiomer of the benzofuran derivative depending upon the choice of ligand, no doubt due to matched and mismatched arrangements in the transition state of the dihydroxylation reaction. Thus, depending on the choice of ligand, it was possible to essentially convert one enantiomer of the benzofuran racemate into the corresponding diol, and the two compounds could then be separated by column chromatography. However, this procedure, even if it worked perfectly is somewhat wasteful as at least 50% of the material must be converted to the diol which is not needed and discarded. In fact, although in theory a 50% yield of the desired enantiomer should be possible, this was certainly found not to be the case when Yamaguchi *et al.* applied this methodology to their system. Four slightly differing benzofuran substrates were resolved and it was found that good ee's were only obtained at the expense of the yield (Scheme 52). Unfortunately, the dihydroxylation reaction did not completely convert one enantiomer before starting to react with the other

and so some of the desired enantiomer was lost in a attempt to ensure that the undesired enantiomer was completely consumed. To obtain ee's in the region of 90%, the yields were typically in the region of 20% for the desired enantiomer.[70]

Scheme 52



The success of the Wacker process, which involved the production of acetaldehyde from ethylene using a Pd^{II} catalyst was the start of an enormous amount of research involving Pd mediated organic transformations.[86] The oxidation of the ethylene in this process is facilitated by a reduction in the catalytic Pd^{II} to Pd^0. The palladium is then reoxidised to Pd^{II} utilising an oxidant such as $CuCl_2$. The resulting CuCl is then reoxidised in the presence of O_2 and so functions as a co-catalyst. This Wacker-type reaction is in essence the process that has been utilised in the Pd mediated reactions as described above. However, it was not long before the usefulness of Pd^0 as a catalyst was investigated and perhaps one of the biggest contributors to research in this area would be Trost, especially in the field of asymmetric allylic alkylations.[86-88]

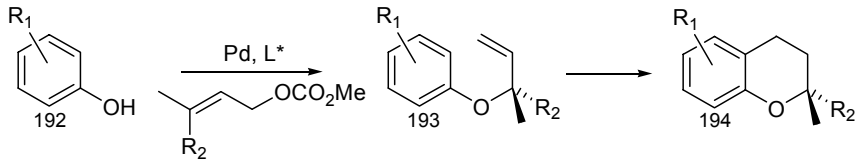
It is not the intention of this literature review to cover all of the work involving Pd^0 mediated transformations, however, in light of the fact that we are interested in producing 2-isopropenyl-2,3-dihydrobenzofuran systems using asymmetric allylic alkylation (AAA) methodology, the next part of the text will focus on Pd^0 mediated transformations leading to these types of compounds.

2.1.6 Asymmetrical Pd(0)-catalysed intramolecular cyclisations

It is interesting to note that there seem to be no publications pertaining to the synthesis of benzofuran systems using a Pd^0 catalyst. The catalytic reactions as described previously using Wacker-type Pd^{II} reactions are the most closely related examples and in the case of the 2-isopropenyl-2,3-dihydrobenzofuran systems, the ee's are by no means satisfactory. However, Trost has investigated the chiral Pd^0 mediated syntheses of the six-membered ring oxygen heterocycles – the chiral chromans.

Trost's initial studies towards the synthesis of chiral chromans was based very much upon research previously done in his group. That is to say, initially *intermolecular* Pd^0 catalysed asymmetric allylic alkylations were performed leading to enantioselective C-O bond formation **193** (Scheme 53). This was then followed by a cyclisation to form the chiral chroman **194**.[89]

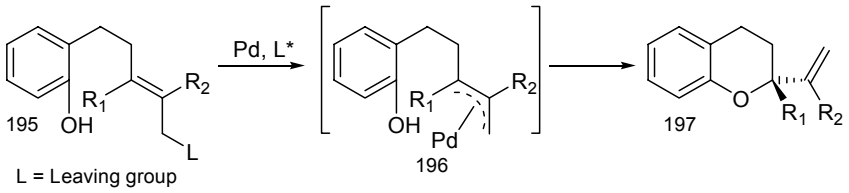
Scheme 53



Trost *et al*. realised a need for an improved strategy as a result of two major problems: Firstly, the ee's for the asymmetric allylic alkylation reactions were less than 90% and secondly, during the following cyclisation step, a small amount of regioisomers formed as a result of competitive attack at the primary allylic terminus.[89] A need for an asymmetrical Pd^0-catalysed intramolecular reaction was realised.

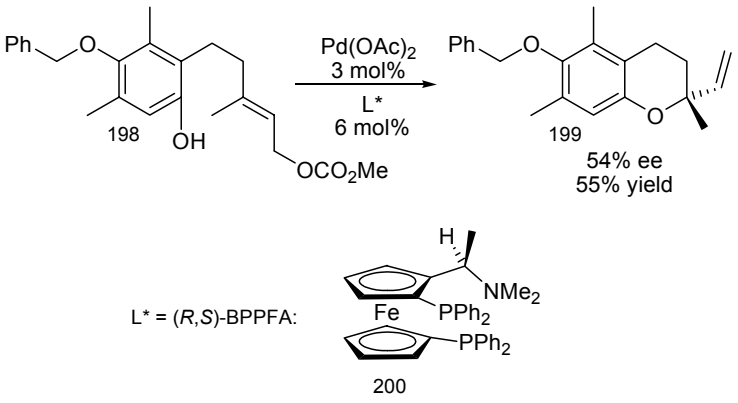
Using a similar strategy, a π-allyl palladium complex should also be obtainable from an olefin **195** containing a suitable leaving group, such as carbonate or acetate, and then *intramolecular* attack by a phenolic oxygen **196** should lead to the desired chroman system **197**, enantioselectively (Scheme 54).[89]

Scheme 54



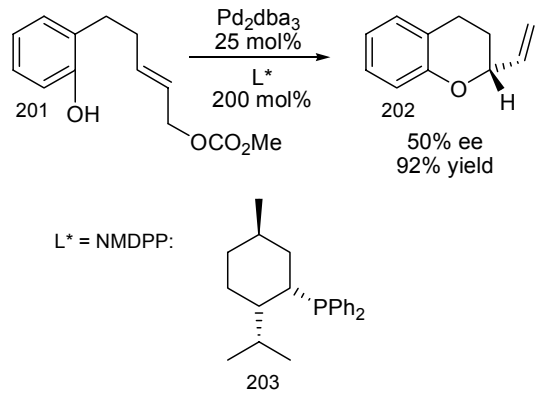
Upon surveying the literature, Trost *et al*. discovered that two other groups had investigated this approach already, but had obtained poor ee's in their reactions. Achiwa *et al*. had studied a variety of chiral ligands in their attempted syntheses of chiral chromans but at best had only managed 54% ee using BPPFA ligand **200**, and the product **199** was only obtained in 55% yield (Scheme 55).[90] Achiwa's proposed that the enantioselectivity for this reaction was as a result of the chiral recognition of the enantiotopic faces of the substrate during the ionisation process.[90] In other words, as the chiral palladium-ligand catalyst approached the substrate, the initial approach and complexation was determined by facio-selectivity imposed by the chiral ligand.

Scheme 55



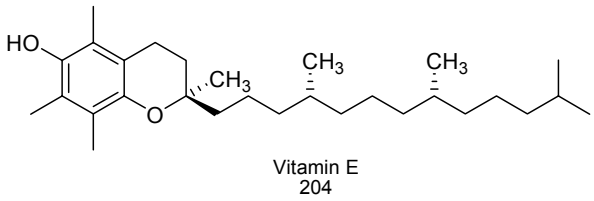
Sinou *et al*. also screened a large number of chiral ligands (Scheme 56) and at best managed to obtain 50% ee when using the NMDPP ligand **203**. Differing from the reason proposed by Achiwa *et al.,* they reasoned that the enantioselectivity had to do with the nucleophilic attack on the already formed π-allyl palladium intermediates.[91]

Scheme 56



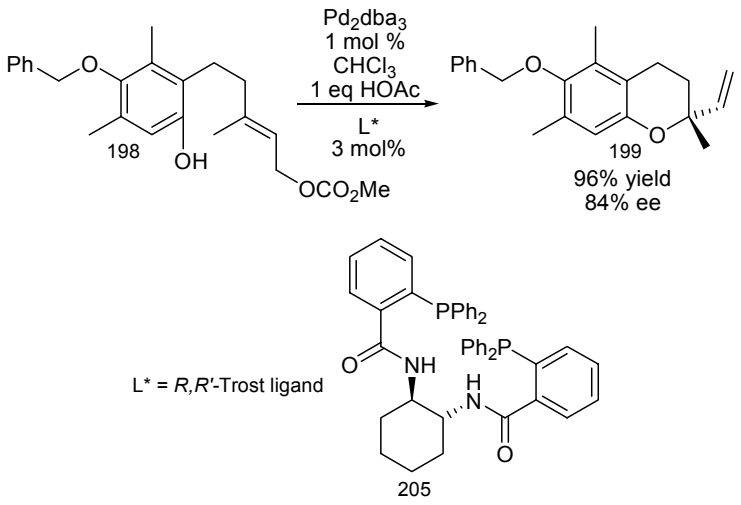
Not disheartened by the seemingly poor enantioselectivity of these reactions, Trost *et al*. began to investigate these chiral cyclisations as a useful method to access the core of vitamin E **204** (Figure 32).[92]

Figure 32



By utilising one of the Trost ligands **205** (Scheme 57), the group was pleased to discover that the desired chroman **199** could be obtained using a Pd π-allyl mediated cyclisation in 96% yield and 84% ee.[92] Moreover, it should also be noted that Sinou *et al*. had in fact already screened this same ligand in their cyclisation procedures, and had yet only obtained 7% ee in their reaction.

Scheme 57



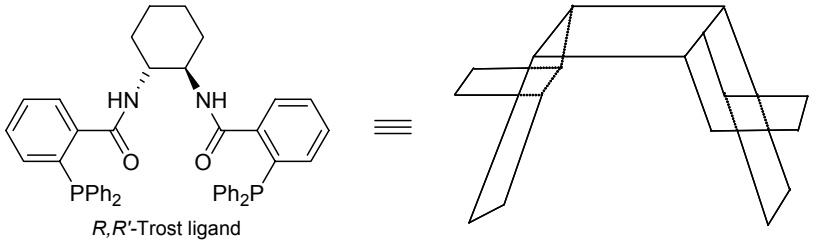
This astounding result in comparison to the work done by Sinou *et al*. prompted Trost to investigate the reaction in a little more detail. Trost proposed that there are at least two possible mechanisms for the catalytic asymmetric alkylation of phenol allyl carbonates: Firstly, the enantioselectivity is derived from the faciotopic discrimination of the Pd-L* complex as it complexes. In other words, the Pd bound to the chiral ligand shows a strong preference for one face of the olefin as it approaches and the subsequent cyclisation is fast enough so that the π-allyl palladium complex thus formed does not have enough time to equilibrate, (which would then result in a racemate). The second possible mechanism could be that the cyclisation step is slow in comparison to the interconversion of the formed π-allyl palladium diastereomer, thus allowing the formed complex to rearrange itself to the thermodynamically more favourable diastereomer, ultimately producing one enantiomer upon cyclisation.

Although Trost and Sinou's conditions were quite similar, and the chiral ligand was the same, the fundamental difference was found to be the one equivalent of acetic acid utilised in Trost's reaction conditions. It was found that if the acetic acid was not used, a drastic drop in ee was observed and in fact, if triethylamine was used instead of acetic acid the reaction began to favour the other enantiomer, though poorly so (8% ee).[92] Were Achiwa's proposals for the enantio-discrimination correct, then the faster the cyclisation, the better the ee should be. However, the opposite is observed. The addition of 1 mole equivalent of acetic acid enhances the ee enormously (84% ee) and thus the second plausible mechanism

makes more sense. The cyclisation reaction is slowed down by acidifying the solution, therefore decreasing the nucleophilicity of the phenolic hydroxyl group. This provides enough time for the complex to equilibrate to the more thermodynamically favoured form and greatly enhances the ee. Another point to emphasise is the fact that in the presence of triethylamine, the ee is not only greatly deteriorated, but slightly favours the opposite enantiomer. This is an indication that the chiral Pd-L* favours complexation onto the 'wrong' side of the olefin initially, and then rearranges by means of a π-σ-π equilibration to the thermodynamically more favoured side after ionisation. Trost explains these deductions using the following working models:[92]

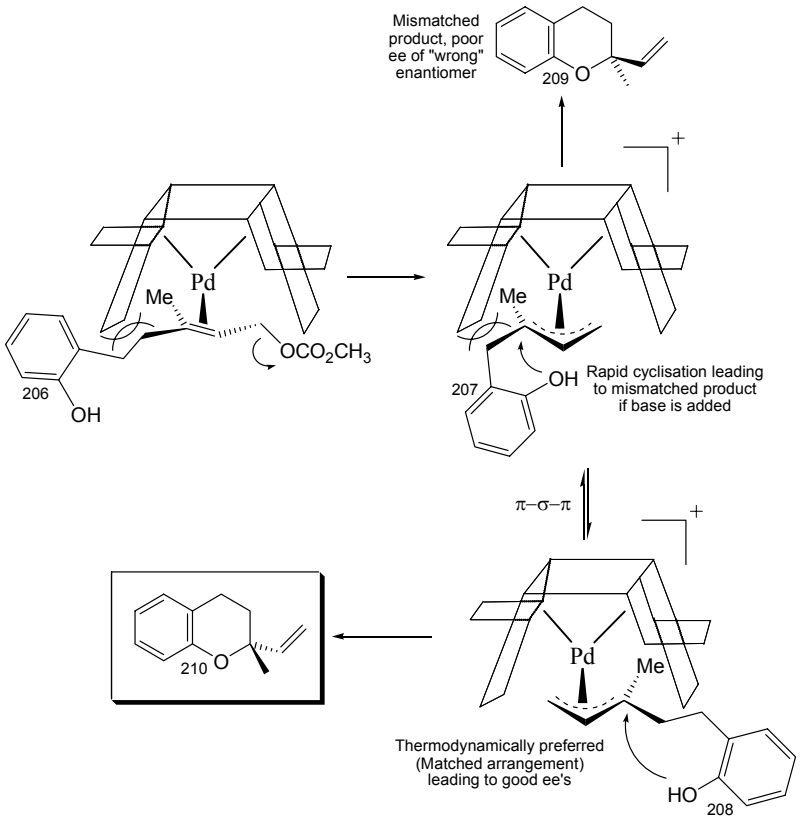
Firstly, the chiral ligand may be spatially represented by the following diagram where the flaps and walls of the scaffold represent the phenyl groups of the triarylphosphine moiety (Figure 33).[92] The scaffold is itself chiral and matches the ligand below.

Figure 33



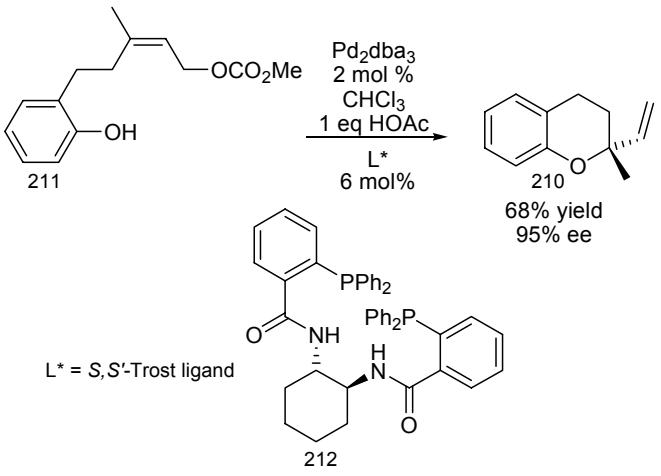
The *trans*-allyl carbonate initially co-ordinates to the Pd-L* in a kinetically matched process (Scheme 58). This is necessary, as the carbonate leaving group must be able to depart from under one of the flaps of the chiral ligand. In this particular case, only one arrangement is possible **206**. However, once the leaving group has departed and the π-allyl palladium complex has been formed **207**, the arrangement is no longer in the most thermodynamically favourable form and therefore rearranges via a π-σ-π process to once again generate a matched arrangement **208**. It is from here that a matched cyclisation can occur, leading to the preferred product **210**. However, if the cyclisation is encouraged by the addition of base, the ee is poor since there is not enough time for the complex to rearrange itself. In fact, if the cyclisation is fast enough, there a preference for a mismatched cyclisation, leading to ee's slightly favouring the opposite enantiomer **209**.[92]

Scheme 58



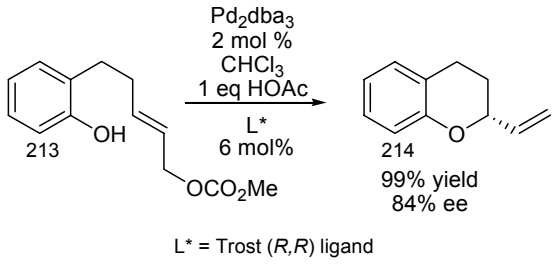
Importantly, the *(Z)*- alkene results in the formation of the opposite enantiomer if the same *R,R'*-Trost ligand is similarly used. Therefore, application of this methodology to *(Z)*- tri-substituted olefin **211** in conjunction with the opposite *S,S'*-Trost ligand resulted in the same enantiomer **210** being formed in excellent ee though somewhat poorer yields (Scheme 59). In fact, it is for this reason that in the synthetic approach to these olefins, one needs to make sure that the compound is either the pure *(E)*- or pure *(Z)*- geometric isomer. Any contamination of geometrical isomers will lead to diminished ee's.

Scheme 59



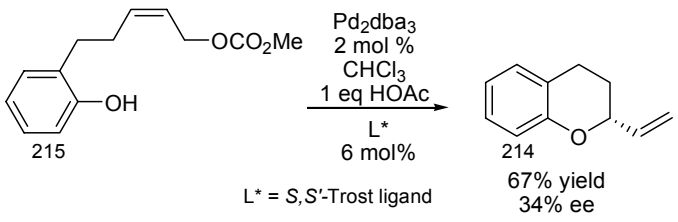
This system is indeed slightly different from the system used by Sinou *et al*. in that a tetra-substituted stereogenic centre is produced as opposed to a tri-substituted stereogenic centre. Trost did apply this methodology to a disubstituted *trans* olefin **213** (Scheme 60) and obtained excellent yields and enantioselectivities of the product now containing a tri-substituted stereogenic centre **214**. Once again, similarly poor and opposite ee's were obtained when base was used or when no acetic acid was used as an additive. [92]

Scheme 60



Interestingly, when the *(Z)*- isomers of disubstituted olefins **215** were subjected to the optimum cyclisation conditions, poor ee's were obtained (Scheme 61).[92]

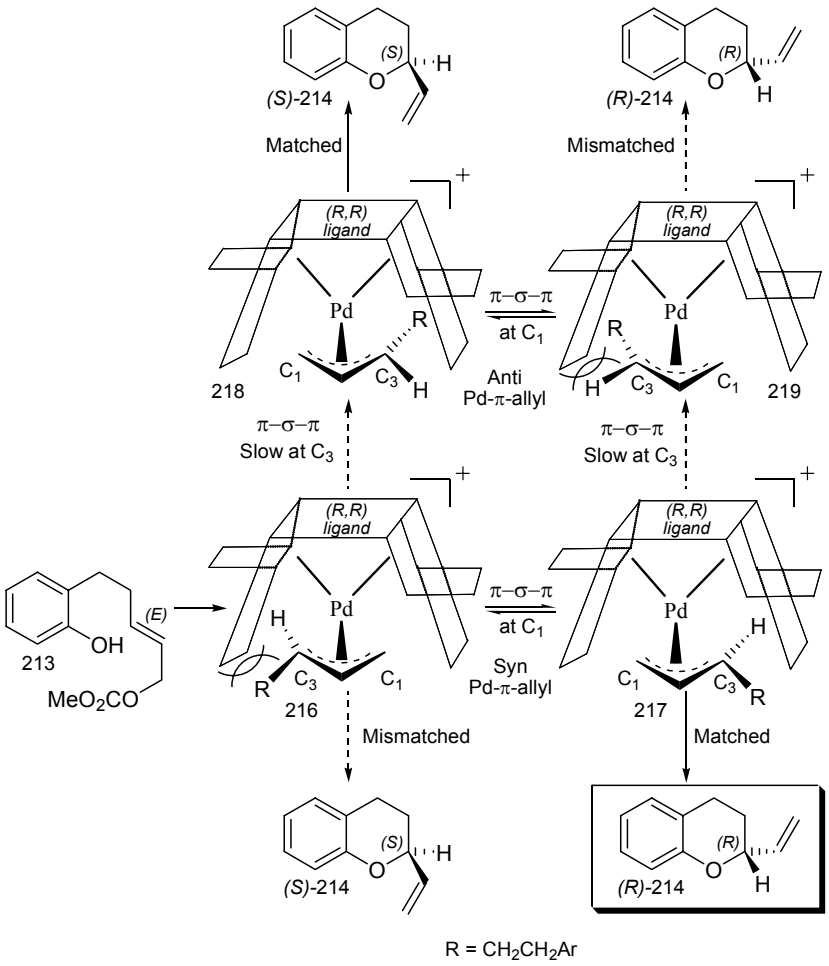
Scheme 61



The reason for this finding can once again be explained by way of the models as described previously. However, one additional consideration that needs to be incorporated into the discussion pertains to the stability of the π-allyl-Pd complex. It is well known that *syn* π-allyl-Pd complexes are thermodynamically more stable than their corresponding *anti* forms.[93] The model below (Scheme 62) depicts the various interchangeable arrangements for the disubstituted *trans* alkene **213**. The initial ionisation of this compound proceeds by means of a matched* process producing the *syn* π-allyl-Pd complex **216**. However, once ionisation has occurred and the leaving group has departed favourably from under the flap, the complex is now no longer in its most thermodynamically favourable arrangement due to steric crowding therefore undergoes a π-σ-π rearrangement generating the more favourable **217**. The phenolic hydroxyl nucleophile can then attack from under the right front flap of the ligand leading to a matched cyclisation, forming ***(R)*-214** in this case. The alternative rearrangement would be the conversion of **216** via a π-σ-π rearrangement to the *anti* π-allyl-Pd complex **218**, and that too could lead to a matched cyclisation. However, the formation of the *anti* π-allyl-Pd complex **218** is thermodynamically disfavoured (R-group in sterically crowded environment) and so does not form a competing reaction, even though **218** could lead to a matched cyclisation. Rearrangement of the less favourable *anti* π-allyl-Pd complex **218** to **219** would lead to a mismatched cyclisation and so this does not occur. Thus, only one pathway is thermodynamically favoured and this is the reason for the pleasingly high ee's when *trans* disubstituted olefins are subjected to cyclisation under Trost conditions.

* The ionisation is a matched process as the leaving group is able to depart from under the flap on the right front section of the ligand.

Scheme 62

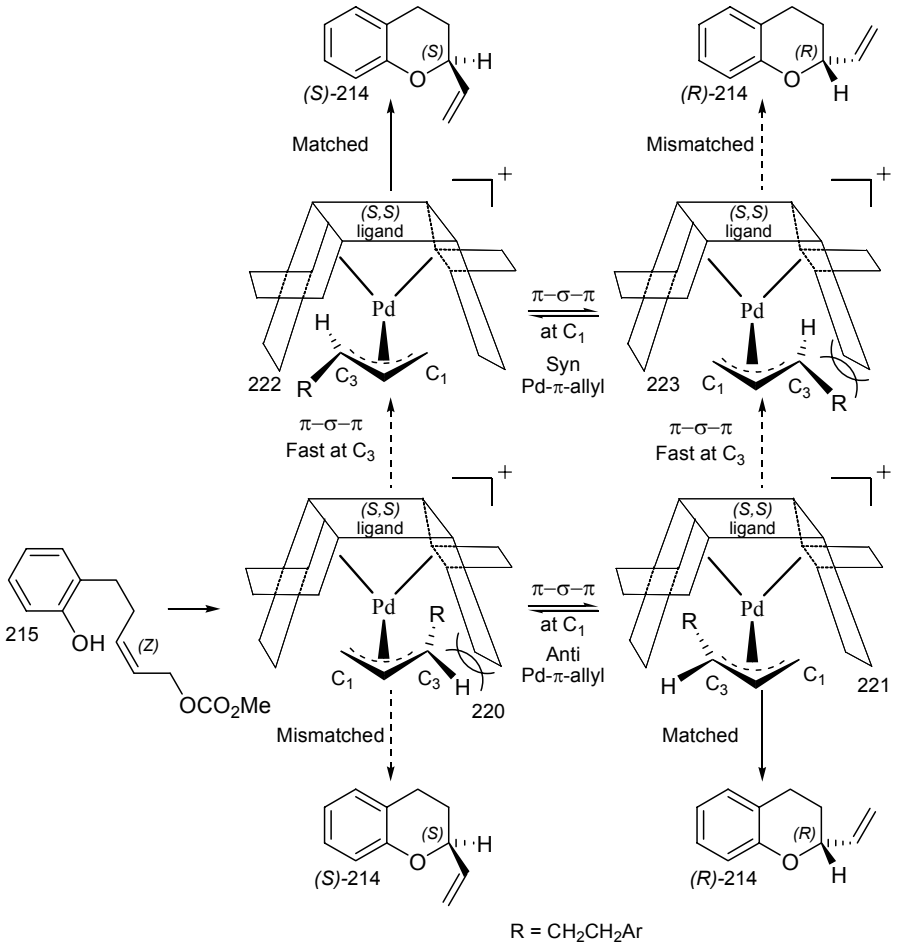


However, when *cis* disubstituted olefins are cyclised poor ee's are obtained and the reason for this is because the initial ionisation leads directly to the thermodynamically disfavoured *anti* π-allyl-Pd complex **220** (Scheme 63). Due to steric factors, **220** cannot undergo cyclisation directly,[*] and therefore either undergoes a π-σ-π rearrangement forming **221** which, although still the less favoured *anti* π-allyl-Pd complex form, can now undergo a matched cyclisation forming ***(R)*-214**. The other alternative is that the initially formed *anti* π-allyl-Pd complex **220** undergoes a π-σ-π rearrangement leading to the *syn* π-allyl-Pd complex **222** which can then cyclise by means of a matched cyclisation forming the opposite enantiomer ***(S)*-214**. Thus, due to the fact that the initial ionisation leads to the

[*] Although **220** looks like the sterically preferred form, in the case of the *anti* π-allyl-Pd complexes, the aryl moiety is extended outwards directly behind the ligand but in the case of **220** cyclisation would require that it curl inward directly into the wall of the ligand.

formation of the thermodynamically less favoured *anti* π-allyl-Pd complex **220**, these two routes compete with each other leading to grossly diminished ee's.[92]

Scheme 63



In summary: in the case of tri-substituted olefins, due to steric influences, slightly higher ee's are obtained using the *cis* alkenes, producing tetra substituted chromans containing a tetra-substituted stereogenic centre. In addition, for tri-substituted olefins the *trans* alkenes also produce tetra-substituted chromans in good ee. In the case of disubstituted alkenes, *cis* alkenes result in extremely poor ee's and the *trans* alkenes result in excellent ee's due to the stability of the π-allyl-Pd complex initially formed. In both cases, the *cis* and *trans* alkenes produce opposite enantiomers when cyclised using the same chiral Trost ligand. Finally, in the case of *trans* alkenes: the *S,S'*-Trost ligand produces the *(S)*- chroman and the *R,R'*-Trost ligand produces the *(R)*- chroman.

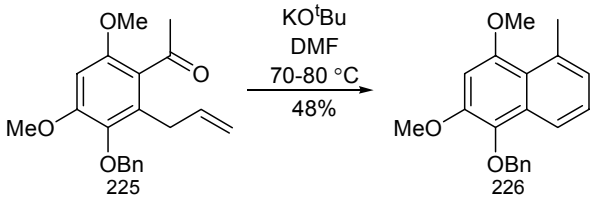
CHAPTER 3 - PLANNED APPROACHES

3.1 TOWARDS CARBAZOLE COMPOUNDS OF INTEREST

3.1.1 An introduction to methodology previously developed in our laboratories

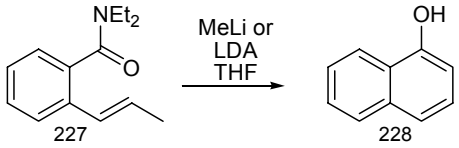
As part of another project previously conducted in our laboratories, whilst attempting to bring the double bond of 2-allyl-3-benzyloxy-4,6-dimethoxyacetophenone **225** into conjugation using KO^{t}Bu at 70 °C in DMF, de Koning inadvertently formed the naphthalene product **226** in a moderate yield (Scheme 64).[94]

Scheme 64



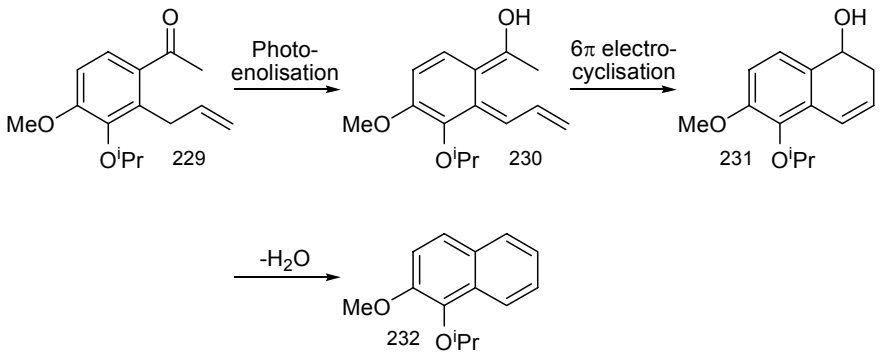
Although this particular type of cyclisation had not been reported before it was quite similar to a cyclisation reported by Snieckus and co-workers in which naphthols **228** were formed from corresponding benzamides **227**, also in the presence of a strong base (Scheme 65).[95]

Scheme 65



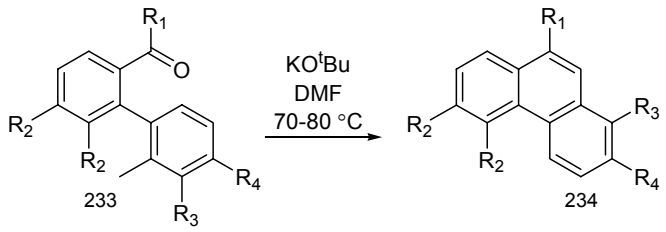
The scope of this new reaction was investigated and soon extended to the synthesis of various substituted naphthalenes. Moreover, it was also discovered that the reaction proceeded better in the presence of light emitted from a high pressure mercury lamp. It was postulated the *o*-allylbenzaldehydes **229** underwent photo-enolisation to the corresponding diene **230** (Scheme 66). This was followed by a 6π-electrocyclisation to afford the alcohol **231** and subsequent dehydration finally afforded the corresponding naphthalene **232**.[94]

Scheme 66



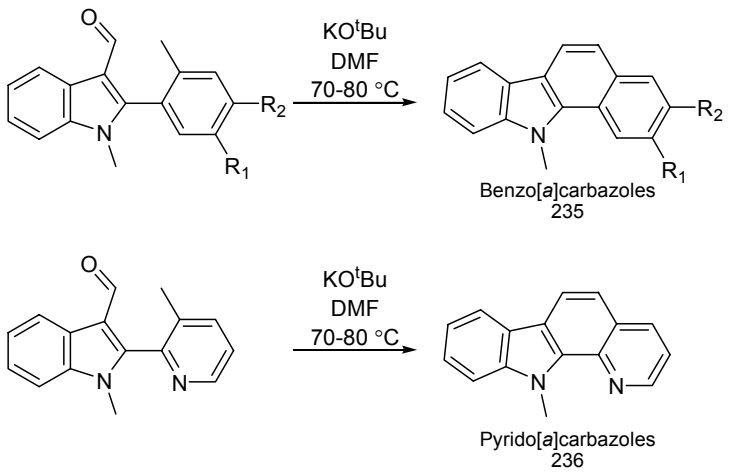
This novel methodology was extended to the synthesis of larger aromatic systems and several substituted phenanthrene derivatives were synthesised (e.g. **234**, Scheme 67) from the corresponding biaryls **233**.[94]

Scheme 67



Further extension of this methodology to indole based systems allowed for the synthesis of several benzo[*a*]carbazoles **235** and pyrido[*a*]carbazoles **236** (Scheme 68). As discussed earlier, the carbazole nucleus is found widely in nature and this new methodology provided a new route to synthesise various substituted forms of these important compounds.[96]

Scheme 68

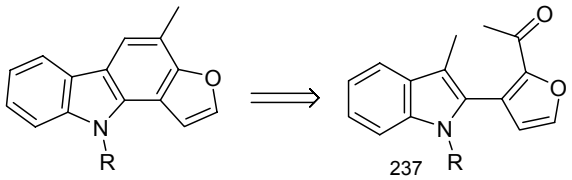


It is this final methodology that interested us as we envisaged that it may be utilised to synthesise furostifoline as will be described below. Should the proposed route be successful, it would constitute one of the shortest total syntheses of this naturally occurring compound.

3.1.2 An envisaged approach for the total synthesis of furostifoline

Since we intended to utilise the methodology developed by de Koning and co-workers,[96] the initial disconnection of furostifoline would have to be at the [*c*] face of the carbazole ring system, leading the to the substrate **237** (Scheme 69), which is similar to the compounds successfully cyclised using the conditions of light and base in DMF.[96]

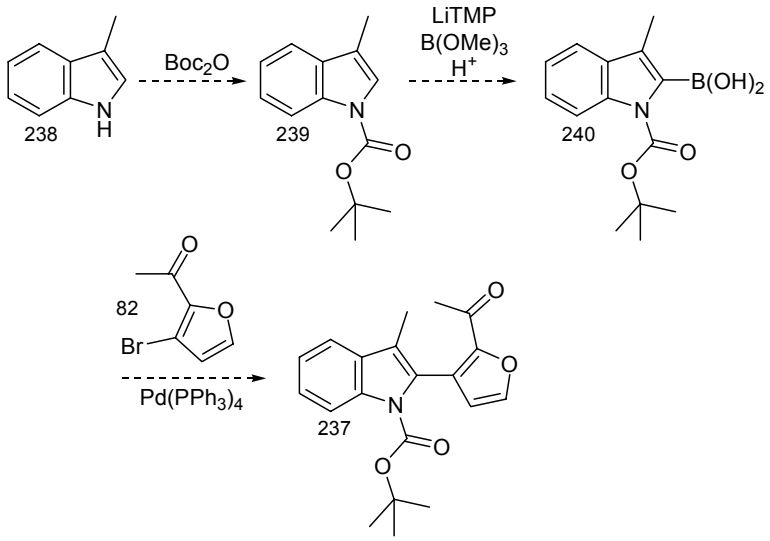
Scheme 69



It was envisaged that **237** could be accessed by starting from readily available skatole **238** (Scheme 70). As an initial step, the attachment of a Boc group to the indole nitrogen, forming **239**, would serve two purposes: Firstly, protection of the reactive indolic nitrogen would be achieved and secondly, the Boc group is ideal for facilitating *ortho* directed metallation. Thus, treatment of the Boc-protected skatole **239** with a hindered lithium base

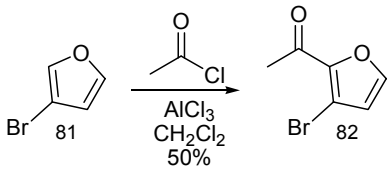
such as lithium-TMP would allow for attachment of a boronic acid forming **240** and reactions of this type have been accomplished before in our laboratories.[96] The intention behind forming the indolo-boronic acid would be to allow for a Suzuki coupling reaction thereby attaching a suitably substituted furan moiety. In our particular case, 2-acetyl-3-bromofuran **82** would be reacted with 3-methylindole-2-boronic acid **240** under Suzuki conditions finally leading to the desired precursor **237**, ready for the light mediated cyclisation.

Scheme 70



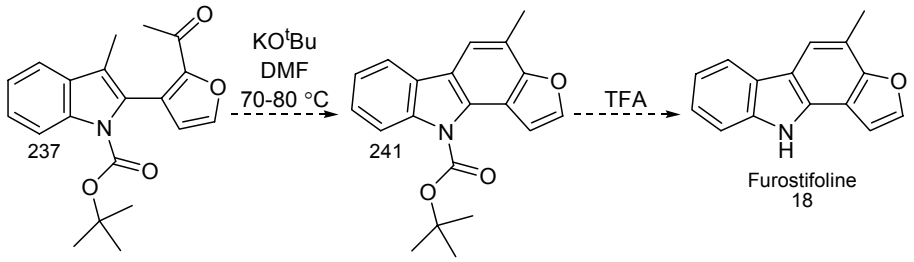
The synthesis of 2-acetyl-3-bromofuran **82** has recently been published by Tanaka *et al.* (Scheme 71).[97] In fact, their intention at the time was to synthesise 5-acetyl-3-bromofuran by means of a Friedel Crafts reaction, treating 3-bromofuran **81** with acetylchloride and aluminium trichloride. Acetylation in the 5-position is what one would expect as this is the more nucleophilic position of the furan ring system. To their surprise, 2-acetyl-3-bromofuran **82** was obtained exclusively in a 50% yield. Nevertheless, this unprecedented reaction would be just what we needed for the construction of our required furan.

Scheme 71



After coupling of the two moieties under Suzuki conditions, we would be in a position to attempt the light mediated cyclisation reaction leading to the carbazole **241** (Scheme 72). Finally, deprotection of the indole moiety under mildly acidic conditions should afford furostifoline **18** in six steps.

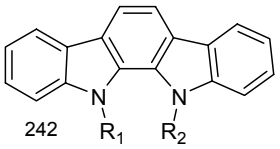
Scheme 72



3.1.3 An envisaged approach to synthesise the indolocarbazole core

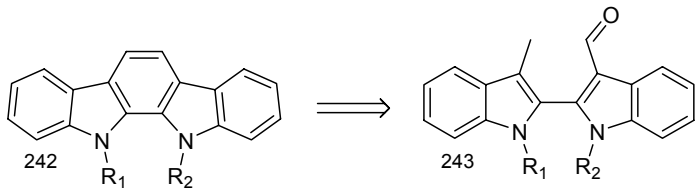
As discussed in the introductory part of this thesis, the indolocarbazole skeleton (**242**, Figure 34) is widely found in many interesting naturally occurring compounds possessing useful biological activity. As an extension of the above goal it seemed feasible that the novel light assisted cyclisation, discovered by de Koning and co workers, might also be useful in the synthesis of indolocarbazole systems.

Figure 34



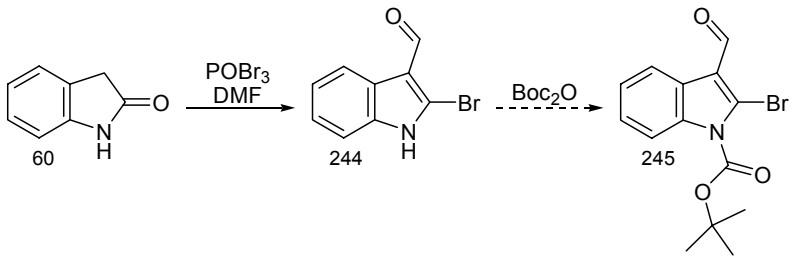
In a similar disconnection to furostifoline, we envisaged that two appropriately functionalised indole moieties could be coupled forming a *bis*-indole **243** (Scheme 73). The necessary features of an aldehyde on the one moiety and an 'aromatic methyl substituent' on the other moiety would provide a system not too dissimilar to those found susceptible to light assisted cyclisation in the presence of KO^{t}Bu.[96] Thus, the key disconnection in our approach would once again be the construction of the double bond, which would form the [*c*]-face of the carbazole system **242**.

Scheme 73



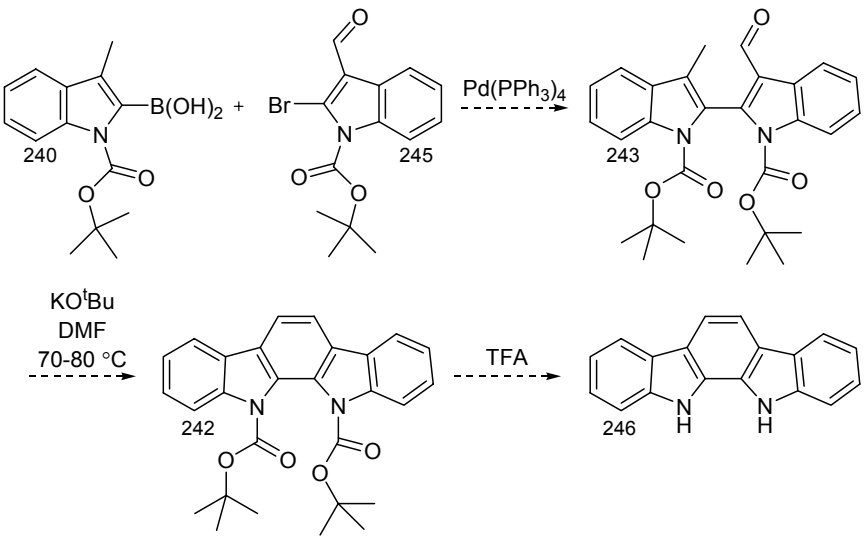
We envisaged that this *bis*-indole system **243**, connected by a biaryl axis could once again be accessed by utilising a Suzuki reaction of two suitably substituted indole units – one being a boronic acid derivative and the other being the required aryl halide derivative. From our planned route to synthesise furostifoline, we already had in mind a feasible procedure to synthesise the 3-methylindole-2-boronic acid derivative **240** and furthermore, there existed literature precedence for the synthesis of 2-bromoindole-3-carbaldehyde derivatives.[98] Thus, according to this procedure, through a modification of the Vilsmeier-Haack reaction, oxindole **60** could be treated with $POBr_3$ and DMF, forming 2-bromoindole-3-carbaldehyde **244** which could then be suitably protected as the Boc-indole derivative **245**, immediately providing us with the aryl-halide moiety required for the Suzuki coupling reaction (Scheme 74).

Scheme 74



The two units (**240** and **245**, Scheme 75) could then be coupled using the Suzuki coupling reaction forming key intermediate **243**. A light assisted cyclisation in the presence of KO^tBu should afford the protected indolocarbazole system **242**. Finally, removal of the Boc protecting groups using mild acid conditions should afford the indolocarbazole core **246**.

Scheme 75



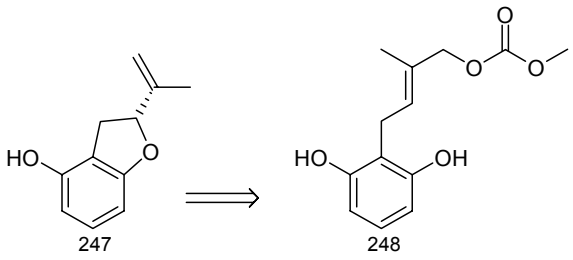
3.2 TOWARDS THE ROTENONE PRECURSOR

3.2.1 An envisaged chiral approach to synthesise 2-isopropenyl-2,3-dihydrobenzofuran-4-ol

As discussed in the introductory parts of this thesis, there are several ways of accessing 2-isopropenyl-2,3-dihydrobenzofuran systems. However, the chiral synthesis of these compounds remains a problem and enantioselectivities on reported syntheses are poor. We envisaged that a Trost approach may lead to high enantioselectivities, even though the Trost chemistry thus far has been limited to 6-membered chroman ring systems.[92]

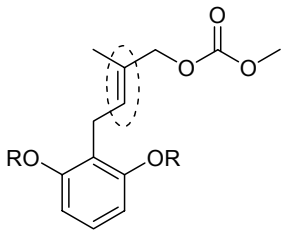
As our key intermediate we envisaged the disubstituted *trans* olefin **248** containing a carbonate leaving group (Scheme 76). It was hoped that this particular intermediate, being similar in structure to Trost's chroman precursors, would undergo a highly enantioselective cyclisation using palladium π-allyl chemistry in the presence of a chiral ligand leading to **247**.

Scheme 76



Of utmost importance in the planning of this particular precursor was that the alkene needed to be synthesised under conditions which would give exclusively one geometrical isomer. As discussed previously, the *(E)*- and *(Z)*- alkenes produce opposite enantiomers when cyclised with the same chiral ligand utilising Trost's conditions. A mixture of *(E)*- and *(Z)*- geometric isomers would therefore lead to diminished ee's.[92] Moreover, for disubstituted alkenes, leading to trisubstituted stereogenic centres, very poor ee's are obtained if the *(Z)*- alkene is used. For our particular system, we will be forming a trisubstituted stereogenic centre, starting from a trisubstituted alkene and so it is important to ensure that the synthetic procedure produces the pure, *(E)*- geometric isomer **249** (Figure 35).

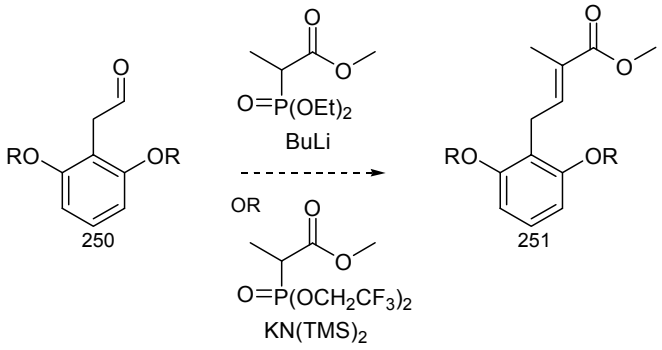
Figure 35



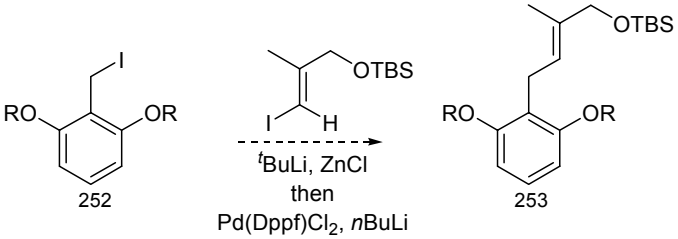
(E)-alkene
249

There are at least three synthetic approaches one may utilise in order to optimise the formation of the *(E)*- geometrical isomer over the *(Z)*- isomer. The Horner-Wadsworth-Emmons reaction is a slight variation on the Wittig reaction, using a phosphonate and a Li base, and normally results in excellent selectivity for the *(E)*- olefin (Scheme 77).[99] A second method is to utilise Still's protocol using trifluoroethyl phosphonoacetate. This procedure is also known to favour the *(E)*- alkene (Scheme 77).[100] Finally, either the *trans* or *cis* alkene ***(E)-*** or ***(Z)-*****253** may be obtained in pure form by coupling an alkyl iodide **252** directly to the correct geometrical vinyl iodide according to the procedure developed by Negishi (Scheme 78).[101]

Scheme 77

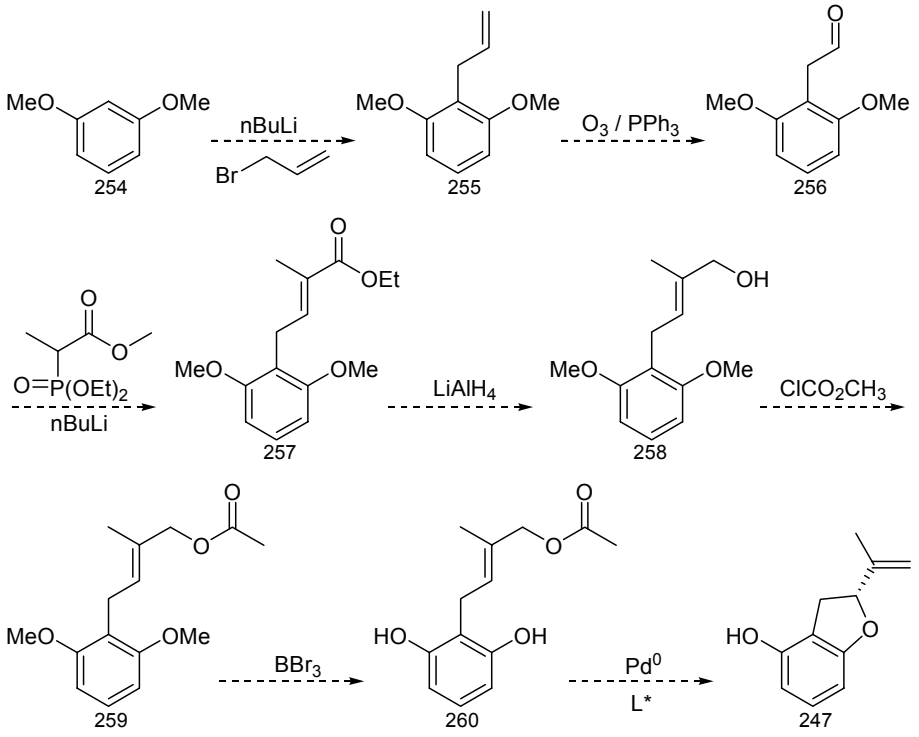


Scheme 78



As an envisaged synthesis for the aldehyde **256**, a logical starting point would be to use readily available dimethoxy benzene **254** (Scheme 79). It is well known that methoxy groups are *ortho* directors and therefore lithiation *ortho* to both groups is easily achieved using *n*BuLi. This would allow for the introduction of an allyl group forming **255** and then ozonolysis of the alkene should cleanly afford the aldehyde **256**. At this point, we will have to investigate one of the coupling procedures as outlined above in order to optimise the formation of the desired *(E)*- alkene **257**. Complete reduction of the alkyl ester moiety to form the alcohol **258** and subsequent conversion of this alcohol to the acetate **259** should facilitate the envisaged Pd π-allyl mediated cyclisation. All that would need to be accomplished before this cyclisation would be the removal of the aromatic methyl protecting groups and reactions of this type can be carried out using reagents such as BBr_3, forming **260**. Finally, with the diol in hand, the chiral Pd π-allyl mediated cyclisation will be investigated as a plausible reaction for forming optically pure 2-isopropenyl-2,3-dihydrobenzofurans, (e.g. **247**). An envisaged problematic step in this synthetic approach may be the selective removal of the aromatic methyl protecting groups **259** in the presence of the acetate. This will have to be investigated and if necessary, the protecting groups may need to be changed to allow for selective removal under milder conditions.

Scheme 79



Upon completion of the envisaged chiral synthesis, all that would remain would be to determine the enantiomeric excess of our final chiral cyclisation step. Unfortunately it would appear that compounds of the type **247** have never been synthesised in a stereoselective manner before and so a simple comparison of specific rotation would not be useful. A possible way to determine ee's would be to subject the final compound to HPLC utilising a column containing a chiral stationary phase.

CHAPTER 4 - AN ENVISAGED LIGHT MEDIATED APPROACH

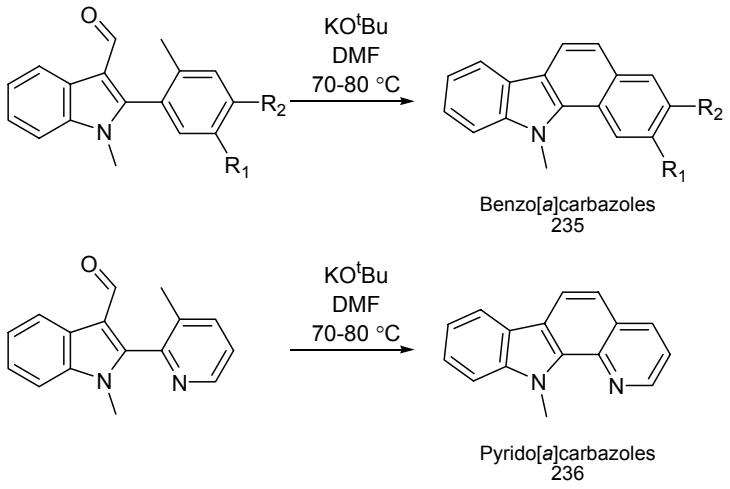
4.1 TOWARDS FUROSTIFOLINE

4.1.1 A planned model study to investigate the feasibility of the light mediated cyclisation

As described in Chapter 3, in our initial approach towards the synthesis of furostifoline we hoped to employ the use of a novel light mediated cyclisation previously developed in our laboratories for similar systems, thereby utilising this reaction to generate the carbazole skeleton of our target molecule.

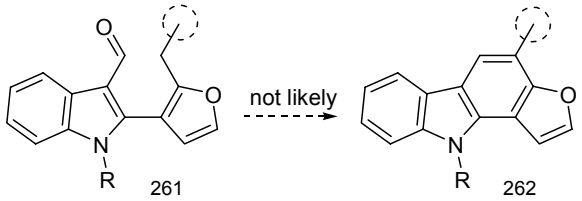
This reaction had been used quite successfully before in our laboratories to synthesise similar carbazoles. For example, as discussed in more detail in the preceding chapter, several benzo[*a*]carbazoles **235** and pyrido[*a*]carbazoles **236** were synthesised in this manner (Scheme 80).[94,96]

Scheme 80



To apply this methodology to our system we would require a similar structural configuration to these examples. Unfortunately, the use of an indole-3-carbaldehyde **261** would not be possible if we wished to obtain the furostifoline structure, mainly due to the required extra methyl functionality in the 4-position of the carbazole (Scheme 81).

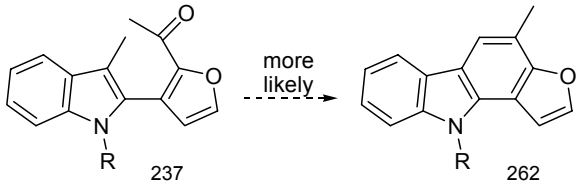
Scheme 81



261 262

However, it was hoped that a reversal of the carbonyl and methyl functionalities, such as in ketone **237** (Scheme 82), would also provide a system likely to undergo the light mediated cyclisation, as it has been shown before that these cyclisations occur using ketones as well as aldehydes.[94,96]

Scheme 82

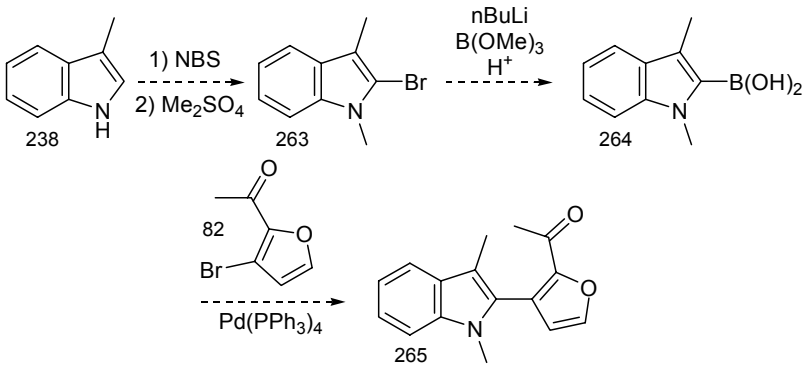


237 262

As a model study, we decided that the *N*-methyl derivative of **237** would be the most easily accessible unit. Thus a synthetic strategy for this compound was formulated.

By utilising a Suzuki coupling reaction, 2-acetyl-3-bromofuran **82** could be coupled to an appropriately substituted indole boronic acid (Scheme 83), in this case 1,3-dimethyl-1*H*-indol-2-ylboronic acid, **264**. It was envisaged that the boronic acid could be synthesised from the corresponding 2-bromo-1,3-dimethyl-1*H*-indole derivative **263**, utilising lithium-halogen exchange as a means of introducing the borate ester. With the boronic acid **264** and the 2-acetyl-3-bromofuran **82** in hand, a Suzuki coupling reaction should provide the indolo-furan precursor containing the required functionality to investigate the light mediated cyclisation reaction.

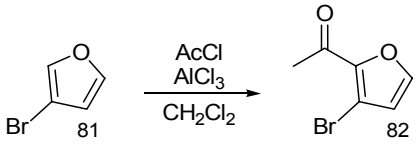
Scheme 83



Should the light mediated cyclisation reaction prove to be successful, then a synthesis with a more appropriate removable protecting group could be undertaken to finally produce furostifoline.

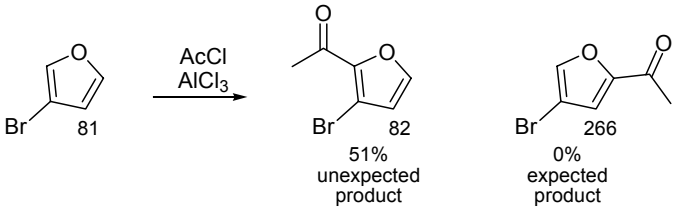
4.1.1.1 Synthesis of 2-acetyl-3-bromofuran – 82

Scheme 84



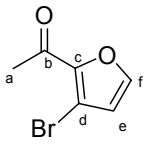
A brief survey of the literature revealed that the synthesis of **82** had previously been carried out by Tanaka and co-workers – albeit by accident! In their synthesis of 2-acetylnaphtho[2,3-*b*]furan-4,9-dione, they required 5-acetyl-3-bromofuran **266** (Scheme 85), which they envisaged synthesising using a Friedel Crafts acylation of 3-bromofuran **81** with acetyl chloride. To their surprise, they obtained exclusively the unexpected product, 2-acetyl-3-bromofuran **82** in 51% yield.[97]

Scheme 85



Unexpected synthesis of 2-acetyl-3-bromofuran by Tanaka *et al*.

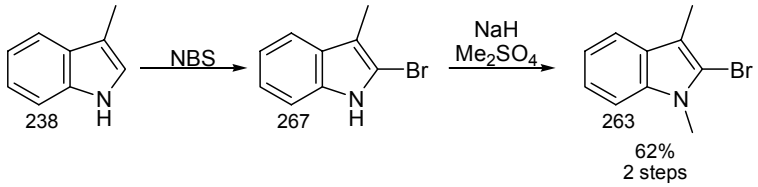
Although this unexpected result caused some difficulties for Tanaka *et al*. it provided us with the methodology to obtain exactly the substitution pattern we required for the synthesis of our key precursor. Thus, freshly distilled acetyl chloride was treated with aluminium trichloride followed by 3-bromofuran **81** producing the desired 2-acetyl-3-bromofuran **82** in excellent yield. It should be noted that for the purification of this product, it was necessary to first column the crude material to remove most of the impurities and then this material was subjected to vacuum distillation, affording the desired product as a white waxy solid. Unfortunately, the material could not be purified adequately by using either column chromatography or distillation alone - both processes were always required. Nevertheless, even with this "double purification", excellent yields (86%) were always obtained.*



Since this Friedel Crafts reaction produces the unexpected 2-substituted product, and Tanaka *et al*. didn't elaborate on their result as it wasn't particularly useful to them, we were concerned that this really was indeed 2-acetyl-3-bromo-furan. Fortunately, a literature comparison of the ^{1}H NMR spectrum coupling constants obtained for the protons on the furan ring proved unambiguously that ^{3}J coupling was occurring (1.75 Hz) between the protons H_f and H_e, these doublets being located at 7.50 ppm and 6.63 ppm respectively – confirming the desired substitution pattern. The presence of the acetyl was clearly indicated by the 3H singlet at 2.55 ppm and moreover by the presence of the carbonyl carbon at 186 ppm in the ^{13}C NMR spectrum.

4.1.1.2 Synthesis of 2-bromo-1,3-dimethyl-1*H*-indole – 263

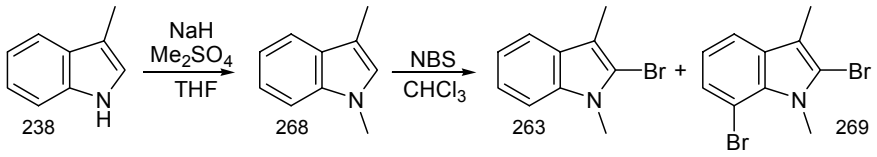
Scheme 86



*The reason for the dramatic increase in yield as compared to the synthesis carried out by Tanaka *et al*. may be attributed to either partial hydrolysis of their acetyl chloride or the 3-bromofuran being somewhat impure, as it is unstable and needs to be stored at –15 °C.

As part of our strategy to ultimately synthesise an appropriately substituted indoleboronic acid, the synthesis of 2-bromo-1,3-dimethyl-1*H*-indole **263** was necessary (Scheme 86). In our initial syntheses of this compound, readily available 3-methylindole **238** was first *N*-methylated forming **268** (Scheme 87). However, subsequent bromination of this protected compound using NBS in chloroform unfortunately always resulted in significant amounts of the undesired 2,7-dibromo product **269** forming, which could not be separated from **263**.

Scheme 87



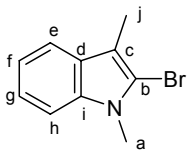
The initial strategy of 1st methylating led to inseparable mixtures

Fortunately, by simply reversing the order of the reactions (Scheme 86), the mono-brominated compound **267** could be synthesised exclusively by capitalising on a slight increase in reactivity of the 2-position of the indole due to the nitrogen not being protected. The crude 2-bromo-3-methylindole **267** was then immediately methylated without attempted purification, forming **263**.* It should also be mentioned that the presence of the methyl group at the 3-position is most important as it blocks this position from bromination. The 3-position is far more reactive in indoles than the 2-position due to electron delocalisation and would normally be the preferred point for bromination. It is possible to brominate the 2-position of indoles without blocking the 3-position but this requires drastic deactivation of the 3-position by attachment of a C≡O moiety onto the indole nitrogen and the use of *t*BuLi to deprotonate the 2-position.[51]

Thus, readily available 3-methylindole **238** (skatole) was refluxed in chloroform in the presence of NBS for 2 hours and the reaction was closely monitored by TLC. After workup, the crude material was concentrated to a dark wax and treated with sodium hydride and dimethylsulfate in THF. Purification of the brominated product was achieved by column chromatography, furnishing 2-bromo-1,3-dimethyl-1*H*-indole **263** as a white waxy solid in an acceptable yield of 62% over the two steps. This compound would

* Purification of the 2-bromo-3-methylindole proved troublesome by column chromatography. Moreover, the compound was unstable in this form and the stability was greatly increased by subsequent protection of the indole nitrogen.

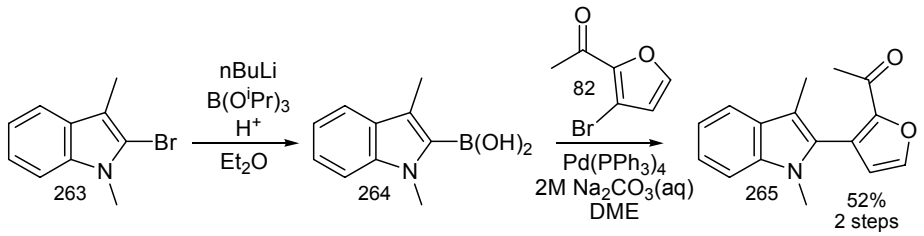
decompose within hours to a dark solid if left at room temperature but could be stored for several months at 0 °C.



The presence of two large singlets in the upfield region of the ^{1}H NMR spectrum and the absence of the more deshielded aromatic singlet which would be present if proton H_b still existed is a clear indication that bromination has occurred at the 2-position of the indole. Proton H_b is ordinarily quite distinctive as a singlet in the ^{1}H NMR spectrum of 1,3-dimethylindole as it is somewhat more upfield than the rest of the aromatic protons, normally occurring in the region of 6.3 ppm. The other aromatic ^{1}H NMR signals are all clustered in the region of 7.0-7.2 ppm with the exception of the more deshielded proton, H_e, appearing as a doublet at 7.47 Hz, slightly more downfield as is typical for these types of compounds.

4.1.1.3 Synthesis of *N*-methyl 2-(2-acetylfuran-3-yl)-3-methylindole by utilisation of the Suzuki reaction – 265

Scheme 88



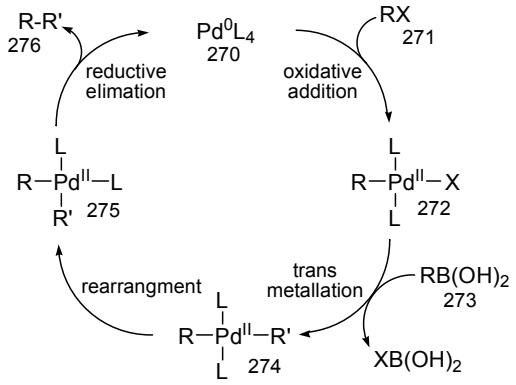
A brief overview of the Suzuki coupling reaction

The Suzuki coupling reaction, also referred to as the Suzuki-Miyaura coupling reaction, is an extremely useful reaction for the coupling of aryl halides to organic boronic acids. In particular, the reaction facilitates the coupling of aryl moieties, thus forming a biaryl bond between these two moieties – a transformation that is not always easily accomplished by means of non-metallic organic chemistry methodology. Moreover, the reaction is facilitated by a catalytic amount of Pd, thereby making it economically feasible as well.

In a cross coupling reaction between an aryl halide and a boronic acid (Scheme 89), the catalytic cycle begins with an oxidative addition of the Pd^0 **270** to the aryl halide **271**, thus

forming a *trans*-σ-palladium(II) complex **272**. This oxidative addition step is often the rate determining step in the catalytic cycle. Generally, oxidative addition is fastest for iodo compounds and very much slower for chloro compounds. Broadly, the reactivity decreases in the order I>OTf>Br>>Cl. The next step in the cycle involves the transmetallation of the organoboron compound **273** to the palladium(II) complex. In this process, the palladium maintains its +2 oxidation state by the process of bond formation to the organic component of the organoboron compound (the boron is exchanged for the palladium in this process) with concomitant loss of the halide acquired during the oxidative addition step. In the next step, there is a rearrangement of the two organic moieties on the palladium, which are effectively *trans* to each other in **274** to form a *cis* arrangement giving **275**. Once this process has completed, the final step in the cycle is the reductive elimination step, in which bond formation occurs between the two organic moieties forming **276**, and the palladium is reduced back to Pd^0 and re-enters the catalytic cycle.

Scheme 89



In summary, the Suzuki coupling reaction facilitates the catalytic Pd mediated carbon-carbon coupling of aryl halides and boronic acids.

For our particular needs, as a precursor to the Suzuki coupling reaction, it was necessary to form the boronic acid from the previously discussed 2-bromo-1,3-dimethyl-1*H*-indole **263**. However, it was soon discovered that this boronic acid rapidly decomposed if it was not kept diluted in solvent. Thus, a strategy was developed involving a solvent exchange process, facilitating the use of the boronic acid in the Suzuki coupling reaction.

Part 1: Synthesis of 1,3-dimethyl-1*H*-indol-2-ylboronic acid - 264

The generation of an aryl boronic acid is achieved by nucleophilic attack of a suitable lithiated aryl moiety onto a borate ester, usually trimethyl borate or triisopropyl borate, thus synthesising the aryl-borate ester which is easily hydrolysed to the corresponding boronic acid using dilute acid. The synthesis of 2-indoleboronic acids requires lithiation at the 2-position of the indole, followed by treatment with a borate ester. The lithiation itself can be accomplished in one of two ways: Either one may employ a suitable *ortho* directing group, such as a Boc protecting group on the indole nitrogen, or the use of lithium-halogen exchange on a suitably halogenated compound may also be used to afford the required boronic acid, as is the case in this particular reaction and hence the need for the synthesis of 2-bromo-1,3-dimethyl-1*H*-indole **263**.

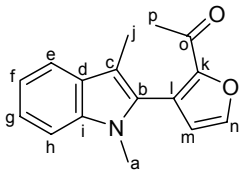
Treatment of 2-bromo-1,3-dimethyl-1*H*-indole **263** with *n*BuLi in diethyl ether at -78 °C followed by the addition of an excess of trimethylborate facilitated the formation of the indolo-borate ester (Scheme 88). This ethereal solution was then treated with 1N HCl rapidly hydrolysing the borate ester to the corresponding boronic acid **264**, easily observable by TLC as the boronic acid is far more polar than the starting 2-bromo-1,3-dimethyl-1*H*-indole. However, it was found that the boronic acid could not be isolated as evaporation of the solvent to afford the neat boronic acid led to rapid decomposition. In order to circumvent this problem, approximately 80% of the ether was removed *in vacuo* and the more concentrated ethereal solution was used directly in the next step.

Part 2: A Suzuki coupling to synthesise *N*-methyl 2-(2-acetylfuran-3-yl)-3-methylindole – 265

The diethyl ether, used as a solvent for the synthesis of boronic acid **264**, was chosen for a very important reason. Normally, THF is used as a solvent in these reactions, however the much lower boiling diethyl ether facilitates an exchange for a higher boiling solvent in the coupling reaction. In this particular case, the Suzuki coupling reaction is a biphasic system employing dimethoxy ethylene glycol (DME) as the organic component and aqueous Na_2CO_3 solution as the aqueous component. The reaction vessel was fitted with a dropping funnel and the slightly concentrated diethyl ether solution containing the boronic acid was added to the dropping funnel and diluted with just slightly more than the desired amount of

DME. By bubbling Ar gas directly into this solution, and with gentle warming the much lower boiling diethyl ether was evaporated, leaving the boronic acid suspended in DME as required. Furthermore, this procedure simultaneously degassed the solution. Once the diethyl ether had been evaporated, the 2-acetyl-3-bromofuran **82** was added to the solution in the dropping funnel and degassing was continued for another 2-3 minutes before the solution was discharged into the reaction vessel, already containing the Pd^0 catalyst in the form of $Pd(PPh_3)_4$. The dropping funnel was then charged with the aqueous sodium carbonate solution and this was similarly degassed for 5-7 minutes and discharged into the reaction vessel. In this way, the boronic acid was introduced into the reaction vessel with the appropriate solvent without ever fully concentrating the compound. Moreover, it was found that the reaction required approximately 3 days at reflux to go to completion and given the sensitivity of the Pd^0 catalyst to oxygen, extreme care needed to be taken in order to ensure that the vessel remained impervious to oxygen for this length of time.

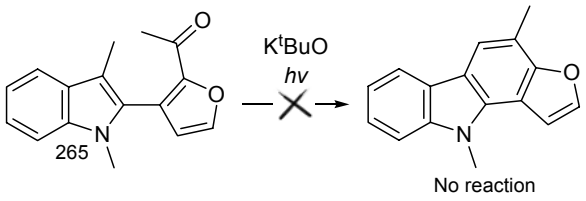
The workup of the reaction and purification by column chromatography proved to be uneventful and the desired coupled product was obtained in a moderate yield of 52% over the two steps. Unfortunately, the sensitivity of the boronic acid even under these careful conditions did not allow for higher yields to be obtained.



The most distinctive feature in the ^1H NMR spectrum is the appearance of three large singlets for the three methyls on the new compound. The two doublets arising from protons H_m and H_n are distinctive with their small coupling constant of 1.64 Hz. The remaining protons on the indole moiety have very much the same configuration as was observed for the precursor, 2-bromo-1,3-dimethyl-1*H*-indole **263**, proton H_e being once again the most deshielded of the indole protons, appearing as a doublet at 7.85 Hz, slightly more deshielded as a result of the attached furan moiety. In the ^{13}C NMR spectrum, the presence of a signal at 187 ppm attests to the presence of the deshielded carbonyl carbon, C_o.

4.1.1.4 Attempted synthesis of *N*-methyl furostifoline using a light mediated cyclisation reaction

Scheme 90



As discussed in detail in the previous chapter, we hoped that the light mediated cyclisation which had proven quite successful for the synthesis of a number of benzo[*a*]carbazoles and pyrido[*a*]carbazoles,[94,96] would also facilitate the formation of a carbazole in our indolo-furan system, leading to furostifoline.

To this end, *N*-methyl 2-(2-acetylfuran-3-yl)-3-methylindole **265** was subjected to KO^{t}Bu in DMF and irradiated with a high pressure Hg lamp at 80 °C to no avail (Scheme 90). Several attempts of this reaction led only to the recovery of some starting material and if the amount of base was increased beyond the normally used four equivalents,[96] or if the temperature was increased this simply led to decomposition of the starting material. Seemingly, furostifoline could not be obtained using this methodology.

4.2 TOWARDS THE INDOLOCARBAZOLE CORE

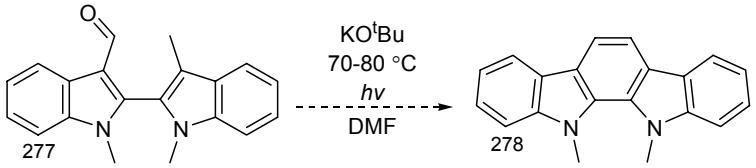
4.2.1 A planned model study to investigate the feasibility of the light mediated cyclisation

In parallel to the study investigating the feasibility of the light mediated reaction as a means to synthesise furostifoline, we also embarked upon a very similar study to investigate the possibility of utilising the same light mediated cyclisation reaction to synthesise the indolocarbazole core, which is found in many biologically interesting natural products, such as staurosporine and rebeccamycin.

Once again, as a first step we envisaged a model study which also employed the use of *N*-methylated indolo moieties, as they are easier to handle and should the study prove successful, the possibility of utilising removable protecting groups instead of the *N*-

methyls would be investigated. The strategy envisaged would be quite similar to that utilised in the furostifoline study and therefore involved setting up a precursor with the required functionality rendering it likely to cyclise under the light mediated conditions. To this end, we envisaged a *bis*-indolo species **277** (Scheme 91), containing the required aryl-methyl on one moiety and the carbonyl on the other. Cyclisation of this molecule should lead directly to the indolocarbazole core **278**.

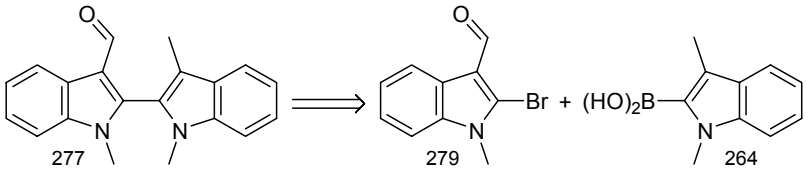
Scheme 91



An envisaged light mediated cyclisation leading to the indolocarbazole core

The synthesis of this key precursor would once again involve a Suzuki coupling reaction to form the bond between the two indole units, and an advantage of this approach would be that the same boronic acid **264** that we used in the furostifoline investigations described previously could be used in this synthesis. This would require that the other indole unit be in the form of the aryl halide, for it to be compatible in the Suzuki coupling. Specifically, 2-bromo-1-methyl-1*H*-indole-3-carbaldehyde **279** would be required as the other component for the Suzuki coupling reaction (Scheme 92).

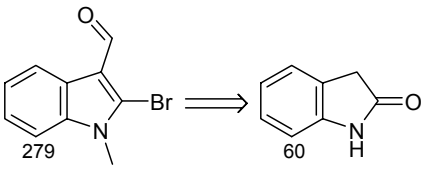
Scheme 92



Required components for the *bis*-indole Suzuki coupling

Fortunately, the synthesis of the required 2-bromo-1-methyl-1*H*-indole-3-carbaldehyde **279** has been accomplished before and this information is published in the literature.[96,98] The compound is readily accessible starting from oxindole **60**, utilising a modification of the Vilsmeier reaction (Scheme 93).

Scheme 93



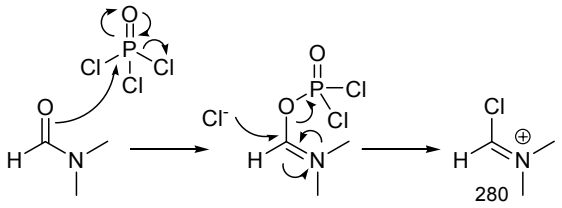
4.2.1.1 Synthesis of 2-bromo-1-methyl-1*H*-indole-3-carbaldehyde using a modification of the Vilsmeier reaction – 279

Mechanism of the Vilsmeier reaction

The treatment of amides with $POCl_3$ or $POBr_3$ leads to the generation of highly reactive iminium cations which are good electrophiles and react rapidly with electron rich aromatic compounds to form an iminium salt. This intermediate can then be hydrolysed using a base thus leading to the corresponding aldehyde.

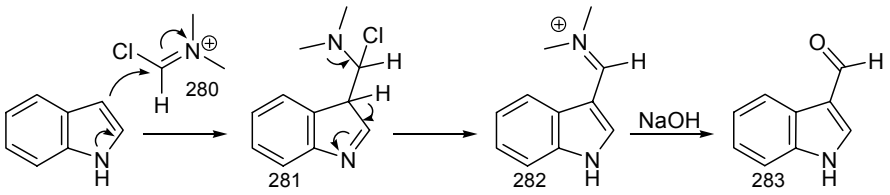
Mechanistically, the process is started by the reaction of $POCl_3$ with DMF (Scheme 94). The P-O bond is an extremely strong bond and provides the driving force for the reaction. Once the P-O bond is established, the liberated chloride anion (or bromide if one is using $POBr_3$) returns to displace the phosphorus, generating the cationic iminium salt **280**.[99,102]

Scheme 94



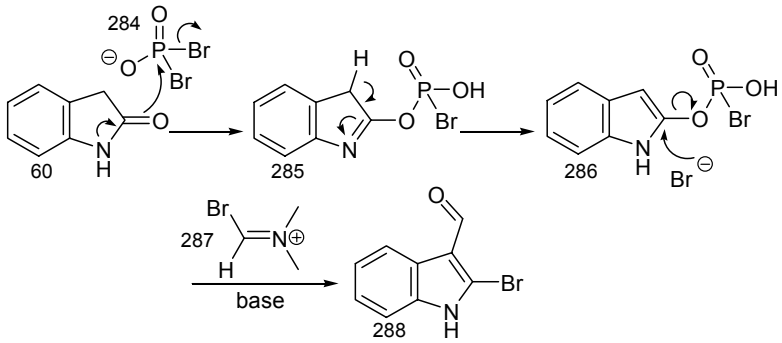
This iminium salt **280** is an excellent electrophile and rapidly reacts with electron rich aromatic compounds (Scheme 95). The indole system is a good nucleophile, reacting preferably at the 3-position as a result of participation of the lone pair on the indole nitrogen and delocalisation within the indole structure. Thus, once the iminium cation has been generated, the indole is added to the reaction and rapidly reacts with the iminium cation, briefly forming the amine **281** which then reverts back to the more stable iminium salt by displacement of the chloride anion to afford **282**. Base hydrolysis of this iminium salt affords the aldehyde **283**.[99,102]

Scheme 95



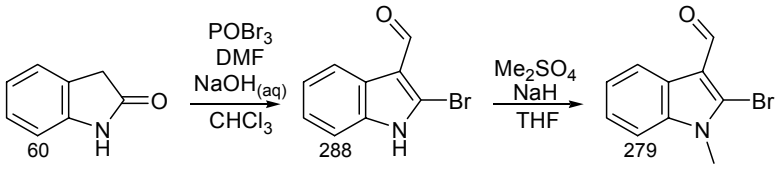
In the case of the our particular reaction, there is a slight modification as we do not start with indole, but rather oxindole **60** (Scheme 96). As before, the iminium salt **287** is first generated from $POBr_3$ and DMF. Oxindole of course is structurally quite different to indole itself. The absence of a double bond connecting the C2-C3 carbons means that electron delocalisation is not possible and the 3-position is therefore not nucleophilic. Thus, upon adding oxindole to the recently prepared iminium salt, the initial reaction is at the C2 carbonyl of oxindole. The phosphorus-oxygen bond is highly stable and so the phosphorus by-product of the original iminium salt generation process **284**, (remembering in this case it would be the dibromophosphor by-product) adds to the oxygen, forming **285** and liberating a bromide anion which returns to displace the phosphorus moiety. This serves two processes: namely, that the 2-position is brominated and the fully aromatic indole system is regenerated in this process after loss of a proton at the 3-position. With the indole structure now intact, the 3-position of the indole is rendered nucleophilic, and the Vilsmeier reaction proceeds as described previously, reacting with the iminium cation **287**. After hydrolysis, the brominated and formylated indole **288** is obtained.

Scheme 96



Synthesis of 2-bromo-1-methyl-1*H*-indole-3-carbaldehyde – 279

Scheme 97

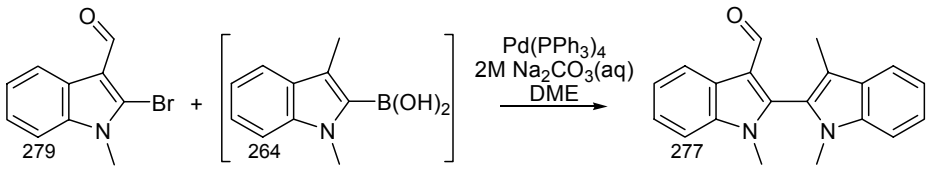


In the first few attempts at this reaction (Scheme 97), the generation of the iminium salt was performed using only a slight excess of DMF in relation to $POBr_3$. Since this procedure is performed in the absence of any solvent, it was found that the salt formed as a white solid and when oxindole (dissolved in chloroform), was added to this solid, dissolution was very slow and often incomplete, leading to diminished yields. This problem was overcome by increasing the amount of DMF to six equivalents in relation to the $POBr_3$, thereby serving as both reagent to generate the iminium salt and as a solvent to keep it in solution. In this way, the subsequent addition of oxindole in chloroform resulted in a homogenous solution and increased the yields obtained.

It was also found that purification of the formylated bromo-indole **288** proved difficult due to its high polarity and so it was not possible to remove all impurities using column chromatography, or by recrystallisation. To circumvent this problem, the crude 2-bromo-indole-3-carbaldehyde **288** was immediately treated with dimethylsulfate and sodium hydride, resulting in the formation and proper purification of 2-bromo-1-methyl-1*H*-indole-3-carbaldehyde **279**, obtained in excellent yields (99% over two steps). The spectroscopic data for this compound were identical to the reported values.[96]

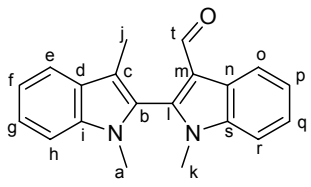
4.2.1.2 Suzuki coupling to form the *bis*-indole system – 277

Scheme 98



With the methodology for the synthesis of 1,3-dimethyl-2-indole boronic acid **264** in hand (Scheme 88), and 2-bromo-1-methyl-1*H*-indole-3-carbaldehyde **279** recently synthesised, it was envisaged that a Suzuki coupling reaction should once again provide the necessary precursor to test the light mediated cyclisation reaction. In this case, the required precursor for the light mediated reaction would need to be 2-(1,3-dimethyl-1*H*-indol-2-yl)-1-methyl-1*H*-indole-3-carbaldehyde **277** (Scheme 98).

Since the boronic acid being utilised in this reaction is identical to that described previously, the same lengthy steps of solvent transfer needed to be performed in order to prevent the decomposition of this compound. Thus, in a very similar procedure, the boronic acid, still dissolved in a small amount of ether was diluted with DME and during the process of degassing by bubbling Ar through the solution and gentle warming, the diethyl ether was removed and the remaining DME solvent rendered oxygen free, a necessity for the Suzuki coupling reaction. This mixture was then discharged into the flask followed by a similarly degassed aqueous sodium carbonate solution. Typically, the best yields were obtained when the reaction was refluxed for two days. Reacting the material for longer did not significantly increase the yields and this was mainly due to the instability of the boronic acid. The elevated temperatures and the presence of the aqueous base resulted in cleavage of the boronic acid moiety and thus significant quantities of 1,3-dimethylindole **268** were always recovered after the coupling reaction. Moreover, the 2-bromo-1-methyl-1*H*-indole-3-carbaldehyde **279** was also found to be unstable at elevated temperatures and this also contributed to the diminished yields obtained for this reaction. Nevertheless, the desired 2-(1,3-dimethyl-1*H*-indol-2-yl)-1-methyl-1*H*-indole-3-carbaldehyde **277** was obtained in a modest yield of 67% over the two steps.

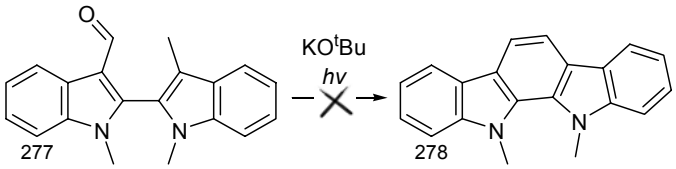


The appearance of 3 large singlets in the ^{1}H NMR spectrum, each integrating for 3 protons corresponding to the three methyl groups, and the presence of the deshielded singlet at 9.69 ppm corresponding to the aldehyde proton H_t were the initial indicators that the coupling reaction had been successful. Unfortunately, due to the similarity of the two moieties of this *bis*-indole, most of the other protons produced overlapping signals which were not easily interpretable. In the ^{13}C NMR spectrum, the deshielded carbonyl carbon at 187 ppm was clearly present and 3 upfield

signals attested to the presence of the 3 methyl groups. Finally, mass determination by high resolution mass spectrometry was in good agreement with the expected value.

4.2.1.3 Attempted synthesis of *N,N'*-dimethyl[2,3-*a*]indolocarbazole using a light mediated cyclisation reaction

Scheme 99



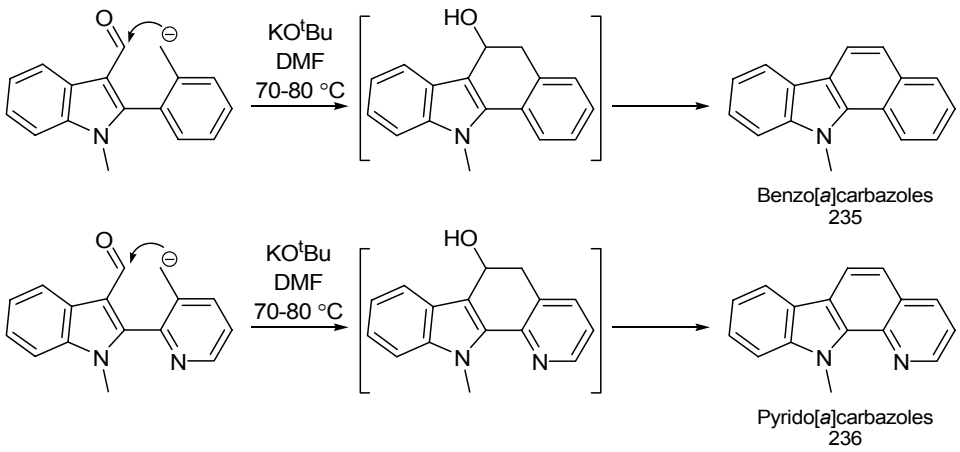
The synthesis of *bis*-indole **277** finally allowed us try the light mediated reaction as a key step in the synthesis of the indolocarbazole core **278** (Scheme 99). The details of this light mediated reaction were discussed in Chapter 1 and the interested reader is requested to refer to this section for more information.

Exposure of 2-(1,3-dimethyl-1*H*-indol-2-yl)-1-methyl-1*H*-indole-3-carbaldehyde **277** to high intensity UV light, in the presence of KO^{t}Bu unfortunately did not result in any reaction taking place. Heating the solution to 80 °C still produced no result and just as was previously observed in the attempted *N*-methyl furostifoline synthesis (Scheme 90), further additions of base and heating to higher temperatures in an effort to force the reaction only resulted in decomposition of the starting material.

4.3 CONCLUDING REMARKS FOR THE LIGHT MEDIATED ROUTE

It is now believed that the previously studied reactions employing a benzylic methyl may have undergone the cyclisation simply by nucleophilic attack of the benzylic carbanion, facilitated by KO^{t}Bu, onto the aldehyde of the indole (Scheme 100). This was then followed by aromatisation through dehydration leading to the previously observed carbazole systems. It is likely that photoenolisation is thus not the mechanism by which these cyclisations are occurring in systems containing a benzylic methyl and an aldehyde or ketone.

Scheme 100



This mechanism would account for the failure of our reactions for the indolo-furan systems as a benzylic methyl is not present and therefore the generation of a benzylic carbanion would not be possible.

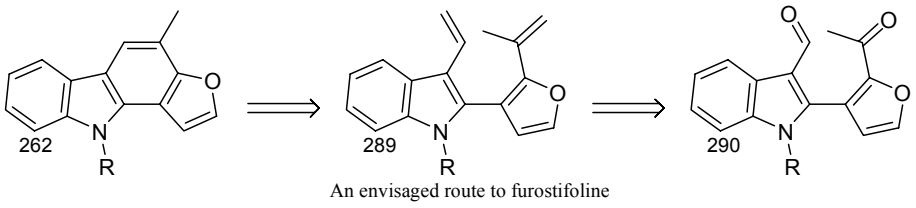
CHAPTER 5 – A METATHESIS APPROACH

5.1 RING CLOSING METATHESIS AS A KEY STEP TO SYNTHESISE FUROSTIFOLINE AND THE INDOLOCARBAZOLE CORE

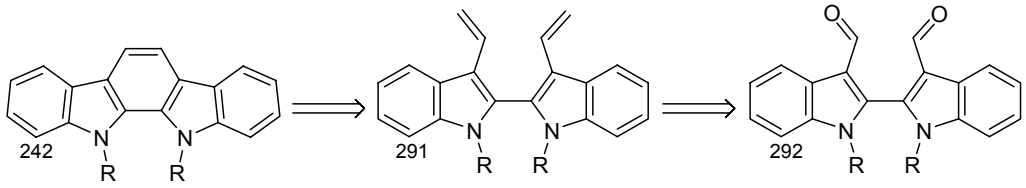
As a consequence of the envisaged light mediated reactions not providing us with the required carbazole systems, for both furostifoline and the indolocarbazole core, we began to plan an alternative strategy to derive these systems. Since a significant amount of work had already been invested in optimising the reactions for the original route, especially the Suzuki coupling reaction, we sought not to deviate too far from our original plan. The problem encountered in the previous syntheses essentially existed in cyclising the two aromatic moieties to form the larger aromatic carbazole system. Therefore we concentrated on alternative methods for cyclising the two moieties. To this end, it seemed that a ring closing metathesis (RCM) reaction may provide a feasible method to form the carbazole systems. Moreover, adapting our current methodology to this new route would require only small changes to our current synthetic strategy.

We envisaged that the dienes **289** and **291** (Scheme 101) would be required as key precursors and they in turn could be derived from their corresponding ketones and/or aldehydes using the Wittig reaction.

Scheme 101



An envisaged route to furostifoline



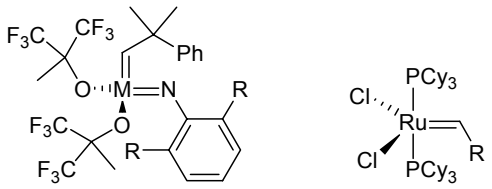
An envisaged route to the indolocarbazole core

5.1.1 The olefin metathesis reaction – background and mechanism

The first significant use of a catalyst to promote the combination of olefins to form new products under relatively mild conditions was pioneered by Karl Ziegler in his reactions involving olefin polymerisation. It was soon discovered that these catalysts sometimes led to other products which were not polymers but rather products formed by the apparent joining of two alkene groups. This process, involving the cleavage and reformation of newly located double bonds leading to new products is now generally referred to as olefin methathesis.[103]

Unfortunately, the early catalysts exhibited poor selectivity for the desired metathesis reaction, leading to a multitude of products and this rendered them somewhat unattractive for use in organic synthesis. However, an increase in research in this area has recently led to the development of catalysts which are both highly reactive and highly selective for the desired combination of two olefins. The initial catalysts **293** (Figure 36), developed by Schrock and co-workers were tungsten or molybdenum alkylidene complexes. However, around the same time, Grubbs and co-workers were developing ruthenium carbene complexes **294** which also showed similar reactivity and selectivity for the olefin metathesis reaction.[103]

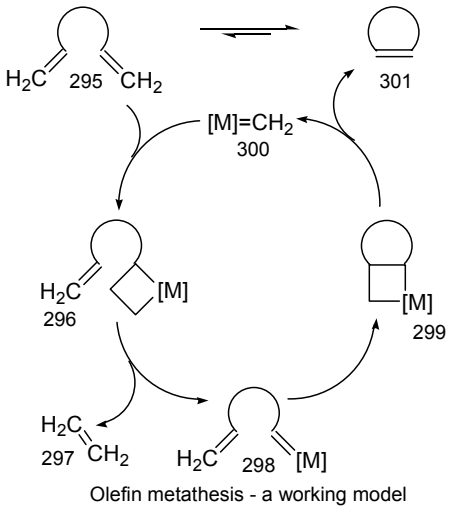
Figure 36



The generally accepted mechanism for the metathesis reaction consists of a series of [2+2] cycloadditions and reversions. The scheme below (Scheme 102) outlines the basic cycle of the reaction, starting with addition of the metal carbene **300** across one alkene of diene **295**, forming the metallo cyclobutane intermediate **296**. A cycloreversion of this ring system leads to elimination of ethene **297** and the formation of the new metallocarbene **298**. Addition of this new carbene across the second olefin forms the next metallo cyclobutane intermediate **299** and a second [2+2] cycloreversion reaction results in the

formation of the new alkene **301** and the liberation of the metal carbene **300** which re-enters the catalytic cycle.[103]

Scheme 102



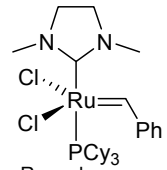
Since all the reaction steps are reversible, the overall reaction needs to be driven forward somehow. In the ring closing metathesis scheme outlined above, the reaction is both entropically driven since ethene is liberated during the reactions, and equilibrium driven since the ethene is volatile, and therefore leaves the system.

A disadvantage of Schrock-type catalysts is their sensitivity toward oxygen and moisture. Therefore reactions utilising this catalyst require rigorously dried and degassed solvents. However, advantageously, these catalysts are particularly reactive and moreover tolerate a wide variety of functional groups. In particular, a mismatch of the hard Mo^{VI} centre with soft sulfur or phosphine functionalities is perhaps the reason why these catalysts react smoothly with alkenes containing these functional groups. The ruthenium based catalysts however, fail to react with these molecules.[103]

The issue of the poorer reactivity of ruthenium based catalysts, especially concerning electron deficient or di- and trisubstituted olefins was addressed in a second generation of these catalysts. By employing stable *N*-heterocyclic carbenes as ligands, the reactivity of these ruthenium based catalysts was greatly increased. Second generation catalysts of the type shown below **302** (Figure 37) exhibit far greater reactivity than the parent Grubbs

carbene catalysts, in some cases displaying better reactivity than the Schrock-type catalysts with the added advantage of their resistance to air and moisture.[103] Catalysts of this type have been used to form tri- and tetrasubstituted double bonds in ring closing metathesis, a feat previously only accomplishable with the Schrock-type catalysts.[103]

Figure 37



Ru carbene metathesis catalyst 302

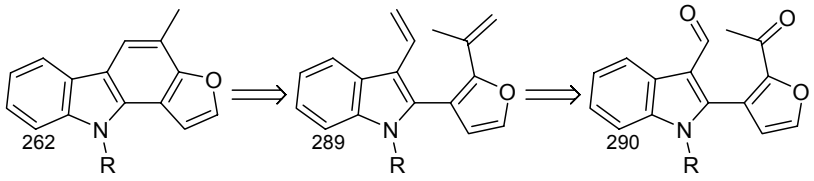
It is this second generation of Grubbs catalysts that we hoped to employ to effect the key step in our syntheses of furostifoline and the indolocarbazole core.

5.1.2 Total synthesis of furostifoline employing metathesis as a key step

5.1.2.1 Outline of the synthetic strategy

As briefly eluded to near the beginning of this chapter, the key precursor we would require for our new furostifoline synthesis would be the diene **289** (Scheme 103), hopefully obtainable using a Wittig reaction on the dicarbonyl **290**. Thus, our previous synthetic route for furostifoline would need to be modified slightly in order to obtain this dicarbonyl compound.

Scheme 103



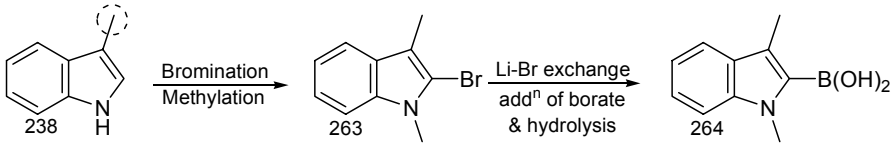
The synthesis of the original 2-acetyl-3-bromofuran moiety **82** would not need any attention as this fragment contains the correct functionalisation. However, the indole moiety would need some attention in order to facilitate introduction the formyl group at the 3-position, as opposed to the methyl group which originally occupied this position. There are several ways in which this could be attained and we envisaged that the most promising

method would be to capitalise on the reactive 3-position of the indole moiety. The nucleophilicity of this position could be exploited in a Vilsmeier formylation, facilitating the introduction of the required aldehyde. In terms of timing, we determined that this functionality could be introduced after the coupling of the furan moiety. Indeed, the furan itself may also be susceptible to reactions of this type and its presence may cause complications,[*] however we envisaged that the unprotected indole would possess a far more reactive 3-position than any other competing electron rich sites on the indole or furan moieties, safely directing the formylation to this position.

This change in strategy required that we prepare a slightly different boronic acid at the start of our synthesis. The methyl group occupying the 3-position of the indole moiety would no longer be required and so a slightly simpler boronic acid was envisaged. Moreover, in the original synthesis which was in fact a model study for that particular route, the nitrogen on the indole moiety was irreversibly protected as the *N*-methyl derivative. In this particular synthesis an analogous methyl-*N*-protection approach would not be possible, for a number of reasons:

In the previous model study, the presence of the methyl at the 3-position of indole moiety not only provided the required functionality for our envisaged light mediated cyclisation, but was also helpful in the synthesis of the corresponding boronic acid moiety. The reason for this is that this methyl effectively blocked the highly reactive 3-position of the indole, allowing for selective bromination at the less reactive 2-position **263**. Lithium halogen exchange using this bromine followed by treatment with a borate ester led to our desired boronic acid **264** (Scheme 104).

Scheme 104

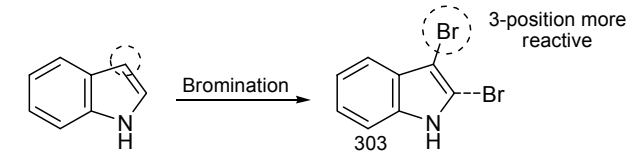


In this new synthesis however, lithium halogen exchange as a means of introducing the boronic acid would not be feasible since the 3-position of the indole moiety is not blocked.

[*] The ketone on the furan is of course added using a very similar reaction, the Friedel Crafts reaction.

Any attempted bromination would certainly result in reaction at this position rather than at the desired 2-position (Scheme 105).

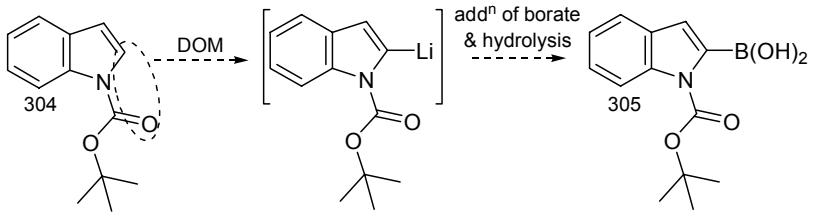
Scheme 105



Bromination not feasible for boronic acid synthesis in new route

To circumvent this problem, we decided to rely on directed *ortho* metallation (DOM) as a means of lithiation and to this end, a Boc protecting group on the indole nitrogen **304** would serve our purposes nicely, facilitating the synthesis of **305** (Scheme 106).

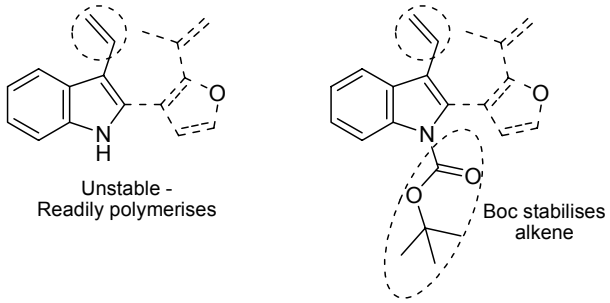
Scheme 106



DOM as a means of selective lithiation leading to correct R-B(OH)$_2$

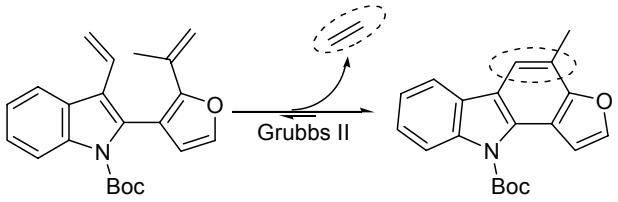
The presence of the Boc protecting group would also serve to circumvent a second important problem arising later in the synthesis. Indoles possessing a 3-vinyl moiety are unstable, and readily polymerise unless the nitrogen of the indole contains an electron withdrawing substituent (Figure 38).[48] Thus the second function of the Boc group would be to stabilise the diene precursor we require for the metathesis reaction near the end of the synthesis.

Figure 38



On the subject of the diene, the metathesis reaction is another step which requires a little more discussion. As mentioned in the brief introduction to the metathesis reaction, it is important to remember that the reaction is essentially reversible and is also sensitive to the steric demands imposed by the substitution pattern on the reacting olefins. Thus, when employing this reaction it is important to ensure that there is a driving force, ensuring that the reaction will proceed in the desired direction and not simply reach a point of equilibrium. The major driving force in ring closing metathesis is the loss of volatile ethene. As long as the ethene continues to leave the system, an equilibrium situation is not possible and this drives the reaction forward. While this phenomenon would be to our advantage, a second driving force for our reaction would be that the formed products would be aromatic, rendering the reverse reaction highly unlikely (Scheme 107). However, as a disadvantage, the methyl on the furan moiety may be the cause of some negative steric influences, inhibiting the reaction. Fortunately there is literature precedence for metathesis reactions performed on other sterically hindered alkenes.[104,105]

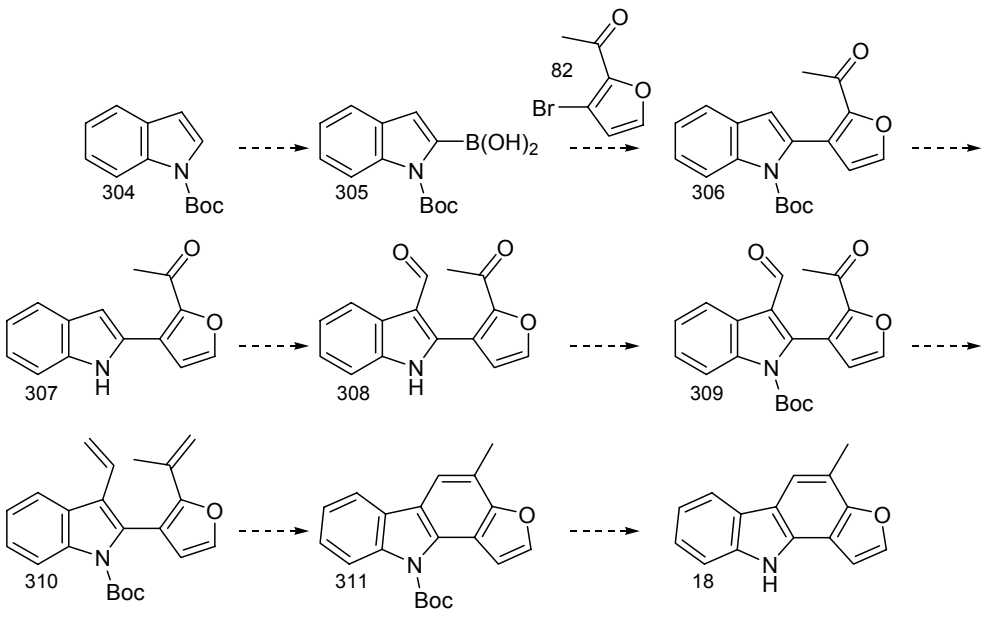
Scheme 107



Loss of ethene and aromatisation should provide the driving force for the metathesis forward reaction

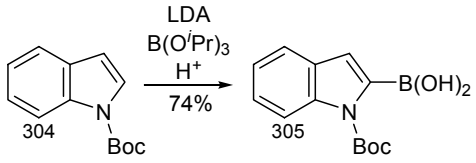
In summary, the entire scheme for the planned synthesis is shown below (Scheme 108). As a starting point, indole will be protected as the *N*-Boc derivative **304** and subsequently converted to the boronic acid **305**. A Suzuki coupling should provide the indole-furan moiety **306** and then removal of the Boc protecting group **307** is envisaged to be necessary in order to ensure that the subsequent Vilsmeier formylation occurs exclusively at the 3-position on the indole moiety, forming **308**. Reprotection of the indole nitrogen with a suitable electron withdrawing protecting group **309** will then be necessary in order to stabilise the future diene **310**, formed from a double Wittig reaction on both carbonyl functionalities. For this purpose, the Boc group will once again be employed. Finally, ring closing metathesis should provide the carbazole ring system **311** and removal of the Boc protecting group would hopefully afford the natural compound, furostifoline **18**.

Scheme 108



5.1.2.2 Synthesis of 1-(*tert*-butoxycarbonyl)-1*H*-indol-2-yl-2-boronic acid – 305

Scheme 109

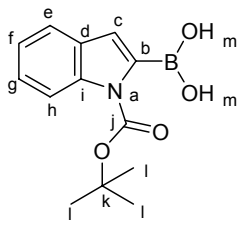


In the preparation of **305**, *N*-Boc-indole **304** was treated with either lithium diisopropylamide or lithium-TMP at -78 °C. Directed *ortho* metallation employing the Boc group facilitated lithiation at the 2-position of the indole moiety. The subsequent addition of trimethyl or triisopropyl borate resulted in a nucleophilic reaction onto the boron and the formation of the indole-borate ester. During the workup process, this borate was easily cleaved to the boronic acid **305** by the careful addition of dilute HCl.

For purification of this boronic acid, crystallisation was found to be the most efficient procedure. In order to achieve this, after the workup, the organic phase (consisting of a mixture of THF and ethyl acetate) was concentrated to about 20% of its original volume and then whilst cooling, hexane was slowly added resulting in precipitation of the desired compound as a white solid. Fortunately, unlike the boronic acid **264** from the previous

route, this particular compound was quite stable and easily handled. Moreover, it could easily be characterised by NMR spectroscopy and stored for several months at 5 °C without discolouration. In this way, 1-(*tert*-butoxycarbonyl)-1*H*-indol-2-yl-2-boronic acid **305** was prepared in multigram quantities and good yields.

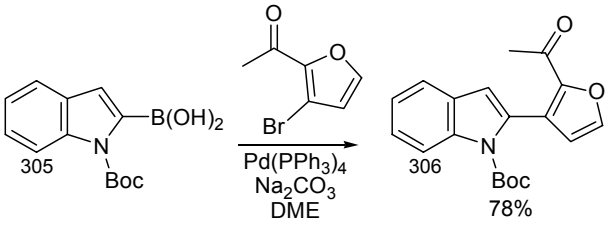
Recently, Vazquez reported a very similar method* for the preparation of this compound using non-cryogenic conditions and good yields were also obtained using this slightly more convenient procedure.[106]



In the ^{1}H NMR spectrum, the presence of the two deshielded doublets can be assigned to the protons H_h at 8.02 ppm and H_e at 7.60 ppm. The large singlet at 7.54 ppm† is due to the equivalent protons on the boronic acid. The absence of the previously employed methyl at the 3-position of the indole (compound **263**) means that a hydrogen now occupies this position. Since no other protons are within coupling range a singlet in the aromatic region should be produced by this new feature. This is indeed attested to by the presence of a singlet at 7.50 ppm for H_c. The two protons H_f and H_g which often produce signals in the form of pseudo-triplets are assigned as two multiplets in this case, occurring in the range 7.38-7.23 ppm. Finally, the large *tert*-butyl singlet is located characteristically upfield at 1.74 ppm. The presence of the carbamate carbonyl is easily assigned in the ^{13}C NMR spectrum at 154 ppm.

5.1.2.3 Synthesis of *tert*-butyl 2-(2-acetylfuran-3-yl)-1*H*-indole-1-carboxylate – 306

Scheme 110

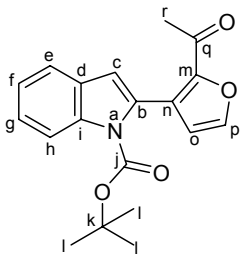


* Vazquez *et al*. treated *N*-Boc indole with LDA followed by triisopropyl borate in THF at 0-5 °C and obtained 96% yield of 1-(*tert*-butoxycarbonyl)-1*H*-indol-2-yl-2-boronic acid.

† This chemical shift for this signal depends on the sample concentration.

The Suzuki coupling of this new boronic acid **305** (Scheme 110) to 2-acetyl-3-bromo furan **82** was made much easier due to the stability of this compound. Nevertheless, a thorough degassing of all solvents and reagents was still necessary in order to ensure that the Pd catalyst did not become poisoned by the presence of oxygen.* Typically, the catalyst was the first reagent to be introduced into the reaction vessel and then after thoroughly degassing the vessel, the attached dropping funnel was charged with DME containing the solubilised boronic acid and furan. Degassing was performed for 10 minutes by bubbling Ar gas directly into the solution before discharging it into the reaction vessel. An aqueous solution containing the sodium carbonate was similarly degassed before being added to the reaction mixture. In this way, it was possible to reflux the reaction mixture for the long reaction times needed (typically 2-3 days) without any degradation of the Pd catalyst. It is also interesting to note that the concentration of the reaction mixture had a profound effect on the stability of the Boc protecting group. In order to preserve the protecting group, it was found that the concentration of the sodium carbonate solution should not exceed 2 M, and that of the DME solution should not exceed 0.25 M with respect to the furan. On the other hand, excessive dilution of the reaction mixture resulted in significantly increased reaction times and this resulted in lower yields owing to cleavage of the boronic acid functionality off the indole moiety, and therefore leading to the recovery of large amounts of *N*-Boc indole **304**. Although this may seem counter intuitive to go to these lengths to preserve the Boc protecting group when the very next step in the reaction sequence is the Boc removal, it was necessary as the Suzuki coupled, yet Boc deprotected product **307** (Scheme 111) had exactly the same R_f as the small amounts of unreacted 2-acetyl-3-bromofuran **82** which was always present at the end of these reactions. This of course rendered purification of this deprotected product difficult and if this material was inadvertently obtained in significant quantities, proper purification necessitated repeating the Boc protection.

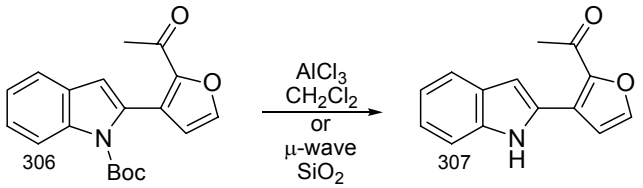
* An insufficiently degassed reaction mixture rapidly changes colour from yellow-orange to black as the palladium is oxidised to Pd^{II}. A vessel that is not properly isolated from the atmosphere produces the same result over a period of time (typically a few hours) leading to termination of the catalytic cycle and diminished yields.



In the ^{1}H NMR spectrum, the presence of two upfield singlets integrating for 3 and 9 protons provides the first indication that the coupling reaction has been successful - the slightly more deshielded singlet corresponding to the methyl protons H_r at 2.37 ppm and the large singlet is unmistakably due to the *tert*-butyl protons, H_l at 1.45 ppm. The remaining protons all occupy the aromatic region of the ^{1}H NMR spectrum and most easily identifiable are the two furan doublets H_p and H_o, at 7.57 ppm and 6.61 ppm respectively. Their small coupling constant of 1.6 Hz is a distinguishing feature. The singlet at 6.67 ppm attests to the presence of proton H_c. The remaining protons on the benzene ring of the indole moiety could only be assigned unambiguously using a combination of an NOE and a COSY spectrum. Irradiation of the *tert*-butyl singlet at 1.45 ppm resulted in a clear response from the aromatic doublet at 8.2 ppm and therefore this signal could be assigned at H_h. Weaker responses were also obtained from the signals corresponding to the furan protons, H_o and H_p, indicating their close proximity to the *tert*-butyl group, mainly due to rotation about the *N*-carbonyl bond. Thus, with proton H_h unambiguously assigned at 8.20 ppm, the other doublet at 7.55 ppm can be assigned to H_e. To assign the internal protons H_g and H_f, a COSY spectrum was required. It was found, as one would expect, that the most deshielded of these two internal protons is H_g, producing a multiplet in the range 7.37-7.31 ppm. Proton H_f, which also produces a multiplet in the range 7.27-7.21 ppm, is less deshielded than H_g. This is expected as H_f is para to the indole nitrogen. Finally, the characteristic signals in the ^{13}C NMR spectrum include the ketone carbonyl C_q at 187 ppm and the carbamate carbonyl C_j, at 150 ppm. The remaining ^{13}C NMR signals were assigned by means of a CH correlated spectrum. An infrared spectrum of the coupled compound clearly showed two carbonyl stretching absorptions at 1732 cm^{-1} and 1674 cm^{-1}, corresponding to the carbonyls of the carbamate and ester respectively.

5.1.2.4 Synthesis of 2-(2-acetylfuran-3-yl)-1*H*-indole – 307

Scheme 111



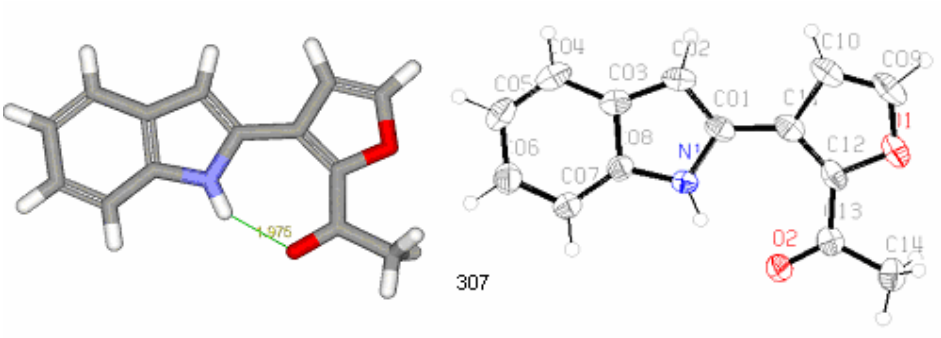
The formylation of indoles using the Vilsmeier reaction and the acylation of indoles by means of the Friedel Crafts reaction normally occurs in the more reactive 3-postion of indoles, even if they are protected. However to ensure that the anticipated formylation of the coupled indolo-furan compound occurred exclusively on the 3-postion of the indole moiety, we decided to remove the protecting group on the indole nitrogen, thus rendering the 3-position far more nucleophilic than any other potentially nucleophilic sites on the furan moiety of this compound. It should be born in mind that the ketone on the furan was introduced using a Friedel Crafts acylation and so it is not too unlikely that this moiety may compete for the iminium cation leading to a mixture of compounds.

Fortunately, the removal of the Boc protecting group (Scheme 111) was easily achieved by either one of the following two methods. The initial Boc deprotections were accomplished by treatment of *tert*-butyl 2-(2-acetylfuran-3-yl)-1*H*-indole-1-carboxylate **306** with a strong Lewis acid, such as aluminium trichloride, in dichloromethane at 0 °C. Although this method provided satisfactory yields in the region of 80%, care had to be taken not to allow the reaction to proceed for longer than was necessary. To this end, the reaction was closely monitored by TLC every 10 minutes until all the starting material had reacted and was then quickly quenched using cold water. Usually, less than 30 minutes was required for the reaction to complete. Interestingly, within a few seconds of adding the $AlCl_3$ to the Boc-indole solution, a colour change to deep red occurred which persisted throughout the duration of the reaction. Upon quenching however, the solution instantly adopted the bright yellow colour of the product, 2-(2-acetylfuran-3-yl)-1*H*-indole **307**. In fact, the bright yellow colour of this new compound made for wonderfully easy chromatography of the product, as one could simply watch the yellow band travelling down the column and collect it as it eluted.

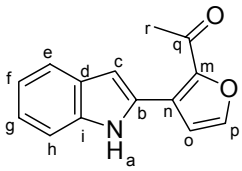
The second method employed to cleave the Boc protecting group made use of the acidic nature of silica gel. To this end, the Boc-protected compound **306** was adsorbed onto a generous amount of silica and carefully dried under vacuum to remove all traces of solvent. Then, by simply heating in a conventional microwave oven, the Boc group was cleaved. As the reaction progressed, the silica gel containing the adsorbed compound gradually changed colour from off-white to bright yellow. An important aspect to note however regarding this procedure was not to allow the silica gel to become too hot as this led to significant decomposition of the product. For this reason, the adsorbate was only subjected to microwave radiation for 30 second bursts with cooling in between. Moreover, agitation of the silica was required as the radiation did not evenly penetrate the entire adsorbate. After each 30 second burst, a sample was taken for analysis by TLC, and so the process was repeated until the reaction had gone to completion. Purification of the product was even easier than the previous procedure as it simply involved loading the adsorbate onto a silica gel column and eluting the product.

On the subject of silica gel chromatography, one would expect that the deprotected indole **307** would be far more polar than its Boc protected precursor **306** and therefore have a much lower R_f. To our surprise, this was not the case and in fact the deprotected compound actually had a slightly higher R_f than the Boc protected compound! The reason for this strange phenomenon may be ascribed to intramolecular hydrogen bonding between the carbonyl oxygen of the furan and the hydrogen on the indole nitrogen. This internal hydrogen bonding minimises the expected hydrogen bonding between the silica gel and the indole nitrogen, accounting for the unexpectedly high R_f of this compound. Since this bright yellow product was very easily recrystallised, an X-ray crystallographic structure was obtained and indeed, a clear hydrogen bonding interaction of 1.98 Å was observed between the indole NH and the ketone on the furan moiety (Figure 39).

Figure 39



In summary, using either procedure, a bright yellow solid was obtained which, although seemingly waxy in physical appearance, actually had a higher melting point than its precursor (137 °C for **307** vs. 98 °C for **306**).



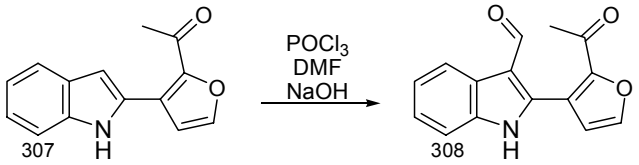
In the ^{1}H NMR spectrum there existed some uncertainty as to the exact assignments of the protons on the benzene ring of the indole moiety. The exact assignment of the doublets H_e and H_h were unclear but fortunately, NOE irradiation of the proton H_a on the indole nitrogen, which appeared as a broad singlet at 11.91 ppm, resulted in a response from the doublet at 7.50 ppm, thereby allowing for assignment of this signal to H_h. Fortunately, the furan doublets from protons H_p at 7.55 ppm and H_o at 7.01 ppm are quite distinguishable from the doublets on the aromatic ring of the indole moiety as a result of their characteristically small coupling constant of just 1.6 Hz. Thus, after assigning H_h by NOE, the only remaining doublet at 7.63 ppm could easily be assigned to H_e. It is interesting to note the effect of the Boc group in that proton H_h is now significantly less deshielded after removal of the Boc group, shifting from 8.20 ppm in **306**, to 7.50 ppm in this deprotected compound, **307**.

Having removed the ambiguity regarding the assignment of the signals for protons H_e and H_h, a COSY spectrum was used to assign the positions of the remaining ambiguous protons, H_f and H_g. A clear coupling was observed between H_h and H_g as well as between H_f and H_e, allowing for assignment of these signals. As per our expectations, the multiplet corresponding to H_g was found to the just slightly more deshielded at 7.25 Hz than the multiplet corresponding to H_f, located at 7.11 Hz. The singlet corresponding to H_c is found

as expected in the aromatic region at 6.92 ppm, and the singlet for the acetyl methyl protons, H_r, is found upfield at 2.66 ppm. The ^{13}C NMR spectrum was assigned using a CH correlated spectrum. The presence of only one deshielded carbonyl carbon belonging to the ketone carbonyl, C_q, attests to the loss of the carbamate carbonyl. The infrared spectrum shows clearly the presence of the indole NH stretch as broad signal in the region of 3253 cm^{-1}, as well as a carbonyl stretch at 1656 cm^{-1}.

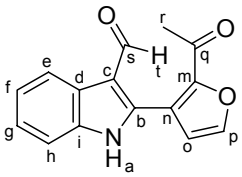
5.1.2.5 Synthesis of 2-(2-acetylfuran-3-yl)-1*H*-indole-3-carbaldehyde – 308

Scheme 112



With the protecting group removed from the indole nitrogen, the Vilsmeier formylation reaction was attempted (Scheme 112). Having gained some experience from the previous Vilsmeier-type reactions, the Vilsmeier salt was once again prepared using a six-fold excess of DMF. In this way the newly formed iminium salt remained in solution and did not present us with the solubility problems previously encountered. On the first attempt at this reaction a slight excess of the Vilsmeier salt was prepared (1.3 equivalents compared to the indole) and the reaction was left to proceed in dichloromethane for 18 hours at room temperature. Using these conditions, the yields were found to be quite poor. On the next attempt, an almost stoichiometric amount of the salt was prepared (1.05 equivalents) and the reaction was monitored closely by TLC. To our surprise, the reaction proceeded remarkably quickly and within a few minutes had seemingly reached a point of termination even though some starting material remained (as determined by TLC). Leaving the reaction for longer only seemed to lead to degradation of the product. Thus, all future reactions were carried out using approximately 1.5 equivalents of the Vilsmeier salt, and importantly, the reaction's progress was always closely monitored by TLC. Upon completion, the indolo-iminium salt was immediately hydrolysed by the addition of an aqueous sodium hydroxide solution, affording the aldehyde **308**.

Developing an efficient method for the purification of the aldehyde turned out to be somewhat more tricky than anticipated. Endless amounts of column chromatography never seemed to remove a bright orange contaminant. In the end, a pure sample of this highly polar compound was obtained by recrystallisation from ethyl acetate/hexane and was used for spectral analysis. However, evaporation of the mother liquor after the recrystallisation revealed a significant amount of the desired carbaldehyde still present, and so it was finally decided that the subsequent protection of this compound should be performed, and the yield based upon the two steps. Thus, in future repetitions of this reaction, the crude material was immediately subjected to Boc protection.



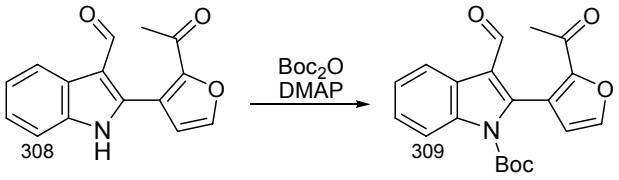
In the ^{1}H NMR spectrum, besides the presence of the highly deshielded and broad singlet produced by the indole nitrogen's proton at 12.68 ppm, a new deshielded singlet is present at 10.50 ppm integrating for one proton, and the familiar singlet usually in the aromatic region around 7 ppm is no longer present. These two pieces of information clearly attest to the presence of the aldehyde, in the desired 3-position on the indole moiety. An interesting observation is the effect the aldehyde has upon the shift of the furan proton H_o, which is shifted significantly downfield and is now found at 7.59 ppm,[*] alongside its partner, H_p, located only slightly more downfield at 7.67 ppm. The protons on the benzene ring of the indole moiety, H_f and H_g produce overlapping signals in the region 7.40-7.27 ppm. The multiplet for H_e (which often appears as a doublet) is significantly shifted downfield to 8.29 ppm[†] and the remaining multiplet for H_h, (which also often appears as a doublet in this series of compounds), is located in a similar position to the precursor at 7.51 ppm. Finally, the methyl protons, H_r, produce the only signal in the upfield region of the ^{1}H NMR spectrum, conspicuous as a large singlet at 2.70 ppm.

[*] In the precursor to this compound, **307**, H_o was located at 7.0 ppm

[†] In the precursor to this compound, this proton was found at 7.63 ppm.

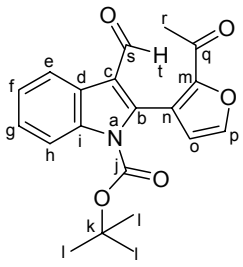
5.1.2.6 Synthesis of *tert*-butyl 2-(2-acetylfuran-3-yl)-3-formyl-1*H*-indole-1-carboxylate - 309

Scheme 113



Following the successful formylation of the indole, it was necessary to once again protect the indole nitrogen and for the reasons mentioned previously pertaining to the stability of the envisaged 3-vinylindole moiety,* an electron withdrawing protecting group was necessary.

As mentioned in the previous step, the difficulties encountered in purifying the indolecarbaldehyde led to the direct protection of crude **308**. Thus, the crude 2-(2-acetylfuran-3-yl)-1*H*-indole-3-carbaldehyde **308** was treated with Boc anhydride in the presence of DMAP, smoothly protecting the indole nitrogen as the carbamate, and facilitating easy purification by chromatography. If necessary, further purification was possible by means of recrystallisation. In this way, yields in the region of 79% were obtained for the desired protected indole carbaldehyde **309** over the two steps (formylation and protection).



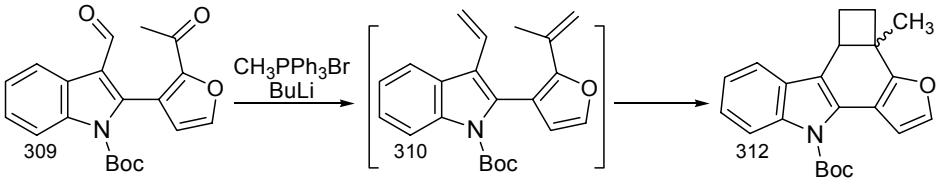
The most notable feature in the ^{1}H NMR spectrum is the increased deshielding of the proton H_h, significantly shifted downfield from 7.51 ppm to 8.18 ppm due to the presence of the electron withdrawing Boc protecting group. Another interesting feature is the upfield shift of the furan proton H_o, shifting from 7.59 ppm in the unprotected precursor to 6.72 ppm. For the most part, the remainder of the ^{1}H NMR spectrum remains largely similar with the exception of the large singlet due to the *tert*-butyl group in the upfield region of the spectrum. The protons H_f and H_g once

* We intend to convert the carbonyls to alkenes using a double Wittig reaction thus forming a 3-vinylindole moiety. These compounds are known to polymerise easily unless an electron withdrawing group is present on the indole nitrogen.

again produce overlapping multiplets in the region 7.45-7.35 ppm and the multiplet produced by H_e is found in the region 8.37-8.34 ppm,* just slightly downfield of H_h. The aldehyde singlet is still present downfield at 9.83 ppm. In the ^{13}C NMR spectrum, interesting features include the presence of an extra carbonyl signal from the carbamate at 150 ppm, as well as the aldehyde and ketone carbonyls, C_q and C_s, located at 186.9 ppm and 186.7 ppm respectively. The large upfield signal at 27.6 ppm attests to the presence of the three equivalent methyl carbons, C_l, on the *tert*-butyl of the Boc protecting group.

5.1.2.7 Unexpected synthesis of *tert*-butyl 2*a*-methyl-1,2,2*a*,10*c*-tetrahydro-6*H*-cyclobuta[*c*]furo[3,2-*a*]carbazole-6-carboxylate – 312

Scheme 114



With the required functionalities now installed on our indole-furan precursor **309**, we turned our attention toward performing the Wittig reaction in order to convert both carbonyls to the corresponding olefins **310** (Scheme 114). Since no problems were expected in this process, we set about using classical Wittig conditions, generating the required ylide from readily available methyl triphenylphosphonium bromide and *n*BuLi. In the first attempt at this reaction, we generated 2.5 equivalents of the ylide with respect to the indole-furan compound (1.25 equivalents of ylide per carbonyl). To our surprise, addition of the dicarbonyl compound to the ylide at 0 °C resulted in a grossly incomplete reaction. By monitoring the progress of the reaction by TLC it soon became apparent that the aldehyde on the indole moiety rapidly converted to the desired olefin.† However, the ketone on the furan seemed far more reluctant to undergo the same reaction, even after leaving the reaction to proceed at room temperature for 18 hours. In order to force the

* The signals for H_e and H_h were unambiguously assigned by NOE.

† As an extension of these investigations, the dicarbonyl **309** was treated with 1.1 eq of methyltriphenylphosphonium bromide and *n*BuLi and the product was isolated, confirming that the aldehyde carbonyl was the first to react with the ylide, as expected. The ketone had not converted to the alkene under these conditions.

reaction to proceed, an additional 5 equivalents of the ylide were prepared and cannulated into the reaction mixture. Analysis of the reaction mixture by TLC indicated that the ketone was now converting to the alkene.* Although the reaction had not gone to completion, we were concerned about the large excess of ylide present in the reaction mixture as this may lead to deprotection of the indole, which would be followed by polymerisation of the newly formed vinyl indole **310**. Therefore, the reaction was quenched and after workup, the presence of a large amount of some poorly soluble material did not bode well for obtaining the desired product in good yield. Nevertheless, the crude material was hastily purified by column chromatography affording a disappointingly small amount of product as a clear oil. However, to our surprise, upon attempting to remove the last of the volatiles under high vacuum, the clear oil rapidly became thick and opaque in colour, suggesting that another reaction had taken place at this point. Furthermore, analysis of the sample at this time (after re-dissolving it in diethyl ether) clearly indicated that although a compound existed at exactly the same R_f as the diene **310**, it no longer had the same brilliant fluorescence under the UV lamp, and several other impurities had also suddenly appeared! This impure material was then columned again and the new compound obtained as an opaque oil.

Initially, the NMR spectra for this unknown compound were confusing. Certainly, there was no evidence of the presence of any alkene protons, disappointingly confirmed by the absence of any signals in the 5-6 ppm region in the ^{1}H NMR spectrum. Moreover, an alarming number of signals in the upfield range of the ^{1}H NMR spectrum initially led us to the incorrect conclusion that the cyclisation had occurred, but the sample was simply not pure. However, the major concerning factor in this regard was that the singlet arising from the methyl protons was not deshielded enough to be characteristic of a benzylic methyl, which should have been the case had the carbazole formed. From the ^{13}C NMR spectrum, it was clear that the ketone and aldehyde carbons were no longer present and more importantly, there were too many signals in the far upfield region where we should only expect to see one, namely the methyl of the furan moiety. Finally, the mass spectrum for this unknown compound was the last piece of evidence needed to solve the puzzle - the mass of this unknown compound was exactly the same as the diene **310**! Yet clearly, the

* The R_f of the diene **310** is much higher than the keto-alkene precursor and brilliantly fluorescent on the TLC plate under the UV lamp.

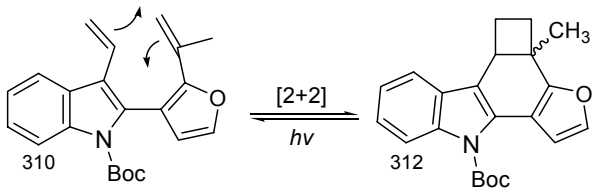
NMR spectra indicated that no alkene protons remained and therefore the only conclusion could be that the metathesis reaction had not occurred and instead a formal [2+2] cycloaddition reaction had taken place resulting in the formation of an interesting indolo cyclobutane derivative **312**. As mentioned previously, after the purification of the diene, on finally concentrating the diene by means of high vacuum, a second reaction had clearly taken place, and this is no doubt the point at which the pericyclic reaction occurred. This cyclobutane adduct **312** would have the same mass as its diene precursor **310**, but of course, would not have any alkene protons.

A direct thermal [2+2] electrocyclisation reaction is symmetry forbidden and therefore this leaves two possibilities regarding the mechanism leading to the cyclobutane product:

- A light mediated [2+2] electrocyclisation
- A thermally mediated π_8 electrocyclisation followed by a π_6 electrocyclisation

As far as the light mediated direct [2+2] cycloaddition is concerned (Scheme 115), the amount of energy available from the natural light is unlikely to be sufficient. Moreover, precisely to circumvent this process should it indeed be the route being followed, the diene **310** was generated in the presence of a minimal amount of light,[*] yet still the cyclobutane product **312** formed upon evacuation of the flask to remove the last traces of solvent after column chromatography.

Scheme 115



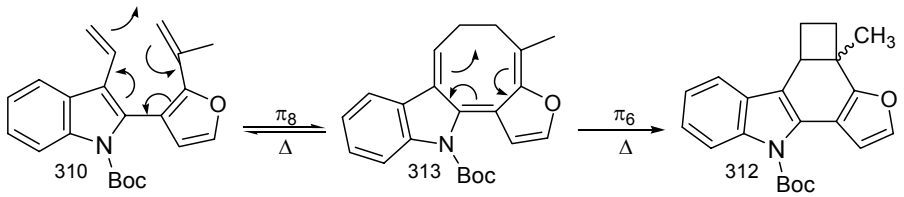
A direct [2+2] cycloaddition is only possible under light mediated conditions

This leaves the thermal process proceeding initially via a π_8 electrocyclisation followed by a π_6 electrocyclisation reaction (Scheme 116). We believe that the initial electrocyclisation reaction forming **313** is a reversible process and no doubt this exists in equilibrium with **310**. However, given enough energy, the second electrocyclisation reaction occurs and this

[*] The reaction was conducted in the absence of sunlight, with only minimal lighting in the laboratory.

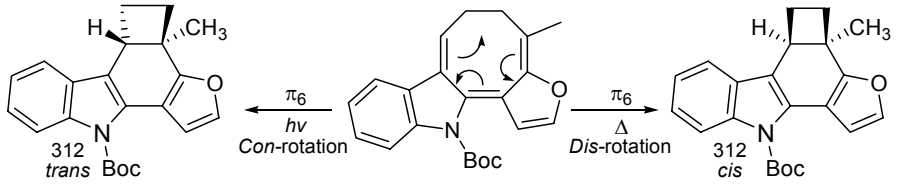
forms the cyclobutane ring system **312** and since this process re-establishes the aromaticity of the indole and furan moieties, it is not reversible.

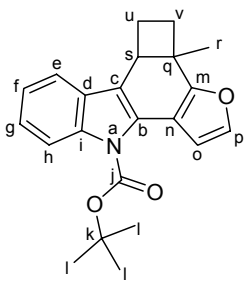
Scheme 116



Furthermore, in terms of the π_8-π_6 electrocyclisation processes, one needs to consider the options of *con*- and *dis*-rotation in the formation of the new bonds (Scheme 117). In the π_8 electrocyclisation process, either a thermally driven conrotatory process or a light mediated disrotation would lead to the same intermediate in light of the fact that the two alkenes are not substituted at their termini where the new σ-bond is forming. However, in the second process, this is not the case: A light mediated π_6 *con*-rotatory σ-bond formation would result in a *trans*-arrangement of the methyl and hydrogen on the bridgehead of the cyclobutane ring, ***trans*-312**. However, a thermally driven *dis*-rotatory process during the new σ-bond formation would lead to the more energetically favourable cyclobutane system ***cis*-312***,* containing a *cis* arrangement of the methyl and hydrogen at the bridgehead.

Scheme 117





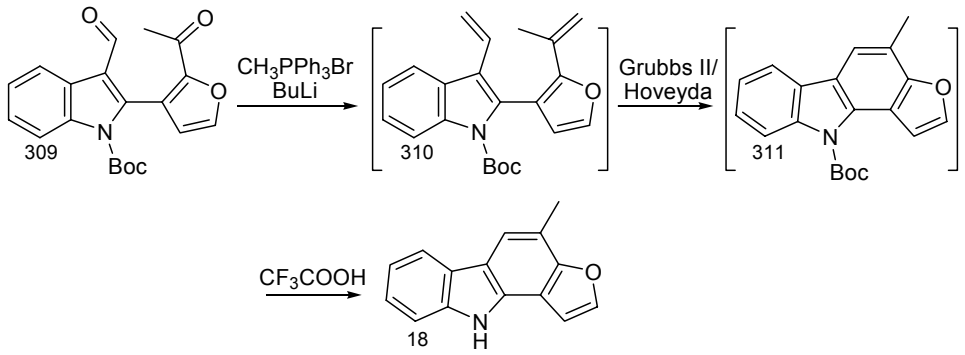
Besides the sudden appearance of several signals in the upfield region of the spectrum, another feature which is immediately obvious in the ^{1}H NMR spectrum of this compound is the fact that although the aromatic signals all seem to be rather familiar in terms of their chemical shifts, these signals suddenly appear far more complicated than they have in the precursors to this compound. At first it was assumed that perhaps a mixture of the *cis* and *trans* cyclobutane adducts was obtained but this seems not to be the case as only two singlets are observed, belonging to the *tert*-butyl protons H_l, located at 1.72 ppm, and the methyl protons H_r, at 1.54 ppm. One would expect to see separate singlets for these same protons at slightly different chemical shifts should there indeed be a mixture of diastereomers. The chemical shift of the signal for the methyl protons was a clear indication that the reaction had not produced the carbazole as desired. If it had, we would have expected the shift to be more representative of a benzylic methyl, in the region of 2.50-3.00 ppm – which is not the case. The most deshielded signal in this spectrum can be assigned to H_h[*] and exists as a multiplet in the region 7.98-7.92 ppm. The furan signals are still characteristically taller than the indole signals and they exist as their usual doublets with a very small coupling constant, and are therefore easily identified. Proton H_p, somewhat more deshielded than its neighbour can be assigned to the doublet at 7.32 ppm with the tiny coupling constant of just 1.9 Hz. The remaining furan proton, H_o produces a doublet at 7.01 ppm with the same coupling constant. Returning to the signals on the benzene ring of the indole moiety, proton H_e produces a multiplet overlapping slightly with the signal from H_p, in the region 7.31-7.28 ppm. Protons H_f and H_g exist as overlapping multiplets in the region 7.21-7.15 ppm. The remaining protons are those associated with the new cyclobutane ring, and are rather more difficult to assign unambiguously. Somewhat deshielded in comparison to these signals is a triplet located at 3.66 ppm and this signal integrating for 1H is assigned to H_s. Following this, the three multiplets in the region 2.66-2.15 ppm account for the remaining four protons, H_u and H_v. In the ^{13}C NMR spectrum the presence of six signals in the region of 26-40 ppm further attested to the six carbons not associated with the aromatic system, namely, the *tert*-butyl carbons, the methyl C_r and the four carbons associated with the

[*] This assignment is made based on all the NOE data obtained for the preceding compounds, and the trends observed.

cyclobutane component. Finally, a high resolution mass spectrum was in good agreement with the expected mass for this compound.

5.1.2.8 Synthesis of furostifoline – 18

Scheme 118



Understanding the unexpected pericyclic reaction previously described prompted a slight modification in our strategy in the hope of still obtaining furostifoline using the metathesis route. Of course, we now had two problems with which to contend: Firstly, the ketone on the furan is reluctant to undergo a Wittig reaction, and the large excess of Wittig reagent needed to force the reaction causes a problem in that under these basic conditions the Boc protecting group could be cleaved. Bearing in mind that by this stage, the aldehyde on the indole moiety has already converted to the corresponding alkene forming a vinyl indole,[*] the loss of the Boc protecting group renders the vinylic indole moiety unstable and amenable to polymerisation.[48] The second problem lies in the fact that the diene **310** (Scheme 118), once in hand, readily undergoes a pericyclic reaction leading to the undesired cyclobutane derivative discussed previously.

Nevertheless, having got this far, we decided to press on in the hope of being able to optimise the conditions and minimise these two undesirable reactions. In order to circumvent the loss of the Boc protecting group we envisaged preparing the Wittig reagent separately and cannulating this ylide into a dropping funnel fitted to the reaction vessel containing the dicarbonyl compound. In this way, we hoped to be able to make small

[*] The aldehyde reacts far more rapidly with the Wittig reagent than the ketone on the furan, forming almost immediately upon addition of the first equivalent of the Wittig reagent.

additions of the ylide and by monitoring the reaction closely by TLC, we hoped that we could limit the excess reagent needed to force the ketone to convert to the olefin. To circumvent the pericyclic reaction, we decided to conduct the Wittig reaction in the presence of a minimal amount of environmental light,[*] and moreover, since it appeared that the irreversible cyclobutane formation reaction proceeded upon removal of the last traces of solvent from the diene, we intended to leave the diene in solvent at all times. Of course, the diene would be in a mixture of ethyl acetate and hexane directly after a short column and this would not be suitable for the metathesis reaction, requiring a solvent exchange. Fortunately, the choice of toluene as a solvent for the metathesis part of the reaction should allow us to remove the ethyl acetate-hexane mixtures using several evaporation-refill cycles. Therefore we intended not to isolate the diene, but rather to carry it directly through to the metathesis reaction after a short column to remove the Wittig impurities.

Thus, with this plan in hand the Wittig reaction was started in the absence of sunlight and with minimal lighting in the laboratory. Initially, a large excess of the ylide was prepared (>10 equivalents) by reacting methyl triphenylphosphonium bromide with *n*BuLi in diethyl ether. In order to ensure that no butyl lithium would be present in the solution and later interfere with the Boc protecting group, a large excess of the phosphonium salt was utilised in this reaction. Whilst the ylide preparation was underway, the dicarbonyl compound was placed into a separate and carefully dried reaction vessel, fitted with a dropping funnel. On the initial attempt, diethyl ether was used as a solvent but it failed to solubilise the dicarbonyl compound **309** (Scheme 118). Fortunately, the addition of an equivolume amount of THF solved this problem. The large excess of ylide of approximately known concentration[†] was then cannulated into the dropping funnel and after cooling the receiving reaction vessel to 0 °C the ylide solution was slowly added to the dicarbonyl solution. As noted before, the conversion of the aldehyde functionality of **309** to the corresponding alkene occurred rapidly, and this could easily be observed by analysis of the reaction

[*] The reaction would be conducted at night, with minimal lighting in the laboratory

[†] Obviously, the amount of ylide generated is known as well as the volume of solvent, allowing for a rough calculation of the concentration of the solution

mixture by TLC.* However, as expected, the conversion of the ketone functionality of **309** to the corresponding alkene proved to be more problematic. Nevertheless, analysis of the reaction mixture by TLC showed the first traces of the diene **310** forming† and so further additions of the ylide were made. Once it appeared that most of the material had converted to the diene **310**, the reaction was quenched to avoid problems pertaining to base deprotection of the indole-Boc group.

Thus, after a quick workup, column chromatography afforded the pure diene **310** in ethyl acetate–hexane fractions. These fractions were combined, diluted with toluene and concentrated to about 20% of the original volume. Toluene was added again and the concentration step repeated. This process of driving off the ethyl acetate and hexane using toluene was repeated four times in the hope of obtaining the diene in nearly pure toluene, without ever having to actually concentrate the unstable compound completely. After this process, analysis of the toluene solution by TLC indicated that the diene was still present, attested to by a brilliantly UV active spot. It should be mentioned at this time that the undesirable cyclobutane compound, derived from the pericyclic reaction has exactly the same R_f as this diene and so the only evidence of having the diene in solution is the brilliantly UV active spot on the TLC plate, and that the diene stains rapidly when the plate is dipped in $KMnO_4$ solution. This is not the case with the cyclobutane derivative **312**.

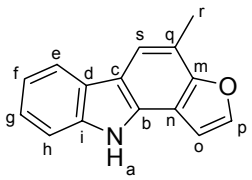
Without delay, the metathesis phase of the two reactions needed to get underway. The toluene solution was thoroughly degassed by bubbling Ar into the solution for 10 minutes. Grubbs II catalyst was added and the reaction was carefully monitored by TLC. Disappointingly, nothing seemed to be happening as the brilliantly UV active spot remained unchanged. The reaction was then heated to 90 °C and after 1 hour there was apparently still no reaction occurring. After 3 hours of maintaining the reaction mixture at 90 °C, another 5 mole % of the Grubbs II catalyst was added and the reaction was heated at 90 °C for another 4 hours. However, still, there seemed to be no product forming and the only spot on the TLC plate was the highly fluorescent spot confirming the presence of the

* Upon conversion of the aldehyde to the alkene, the R_f increased notably. Moreover, the new compound did not stain well using DNPH dip but stained remarkably well in $KMnO_4$ – a commonly noted feature in all olefinic compounds prepared

† A brilliantly UV active spot, of yet higher R_f than its precursor

diene. At this point, it was decided that perhaps the alkenes were too electron deficient and were not suitable substrates for the Grubbs II catalyst. The Hoveyda-Grubbs metathesis catalyst is well known to react better with electron deficient alkenes[107,108] than the Grubbs II catalyst and so 5 mole % of this catalyst was added to the reaction mixture and it was heated for 18 hours at 90 °C. Analysis of the reaction mixture after this time indicated that the highly fluorescent diene was still present. However, upon staining the plate with $KMnO_4$ dip, the diene stained rapidly and without heating as expected, but when the plate was heated, another yellow spot appeared, almost not visible due to a significant amount of overlap with the remaining diene. Without a doubt though, the different rates of staining clearly suggested that another compound existed in the solution.

The reaction mixture was concentrated and purification by column chromatography was not successful, affording a number of compounds all with the same R_f. A ^{1}H NMR spectrum of this mixture clearly indicated that the undesired cyclobutane derivative **312** was present, yet there also seemed to be significant amounts of at least one other compound. At this point, it was decided to proceed with the Boc deprotection in the hope of obtaining new compounds of suitably different R_f, rendering them separable by column chromatography. To this end, the mixture of compounds was dissolved in dichloromethane and treated with trifluoroacetic acid, affording several unidentifiable compounds in small amounts, and one compound in a somewhat larger amount. ^{1}H NMR spectral analysis of this compound confirmed that we had in fact obtained furostifoline **18**, although in a poor yield of only 5% (10 mg) over the three steps. The ^{1}H NMR spectrum of this compound was in exact agreement with that obtained by Knölker in this compound's first total synthesis, and Furakawa and co-workers, who first isolated the alkaloid from the root bark of *Murraya euchrestifolia*.[12,39]



The most notable feature in the ^{1}H NMR spectrum is the loss of the aldehyde signal, replaced by a new singlet in the aromatic region of the spectrum, namely H_s, found at 7.77 ppm. Pleasingly, the methyl protons H_r are now found in the expected region for benzylic protons, at 2.66 ppm. (In the troublesome cyclobutane derivative **312**, these methyl protons were found at a worrying 1.54 ppm.) A highly deshielded and broad singlet at 8.24 ppm attests to the presence of the proton on the indole nitrogen, H_a.

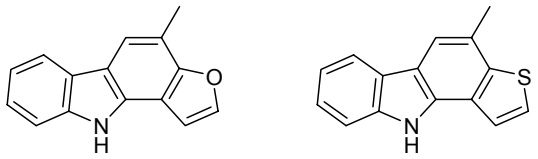
As for the remaining protons, the characteristics are rather similar to the spectra for the precursors seen thus far. The furan protons H_p and H_o are conspicuous by their small coupling constant of just 2.14 Hz, found at 7.71 ppm and 6.98 ppm respectively. The signal for H_e is somewhat deshielded from the other aromatic signals, this doublet is found at 8.04 ppm. Protons H_g and H_f produce multiplets at 7.36 ppm and 7.24 ppm respectively. Finally, H_h is located somewhat more upfield in comparison to the Boc protected indolo-furan precursors in this series of compound, found at 7.47 ppm.

5.1.3 Total synthesis of a thio-analogue of furostifoline employing metathesis as a key step

Since the synthesis of furostifoline proved to be far more troublesome than anticipated one may question as to why we now opted for more punishment by embarking upon a synthesis of the thio-analogue of furostifoline using a similar synthetic route. The method behind the madness lies in the fact that the synthesis of this thio-analogue began quite some time before the troublesome Wittig and metathesis steps and was run concurrently to the previously discussed synthesis. Indeed, had we completed the sequence of steps previously described before starting this particular synthesis then certainly, these plans would have been posthumously binned! That would have been a great shame because as it turns out, the simple act of replacing the oxygen in the furan moiety with a sulfur made a world of difference in the outcome of the metathesis reaction.

Thus blissfully unaware of the problems that lay ahead in the furostifoline synthesis we decided to embark upon a synthesis with a thiophene equivalent of the acetylfuran. Moreover, we hoped that the same synthetic strategy as was being employed to synthesise furostifoline would prove successful in the synthesis of its thio-analogue. For simplicity, we shall simply refer to this thio analogue as 'thiofurostifoline' **314** (Figure 40).

Figure 40



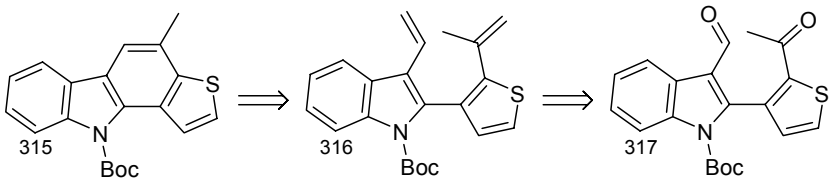
Furostifoline
18

Thiofurostifoline
314

5.1.3.1 Outline of the synthetic strategy

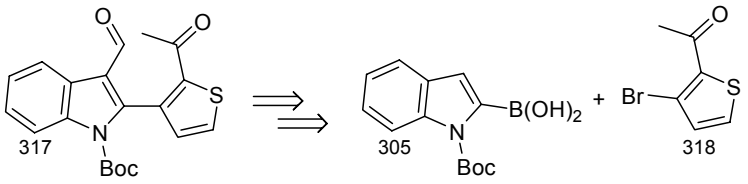
In the synthesis of thio-furostifoline **314**, we hoped to employ essentially the same methodology we were developing for the synthesis of furostifoline **18**. Thus, we hoped to use metathesis to construct the carbazole ring system from a suitably fused indolo-thiophene diene **316** (Scheme 119). The diene we once again envisaged obtaining from the corresponding dicarbonyl compound **317**.

Scheme 119



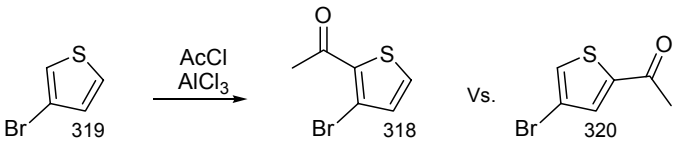
We envisaged that the construction of this coupled thiophene-indole moiety **317** should be possible utilising the same methodology as was being employed for furostifoline **18**. For this reason, a detailed description won't be repeated in this section however in short, an appropriately substituted thiophene moiety **318** should be amenable to a Suzuki coupling with the previously prepared indole boronic acid **305** and then the transformations involving deprotection, formylation and reprotection should afford **317** (Scheme 120).

Scheme 120



One concern however pertained to the acetylation of 3-bromothiophene **319** as once again we needed the acetylation to occur in the 3-postion to afford **318** (Scheme 121), just as we had accomplished with the furan moiety **82**, employed in the furostifoline synthesis. Although the acetylation of the furan had set a good precedent for this reaction to be successful, it had to be born in mind that the originally published acetylation of the furan, occurring in the 3-postion was not what Tanaka *et al*. expected.[97] Consequently, there existed the possibility that the thiophene may acetylate in the expected 2-position giving **320** under the same conditions.

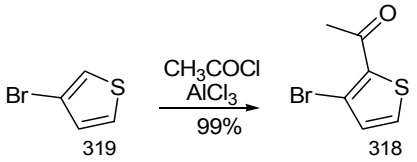
Scheme 121



Acetylation of 3-bromothiophene may not provide the required product - 2-acetyl-3-bromothiophene

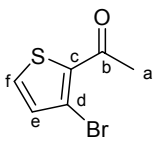
5.1.3.2 Synthesis of 2-acetyl-3-bromothiophene –318

Scheme 122



Having optimised the Friedel Crafts acylation for the furan from the reported 50% yield[97] to consistently obtaining quantitative yields we set about the acylation of commercially available 3-bromothiophene **319** using these same optimised conditions (Scheme 122). To this end dichloromethane was cooled to 0 °C and the acylating cation was preformed by the addition of freshly distilled acetyl chloride to aluminium trichloride. After about 15 minutes, the aluminium trichloride had reacted and no trace of the undissolved Lewis acid could be seen in the dichloromethane. The 3-bromothiophene **319** was added slowly and it was found that the yields were maximised if the temperature was maintained at 0 °C for 30 minutes after the addition. Thereafter, the solution was allowed to warm to room temperature. After 1 hour at room temperature the reaction was complete and could be quenched by cooling the solution to 0 °C once again and carefully adding ice-water.

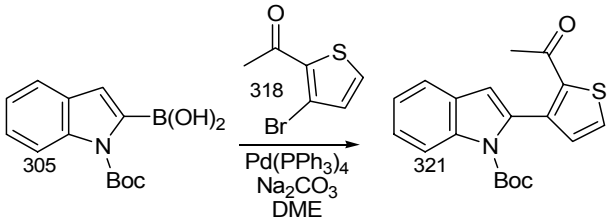
The behavioural similarity between the furan and the thiophene in this particular reaction was remarkable, including the previously observed phenomenon where the crude mixture could not be purified by column chromatography or distillation alone. In order to obtain a pure white waxy solid, the crude material had to first be columned to afford a slightly orange solid and then distillation at reduced pressure afforded the desired 2-acetyl-3-bromothiophene **318** in quantitative yields.



The ^{1}H NMR spectrum for this compound is almost identical to its oxygen analogue with perhaps one major exception: The furan version **82** of this compound produced doublets for protons H_f and H_e with small coupling constants (≈1.6 Hz). An observable difference in the ^{1}H NMR spectrum of this compound **318** is the larger coupling constant for these doublets (5.2 Hz). The methyl protons, H_a produce a singlet in the upfield region of the spectrum at 2.70 ppm and the doublets for the aromatic protons H_f and H_e are located downfield at 7.52 ppm and 7.11 ppm respectively. Pleasingly, the coupling constant of 5.2 Hz between these two doublets attests to the fact that the acylation has indeed occurred at the 2–position, consistent with what we had observed for the furan equivalent **82**. The ^{13}C NMR spectrum clearly shows the deshielded carbonyl carbon at 190 ppm and the quaternary carbon, C_c, bonded to the sulfur and acetyl units is found quite deshielded at 139 ppm. The two CH carbons on the thiophene ring are found at 134 ppm for C_f and 114 ppm for C_e. By virtue of the bromine bonded to C_d, this carbon is found somewhat upfield at 114 ppm and finally, the methyl on the acetyl moiety, C_a, is located in the upfield region at 30 ppm.

5.1.3.3 Synthesis of *tert*-butyl 2-(2-acetylthiophen-3-yl)-1*H*-indole-1-carboxylate by Suzuki coupling – 321

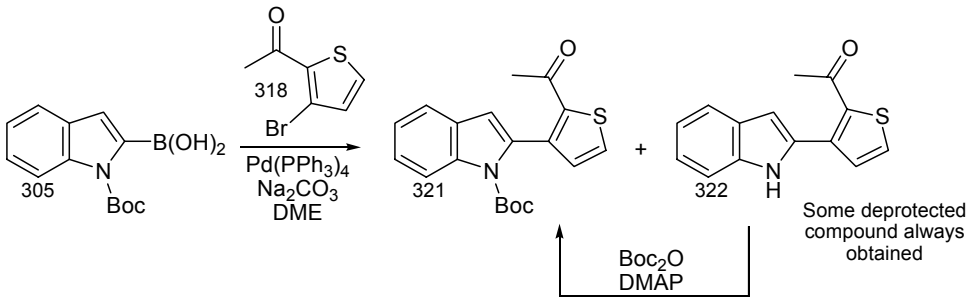
Scheme 123



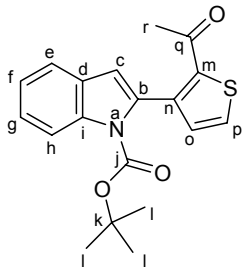
For the coupling of the indole **305** and thiophene **318**, (Scheme 123), we once again envisaged utilising a Suzuki coupling reaction as we had already optimised the conditions for the furan equivalent. Moreover, we would utilise the same indole boronic acid as we had previously used in the furostifoline synthesis. The degassing technique we had previously employed had proven to be most effective and so in preparation for this reaction the reagents were similarly degassed. To this end, the reaction vessel, fitted with a dropping funnel was thoroughly degassed and then the $Pd(PPh_3)_4$ catalyst was added to the flask. The dropping funnel was charged with DME and the Boc protected indole-2-boronic

acid **305** was added to this solvent. By gently bubbling Ar gas into the solvent, dissolution of the boronic acid was facilitated as was the removal of all undesired oxygen. After about 5 minutes of degassing, the 2-acetyl-3-bromothiophene **318** was added and it too rapidly dissolved into the solution which was still being agitated by the bubbling Ar. After a further 2 minutes of degassing, the solution containing both components required for the Suzuki coupling reaction was discharged into the reaction vessel. The dropping funnel was loaded with aqueous sodium carbonate solution and this solution was similarly degassed before being discharged into the reaction vessel. In this way, all reagents added to the reaction vessel could be thoroughly purged of oxygen and the inadvertent introduction of oxygen upon addition of the reagents to the reaction vessel was avoided. This careful procedure to avoid introducing oxygen and poisoning the catalyst was necessary, especially in this particular Suzuki reaction as the thiophene seemed to react somewhat slower than its furan equivalent. This may be attributed to the sulfur being less electronegative than oxygen and therefore rendering the oxidative insertion of Pd between the carbon and the bromine somewhat less reactive than was observed for the furan. Typically, the reaction was refluxed for 3 days in order to maximise the yield. It was found that reaction times exceeding this did not increase the yield as under these conditions, cleavage of the boronic acid functionality occurred from the indole moiety. Therefore, it was quite normal to recover significant amounts of *tert*-butyl 1*H*-indole-1-carboxylate **304** after the reaction. Moreover, the Boc protecting group was not completely inert under the conditions of elevated temperature and strong base and so these long reaction times also facilitated some deprotection of the indole. This unfortunately led to small amounts of the coupled, yet Boc deprotected compound **322** being obtained (Scheme 124). One may envisage that this would not be problematic as the very next step in our planned sequence was in any event this exact deprotection. The complication however arose out of the fact that this deprotected species had exactly the same R_f as the small amount of remaining 2-acetyl-3-bromothiophene which always persisted as a result of the coupling reaction not proceeding to completion. Thus purification of **322** was not possible. To overcome this problem and to optimise the yield for the coupling reaction, the crude material was always treated with a small amount of Boc anhydride and DMAP to reprotect any material that had spontaneously deprotected (Scheme 124), thus facilitating proper purification by column chromatography.

Scheme 124



In this way, the coupled and protected indole-thiophene compound **321** could be isolated in good yields.

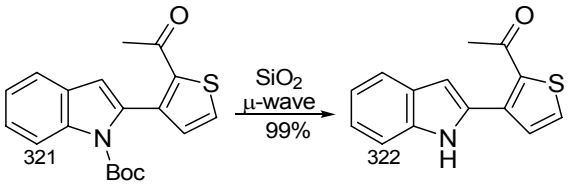


The presence of two singlets in the upfield region of the ^{1}H NMR spectrum was an immediate indication that the two moieties had coupled successfully. The large singlet at 1.34 ppm attested to the three methyls on the *tert*-butyl of the Boc group and slightly deshielded in comparison, the acetyl methyl's singlet is found at 2.19 ppm. The two doublets arising from the protons on the thiophene ring are quite distinct on the spectrum and this is a characteristic feature throughout this series of compounds. Even though they no longer have the small coupling constant which was a distinctive feature on the furan set of compounds, these thiophene doublets were always taller than the other aromatic signals and produce coupling constants in the region of 5 Hz. Thus, protons H_p and H_o are located at 7.55 ppm and 7.07 ppm respectively, with a coupling constant of 5.0 Hz. The proton in the 3-position of the indole moiety, H_c, does not couple to any other protons and produces the least deshielded signal of all the aromatic protons. Its singlet is found at 6.58 ppm. Finally, the four aromatic protons on the benzene ring of the indole moiety are similarly arranged as per the furan analogue of this compound and therefore NOE experiments conducted on furan analogue are useful in assigning these protons. Proton H_h is the most deshielded signal, a doublet occurring at 8.29 ppm. Somewhat less deshielded, the doublet from H_e is found overlapping with the doublet from H_p at 7.55 ppm. Finally, the multiplets produced by protons H_g and H_f are located in the regions 7.39-7.33 ppm and 7.29-7.24 ppm respectively. In the ^{13}C NMR spectrum, the most noticeable signals are the highly deshielded carbonyl signals arising from the ketone, C_q, at 191 ppm and the carbamate, C_j,

at 150 ppm. The remaining four quaternary carbons are located in the region 138-129 ppm. In the infrared spectrum, two distinct carbonyl stretch absorptions are visible, the carbamate carbonyl at 1733 cm^{-1} and the ketone carbonyl at 1656 cm^{-1}.

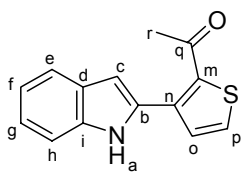
5.1.3.4 Removal of the Boc protecting group to synthesise 1-(3-(1*H*-indol-2-yl)thiophen-2-yl)ethanone – 322

Scheme 125



In preparation for the Vilsmeier formylation to introduce a carbonyl in the 3-position of the indole moiety, we once again decided that it would be wise to deprotect the indole nitrogen, rendering the 3-position far more nucleophilic and thereby circumventing any possible competing reactions at other electron rich sites. In the route employing the furan, several methods for this deprotection were investigated and it was found that microwave irradiation of the Boc-material adsorbed onto silica gel proved to be the most effective, and most convenient method of deprotection. The acidity of the silica in conjunction with the localised heating easily facilitated cleavage of the carbamate.

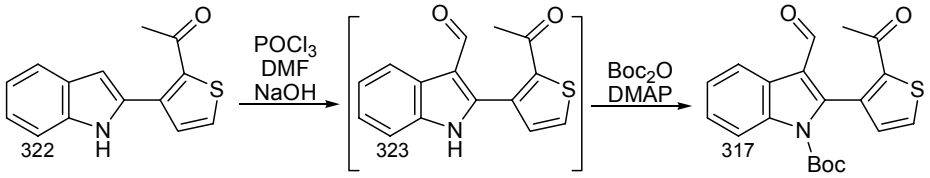
The Boc protected material **321** (Scheme 125) was therefore adsorbed onto a generous amount of silica gel and all traces of solvent were removed *in vacuo*. The adsorbate was then subjected to microwave radiation in bursts lasting 30 seconds. After each burst, the powder was agitated to evenly distribute the protected and unprotected material and a sample was taken to determine the progress of the reaction by TLC analysis. The process of heating for 30 seconds, agitating the adsorbate and allowing to cool, followed by TLC analysis was repeated until all the starting material had been consumed. As the reaction progressed, the adsorbate changed colour from off–white to yellow. Once the reaction was complete the desired product was simply eluted off the silica. In this way, the pure, unprotected indolo-thiophene **322** was obtained in excellent yields.



The appearance of a broad singlet downfield at 12.31 ppm in the ^{1}H NMR spectrum is a clear indication of the free amine proton, H_a, on the indole. Based on NOE experiments performed on the furan analogue of this compound, and since the NMR spectra of the two compounds are very similar, it is possible to assign the doublet produced by H_h as the less deshielded of the two doublets arising from the benzene ring of the indole moiety. Thus, H_h produces a doublet at 7.51 ppm and H_e produces a doublet at 7.64 ppm. Proton H_g produces a multiplet in the region 7.28-7.22 ppm and H_f, being para to the nitrogen produces the least deshielded signal for the four protons on the indole's benzene ring, appearing as a triplet at 7.12 ppm. The doublets produced by protons H_p and H_o on the thiophene moiety are always distinctive and these signals occur at 7.70 ppm and 7.54 ppm, with their characteristic coupling constant of 5.31 Hz. The last aromatic proton, H_c, shows some long range coupling and therefore appears as a poorly resolved doublet at 6.97 ppm. Finally, the methyl of the acetyl moiety is found as an upfield singlet, at 2.72 ppm. In the ^{13}C NMR spectrum, it is clear that only one carbonyl carbon is present now, namely C_q on the acetyl moiety, found at 192 ppm. Besides this carbonyl signal, only four other quaternary carbons are visible in the spectrum, attesting to the loss of the Boc protecting group.* In the infrared spectrum, a clear broad NH stretch absorption is observed at 3178 cm^{-1}.

5.1.3.5 Vilsmeier formylation to synthesise *tert*-butyl 2-(2-acetylthiophen-3-yl)-3-formyl-1*H*-indole-1-carboxylate – 317

Scheme 126



The Vilsmeier formylation had proven to be a most successful method for introducing the required carbonyl functionality and we were confident that the reaction would work just as

* The quaternary carbon signal arising from the *tert*-butyl group on the Boc was always distinctive in the region of 80-90 ppm.

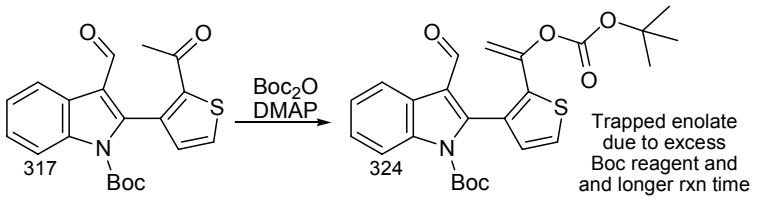
well on this thiophene analogue **322** (Scheme 126). Moreover, due to the problems encountered in purification of the newly formylated, yet still unprotected indolo-furan compound **306**, we decided in this reaction not to attempt purification of the unprotected compound **323** but rather to immediately subject the crude material to Boc protection after the formylation.

As learned from the previous reactions, in preparation of the Vilsmeier salt, a six fold excess of DMF was utilised relative to the amount of $POCl_3$ in order to keep the newly formed iminium salt in solution. It was previously found that if a stoichiometric amount of DMF was utilised, the iminium salt formed as a white solid. When the indole, dissolved in dichloromethane was added to this salt it took too long for the iminium salt to dissolve completely and this resulted in diminished yields. The reason for this is that it was also found that the reaction time should be kept to a minimum to avoid side reactions with the newly formed product. Thus, the excess DMF maintained the iminium salt in solution and the subsequent addition of the indole in dichloromethane resulted in an instantly homogenous solution. The rapid reaction that ensued was then closely monitored by TLC and usually the starting material had all been converted to the salt within 30 minutes. Without further delay, this salt was hydrolysed using sodium hydroxide to form the aldehyde **323**.

With the crude aldehyde **323** in hand, we immediately embarked upon protection of this material without further purification. Normally, in the case of the furan equivalent this protection step was set up and within 1 hour the reaction was deemed to be complete and the material could be isolated and purified. However, on this one particular occasion involving protection of this thiophene compound **323** the reaction was left to proceed for 18 hours, in the presence of an excess of the Boc anhydride reagent. To our surprise, analysis of the reaction mixture after this time indicated that the crude aldehyde had indeed all reacted, but two products had formed, and seemingly of approximately equal amounts as gauged by the intensity of the spots on the TLC plate. Isolation of both compounds revealed that one of them was the desired protected aldehyde **317** but the other product was initially quite baffling regarding its structure. Moreover, this new compound was isolated in a significant amount, almost equalling the mass of the desired compound. It was not surprising then that the yield calculated for the desired aldehyde was only 50%.

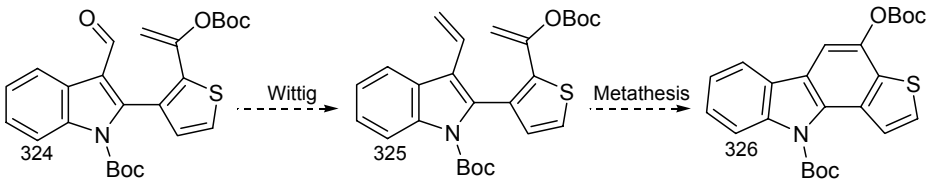
An immediately obvious feature in the ^{1}H NMR spectrum of this new compound was the existence of two *tert*-butyl singlets, suggesting the presence of two Boc groups. Moreover, the usual indole signals appeared as normal as did the easily identifiable doublets arising from the thiophene moiety. Also of interest was the fact that a highly deshielded singlet characteristic of an aldehyde proton indicated that this new compound had indeed formylated, as intended. Finally, the presence of two doublets in the alkene region, as well as the fact that we were suddenly missing the singlet from the methyl protons of the acetyl provided the final clues as to what had gone wrong with approximately half the formylated material. During the protection step, the combination of an extended reaction time, and the presence of excess Boc anhydride had resulted in significant conversion of the initially desired material's ketone moiety to its corresponding trapped enolate **324** (Scheme 127). This accounted for the poor yield of the intended reaction, and in the ^{1}H NMR spectrum, accounted for the presence of the alkenyl protons, the presence of a second Boc protecting group and the absence of the expected methyl signal.

Scheme 127



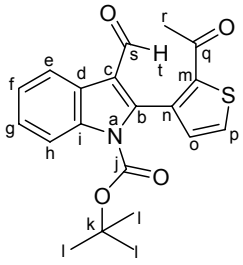
This oversight in the protection step provided us with an interesting, though somewhat undesirable result. Nevertheless, we had inadvertently generated an alkene **324** and we considered the possibility of also transforming the aldehyde functionality on this compound to its corresponding alkene **325** (Scheme 128). A metathesis reaction may then allow us to synthesise an analogue of thiofurostifoline **326**, containing a hydroxyl moiety instead of a methyl.

Scheme 128

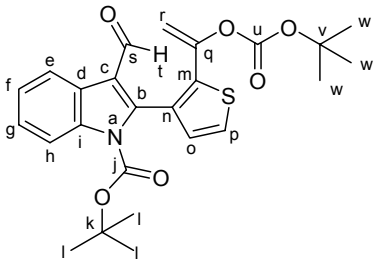


A possible use for this new compound leading to a hydroxy version of thiofurostifoline

In summary, if one includes the amount of material obtained for both compounds, and considers the amount of the starting indole, the yield of 85% is excellent over the two steps. Unfortunately, 35% of this material continued to react with the excess Boc reagent forming our new alkene!



The presence of a highly deshielded singlet at 9.65 ppm is a welcome sight as it attests to the presence of the aldehyde proton, H_t. The presence of this new formyl group of course means that the only aromatic singlet, present in all the preceding compounds in position H_c in this series, is no longer present. The presence of the Boc protecting group has a profound effect on the chemical shift of the doublet, H_h, now found significantly downfield at 8.25 ppm. The signal from the other doublet on this benzene ring, H_e is characteristically still the most deshielded of the indole protons and it is found at 8.36 ppm. The multiplets arising from protons H_f and H_g overlap in the region 7.48-7.38 ppm. The doublets from the protons on the thiophene ring are always easily observed and they are located at 7.68 ppm for H_p and 7.20 ppm for H_o with their characteristic coupling constant in the region of 5 Hz. Finally, the remaining upfield signals are limited to two singlets, namely that of the acetyl methyl protons, H_r, at 2.31 ppm and the *tert*-butyl protons, H_l, at 1.37 ppm. In the ^{13}C NMR spectrum, the two highly deshielded signals attest to the presence of the aldehyde and ketone, with the ketone found just slightly more downfield at 189 ppm and the aldehyde at 187 ppm. The remaining carbonyl signal, belonging to the carbamate, C_j, is found at 149 ppm. The remaining six aromatic quaternary carbons are all easily visible in the spectrum in the region 143-120 ppm. The only non-aromatic quaternary carbon, C_k, is found somewhat more upfield at 85 ppm.

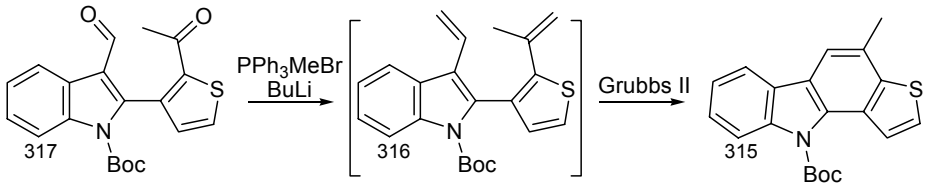


In the trapped enolate **324**, the alkene protons H_r are very distinctive. Proton H_r *trans* to the carbamate oxygen is found slightly more downfield at 5.18 ppm, whereas H_r *cis* to this oxygen is less deshielded at 5.01 ppm. The presence of the extra *tert*-butyl signal, just slightly upfield of the characteristic *N*-Boc observed thus far attests to the presence of the protons, H_w, at 1.14 ppm. The more familiar *tert*-butyl signal for the other

N-Boc protecting group is found in its characteristic location of 1.36 ppm. The remaining aromatic protons do not differ significantly from the acetyl compound **317**, perhaps with the exception of the thiophene proton, H_p, found somewhat less deshielded than usual at 7.33 ppm. The remaining doublet for the thiophene moiety, H_o, is found at 7.01 ppm. On the indole moiety, the signals for protons H_f and H_g exist as overlapping multiplets and protons H_e and H_h produce multiplets in the regions 8.37-8.34 ppm and 8.31-8.29 ppm respectively. Finally, the aldehyde proton, H_t, produces a characteristically deshielded singlet at 9.67 ppm.

5.1.3.6 Wittig reaction, followed immediately by RCM to synthesise *tert*-butyl 4-methyl-10*H*-thieno[3,2-*a*]carbazole-10-carboxylate – 315

Scheme 129



The problems previously experienced with this reaction in our synthesis of furostifoline resulted in this particular set of transformations being approached with rather diminished enthusiasm. The fact that all of the reactions thus far for this series of compounds containing the thiophene had so closely resembled the furan analogues did not bode well for these final transformations. Nevertheless, having come this far in this series, these final three steps *en route* to thiofurostifoline had to at least be attempted.

With the knowledge in hand that the ketone moiety in **317** (Scheme 129) would be resistant to the Wittig reaction, we immediately set about preparing a large excess of the methyl ylide that would be required to convert both carbonyls to the corresponding alkenes. As before, once prepared, this ylide was cannulated into a dropping funnel so that it could be added in portions, whilst closely monitoring the reaction by TLC. Although we expected that an excess of the ylide would be required, we needed to once again exercise caution in that the excess ylide would deprotect the Boc protecting group. Since by that stage the aldehyde of **317** would already have converted its corresponding alkene, the loss of the Boc protecting group would render our molecule susceptible to polymerisation and

lead to diminished yields, as had occurred *en route* to furostifoline. The best we could hope for was to add the ylide in portions, and after each addition the reaction would be monitored by TLC and as soon as most of the material had been converted to the diene, the material would be hastily purified and subjected to metathesis.

Moreover, since we were still not sure that the electrocyclisation reaction in the furan analogue, leading to the undesired cyclobutane product, was not truly a light induced [2+2] cycloaddition reaction, we once again took precautions against exposing our two-step reaction to sunlight.

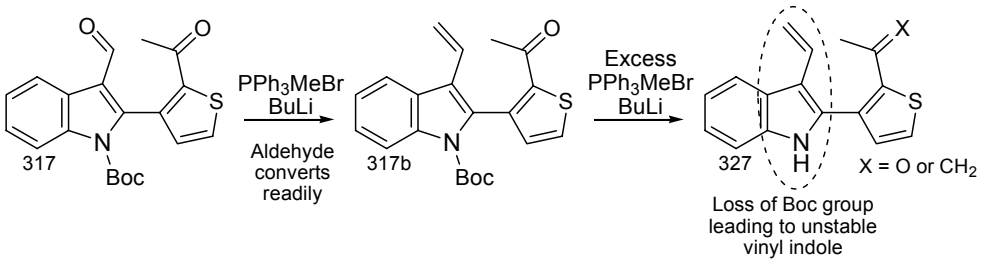
In the absence of sunlight, and with minimal lighting in the laboratory, the addition of the first few equivalents of the ylide resulted in the dicarbonyl **317** rapidly converting to the mono-alkene as the aldehyde readily reacted. This transformation could easily be followed by analysis of the reaction mixture by TLC. Once all of the dicarbonyl **317** had been consumed, by TLC it was clear that we had almost exclusively the mono-ene, and only traces of the desired diene **316** could be observed on the TLC, glowing brilliantly under UV light at a much higher R_f. As before, the ylide was added in portions and the reaction monitored closely. The formation of the diene, although reluctant, seemed slightly easier in the thiophene analogue as compared to the furan compound. However, a point was reached where further additions of ylide did not seem to be effectively converting the last traces of ketone to alkene and we became concerned that further additions of ylide may result in significant Boc deprotection. Thus, without having fully converted the mono-ene to the desired diene **316**, the reaction was hastily worked up and purified by column chromatography after adsorption of the crude material onto silica gel.

Having learned that concentration of this precious diene **316** until neat results in rapid decomposition to the cyclobutane adduct, we undertook to transfer the diene into the required toluene solvent without ever fully concentrating the material. Fortunately, the high boiling point of toluene rendered this task relatively simple. The combined ethyl acetate-hexane fractions containing the diene were evaporated *in vacuo* to approximately 20% of the original volume and then a generous amount of toluene was added. The mixture of solvents was once again concentrated *in vacuo*, and toluene was again added. This process of driving off the lower boiling solvents using toluene was repeated four times and

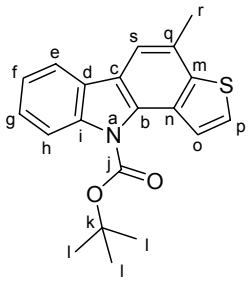
finally, the diene, essentially now in toluene, was concentrated to about 10 ml, thoroughly degassed and treated with 5 mole % Grubbs II catalyst at room temperature. To our amazement, without warming, the diene immediately began reacting and a new compound was evident upon monitoring the reaction by TLC! Although the R_f of the product was very similar to that of the starting material, it was nevertheless unmistakable that a new compound was forming. After 3 hours, it seemed as though the transformation was complete however, in light of the fact that the spots were overlapping on the TLC, another 5 mole % catalyst was added and the reaction was left to proceed for 18 hours, just to be sure. After workup and purification, the desired carbazole **315** was isolated in 40% yield.

The metathesis reaction for the thiophene analogue seemed to proceed quite smoothly and the poor yield can almost certainly be attributed to the difficulties in preparation of the diene compound **316**. The problem lies in the fact that the aldehyde functionality of **317** readily converts to the corresponding alkene **317b** (Scheme 130), but the ketone functionality of **317** is resistant to the Wittig reaction. The excess ylide needed to force the ketone to convert results in loss of the Boc protecting group, and with the aldehyde already converted to the alkene, this vinyl indole **327** begins to polymerise and it is here that material is lost, leading to a poor overall yield.

Scheme 130



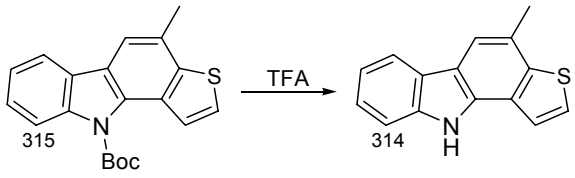
Nevertheless, although the yield over the two steps was not ideal, we were ecstatic at having synthesised this protected form of thiofurostifoline.



The position of the methyl protons, H_r, at 2.67 ppm in the ^{1}H NMR spectrum provides the immediate relief that we do indeed have a benzylic methyl and that we have not synthesised the cyclobutane product.* Another feature in the ^{1}H NMR spectrum which attests to the formation of the carbazole system is the presence of the aromatic singlet at 7.70 ppm, produced by proton H_s. The remaining signals in the spectrum are all quite familiar: The doublets produced by the protons on the thiophene ring are once again quite distinctive and the aromatisation of the entire system has not radically altered their coupling constant which is still in the usual region of 5 Hz. These signals are located at 7.47 ppm for H_o and H_p is located at 8.16 ppm, overlapping with the most deshielded proton on the benzene ring of the indole moiety, H_h. The other doublet arising from this ring is produced by proton H_e, slightly more upfield at 7.95 ppm. The last two aromatic signals arising from protons H_g and H_f are multiplets, in the regions 7.45-7.39 ppm and 7.36-7.31 ppm respectively. Finally, the unmistakable *tert*-butyl signal, for protons H_l, is located upfield at 1.76 ppm. In the ^{13}C NMR spectrum, the deshielded quaternary carbon signal attests to the presence of the carbamate carbon, C_j, at 151 ppm. Pleasingly, no another carbonyl signals are present. Finally, the mass spectrum of this compound provides the evidence that the metathesis reaction was indeed successful, cleaving away the two alkenyl carbons thus affording a product lower in mass than the troublesome cyclobutane adduct. The result of the mass spectral analysis of 337.1138 amu correlates nicely with the expected mass of 337.1136 amu.

5.1.3.7 Boc deprotection affording thiofurostifoline - 314

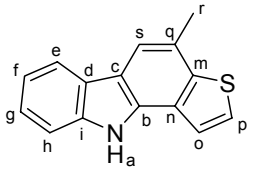
Scheme 131



* The cyclobutane product does not have a benzylic methyl and so its shift in the ^{1}H NMR spectrum in the region 1.54 ppm.

With only a small amount of the protected carbazole in hand, the less convenient, though somewhat milder deprotection of the Boc substituent utilising TFA was opted for in lieu of the silica and microwave irradiation method.

In order to carry out this reaction, the protected version of thiofurostifoline **315** (Scheme 131) was dissolved into dichloromethane and treated with 3 equivalents of trifluoroacetic acid at room temperature. To our surprise, after 1 hour no reaction had taken place and so the solution was warmed to reflux. Still no reaction seemed to be occurring upon analysis of the solution by TLC. Whilst continuing with warming, the solution was gradually concentrated by blowing away the dichloromethane vapour using a gentle stream of Ar gas. Finally, as the solution became more concentrated the reaction proceeded smoothly, affording a single new compound. The solution was diluted with dichloromethane and neutralised with an aqueous bicarbonate solution. After purification, thiofurostifoline **314** was obtained as a white solid in 75% yield.



In the ^{1}H NMR spectrum, the presence of a broad singlet at 8.39 ppm corresponding to the indole nitrogen's proton, H_a, and the upfield shift (7.95 ppm to 7.50 ppm) of the doublet arising from proton H_h is a clear indication that the Boc group had been removed. On the aromatic ring, the most deshielded proton, H_e, produces a doublet characteristically at 8.08 ppm and the protons H_g and H_f produce multiplets in the region 7.43-7.38 ppm and 7.29-7.25 ppm respectively. The only aromatic proton not able to couple with any other protons, H_s, produces a singlet at 7.84 ppm. The protons on the thiophene ring system, H_p and H_o, produce their characteristic doublets at 7.63 ppm and 7.54 ppm with a coupling constant of 5.5 Hz. Finally, the only upfield signal is the singlet produced by the methyl protons, H_r, in the benzylic region of 2.71 ppm. In the infrared spectrum, a clear NH stretch is observed at 3414 cm^{-1}, and finally, analysis of this compound by mass spectrometry affords an accurate mass of 237.0606 amu, in good agreement with the expected mass of 237.0612 amu.

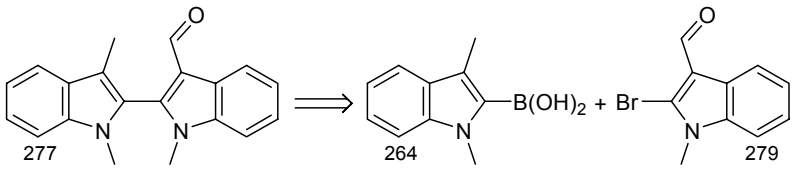
5.1.4 Synthesis of the indolocarbazole core – a metathesis approach

5.1.4.1 Outline of the strategy

In the syntheses of furostifoline and its thio-analogue, thiofurostifoline, the key steps involved a Suzuki coupling reaction to combine the two essential moieties – namely the indole and thiophene or furan moieties and then finally, a metathesis reaction could be regarded as the second key step – cyclising the two moieties together, and forming the necessary carbazole skeleton.

In the previous attempted synthesis of the indolocarbazole system (Scheme 132), a Suzuki coupling reaction was also employed to connect the two indole moieties, **264** and **279**. However, as previously discussed, this route did not lead to the indolocarbazole core as the light mediated cyclisation methodology could not be applied to this particular system (Chapter 4).

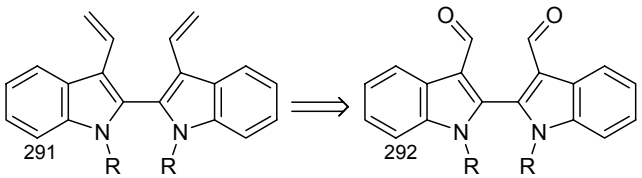
Scheme 132



Previous methodology which required 3-methyl and 3'-aldehyde functionalisation

With the metathesis methodology in mind, we envisaged now that we would once again need a coupled *bis*-indole system (Scheme 133). However, the fundamental difference would be that in the earlier approach, one moiety possessed an aldehyde substituent in the 3-position and the other moiety possessed a methyl substituent in its 3-position. In this new approach, as we intended to synthesise a diene using a Wittig reaction, we envisaged that we would need aldehyde functional groups on both moieties **292**.

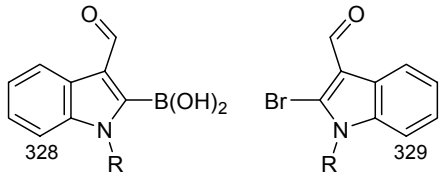
Scheme 133



The new metathesis route would require aldehydes on both moeities

The synthesis of this dicarbonyl compound presented a slight problem if we wished to utilise our previous strategy involving a Suzuki coupling reaction to join the two moieties. The reason for this is due to the fact that one unit would need to be in the form of a boronic acid **328**, and the other would need to be in the form of an aryl halide **327** (Figure 41).

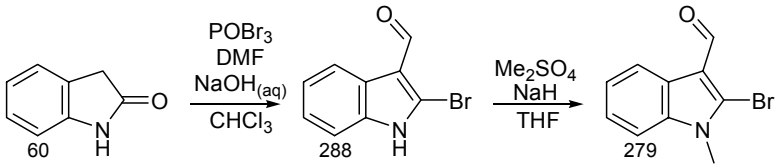
Figure 41



Reagents required for Suzuki coupling

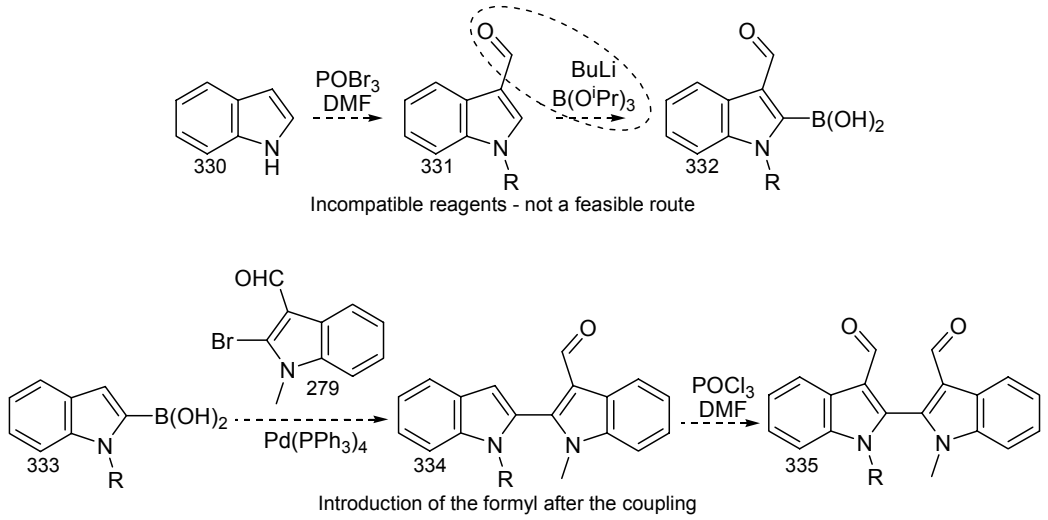
The synthesis of the aryl halide would not be a problem and in fact we have already developed methodology for this. As previously discussed in the earlier synthesis of these *bis*-indole compounds, oxindole **60** was readily converted using a modified Vilsmeier reaction to 2-bromo-1-methyl-1*H*-indole-3-carbaldehyde **279** (Scheme 134).

Scheme 134



Naturally, we envisaged that should we embark upon this particular route, the second step involving protection of the indole nitrogen could be accomplished equally well using a Boc protecting group instead of a methyl. So, the synthesis of this particular compound did not pose a problem. However, in the synthesis of the boronic acid, we realised that we would have to adopt a somewhat lengthy route. Although it is very easy to synthesise 3-formylindole **331** utilising a Vilsmeier reaction on indole,[48] the presence of the formyl group prior to generating the boronic acid **332** would pose a problem as it would be incompatible with the *n*BuLi employed in the subsequent reaction where the boronic acid is generated (Scheme 135). Thus, we would have to first generate the boronic acid without any further functionality on the indole system **333**, and after coupling the two indole moieties together forming **334**, the second formyl group could be introduced **335**.

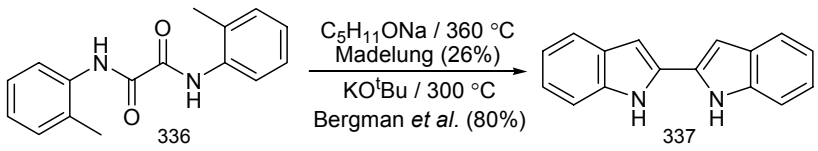
Scheme 135



Although this second route seemed feasible, we decided to scrutinise the literature in the hope of finding methodology to synthesise *bis*-indoles using a more direct route. Also realising that the compound we were after could be symmetrical, we saw no problem in performing a double formylation if necessary – we would then simply need ready access to an unsubstituted *bis*-indole system.

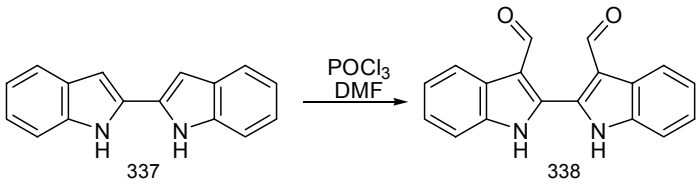
A brief survey of the literature quickly identified a suitable reaction for our purposes. In 1995 Bergman *et al*. published a paper in which they utilised a modified version of the Madelung synthesis to synthesise 2,2'-biindolyl **337** (Scheme 136). The original synthesis of this *bis*-indole **337**, published in 1912 by Madelung employed the use of sodium *n*-amylate and oxalyl-*o*-toluidide at 360 °C, forming *bis*-indole in a reaction which now bears his name.[109,110] Unfortunately, the yield for the reaction under these harsh conditions was rather poor. Bergman *et al*. modified the base required to deprotonate the benzylic position, and thus managed to effect the reaction at lower temperatures, significantly improving the yield.[111]

Scheme 136



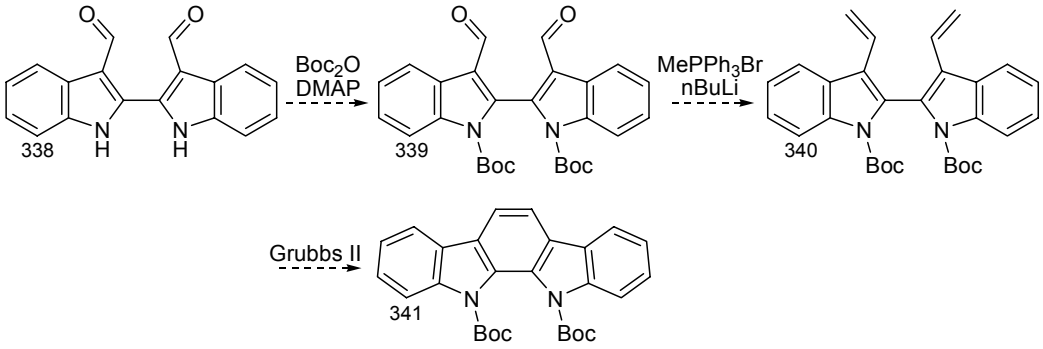
Moreover, the double formylation of this *bis*-indole compound **337** was also discussed in the paper by Bergman *et al*.[111] and as expected, the conditions are analogous to the Vilsmeier conditions one would employ for formylating indole itself (Scheme 137).[48]

Scheme 137



Thus, with this promising methodology in hand it remained for us to synthesise the *bis*-indole-carbaldehyde **338** and then suitably protect both indole nitrogens with electron withdrawing protecting groups **339** (Scheme 138). Following this, a double Wittig reaction forming the diene **340** should put us in a position to try metathesis as a means of cyclising the *bis*-indole system, thereby leading to the indolocarbazole core **341** we desired.

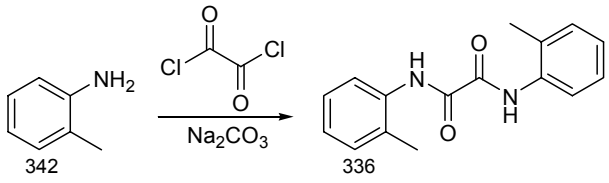
Scheme 138



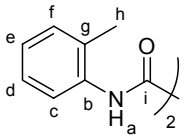
An envisaged route starting from the symmetrical *bis*-indole-3-carbaldehyde

5.1.4.2 Synthesis of oxalyl-*o*-toluidide – 336

Scheme 139



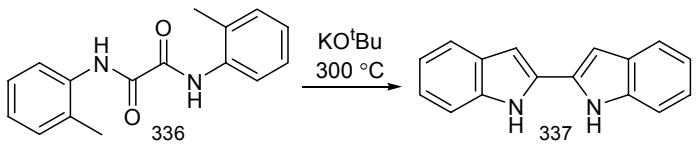
At the outset we needed to prepare oxalyl-*o*-toluidide which we required for the Madelung-type synthesis. To this end, oxalyl chloride was slowly added to a solution of *o*-toluidine **342** in THF, also containing finely powdered sodium carbonate to react with the HCl produced (Scheme 139).* Fortuitously, the *bis*-amide **336** formed immediately and was seemingly completely insoluble in THF, precipitating from solution as it formed. Once all the oxalyl chloride had been added, the product was simply filtered and washed with a small amount of water to remove any salts and then washed with a small amount of ethyl acetate to remove any excess *o*-toluidine. Analysis of the product by ^{1}H NMR spectroscopy indicated that it was quite pure and further purification was not necessary. In this way, the required oxalyl-*o*-toluidide **336** was synthesised in quantitative yields and obtained as a white crystalline material.



The NMR spectra for this compound are pleasantly straightforward due to its C_2 symmetry. In the ^{1}H NMR spectrum, the amide singlet is characteristically broad and deshielded, at 9.37 ppm. There is significant overlap in the signals arising from the aromatic ring protons however, H_c is found slightly downfield of the other protons and produces a doublet at 8.09 ppm. Protons H_f and H_d produce overlapping multiplets in the region 7.31-7.24 ppm and H_e produces a multiplet in the region 7.17-7.12 ppm. Finally, the benzylic methyl protons, H_h are attested to by the upfield singlet at 2.39 ppm. In the ^{13}C NMR spectrum, the most notable signals are those belonging to the carbonyl carbon, C_i, found downfield at 158 ppm and in contrast, the benzylic methyl, C_h, is found upfield at 17 ppm. In the aromatic region of the spectrum, the two quaternary carbons are easily identifiable as C_b at 134 ppm and therefore C_g at 128 ppm. The remaining four signals in this region are all aromatic CH's.

5.1.4.3 2,2'-Biindolyl using a Madelung-type reaction – 337

Scheme 140



* The oxalyl chloride was added to the *o*-toluidine and not the other way around, thus ensuring that the majority of the product formed was indeed the *bis*-amide adduct **336** that we desired.

Bergman *et al*. vastly improved this very old procedure for the synthesis of *bis*-indole **337** by employing KO^{t}Bu as a base instead of sodium amylate (Scheme 140).[111] In this procedure, which we also utilised to synthesise the same compound, the strong base allows for deprotonation of the benzylic protons leading to a nucleophilic attack on the amide carbonyl. At the elevated temperature, this attack is immediately followed by dehydration leading to the *bis*-indole system.

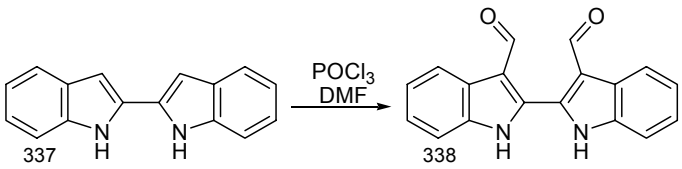
Although Bergman *et al*. claim to have obtained yields in the region of 80%, our yields for this reaction were typically in the region of 65%. This may be attributed to the fact that this reaction may be described quite simply as 'messy'. In fact, the reaction is set up by initially forming a slurry of the oxalyl-*o*-toluidide in ^{t}BuOH solvent and the base, KO^{t}Bu. This slurry is then gradually heated to 225 °C during which time the solvent evaporates and the KO^{t}Bu sublimes from the reaction mixture! Nevertheless, once the temperature of the reaction mixture reaches 270 °C, a vigorous reaction begins to take place and the water eliminated during the dehydration step suddenly finds itself in an environment of nearly 300 °C, and is therefore in a big hurry to leave, sputtering the slurry up onto the sides of the reaction vessel. After a few attempts at this reaction it was found that better yields were obtained by actually 'blowing off' the emitted solvent and KO^{t}Bu using a gentle stream of Ar up a flue connected to the top of the reaction flask. Given the nature of this reaction, better yields would probably be obtained when performing it on a larger scale.[*] On the smaller scale, as in our case involving 1-2 g reactions, the sputtering of the reaction slurry leads to losses which more significantly affect the overall yield.

Nevertheless, the yields in the region of 65% which we were obtaining provided us with more than enough material to continue. However, the *bis*-indole proved to be insoluble in most organic solvents as well as water and therefore proved rather difficult to handle from a purification point of view. Bergman *et al*. utilised a mixture of dioxane and acetic anhydride to recrystallise their material however we found it more convenient to crystallise the material from hot pyridine. All future preparations of this compound did not include any subsequent purification steps as we found it more convenient to simply proceed with the next step.

[*] Bergman *et al*. were conducting these reactions on scales in excess of 100 g.

5.1.4.4 2,2'-Biindolyl-3,3'-dicarboxaldehyde – 338

Scheme 141



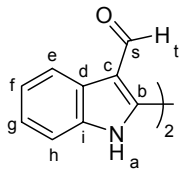
The formylation of indoles at the 3-position is well known and we decided that this methodology should work equally well on our *bis*-indole system **337** (Scheme 141).[48] However, the formylation conditions we employed previously on the indolo-furan and indolo-thiophene systems involved generating the iminium salt by the addition of $POCl_3$ to 6 mole equivalents of DMF,* and then the indole unit, dissolved in dichloromethane was added to the Vilsmeier salt. However, in this particular reaction, given the poor solubility of the *bis*-indole in dichloromethane, this reaction was performed by generating the Vilsmeier salt in an excess of DMF as before, and then the *bis*-indole, also dissolved into DMF, was added to the iminium salt solution.

As was observed with the other indole compounds, this reaction proved to be very rapid even at 0 °C. Within 1 hour the reaction was complete and was quenched by the addition of water. The doubly formylated material also proved to be very insoluble in most organic solvents however fortuitously, this reaction afforded the desired product with an acceptable purity, obviating the need for further purification. Thus, directly after the reaction, the hydrolysis of the iminium salt to the *bis*-indole by the addition of aqueous NaOH resulted in the desired product simply precipitating from the water-DMF mixture as an off-white solid. After several water washings to remove any excess NaOH, the product was dried and appeared to be of excellent purity as determined by NMR spectroscopy. In this way, the desired doubly formylated *bis*-indole **338** was obtained in excellent yields.

Bergman *et al*. have also synthesised **338** utilising a similar procedure.[111] The major difference in their procedure is that they allow the reaction to continue for 40 hours!

* The excess DMF provided a suitable solvent for the newly formed iminium salt. By keeping the salt in solution, better yields were obtained for the Vilsmeier reaction.

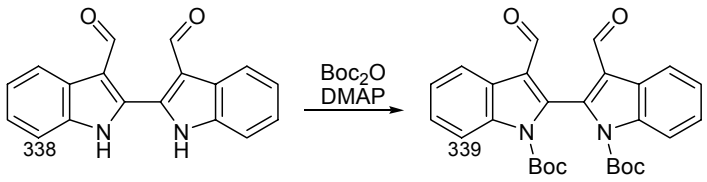
However, they also report obtaining a pale yellow solid directly from the reaction which was deemed pure by NMR. After recrystallisation from pyridine, they obtain a white solid.



In the ^{1}H NMR spectrum the NH signal is remarkably deshielded, occurring as a broad singlet at 14.94 ppm. The aldehyde signal, is located somewhat further upfield at 10.34 ppm. The aromatic protons on the benzene ring of the indole are scattered in their familiar locations. The most deshielded of these, H_e, produces a doublet at 8.01 ppm and slightly upfield at 7.69 ppm, proton H_h also produces a doublet. The remaining protons, H_f and H_g produce overlapping multiplets in the region 7.46-7.36 ppm. In the ^{13}C NMR spectrum, a deshielded signal at 185 ppm attests to the presence of the two equivalent aldehyde carbons. The remaining carbon signals are all characteristically in the aromatic region as we would expect for this compound.

5.1.4.5 *N,N'*-Di-*tert*-butylcarboxylate-2,2'-biindolyl-3,3'-dicarboxaldehyde – 339

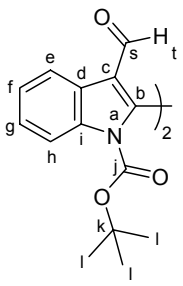
Scheme 142



The *bis*-indole **337** and its subsequently formylated analogue **338** were found to be insoluble in most solvents, and this included THF, our solvent of choice for the Boc protection. However, pleasingly, upon the addition of Boc anhydride to the insoluble 2,2'-biindolyl-3,3'-dicarboxaldehyde **338** (Scheme 142), followed by a catalytic amount of DMAP, the protection of the small amount of material in solution was very rapid, and the resulting shift in equilibrium was just as rapid. Within a few minutes, the solution was completely homogeneous and an analysis of the reaction mixture by TLC indicated that all the material had reacted.[*] After the usual workup procedure, the protected *bis*-indole **339**

[*] The unprotected *bis*-indole compounds do not move on a TLC plate using ethyl acetate/hexane mixtures and produce a distinct UV active spot on the baseline.

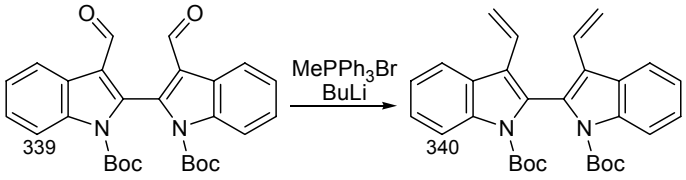
was easily purified by column chromatography affording the desired compound as a white solid. Moreover, no trace of the mono-protected analogue was observed and so the desired *N*,*N*'-di-*tert*-butyldicarboxylate-2,2'-biindolyl-3,3'-dicarboxaldehyde **339** was isolated in excellent yields as a white solid.



The presence of a large *tert*-butyl singlet at 1.26 ppm, and absence of the highly deshielded broad singlet attests to the successful protection of both indole nitrogens. As a result of the electron withdrawing nature of the Boc protecting group, protons H_h are slightly more deshielded, and this doublet is now located at 8.33 ppm. The other doublet from the aromatic indole proton H_e, has hardly moved in comparison to the unprotected analogue, now just slightly downfield at 8.44 ppm. The aldehyde proton, H_t, produces a deshielded singlet at 9.83 ppm. In the ^{13}C NMR spectrum, the presence of the carbamate carbonyl, C_j, results in a new deshielded signal at 149 ppm. Another new feature is the presence of the quaternary carbon, C_k, at 85 ppm.

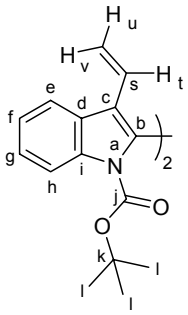
5.1.4.6 *N,N'*-Di-*tert*-butylcarboxylate-2,2'-biindolyl-3,3'-divinyl – 340

Scheme 143



In our previous Wittig reactions involving the indolo-furan and indolo-thiophene compounds, the aldehyde functionality on the indole moieties had smoothly converted to the corresponding alkene and it was the ketone functionality on the furan and thiophene that had proven to be problematic. On this *bis*-aldehyde compound **339** (Scheme 143) however, we hoped that the formation of the diene would be more easily accomplished, since we are not burdened with any ketone functionalities. Fortunately, the aldehyde groups reacted smoothly with just 1.25 equivalents of ylide per aldehyde, forming the diene **340** after 18 hours at 0 °C. The starting material was easily consumed using these mild conditions, as attested to by a single brilliantly UV active spot on the TLC plate. Moreover, unlike the indolo-furan and indolo-thiophene analogues, it was found that this

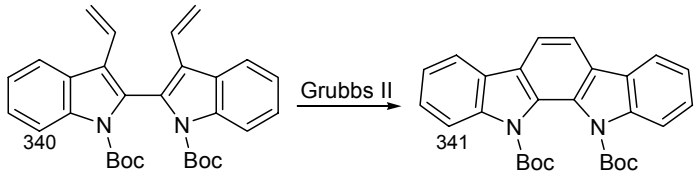
divinyl-indole could be purified by column chromatography and isolated as a clear oil - provided it was kept cool, thereby facilitating limited characterisation. In this manner, the divinyl *bis*-indole **340** was obtained in quantitative yields as a clear oil.



The presence of three signals in the midfield region of the ^{1}H NMR spectrum is confirmation that the alkene is present – and moreover, once again the spectrum correlated to only one indole moiety, indicating that the new molecule is symmetrical and that the Wittig reaction had taken place on both aldehydes as desired. Due to the loss of the aldehyde, the most deshielded signal is now the doublet from protons H_h, at 8.40 ppm. Slightly upfield of this the other indole doublet is located at 7.92 ppm, produced by proton H_e. The remaining indole protons, H_g and H_f produce multiplets in the regions 7.44-7.38 ppm and 7.36-7.30 ppm respectively. The alkene protons produce three separate signals: The most deshielded of these is a doublet of doublets at 6.46 ppm resulting from proton H_t, with coupling constants of 17.97 Hz and 11.63 Hz as a result of *trans* coupling to H_v and *cis* coupling to H_u respectively. Slightly upfield of this signal at 5.74 ppm, proton H_v produces a doublet of doublets with coupling constants 17.97 Hz, as a result of coupling to H_t, and a tiny geminal coupling constant of just 1.11 Hz, coupling to H_u. Similarly, proton H_u produces a doublet of doublets at 5.26 ppm with coupling constants 11.63 Hz and 1.12 Hz, as a result of coupling to H_t and geminal coupling to H_v.

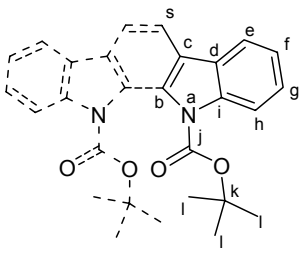
5.1.4.7 Di(*tert*-butyl) indolo[2,3-*a*]carbazole-11,12-dicarboxylate – 341

Scheme 144



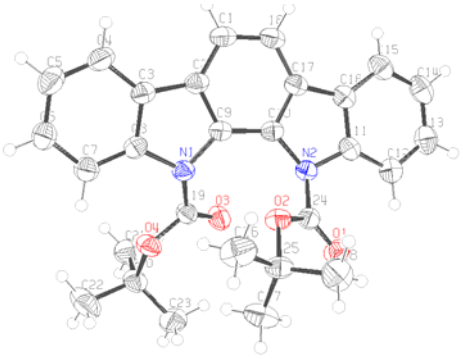
Having successfully completed the Wittig reaction, and with the diene safely in hand, a metathesis reaction was all that we required to form the desired indolocarbazole system **341** (Scheme 144). To this end, the diene **340** was dissolved in toluene and the solution was thoroughly degassed by bubbling Ar below the surface of the liquid for 10 minutes. Finally, 5 mole % of Grubbs II catalyst was added and the solution was stirred at room

temperature under Ar. Disappointingly, analysis of the reaction mixture by TLC after 1 hour indicated that no reaction was taking place and once again it seemed as though the indole-based substrate was proving to be resistant to the metathesis reaction. The reaction mixture was heated to 80 °C and after 1 hour, TLC analysis clearly indicated that the starting material was being consumed and a new compound was forming. The reaction was thus left to proceed under Ar at 80 °C for 18 hours. After this time, TLC analysis indicated that a small amount of starting material still remained and so another 5 mole % of Grubbs II catalyst was added and the reaction was given another 4 hours to react at 80 °C. Eager to confirm that the new spot was indeed the desired product, the reaction was then concentrated and purified by column chromatography even though TLC analysis indicated that a small amount of starting material was still present. This new compound was indeed the desired indolocarbazole **341** and was isolated and recrystallised affording a white crystalline material. As expected, not all of the diene had reacted and this remaining starting material was isolated as well. Overall, a 63% yield was obtained for the desired indolocarbazole or, if one takes into account the recovered starting material, a 74% yield was obtained.



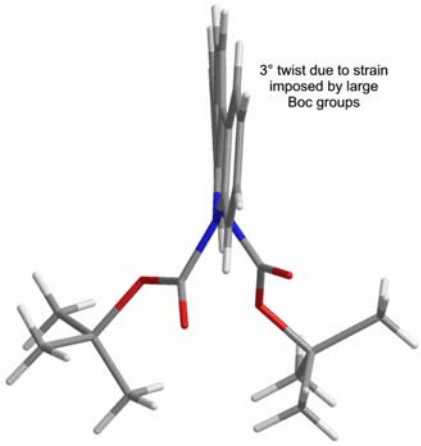
In the ^{1}H NMR spectrum, a new singlet produced by aromatic proton, H_s, and the doublet produced by proton H_e, overlap in the region 8.04-8.01 ppm. The most deshielded proton, H_h, produces a doublet at 8.27 ppm. Protons H_g and H_f produce multiplets and these signals are found at 7.51-7.46 ppm and 7.41-7.36 ppm respectively. Finally, the large *tert*-butyl singlet is in its usual region at 1.63 ppm. In the ^{13}C NMR spectrum, the expected twelve signals are observed. The most deshielded carbon signal is also a quaternary carbon and can be easily assigned to the carbonyl of the carbamate, C_j. Finally, the only quaternary carbon in the midfield region of the spectrum can be assigned to the *tert*-butyl carbon, C_k. Analysis by high resolution mass spectroscopy revealed an observed mass of 456.2011 amu, in good agreement with the expected mass of 456.2049 amu.

Figure 42



The wonderful crystalline nature of this compound rendered it amenable to analysis by X-ray crystallography (Figure 42). To this end, the material was easily recrystallised from ethyl acetate-hexane affording clear needle-like crystals. The crystallographic analysis of this structure afforded an excellent goodness of fit of 0.963 and an R factor of 5.5%. The space group of this compound was found to be monoclinic, P2(1)/n.

Figure 43



Some interesting features observed in the crystal structure include the fact that the bulky Boc protecting groups apply a significant amount of ring strain on the indolocarbazole skeleton (Figure 43). This structure, which is normally quite planar (as in for example Rebeccamycin and Staurosporine) now possesses a 3° twist across the structure. As one would expect, the bulky Boc protecting groups are arranged pointing away from each other, mostly facilitated by an inverse arrangement of the trigonal planar geometry of each of the indole nitrogen atoms.

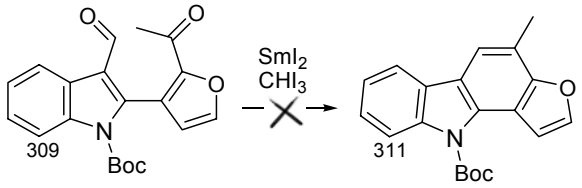
5.2 OFF THE BEATEN TRACK – REACTIONS CONDUCTED OUT OF INTEREST OR REACTIONS NOT LEADING ANYWHERE

As in any linear synthesis, one is often presented with unexpected results that might be worth investigating further. Or indeed, as a planned synthesis progresses one often comes up with new ideas that deviate slightly from the envisaged route and these ideas are often explored. In the preceding three subsections, the total synthesis of furostifoline, its thio analogue, thiofurostifoline and the indolocarbazole core were presented. However, during the course of the respective syntheses other reactions were investigated which either failed to produce significant results or ultimately led to a dead end. So as not to distract the reader with all sorts of sundry reactions these were not presented in the three previously discussed syntheses. However, for completeness, a select few ideas which were investigated shall be presented here.

5.2.1 *En route* to furostifoline and thiofurostifoline

5.2.1.1 Attempted coupling of the carbonyl moieties by means of a samarium diiodide mediated reaction

Scheme 145



The samarium mediated version of the McMurry coupling is a well known reaction and is often preferable to the McMurry coupling in that the reaction is somewhat milder and more tolerant of sensitive functional groups.[112] Although at this stage in our synthetic strategy we intended to facilitate the cyclisation using the metathesis route, it nevertheless seemed a waste not to at least attempt several carbonyl coupling reactions in the hope that we may find a shorter route to the furanocarbazole and thiophenylcarbazole systems. Thus we initially investigated the samarium mediated coupling reaction (Scheme 145).

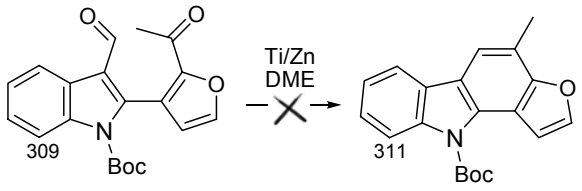
Samarium mediated couplings of indole-carbaldehydes are not well precedented and this did not bode well for our intended coupling. Nevertheless, the samarium diiodide solution

needed for this reaction was prepared from samarium metal and triiodomethane in THF. Although several methods for preparing samarium diiodide were investigated we found that the addition of triiodomethane to samarium metal in dry and thoroughly degassed THF, followed by ultrasonic agitation of the solution conveniently afforded the deep blue solution required for our reaction.

At the first attempt of the reaction, the dicarbonyl compound **309** (Scheme 145), also in dry and thoroughly degassed THF was added dropwise to the samarium diiodide solution and the deep blue colour soon disappeared once all the indolo-furan had been added. However, disappointingly, analysis of the reaction mixture by TLC at this point indicated that only baseline material was present and so not surprisingly, no useful compounds were isolated from this reaction, not even traces of starting material. In the hope that perhaps the addition of the indolo-furan **309** to the samarium solution resulted in too large an excess of samarium initially, the reaction was repeated with the reverse order of addition. Thus, a deep blue samarium diiodide solution was prepared as described before and this solution was cannulated into a dropping funnel and added dropwise to **309**. As each blue drop fell into the reaction mixture the colour rapidly disappeared, an indication that the samarium diiodide was indeed reacting with the starting material. Once half the samarium had been added, the reaction mixture was analysed by TLC and disappointingly all that was observed was some starting material and a large spot on the baseline. Nevertheless, the samarium solution was added slowly until the all of the indolo-furan **309** had reacted. At this point, analysis of the reaction mixture by TLC indicated that only baseline material was present. Just for good measure, the reaction was then heated to reflux for 1 hour in the hope that magically, the desired carbazole would somehow spring to life from the baseline mess that could be observed on the TLC. This of course, did not happen.

5.2.1.2 Attempted McMurry coupling of the indolo-furan dicarbonyl compound

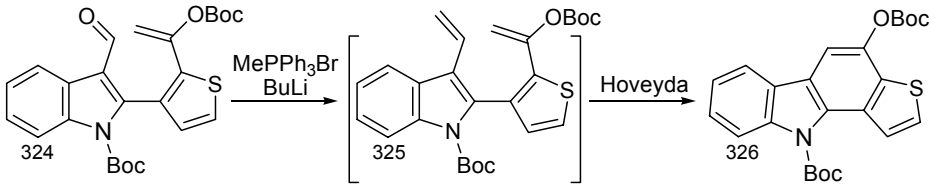
Scheme 146



Having found a not-so-useful method of rapidly destroying indole compounds using samarium, we next decided to investigate the more traditional method for carbonyl coupling, the McMurry reaction (Scheme 146).[113] In this particular case, the preparation of the required Ti^0 was achieved by reduction of $TiCl_4$ using activated Zn dust in DME, prior to the addition of the indolo-furan starting material **309**. During this process, a wonderful sea-blue colour was observed once the $TiCl_4$ was added to the Zn, and then the DME was heated to reflux according to the procedure by Coe and Scriven.[113] Once the reduction was complete, the solution was cooled to -10 °C and the indolo-furan was added in one portion and the solution was again heated to reflux for 2 hours. Analysis of the reaction mixture revealed a multitude of new compounds. Clearly, the powerful Lewis acid had proven to be rather too much for the indolo-furan and the second method for rapid destruction of our precious material had just been uncovered.

5.2.1.3 Carbazole formation by metathesis from inadvertently prepared *tert*-butyl 2-(2-(1-(*tert*-butoxycarbonyloxy)vinyl)thiophen-3-yl)-3-formyl-1*H*-indole-1-carboxylate

Scheme 147



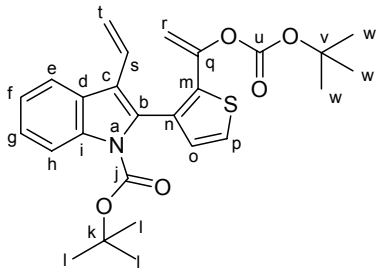
Previously, we discussed an inadvertent preparation of trapped enol **324** as a result of adding too much Boc anhydride to *tert*-butyl 2-(2-acetylthiophen-3-yl)-3-formyl-1*H*-indole-1-carboxylate **317** (Scheme 130). Although at the time this seemed to be a rather annoying error it did however present us with an interesting variation on the thiofurostifoline compound we had in mind. If we could carry out a similar metathesis reaction on this compound we would have found a convenient way of preparing the oxygen substituted analogue of thiofurostifoline **326** (Scheme 147) as opposed to the methyl version. Moreover, as discussed previously, during the Wittig step, it is the ketone that is resistant to olefination and this requires a large excess of ylide, leading to losses in yield. However in this particular case, the 'ketone' has already been converted to an alkene as it is in the form of the trapped enol. Thus, all we would need from the Wittig reaction is the

conversion of the aldehyde **324** to the olefin **325** and this reaction should not pose a problem. We would then be in a position to carry out a metathesis reaction.

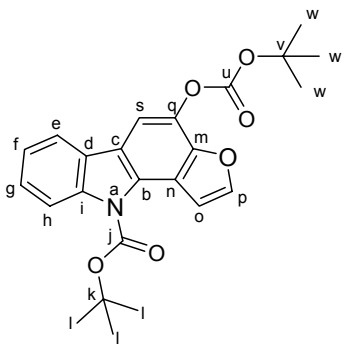
Consequently, the methyl ylide was generated as before by treating methyl triphenylphosphonium bromide with *n*BuLi forming a yellow solution and this solution was cannulated into a dropping funnel. This ylide solution was added dropwise to **324**, dissolved in THF and at 0 °C. The reaction was carefully monitored by TLC after each small addition of ylide solution and as soon as all the starting material had been converted the reaction was quenched by the addition of ice cold water. Since these dienes were previously found to be very unstable we once again adopted the technique of avoiding concentrating the reaction mixture completely. Thus, the crude diene solution **325** was concentrated to 20% of its original volume and then adsorbed onto silica gel and quickly purified by column chromatography. The fractions containing the diene were then collected and once again concentrated to about 20% of the original volume and finally, the solution was diluted with toluene and concentrated again. Toluene was in fact added three times and the solution concentrated to 20% of the original volume after each addition, in this way driving off the lower boiling solvents, ensuring that the diene was dissolved in toluene only. This entire process, including the Wittig reaction was performed in the absence of sunlight, and with minimal lighting in the laboratory.

With the diene in toluene, the metathesis part of the two step process could be attempted. Since the Hoveyda-Grubbs catalyst had proven useful in the synthesis of furostifoline, we decided to use it in this reaction as well. Thus, 5 mole % of the catalyst was added and the solution was immediately heated to 80 °C. TLC of the reaction mixture 1 hour later indicated that a new product was forming and so the reaction was left to proceed for another 5 hours. After this time, is appeared that the reaction was not progressing any further even though some starting material still seemed to be present and so another 5 mole % of Hoveyda catalyst was added and the reaction mixture was left to react for 18 hours at 80 °C. Analysis of the reaction mixture indicated that a small amount of the diene still seemed to be present but nevertheless, the reaction mixture was concentrated and purified by column chromatography. Two products were isolated, and disappointingly, both were in very small amounts. As expected, the one compound was indeed the diene, as the metathesis reaction had not gone to completion. The other compound was the desired

carbazole **326**, however, only 17 mg of this compound was isolated from the two step reaction corresponding to a dismal 9% yield. An interesting point to note though is that fact that we were able to isolate the small amount of unreacted diene **325**. In the previous cases with compounds of this type, the diene spontaneously underwent an electrocyclisation reaction affording the cyclobutane derivative as previously discussed.



The presence of a new double doublet at 6.46 ppm, and the loss of the highly deshielded singlet formerly at 9.67 ppm confirmed that the aldehyde had been converted to the alkene as planned. Proton H_s, now in quite a different environment couples to the new protons H_t, forming a double doublet with coupling constants of 18.0 Hz and 11.7 Hz. Fortunately, the two alkenes produced signals that did not overlap and so comparison of the coupling constants for protons H_t and H_r allowed for unambiguous assignment of these signals. It was found that H_t *trans* to H_s was the most deshielded of these four signals, producing a doublet at 5.71 ppm with the slightly larger coupling constant of 17.9 Hz. Its geminal partner, H_t *cis* to H_s was attested to by the presence of a slightly more upfield doublet at 5.26 ppm and having a coupling constant of 11.8 Hz. Unfortunately, the small coupling one would normally expect to see between these two geminal H_t protons was not observed. However, this phenomenon was observed for the protons H_r on the more substituted olefin. It is assumed that the slightly more deshielded of these two doublets would be H_r *trans* to the oxygen of the carbonate, found at 5.05 ppm and having a small geminal coupling constant of 2.6 Hz. Its geminal partner, *cis* to the carbonate is slightly upfield at 4.91 ppm with a coupling constant of 2.5 Hz. As for the remaining protons, the signals are all in their familiar locations with perhaps the exception being a second, slightly more deshielded large singlet in the upfield region at 1.32 ppm – a reminder of the second Boc group.

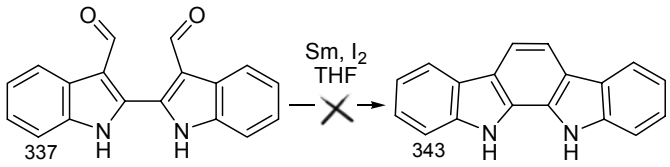


The formation of the carbazole results in a considerably less complicated spectrum as compared the diene precursor. The two most deshielded signals, belonging to H_p and H_h once again overlap in the region 8.17-8.14 ppm. A clear indication that the metathesis reaction has proceeded is the presence of the new aromatic singlet at 7.83 ppm, corresponding to H_s. Proton H_e produces a doublet at 8.00 ppm, and protons H_g and H_f produce triplets at 7.46 ppm and 7.38 ppm respectively. Interestingly, although these protons generally produce multiplets (as one would expect) once the carbazole is formed these signals appear as triplets and this same phenomenon was observed for thiofurostifoline. Finally, the remaining thiophene proton, H_o produces a doublet at 7.51 ppm. Unambiguous assignment of the two large upfield singlets corresponding to the *tert*-butyl protons H_w and H_l was done by comparison of this spectrum to that obtained for the closest analogue to this compound, thiofurostifoline, which similarly possesses the *N*-Boc but contains a methyl at the 4-position of the carbazole instead of the second Boc functionality. In thiofurostifoline protons H_l produced a singlet at 1.76 ppm. For compound **326**, two *tert*-butyl signals are located at 1.78 ppm and 1.48 ppm. Therefore, the signal at 1.78 ppm is assigned to the protons H_l and the signal at 1.48 ppm is assigned to H_w.

5.2.2 The indolo-carbazole series of compounds

5.2.2.1 Attempted coupling of the carbonyl moieties utilising a samarium diiodide mediated reaction

Scheme 148



A samarium mediated carbonyl coupling was also attempted on the *bis*-indole carbaldehyde **337** (Scheme 148). In light of the fact that the Boc protecting groups may have interfered in the previously attempted samarium reaction (Scheme 145), the reaction was attempted on the unprotected *bis*-indole **337** in the hope of obtaining indolocarbazole

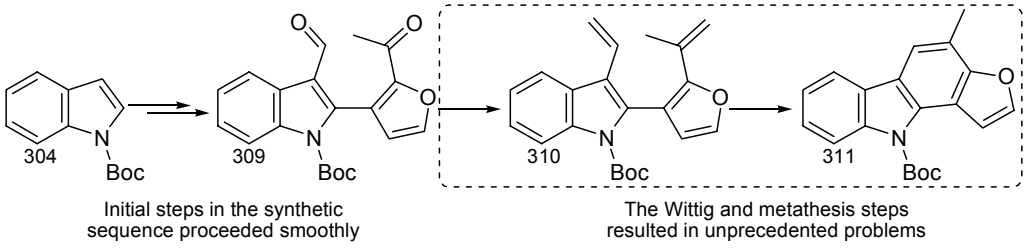
343. To this end, a samarium diiodide solution was prepared by adding iodine to samarium metal in THF and subjecting the heterogeneous mixture to ultrasonic agitation for 0.5 hour. During this time, the solution became deep blue in colour. The samarium solution was then cannulated into a dropping funnel and added slowly to a dilute solution of the *bis*-indole **337** in THF. Unfortunately, analysis of the reaction mixture revealed a multitude of decomposition products.

5.3 CONCLUDING REMARKS PERTAINING TO THE SYNTHESIS OF VARIOUS CARBAZOLES

Our initial intention to synthesise the indolocarbazole core and furostifoline using the light mediated approach unfortunately did not proceed as we had hoped it would. As was discussed previously, the reason for this is no doubt due to the lack of any suitably acidic protons in a benzylic-type position on our indole precursors. However, since we had developed successful synthetic sequences leading up to the precursors for the light mediated reaction we did not wish to discard all this work and therefore sought an alternative method whereby we could still obtain the desired carbazoles, yet continue to employ a similar synthetic strategy. To this end, metathesis seemed a viable option.

In the synthesis of furostifoline, the sequence of steps leading up to the metathesis reaction proceeded as planned (Scheme 149). However, the final two steps which involved the conversion of both carbonyls to olefins followed by metathesis were fraught with unprecedented problems.

Scheme 149



These problems consist of three major incidents over these two final steps in the conversion of the carbonyls to the corresponding to olefins using the Wittig reaction, and then metathesis of the diene to obtain the desired carbazole. In the Wittig reaction, it was

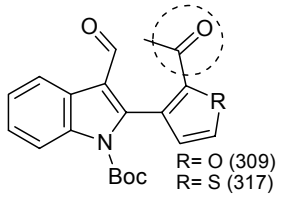
found that the aldehyde functionality rapidly converted to the desired olefin, using just over one equivalent of the methyl ylide. However, the ketone attached to the furan resisted olefination and had to be forced by the addition of up to ten equivalents of ylide. Unfortunately, these basic conditions also facilitated the deprotection of the vital electron withdrawing Boc protecting group. Since the aldehyde on the indole had already converted to the alkene, this unprotected vinyl indole rapidly polymerised leading to diminished yields. However, usually, the reaction did produce some of the diene with the indole nitrogen's Boc group still in place, and it is here that the second problem came to the fore. Complete evaporation of the solvent containing the diene led irreversibly to the cyclobutane adduct, no doubt via a π_8 electrocyclisation followed by an irreversible π_6 electrocyclisation reaction. Although these electrocyclisation steps ultimately lead to a strained cyclobutane adduct, the reestablishment of the aromaticity of the indole as well as the furan ring systems renders the π_6 electrocyclisation irreversible. To some extent, this problem could be overcome provided the diene was never fully concentrated. Solvation of the molecule seemed to inhibit at least the second irreversible π_6 electrocyclisation reaction. This of course did mean that a solvent exchange process was required to perform the metathesis reaction – and it is in this reaction where the third problem arose. The indolo-furan diene seemed virtually unreactive in the presence of the Grubbs II metathesis catalyst and the reaction had to be forced to proceed by the addition of the Hoveyda-Grubbs catalyst, as well as by raising the reaction temperature to 90 °C. In light of the fact that the indolo-thiophene diene, and the *bis*-indolo diene did not exhibit this final metathesis problem led us to the conclusion that perhaps the nearby oxygen on the furan is capable of co-ordinating with the ruthenium catalysts, adversely affecting the reaction. Another effect of the oxygen on the furan could be the withdrawing of electron density from the adjacent alkene, which would also impede the metathesis reaction Sadly, the combination of these three problems over the final two steps led to furostifoline being obtained in only a very poor yield.

The synthesis of the thio-analogue of furostifoline also proceeded smoothly right up to the point of performing the Wittig and metathesis reactions. Regarding the Wittig reaction, the same problems were encountered in terms of the thiophene ketone resisting olefination, leading to deprotection and diminished yields as well as the fact that having obtained some of the diene, evaporation of the solvent resulted in the same π_8-π_6 electrocyclisation

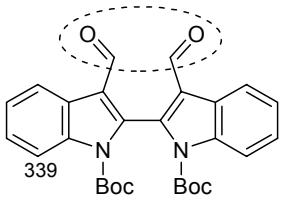
reactions. However, by working very carefully, a modest amount of the diene could be obtained. What is interesting is that the metathesis reaction on this particular compound proceeded wonderfully using the Grubbs II catalyst. Even at room temperature the formation of the desired carbazole occurred readily once again reinforcing the belief that in the case of furostifoline, the metathesis reaction was being hampered solely as a result of the oxygen in the furan, as this is the only difference in functionality between these two compounds. Thus, regarding the thio-analogue of furostifoline, the effect of having to deal with only two problems over the last two steps resulted in a drastically improved yield of the desired carbazole.

Finally, regarding the synthesis of the indolocarbazole from the *bis*-indole, we were very pleased to discover that none of the recently discussed three problems occurred over the last two steps. As far as the Wittig reaction is concerned, this particular compound differed from furostifoline and thiofurostifoline in that the *bis*-indole contained two aldehyde functional groups, as opposed to an aldehyde and the troublesome ketone (Figure 44). Conversion of the aldehydes to the corresponding olefins proceeded smoothly and required just over one equivalent of ylide per aldehyde.

Figure 44



The precursors to furostifoline and its thio-analogue contain the troublesome ketone

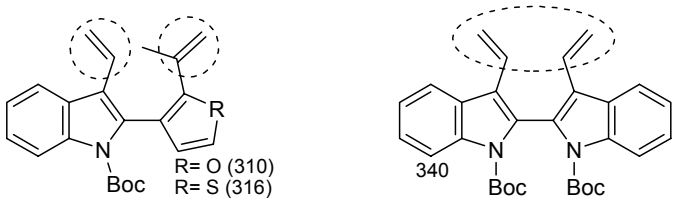


The Wittig reaction proceeded smoothly on on the *bis*-indole which contained only aldehydes

Moreover, the second problem, being that of the π_8-π_6 electrocyclisations following the formation of the diene was simply not observed for the *bis*-indole **340** (Figure 45) and in fact, not only could this diene be concentrated to neat, but limited characterisation was possible provided the diene was kept relatively cool. In theory, the *bis*-indole diene should be able to undergo exactly the same π_8-π_6 electrocyclisations as was observed for the indolo-furan **310** and indolo-thiophene **316**. A possible reason for the stability of the *bis*-indole diene may be have something to do with the symmetry of the molecule, rendering both alkenes electronically equivalent. In the case of the indolo-furan and indolo-thiophene

dienes, this is not the case and a difference in the electronics of alkenes may be the driving force starting the reaction, with the more electron rich alkene attacking the less electron rich alkene.

Figure 45



Non-equivalent alkenes

Symmetry in the *bis*-indole - alkenes equivalent

Finally, with no nearby oxygens to hamper the metathesis reaction, the formation of the desired carbazole from **340** was easily accomplished using the Grubbs II catalyst. However this reaction required heating to 80 °C before it proceeded. No doubt, this is simply due to the larger steric demands imposed by two bulky Boc groups which are required to come into close proximity for the metathesis reaction to occur – forming the carbazole system.

In summary, using metathesis several interesting carbazole systems were synthesised. However, the problems pertaining mainly to the stability of the indolo-furan and indolo-thiophene dienes requires some attention. Perhaps the Boc protecting group is not the best option in this case and a more robust protecting group should be employed to survive the rather harsh conditions involved in the Wittig reaction.[*] However, it is important to bear in mind that this new protecting group should also be significantly electron withdrawing so as to stabilise the vinylic indole once it has formed. To this end, perhaps the use of a tosylate protecting group may be a good choice.

[*] Although not discussed in this thesis, the Tebbe reaction was also attempted on the indolo-thiophene **317** as an alternative method to synthesis the required diene – unfortunately, this reaction was not successful and only led to decomposition of the starting materials.

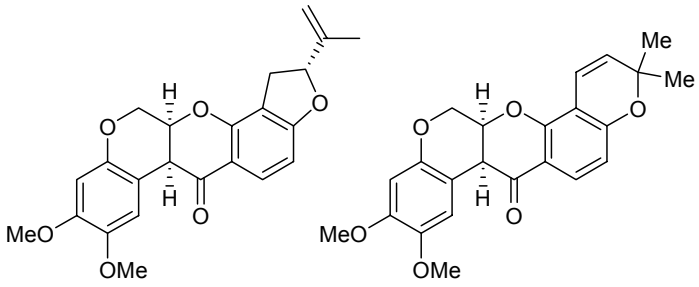
CHAPTER 6 – BENZOFURAN BASED NATURAL PRODUCTS

6.1 ASYMMETRIC SYNTHESES OF TWO BENZOFURAN COMPOUNDS AS VALUABLE ROUTES TOWARDS THE SYNTHESIS OF SEVERAL NATURAL PRODUCTS

6.1.2 Towards the synthesis of rotenone – a collaborative study

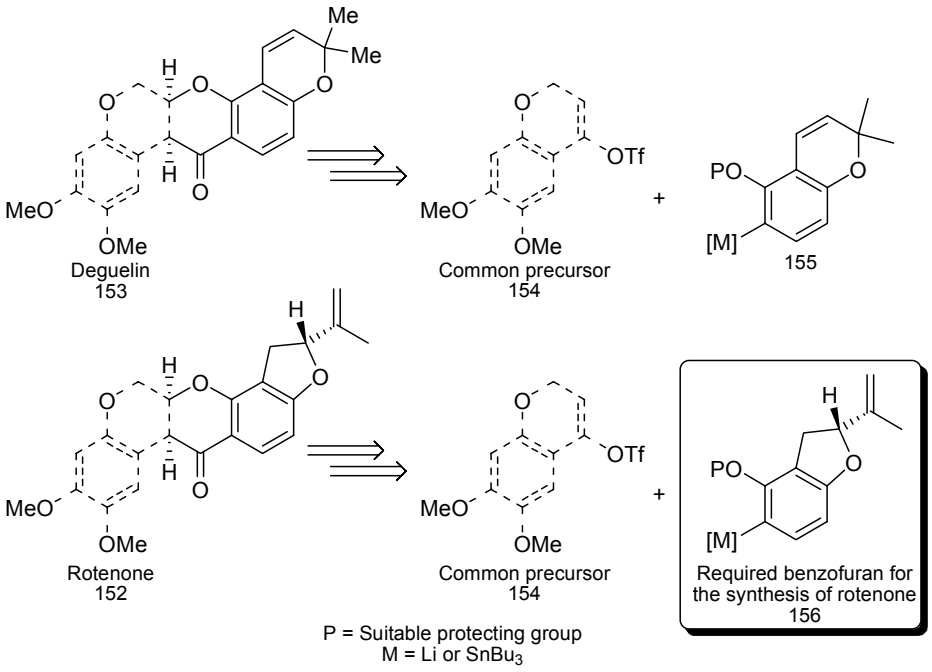
As part of a collaboration between ourselves and the University of Köln, a project was initialised in order to synthesise the rotenoid, rotenone **152** (Figure 46). In the approach towards the synthesis of rotenone, we hoped to capitalise on existing work being done in the Köln laboratories towards the synthesis of a similar compound, deguelin **153**.[114]

Figure 46



Rotenone and deguelin share a common dimethoxychroman moiety **154** (Scheme 150) and differ only in that deguelin contains a benzopyran moiety **155** rather than the benzofuran moiety **156** of rotenone. Moreover, in their approach toward deguelin, Schmalz *et al*. envisaged a convergent procedure whereby the chroman and benzopyran moieties would be synthesised separately, and then appropriately coupled *en route* to the desired product. This same approach was envisaged to be useful for the synthesis of rotenone and since Schmalz *et al*. were already developing methodology to synthesise the appropriate common chroman **154** for their deguelin work, we undertook to develop a viable synthesis of the remaining moiety, the chiral benzofuran unit **156**.

Scheme 150



An envisaged disconnection to synthesise rotenone employing a common precursor

6.1.3 Asymmetric synthesis of the required chiral benzofuran - a rotenone precursor

6.1.3.1 Outline of the synthetic strategy

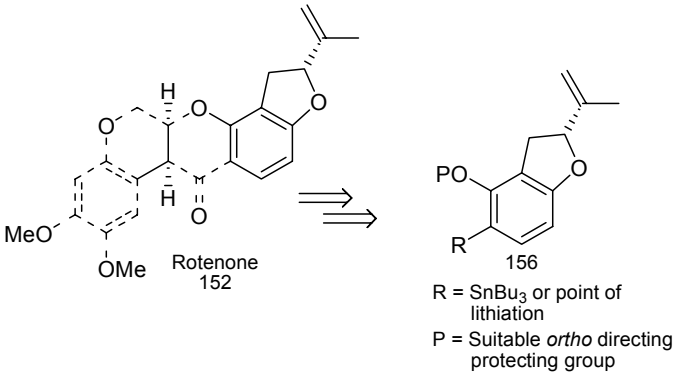
In our approach towards this benzofuran unit we hoped to utilise methodology developed by Trost to asymmetrically cyclise an appropriately substituted phenol, thereby affording the required benzofuran **156**. Although the asymmetric Trost methodology has been thoroughly explored for the synthesis of chiral chromans,[92] to our knowledge, its use in the synthesis of chiral benzofurans has not previously been reported.

As a synthetic target, there were two main requirements that we needed to consider in planning our synthesis of the benzofuran compound if it were to be a suitable precursor for rotenone. Obviously, the introduction of the required stereogenic centre, in good enantiomeric excess was essential. However, once synthesised, the chiral benzofuran moiety would need to be attached to the chroman **154** which Schmalz *et al*. were busy synthesising. It was envisaged that this attachment could be accomplished using one of two methods: As one approach, a Pd mediated carbonylative coupling could be employed

between the two units, which would simultaneously introduce the required carbonyl functionality. In order to facilitate this reaction, our chiral benzofuran unit **156** would require a tributyl tin functional group at the 5-position (Scheme 151). Alternatively, the chroman unit could be modified to form the Weinreb amide, then the addition of the chiral benzofuran could be achieved after appropriate lithiation of the benzofuran moiety **156**, also at the 5-position. Moreover, the ethereal oxygen in the pyranone ring system in rotenone **152** would have to be incorporated into the benzofuran synthesis, as it could not be introduced as part of the chroman moiety.

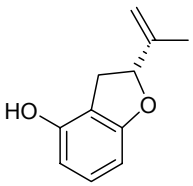
The requirement for the extra oxygen functionality in the benzofuran is actually rather fortuitous as this allows for the synthesis of either the tin-substituted benzofuran moiety, or allows for appropriate lithiation to facilitate addition to the Weinreb amide. The reason for this is that we could plan to synthesise the appropriate benzofuran with the oxygen in the 4-position, as required, and then suitably protect this oxygen with an *ortho* directing group facilitating either the synthesis of the correct tin adduct, or simply, *ortho* lithiation on its own and addition of the chroman moiety as the Weinreb amide should result in the coupling of the two critical moieties.

Scheme 151



Thus, our target as a suitable rotenone precursor needed to be *(R)*-2-isopropenyl-2,3-dihydrobenzofuran-4-ol **247** (Figure 47).

Figure 47



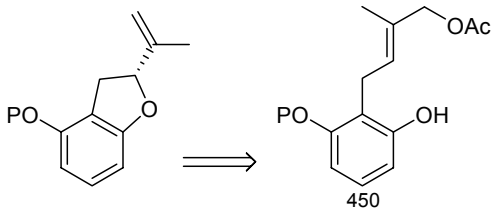
247

6.1.3.2 A planned synthesis of *(R)*-2-isopropenyl-2,3-dihydrobenzofuran-4-ol – a disconnection approach

In our retro-synthetic strategy for the desired chiral benzofuran, there were two main features we needed to keep in mind: Firstly, we wished to utilise an asymmetric Trost-type cyclisation to form the chiral benzofuran and secondly, the final compound would need to have the required oxygen functionality in the 4-position.

For the Pd π-allyl mediated cyclisation, we required exclusively the *trans* allyl-acetate compound **450** (Scheme 152) where nucleophilic phenolic attack onto the intermediate chiral Pd π-allyl complex would afford the desired benzofuran as a single enantiomer.

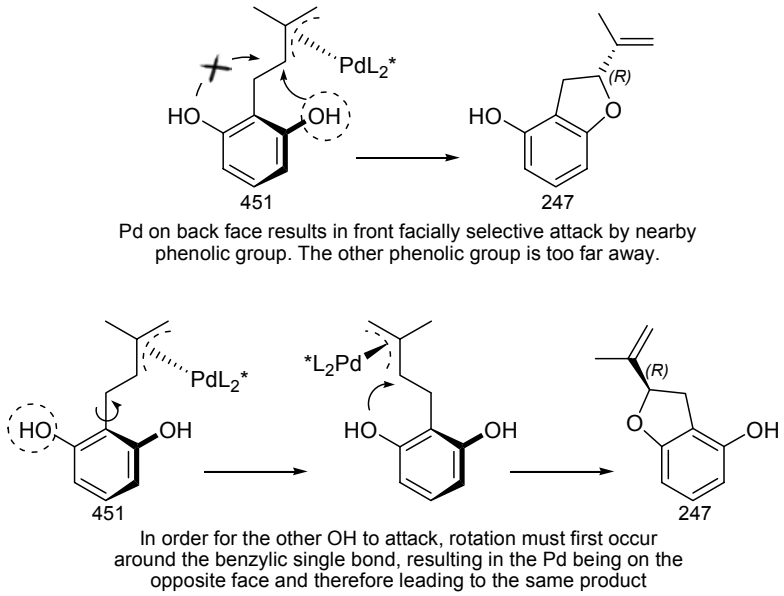
Scheme 152



450

At this point, we needed to plan the introduction of the extra oxygen functionality. After some consideration, it became clear that a precursor of the type **451** (Scheme 153), where both phenolic moieties in the unprotected form would still result in the same desired product. Either phenolic group could act as the nucleophile and we would still only obtain one enantiomer in light of the fact that the π-allyl Pd complex would have to rotate around the benzylic single bond if it were to react with the 'other' phenol group. Thus, attack from the other phenol would not result in an inversion of stereochemistry as rotation about the benzylic single bond to facilitate the attack would also result in the π-allyl Pd complex being on the opposite side to its original position, leading to the same product.

Scheme 153



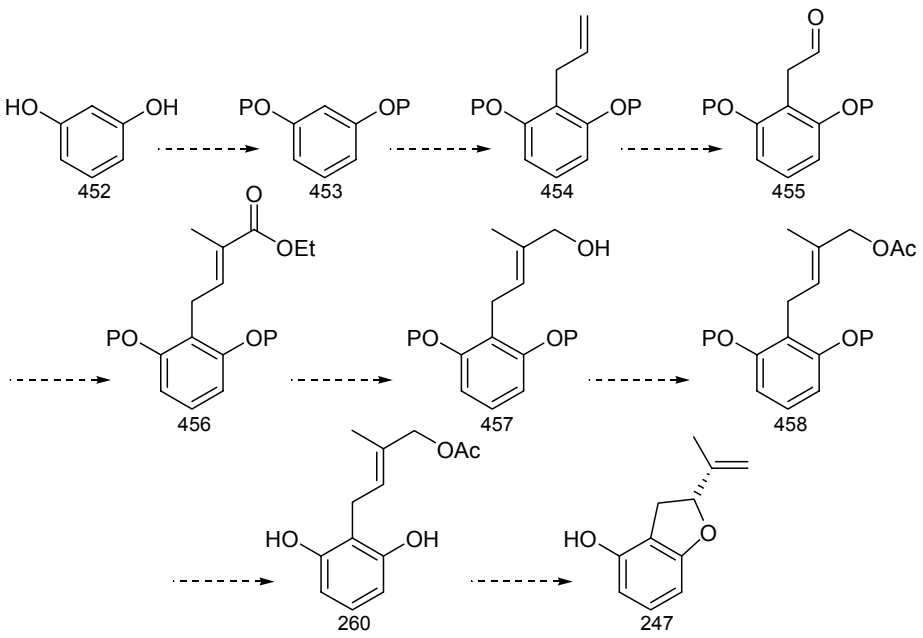
The fact that either phenol could attack and still lead to only one enantiomer has an enormous implication on our synthesis in that we would not need to differentiate between the phenolic substituents. To differentiate between these two phenols would introduce complications as two different protecting groups would have to be introduced at the outset and this would not only lead to extra steps in the synthesis, but the selective protection of one hydroxyl group would not be efficient, and this would result in poor yields right at the outset of the synthesis. It also meant that we would not have to introduce the second phenol later in the synthesis. In fact, the two phenol functionalities could be present from the start. We envisaged that we could start our syntheses from readily available resorcinol.

Thus, with a suitable starting material in mind, a synthetic pathway was planned (Scheme 154). Firstly, resorcinol **452** would need to be suitably protected **453** and although it would not be necessary to differentiate between the protecting groups on the two alcohols, the choice of a suitable protecting group would still require some thought. The reason for this is that the second step in the synthesis would make use of the 1,3-diol functionality to introduce an allyl moiety at the 2-position **454** of the benzene ring and so suitable *ortho* directing protecting groups would need to be employed. However later in the synthesis, prior to the Pd π-allyl cyclisation, the protecting groups on the phenols would need to be cleaved in order to facilitate the furan ring formation. In light of the fact that at this point

we would also have an allyl acetate present which we would need to keep intact, acid cleavage of the phenolic protecting groups would not be an option. In fact, the choice of protecting groups warrants a small discussion in this PhD, this will be done after discussing our synthetic strategy. In continuation – with the allyl group in place and the phenols still protected, we envisaged that we could obtain our required *trans* allyl-acetate functionality using a Horner-Wadsworth-Emmons reaction. Therefore, to facilitate this we would need to convert the allyl group into an aldehyde **455** by ozonolysis and then the envisaged modified Wittig-type reaction with an appropriate phosphonate should afford exclusively the *trans* ester **456**.[115,116] Reduction of this ester to the alcohol **457** and conversion to the *O*-acetate **458** would almost put us in a position to carry out the chiral π-allyl Pd cyclisation, and it is here that the sequence could become somewhat tricky. At this point, we would need to remove the protecting groups from the two phenolic functionalities without cleaving the *O*-acetate, thereby forming **260**, as the acetate is required to be present for the subsequent Pd π-allyl cyclisation. The protecting groups on these two phenolic hydroxyls must also be able to facilitate *ortho*-lithiation at the start of the synthesis, and so this would rule out benzyl protecting groups for example.[*] Therefore, the only logical choice would be to employ silyl protecting groups as these could be removed using TBAF. However, their stability in the presence of *n*BuLi would have to be investigated as well as their effect on the initial allylation which required that the *O*-silyl groups act as *ortho* directors.

[*] In addition, removal of these benzyl protecting groups under hydrogenation conditions may result in problems regarding the stability of the *trans* alkene, required for the π-allyl palladium cyclisation

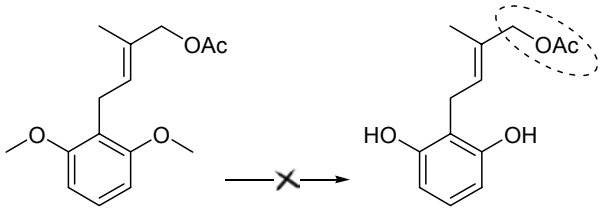
Scheme 154



A planned synthesis for the required *R*-benzofuran

It should also be mentioned that we initially began our synthetic investigations using methoxy protecting groups and although these protecting groups worked superbly as *ortho* directors, this route came to an abrupt halt as their removal at the allyl-acetate stage proved to be problematic (Scheme 155). Although several methods were investigated to cleave these groups using Lewis acids such as BBr_3 and $AlCl_3$, the acetate never survived these reactions and so the most obvious choice of protecting group proved rather unhelpful. In light of the fact that this synthetic route did not lead to the desired product, its detailed discussion has been omitted from this thesis.

Scheme 155

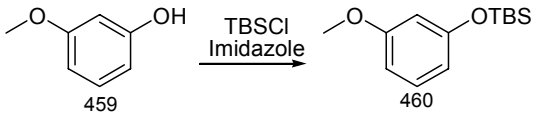


Initial investigations employing methoxy protecting groups for the phenolic hydroxyls revealed that they could not be cleaved without also destroying the required acetate

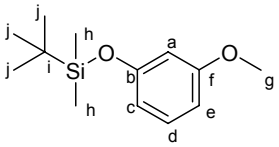
Therefore, at the outset, an investigation into the most effective phenolic protecting group was of the utmost importance.

6.1.3.3 Synthesis of *tert*-butyl(3-methoxyphenoxy)dimethylsilane – 460

Scheme 156



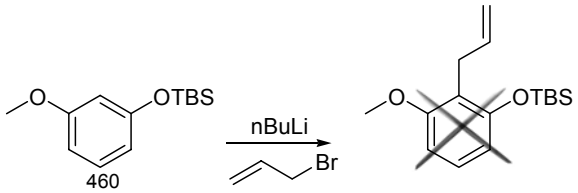
As part of an initial model study to investigate the ability of the *tert*-butyldimethylsilyl protecting group to act as an *ortho*-director for the envisaged lithiation reaction, we decided to protect readily available 2-methoxyphenol **459** (Scheme 156). To this end, **459** was dissolved in acetonitrile and treated for 18 hours with TBSCl and imidazole. As expected the reaction proceeded smoothly and after purification, the silyl protected analogue **460** was obtained in an excellent yield as a clear oil.



In the ^{1}H NMR spectrum the presence of a large singlet at 1.03 ppm and another at 0.24 ppm attests to the presence of the TBS protecting group and these signals correspond to the *tert*-butyl group, H_j, and the equivalent methyl protons, H_h, respectively. The signal for the protons on the methoxy substituent H_g, is located further downfield at 3.80 ppm. As for the protons on the aromatic ring, only H_d can be assigned without ambiguity based upon the ^{1}H NMR and ^{13}C NMR spectra alone. This proton produces the most deshielded signal, located at 7.14 ppm and strangely, even though the ring is not symmetrical, protons H_c and H_e are in such similar chemical environments that H_d produces a perfect triplet. Unfortunately, although one would expect H_a to also be easily identifiable, its singlet is seemingly buried beneath another multiplet, and is therefore not clearly discernable. In the ^{13}C NMR spectrum, a characteristic feature is the negative chemical shift of the signal produced by the two equivalent methyls, C_h, attached to the silyl. Their signal is found at -4.4 ppm.

6.1.3.4 Attempted synthesis of (2-allyl-3-methoxyphenoxy)(*tert*-butyl)dimethylsilane

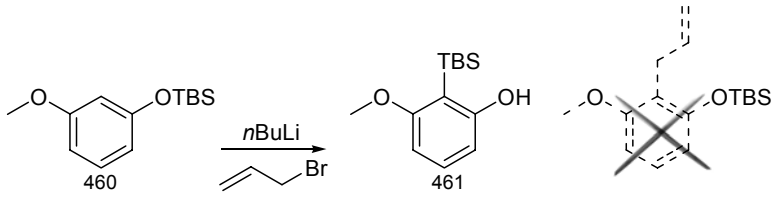
Scheme 157

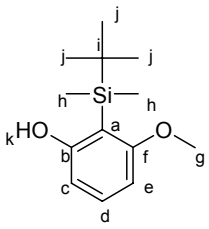


Having obtained the silyl protected 3-methoxyphenol derivative in good yield, the stability of the silyl group in the presence of *n*BuLi could be tested, as well as the ability of the *O*-silyl group to participate in *ortho* directing the lithiation of the benzene ring. *Ortho* directed lithiations of this type have been conducted in our laboratories before using 1,3-dimethoxybenzene allowing for allylation at exclusively the 2-position, in good yields.

To this end, *tert*-butyl(3-methoxyphenoxy)dimethylsilane **460** (Scheme 157) was treated with *n*BuLi at -10 °C for 90 minutes to allow lithiation to occur and then allyl bromide was added dropwise in the hope of nucleophilic displacement of the bromide, facilitating addition of the allyl group to the benzene in the 2-position. After workup of the reaction, column chromatography afforded only one product, but in a disappointingly small amount. Moreover, the ^{1}H NMR spectrum of this new compound was certainly not consistent with what we would have expected. At first glance, it was clear that the alkene signals which should have been quite conspicuous, were simply not present. The silyl protecting group on the other hand seemed to have survived the reaction as the singlets corresponding to the *tert*-butyl and methyl groups were clearly present. Moreover, the ^{1}H NMR spectrum simply did not indicate that we had the correct number of protons for the desired product and in fact, the number of protons was the same as the starting material, although we very clearly had a different product. Finally, the fact that only three aromatic protons were clearly present in the ^{1}H NMR spectrum, even though no allyl group had been added led us to the conclusion that the silyl group had migrated from the oxygen to the carbon, no doubt immediately after lithiation (Scheme 158). Thus, we had inadvertently synthesised 2-(*tert*-butyldimethylsilyl)-3-methoxyphenol **461** in 13% yield.

Scheme 158





In the ^{1}H NMR spectrum, the presence of the silyl group is clearly attested to by the large *tert*-butyl singlet at 0.94 ppm, and the singlet corresponding to the equivalent methyl protons, H_h at 0.38 ppm. A new feature in the spectrum is the -OH singlet, H_k, at 5.03 ppm. The three remaining protons on the benzene ring produce signals that are well resolved and once again, the most deshielded of these is the triplet observed for H_d. Protons H_c and H_e produce doublets as expected, yet quite well resolved from each other at 6.44 ppm and 6.37 ppm.

6.1.3.5 A change of plan regarding the protecting group strategy

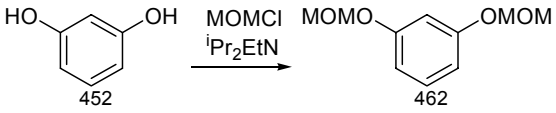
The instability of the silyl group under the lithiation conditions presented a problem in the synthetic sequence. In order to introduce our allyl group, needed for the rest of the synthesis, it is necessary to exploit the 1,3-diol substitution on the benzene ring to effect *ortho* directed lithiation. When these phenolic groups are protected as the methoxy derivatives, this reaction proceeds smoothly. Unfortunately, it was found during the initial studies that these methoxy protecting groups could not be selectively removed without also affecting the acetate, which we would need to keep. Cleavage of the acetate as well leads to complications as it then becomes necessary to first reprotect the more reactive phenolic groups, re-establish our desired acetate, then remove the phenolic protecting groups once again.

In light of the fact that we now know that starting with the silyl protecting group already in place is not a viable option, it became apparent that a protecting group 'switch' would be necessary at some point in our route. At the start, we would need a protecting group capable of facilitating the required *ortho* lithiation but then this group would have to be removed at a certain point and another protecting group introduced which could later be cleaved without the need for acid or Lewis acid reagents. A silyl group would certainly

suffice as the second protecting group. As for the initial protecting group we surmised that a MOM protecting group would serve satisfactorily. The ability of this group to effect *ortho* lithiation on a substituted benzene ring is well known and it can be cleaved relatively easily under acid conditions. This of course means that the timing for the protecting group switch would have to be at a point in our synthesis when no other acid sensitive groups would be present. Therefore, it was decided that directly after the allylation, the MOM protecting groups would be removed and be replaced by silyl protecting groups, which should last for the rest of the planned sequence. The only concern regarding this new strategy was the slight possibility that under the acidic conditions, combined with some heating as would be required to remove the MOM groups, isomerisation of the allyl alkene may occur, driven by the thermodynamic preference of this functionality to be in conjugation with the benzene ring.

6.1.3.6 Synthesis of 1,3-*bis*(methoxymethoxy)benzene – 462

Scheme 159



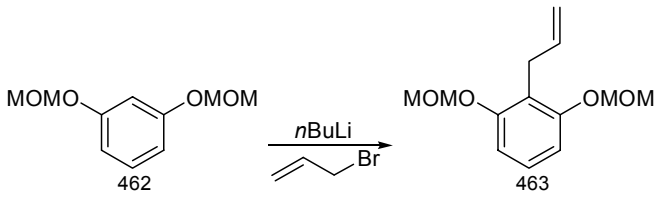
The double protection of resorcinol **452** as the *bis*-methoxymethyl ether **462** is well known.[117,118] Various bases have been utilised in this reaction including strong bases such as *n*BuLi as well as milder bases such as diisopropylethylamine. It is this milder method which we decided to use, employing the amine base along with methoxymethylene chloride to protect both phenols of resorcinol (Scheme 159). To this end, resorcinol was added to dichloromethane solvent, however it was found that the polar compound was not completely soluble in this solvent.* In the initial attempts at the reaction, poor yields were obtained for the desired product **462**, (less than 20%) and large amounts of an insoluble polymeric material were recovered. After some experimentation, it was found that the best yields were obtained if the amine and MOMCl were added simultaneously to the reaction mixture using two separate dropping funnels. Once formed however, purification of the doubly MOM protected compound **462** was easily achieved by either column

* Resorcinol is in fact more soluble in THF however dismal yields were obtained when this reaction conducted in THF as solvent.

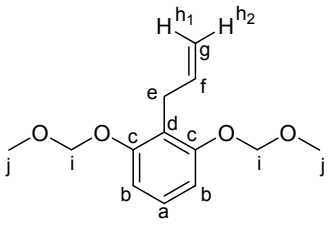
chromatography or bulb to bulb distillation, affording the desired compound as a clear oil in yields of 60-70%. The NMR data for **462** were identical to that reported in the litereature.[117]

6.1.3.7 Synthesis of 2-allyl-1,3-*bis*(methoxymethoxy)benzene – 463

Scheme 160



The MOM protecting group is reputed to be an excellent *ortho* director and we were optimistic that in this particular reaction it would facilitate the introduction of the allyl group at the desired 2-position. To this end, *bis*-MOM protected resorcinol **462** was treated with *n*BuLi in THF at -10 °C (Scheme 160). The solution gradually changed colour from clear to bright yellow as the lithiation occurred and after approximately 90 minutes, allyl bromide, in THF, was added dropwise and the reaction was left to proceed for 18 hours. Analysis of the reaction mixture after this time clearly showed that a new compound had formed having a slightly higher R_f than the *bis*-MOM adduct, although the reaction appeared not to have gone to completion as some of the starting material still remained. Nevertheless, after workup and purification which proved uneventful, the desired allylated compound **463** was obtained in 78% yield as a clear oil.

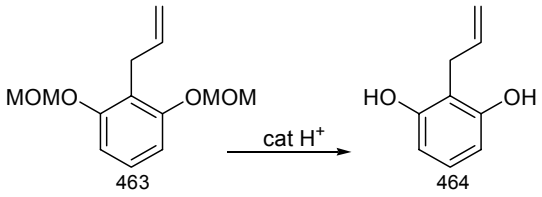


The symmetry about the benzene ring makes for a slightly more simplified ^{1}H NMR spectrum as compared to the previous model study examples. Proton H_a now legitimately produces a triplet as its neighbours, H_b, are equivalent by virtue of the symmetry associated with the benzene ring. The triplet for H_a occurs as the most deshielded signal at 7.09 ppm and the doublet for protons H_b is found slightly upfield at 6.77 ppm. The most interesting signal on the spectrum is that for the alkene proton H_f, producing a tdd due to coupling with the adjacent methylene protons H_e, as well as the two non-equivalent geminal alkene protons, H_{h1} and H_{h2}. This interesting signal occurs at 5.96 ppm and its three coupling constants correspond nicely

with the coupling constants obtained for each of the individual coupling partners. The doublet for the methylene protons H_e, unfortunately overlaps with the large singlet associated with the methyl protons H_j, in the region 3.48-3.46 ppm. Finally, the deshielded methylene protons H_i, produce a singlet at 5.17 ppm.

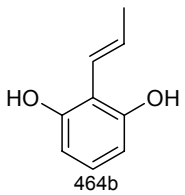
6.1.3.8 MOM deprotection, forming 2-allylbenzene-1,3-diol –464

Scheme 161



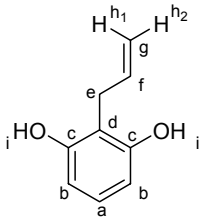
The exact timing regarding the removal of the MOM protecting groups of **463** was a matter which required some experimentation. We envisaged that in this synthetic route, there would be two points at which the MOM protecting groups could be removed and replaced by silyl protecting groups. One of the points would be now, with the allyl group in place, although we did have a concern that the prolonged acidic conditions and heating, required to remove the MOM groups, may result in some isomerisation of the double bond to the more conjugated position **464b** (Figure 48). The only other point at which we envisaged that the MOM groups could be removed would be right after the next step in the sequence, namely, after conversion of the allyl group of **463** to the corresponding aldehyde by means of ozonolysis. Following that, there would not be an opportunity to remove the MOM groups as the molecule would contain acid sensitive ester groups or other free hydroxyl groups which would interfere in this process.

Figure 48



Therefore, to investigate the efficiency of the acid catalysed MOM hydrolysis at this point in the synthetic sequence, 2-allyl-1,3-*bis*(methoxymethoxy)benzene **463** was dissolved in

methanol and a catalytic amount of HCl was added (Scheme 161). After stirring the reaction at room temperature for several hours it appeared by TLC analysis that the starting material was not reacting and so the reaction mixture was heated to reflux. After another hour at this temperature, two new spots at lower R_f values suggested that the reaction was proceeding smoothly and most likely the two new compounds were the completely deprotected species as well as the mono-deprotected species. This assumption was confirmed once the reaction was left to continue at reflux for 18 hours resulting in total consumption of the starting material and only a trace amount of the presumed mono-deprotected species remained, as determined by TLC. The solvent was removed *in vacuo* and the crude oil thus obtained dried using magnesium sulfate after redissolving the crude material in ethyl acetate. The crude material could then be purified by column chromatography and in this way, quantitative yields of the desired diol were obtained. On a larger scale however, it should be noted that the reaction could take some time to complete - up to two days in fact for masses in the range of about 5 g. It was also found that the catalytic amount of acid used initially would evaporate during this time and so approximately every 12 hours, a few drops of HCl needed to be added to the reaction. However, it is important to note that the loss of the acid should not be countered by simply adding a larger quantity of HCl at the start of the reaction, as it was found that this approach led to drastically decreased yields.

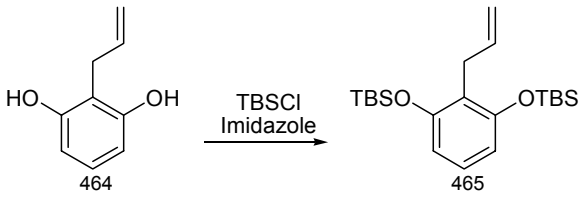


In the ^{1}H NMR spectrum, the loss of the MOM protecting groups is immediately apparent by absence of the two singlets associated with the methyl and CH_2 components of this protecting group. As can be seen in the ^{1}H NMR spectrum, purification of this diol proved not to be as efficient as was originally thought as tiny signals indicated the presence of an impurity. This impurity could not be removed even after repeated column chromatography and this is not surprising, as the presence of two tiny doublets in the alkene region possibly indicates that the impurity is indeed a trace amount of the isomerised product **464b**. Fortunately, according to the ^{1}H NMR spectrum, this isomer accounted for less than 5% of the material. The presence of the interesting tdd signal at 6.02 ppm once again attests to the presence of proton H_f, coupling to the non-equivalent geminal protons H_h, as well as to the methylene protons, H_e. These protons in turn couple to H_f with concurring coupling constants. The geminal alkene protons, H_h, unfortunately

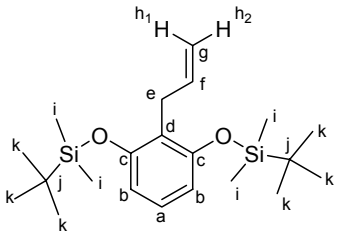
produce overlapping signals in the region 5.20-5.11 ppm. On the benzene ring, the protons H_b are equivalent and therefore a triplet is observed for proton H_a at 6.97 ppm. Protons H_b in turn produce a doublet at 6.43 ppm. In the IR spectrum, a broad OH stretch is observed at 3413 cm^{-1}.

6.1.3.9 Protection of the diol as the *bis*-silyl ether, 2-allyl-1,3-*bis*(*tert*-butyldimethylsilyloxy)-benzene – 465

Scheme 162



In order to continue along our planned synthetic route, we now required to protect the diol **464** as the *bis*-silyl ether **465** (Scheme 162). The removal of *tert*-butyldimethylsilyl protecting groups under non-acidic conditions is well known and this would be required near the end of our sequence. Thus, treatment of **464** with 2.5 equivalents of TBSCl afforded the desired doubly protected analogue **465**. Although the crude material was obtained as an oil, purification by distillation was not attempted for fear of isomerising the double bond at elevated temperatures. Purification by column chromatography however, proved uneventful and the desired compound was obtained as a colourless oil in good yield.

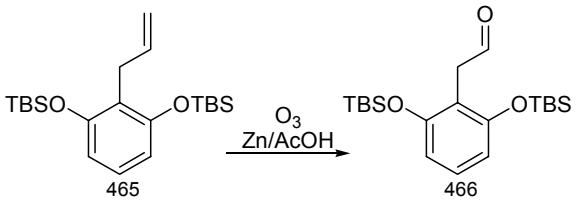


In the ^1H NMR spectrum the presence of two large singlets in the upfield region attested to the presence of the two TBS protecting groups. Due to the symmetry of this molecule these protecting groups are equivalent and so only one large singlet is observed for the protons H_k, at 1.01 ppm and similarly, protons H_i produce a singlet slightly upfield at 0.23 ppm. The benzylic methylene protons, H_e, are located in their expected region at 3.39 ppm, producing a doublet as a result of coupling to H_f. In fact, a closer inspection of this doublet reveals very slight shoulders on the peaks, no doubt due to weak long range coupling through the double bond to the geminal protons H_h. Proton H_f once again

produces a clear tdd at 5.93 ppm as a result of coupling to the equivalent protons H_e, as well as to the non-equivalent geminal protons, H_h. In this molecule, these geminal protons produce overlapping signals in the region of 4.94-4.88 ppm. Finally, the two equivalent protons, H_b, couple to H_a producing a doublet at 6.45 ppm and H_a produces a triplet at 6.93 ppm.

6.1.3.10 Ozonolysis to form 2-(2,6-*bis*(*tert*-butyldimethylsilyloxy)-phenyl)acetaldehyde – 466

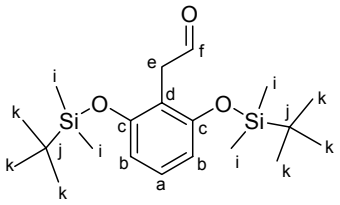
Scheme 163



With the silyl protecting groups in place, the next step required conversion of the alkene **465** to the aldehyde **466** (Scheme 163). There are two well known methods for this procedure:[102] One could convert the alkene to the corresponding diol using osmium tetroxide and then cleavage of this 1,2-diol system with sodium periodate would afford the corresponding aldehyde. The second procedure involves treatment of the alkene with ozone, resulting in a pericyclic reaction followed by a rearrangement leading to the ozonide. This ozonide can then be reduced using a number of methods to form the corresponding aldehyde. It was by utilisation of this second procedure that we hoped to form our desired aldehyde.

A complication we wished to circumvent was the over-oxidation of our electron rich aromatic ring and so the reaction was cooled to -84 °C using a frozen acetone slurry cooling bath. The addition of ozone was also performed for short periods of time (typically 2 minutes) and after each addition, the remaining ozone in the solution was quickly dispersed by bubbling N_2 gas into the reaction mixture. The progress of the reaction was then determined by TLC analysis. This procedure was repeated until only trace amounts of the starting material remained. The ozonide was then reduced by the addition of an excess amount of triphenylphosphine. Unfortunately, this proved to be a problematic, as although

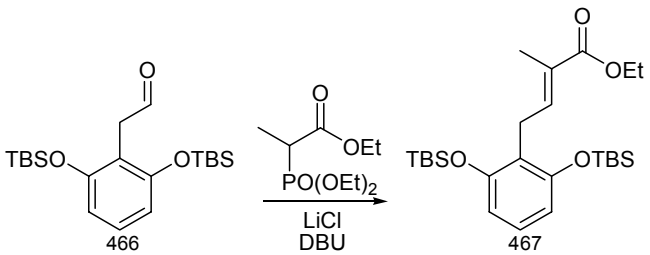
the PPh_3 did indeed reduce the ozonide to the aldehyde as planned, the excess PPh_3 proved impossible to separate from the aldehyde **466** as it had exactly the same R_f! Thus, the reaction was repeated and a zinc-acetic acid reduction was employed, effectively reducing the ozonide and allowing for purification by column chromatography. It should also be mentioned, that dimethylsulfide was previously found to be an ineffective reductant for this system.* In this way, the desired aldehyde could be obtained in excellent yields and existed as an oil at room temperature, or a white waxy solid at refrigeration temperatures.



The appearance of a new signal in the ^1H NMR spectrum at 9.61 ppm, and the absence of the three alkene signals is immediately apparent, and attests to the formation the aldehyde. Shoulders on this signal indicate very weak coupling of this aldehyde proton, H_f, to the adjacent methylene protons, H_e. Similarly, the methylene protons couple only very weakly to the aldehyde proton and produce a doublet at 3.65 ppm with a coupling constant of just 1.5 Hz. The silyl protecting groups produce their large singlets at 0.98 ppm and 0.23 ppm for protons H_k and H_i respectively. The protons on the benzene are characterised by a triplet for proton H_a at 7.03 ppm and a doublet for equivalent protons H_b, at 6.51 ppm. In the ^{13}C NMR spectrum, a signal at 201 ppm is indicative of the carbonyl carbon and in the IR spectrum, a strong absorption at 1729 cm^{-1} is observed due to the C=O stretch.

6.1.3.11 Horner-Wadsworth-Emmons reaction to synthesise *(E)*-ethyl-4-(2,6-*bis*(*tert*-butyl-dimethylsilyloxy)phenyl)-2-methylbut-2-enoate – 467

Scheme 164



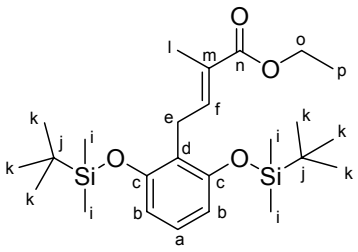
* In our initial studies we employed an equivalent compound which had methoxy protecting groups instead of the silyls. It was found that dimethyl sulfide did not reduce the ozonide of this compound after ozonolysis. In fact, the ozonide proved to be quite stable and could easily be purified by column chromatography and characterised by NMR spectroscopy. Hence the reason for using PPh_3 as a reductant.

With the aldehyde in hand, a Horner-Wadsworth-Emmons reaction was the next step to be carried out and as one of the key reactions in the planned synthetic sequence, the formation of the *(E)*- isomer exclusively was crucial for good enantioselectivity during the planned Pd π-allyl cyclisation, which was to follow later. Wittig reactions can be either *(E)*- selective or *(Z)*- selective depending on the nature of the ylide. Typically, unstabilised ylides lead to the formation of mainly the *(Z)*- alkenes as a result of the kinetically preferred *syn* arrangement of the oxaphosphetane ring intermediate. However, for stabilised ylides, i.e., ylides wherein the anion may be stabilised by conjugation into a carbonyl system, the formation of the oxaphosphetane ring system is reversible due to this added stability of the anion and so kinetic control no longer dominates and thermodynamically, the *anti* arrangement of the oxaphosphetane ring intermediate dominates, resulting in the major product being the *(E)*- alkene.[102,115,116]

For our particular reaction, the required phosphonate ester was not available and needed to be synthesised. Fortunately, this was easily accomplished by refluxing triethylphosphite with at least a two fold excess of ethyl 2-bromopropanoate, in the absence of any solvent. Typically, the formation of the phosphonate needed to be conducted a reflux for at least 72 hours as it proceeded rather slowly. Moreover, a large excess of ethyl 2-bromopropanoate was required to ensure that all the triethylphosphite reacted, as the boiling point of the triethylphosphite and that of the desired product were too close to allow for purification of the product by distillation. However, the boiling point of ethyl 2-bromopropanoate on the other hand was significantly lower than that of the desired phosphonate ester and so since this reagent could easily be separated from the desired phosphonate, it was always used in excess to ensure complete consumption of the triethylphosphite.

In order to perform the modified Wittig reaction, the phosphonate ester was treated with DBU and LiCl in acetonitrile (Scheme 164). Dissolution of the LiCl salt took several minutes and only occurred after the addition of the DBU. Finally, the aldehyde **466**, dissolved in acetonitrile was added in one portion resulting in an exothermic reaction. During future repetitions of this reaction on a larger scale, a water bath at about 5 °C was employed to prevent the reaction mixture becoming too hot and this seemed to improve the yields obtained for the reaction. Once the aldehyde had been added, the reaction was

stirred at room temperature for 18 hours. It was found for these reactions that complete consumption of the aldehyde very rarely occurred, even when the amounts of the other reagents were increased. Moreover, since the desired product **467** had a similar R_f to the aldehyde **466**, purification by column chromatography needed to be conducted with extra care and often more than once in order to obtain the desired product in good purity. Nevertheless, this procedure proved to be quite successful as it afforded exclusively the desired *(E)*- alkene* **467**, in good yields.

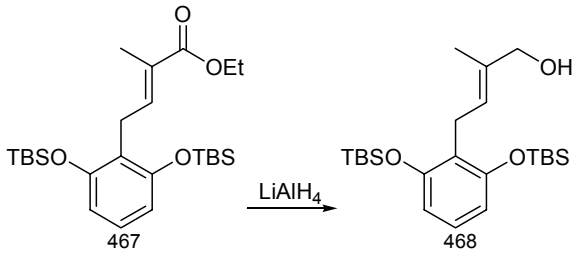


In the ^{1}H NMR spectrum, the appearance of new singlets attested to the presence of the ethyl propanoate moiety. Interestingly, the single alkene proton, H_f, is significantly more deshielded in comparison to what was observed for this proton in the allyl precursors to this compound, no doubt due to conjugation of the alkene into the carbonyl system. Proton H_f produces a poorly resolved triplet at 6.81 ppm. In the aromatic region of the spectrum, protons H_a and the equivalent protons, H_b are attested to by a triplet at 6.94 ppm and a doublet at 6.46 ppm, respectively. In the mid-region of the ^{1}H NMR spectrum, a quartet at 4.14 ppm integrating for two protons is a new feature and this can be assigned to protons H_o. Slightly upfield of this signal at 3.49 ppm is the doublet for protons H_e, coupling to H_f. Fortunately, assigning the methyl signals for protons H_l and H_p is easily accomplished based upon multiplicity. The singlet at 1.92 ppm and triplet at 1.23 ppm, correspond to H_l and H_p, respectively. Using a CH correlated NMR spectrum, all the carbon signals could be assigned.

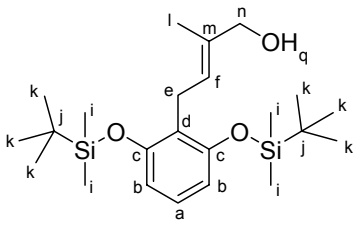
* The geometry of the alkene was not actually determined at this stage, but rather at the acetate stage two steps further. The acetate allowed for more definitive results from NOE experiments.

6.1.3.12 Synthesis of *(E)*-4-(2,6-*bis*(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-en-1-ol – 468

Scheme 165



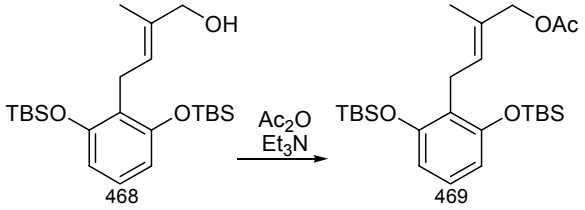
With the alkene in place we now needed to perform two functional group transformations on our molecule **467** to facilitate the Pd π-allyl mediated chemistry. Firstly, the ester would need to be reduced to the corresponding alcohol **468** (Scheme 165). On treating **467** with $LiAlH_4$ in THF it initially appeared as though the reaction was proceeding smoothly, as analysis of the reaction mixture by TLC indicated a single new product forming at a lower R_f. However, before all the starting material could be consumed, two new spots began to appear, and with time, these extra compounds increased in amount. At this point the reaction was quenched by the addition of water and after isolating the compounds, it was determined that the silyl protecting groups were not inert to the reducing agent and were being cleaved to afford the correspond phenols during the reduction. This of course would pose a major problem. Indeed, selectively reprotecting the phenols in the presence of a free primary aliphatic hydroxyl is possible, but we certainly did not wish to go through another back-and-forth protecting group sequence. Fortunately, by simply lowering the reaction temperature to 0 °C, it was found that the rate of reduction of the ester was not significantly altered, however, the silyl protecting groups proved to be far more stable at this lower temperature. Provided the reaction was performed at 0 °C, and the progress monitored closely by TLC to avoid unnecessarily prolonged exposure to the $LiAlH_4$, the desired primary alcohol with the silyl protecting groups intact, could be obtained in good yield.



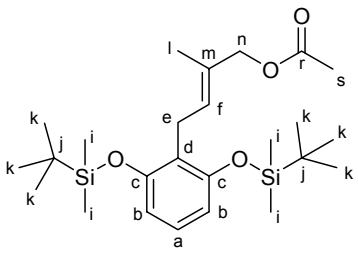
In the ^{1}H NMR spectrum, the absence of the carbonyl means that delocalisation of the alkene no longer occurs, and the alkene proton, H_f is shifted back upfield to 5.46 ppm. Since the methyl group of the ester is no longer present, the remaining methyl protons, H_l, are easily assigned as the singlet at 1.78 ppm. The new methylene protons, H_n, produce a singlet at 3.96 ppm. The alcohol proton, H_q, produces a singlet at 2.17 ppm. In the infrared spectrum, a broad OH stretch is observed at 3331 cm^{-1}.

6.1.3.13 Synthesis of *(E)*-4-(2,6-*bis*(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-enyl acetate - 469

Scheme 166



In order to facilitate the envisaged Pd π-allyl mediated cyclisation, the hydroxyl functional group needed to be converted into a suitable leaving group. Typically, in Trost's chemistry an acetate served this purpose well and so we decided to adhere to the same methodology (Scheme 166). The conversion of the primary hydroxyl group was easily accomplished by treating **468** with acetic anhydride and triethylamine at room temperature in THF. After 4 hours the reaction was complete as determined by TLC analysis and the reaction was quenched by the addition of ice-cold water. After extraction and purification by column chromatography the desired acetate **469** was obtained in good yield as a clear oil.



In the ^{1}H NMR spectrum the presence of the acetate is immediately apparent by the new singlet at 2.04 ppm, corresponding to the methyl protons, H_s. Just slightly upfield of this singlet is another singlet, also integrating for three protons corresponding to the methyl protons, H_l. Unambiguously distinguishing between these two signals

was possible by comparison of the chemical shift for protons H_l in the absence of the acetate (molecule **468**) as well as by utilising a CH-correlated spectrum. One would expect the ^{13}C NMR signal for C_s, adjacent to a carbonyl to be somewhat more downfield than the carbon, C_l. This is indeed the case as C_s occurs at 21 ppm in the ^{13}C NMR spectrum and C_l at 14 ppm. As for the remaining protons little has changed in the ^1H NMR spectrum, except of course that the OH signal is no longer present. In the mid-region of the ^1H NMR spectrum the methylene protons, H_n produce a singlet at 4.40 ppm, as no extended coupling is observed through the double bond. Protons H_e couple to H_f, resulting in a doublet at 3.37 ppm. The alkene proton is found at 5.52 ppm and produces a poorly resolved triplet due to coupling to H_e. On the aromatic ring, equivalent protons H_b couple to H_a resulting in a doublet at 6.45 ppm and in return, proton H_a couples to these equivalent protons producing a triplet at 6.91 ppm. Finally, the silyl protecting group cannot be missed as the two large singlets associated with this group are found at 0.99 ppm and 0.23 ppm for protons H_k and H_i respectively. In the IR spectrum, the absence of the OH stretch and the new appearance of a C=O stretch confirm that the correct functionality is in place.

En route to this compound, we previously discussed the synthesis of the Horner-Wadsworth-Emmons product, *(E)*-4-(2,6-*bis*(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-en-1-ol **467** (Scheme 164), and mentioned that only the *(E)*- isomer was obtained. In fact, at that time, NOE experiments were conducted on that Wittig product **467** however the results thereof were not conclusive. The reason for this is because in the *(E)*- isomer **467** (Figure 49), there are no protons in close proximity with the alkene proton H_f. Thus, irradiation of proton H_f in a NOE experiment only shows a response from the silyl protecting group protons, and nothing from the ethyl propanoate chain. This is of course expected as the *(Z)*- isomer would indeed show a response due to the fact that in such a scenario, the H_f proton would be in close proximity to H_l, and a response would then have been observed. However, confirming the geometry by the absence of any response from H_l is not definitive. Therefore, having completed the reduction of the Wittig ester, and formed the corresponding acetate **469**, we were in a better position to repeat the NOE experiments as now, we had protons which should be in close proximity to H_f, and therefore should provide a clear response on irradiation of H_f in a NOE experiment. This was indeed found to be the case as irradiation of H_f resulted in a clear response being observed for protons H_n as well as for the methyls upon the silyl protecting groups (Figure

50). Moreover, no response was observed from protons H_l, confirming that we had formed the *(E)*- isomer exclusively.

Figure 49

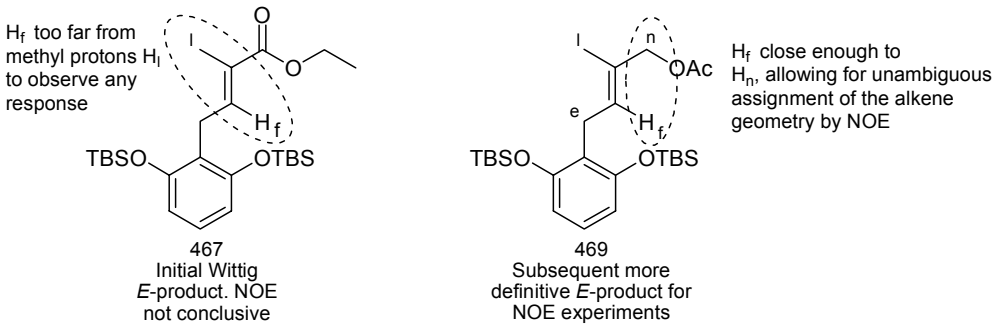
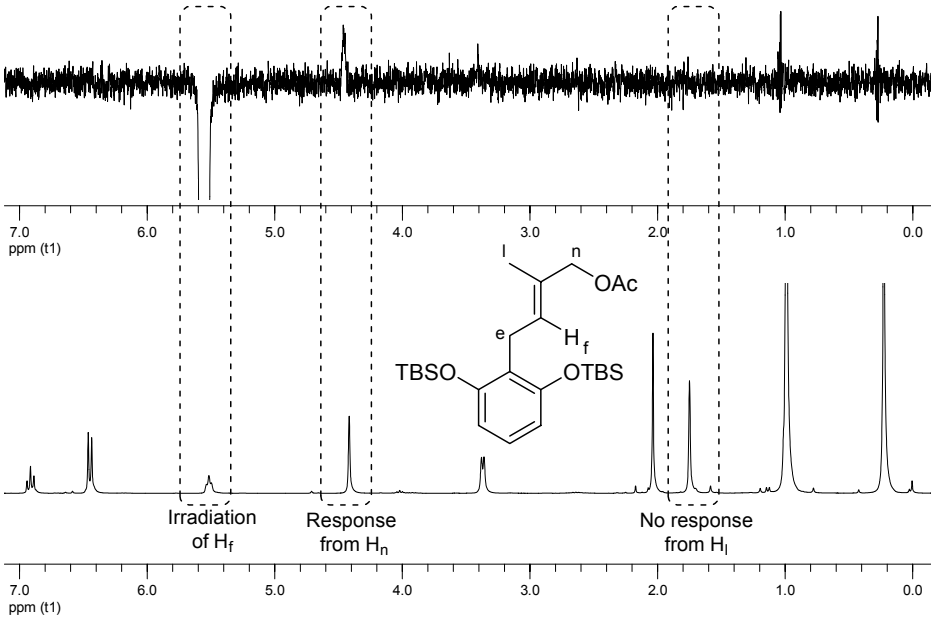


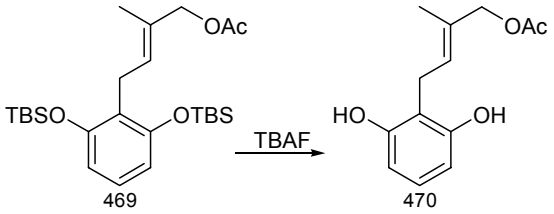
Figure 50



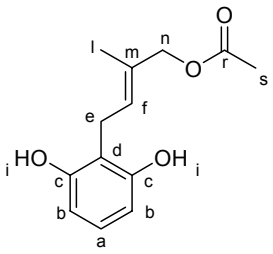
NOE irradiation of H_f clearly indicates *E*-alkene geometry

6.1.3.14 Synthesis of *(E)*-4-(2,6-dihydroxyphenyl)-2-methylbut-2-enyl acetate – 470

Scheme 167



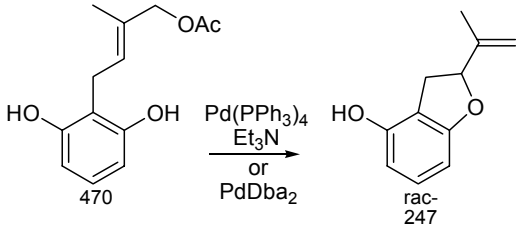
Having finally synthesised the desired benzofuran precursor with all the correct functional groups in place to attempt the Trost chemistry, all that remained was to remove the silyl protecting groups. To do this, we envisaged that a non-acidic deprotection using TBAF would afford the diol, without affecting the required acetate group (Scheme 167). Thus, the *bis*-silyl protected compound **469** was dissolved in THF and as a precaution the reaction was cooled to 0 °C by means of an ice bath. Two mole equivalents (one per silyl protecting group) of TBAF was added in one portion and after 5 minutes the reaction's progress was checked by TLC. To our surprise, all of the starting material had already been consumed and only one new spot had formed at a much lower R_f. The reaction mixture was immediately diluted with water and thoroughly extracted with ethyl acetate. After purification by column chromatography the desired diol **470**, with the acetate still in place was obtained in excellent yield as a viscous colourless oil.



The absence of the two large singlets in the upfield region of the spectrum is an immediate indication that the silyl groups are no longer present. Interestingly, the signal for the two equivalent phenoxyl protons, H_i, was not immediately evident as they did not produce a clear sharp signal as had been observed for the earlier allyl diol **494** (Scheme 161). In this particular compound, a very broad signal is observed for these two protons over the region 6.20-5.00 ppm, overlapping with the signal from H_f, which produces a triplet at 5.60 ppm. As for the rest of the ^1H NMR spectrum, little has changed in comparison to the silyl protected precursor.

6.1.3.15 Synthesis of racemic (±)-2-isopropenyl-2,3-dihydrobenzofuran-4-ol by Pd π-allyl chemistry – *rac*-247

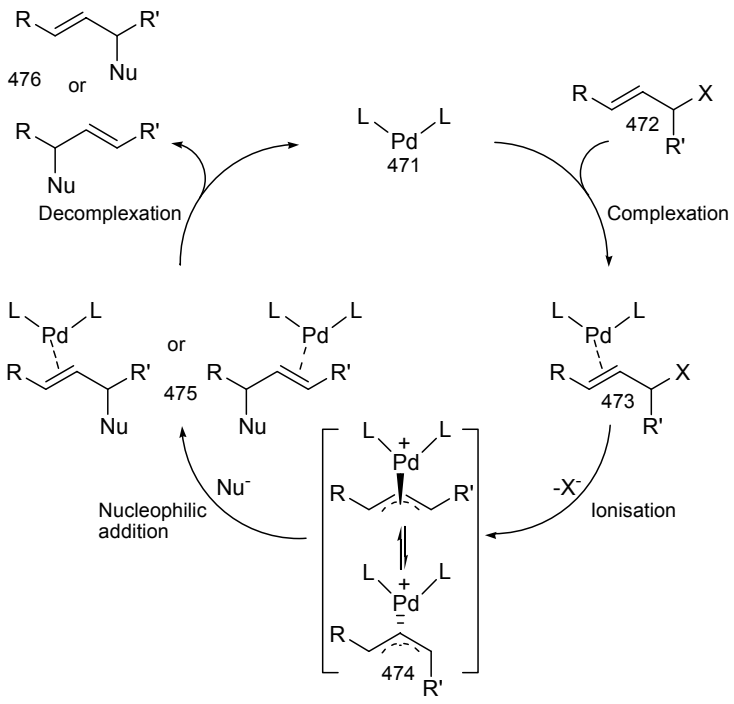
Scheme 168



As the first approach to the Pd π-allyl chemistry, we decided to investigate an achiral cyclisation in order to confirm that the reaction would indeed proceed to generate the 5-membered ring (the dihydrobenzofuran) as well as it had done for Trost's 6-membered chromans.[89,92]

The catalytic cycle for this intramolecular cyclisation is very similar to the intermolecular π-allyl palladium nucleophilic substitution reactions which have also been extensively studied by Trost. If one considers the catalytic cycle as shown below (Scheme 169), the first step in the catalytic cycle is complexation of Pd **471** onto the electron rich olefin **472** followed immediately by ionisation thus setting up the electrophilic Pd π-allyl complex **474**.[119,120] In the example shown below, attack of a nucleophile could occur from either side of the Pd π-allyl complex. Following this, decomplexation of the Pd occurs resulting in the formation of either (or both) of the olefinic compounds **476**.

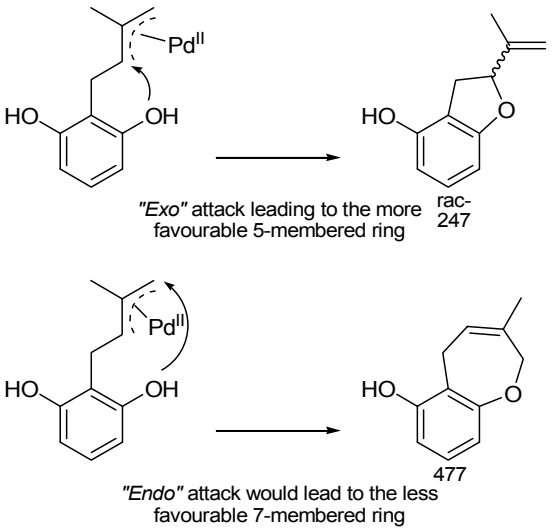
Scheme 169



Catalytic cycle for π-allyl Pd mediated nucleophilic substitution

It is this issue of the regioselectivity of the nucleophilic attack which needs some consideration for our particular system (Scheme 170). We desire to obtain the dihydrobenzofuran system and so require preferential *"exo"* nucleophilic attack, leading to the 5-membered ring system ***rac*-247**. Although the alternative *"endo"* attack is theoretically possible, it would lead to a 7-membered ring system **477** which is a thermodynamically less favourable system. Therefore we anticipate that the desired 5-membered ring system will predominate.

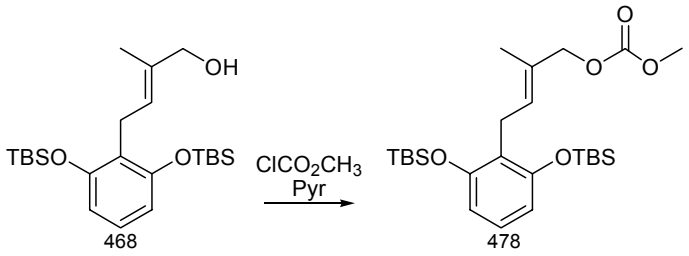
Scheme 170



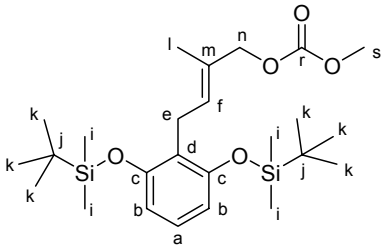
Thus, with a strong precedent for the formation of the desired benzofuran ring system, we set about investigating this reaction. As a first attempt, we envisaged that $Pd(PPh_3)_4$ would be a suitable catalyst as it met the requirements of being a source of Pd^0 and contained phosphorus-based ligands. Therefore, treatment of the acetate **470** (Scheme 168) with this catalyst in THF, in the presence of triethylamine to neutralise the acetic acid which would be produced, resulted in only trace amounts of the desired product being obtained. However, when switching to $PdDba_2$ as a source of Pd^0, and adding triphenylphosphine separately as the ligand source, the yield for the reaction was improved. In order to conduct the reaction using this approach, the actual catalyst, which is really still $Pd(PPh_3)_4$, was preformed by first adding the $PdDba_2$ to thoroughly degassed DMF, resulting in a dark red solution. Four equivalents of triphenylphosphine in relation to the Pd was then added and as the ligand exchange occurred, the colour of the solution gradually changed from deep red to yellow as the Dba ligand was displaced by the PPh_3, forming $Pd(PPh_3)_4$. The acetate was then added followed immediately by triethylamine and using this procedure, the yield was improved to a dismal 22%. This yield could not be improved upon and it was decided that a slightly different strategy would need to be employed.

6.1.3.16 Synthesis of *(E)*-4-(2,6-*bis*(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-enyl methyl carbonate – 478

Scheme 171



At this point it was decided that perhaps the leaving group required for the formation of the π-allyl Pd complex should be changed. It is possible that once liberated, the acetate anion could re-attack the Pd-complex, simply reverting back to the starting material and this may account for the poor yields. By changing the leaving group to a carbonate, this problem would be overcome as elimination of the carbonate would immediately result in this functional group decarboxylating, producing carbon dioxide and methanol, circumventing any return attack and hopefully leading to better yields. This new strategy would mean returning to a few steps earlier in the synthetic sequence to apply the appropriate protecting group after reduction of the ester **468** (Scheme 171). To this end, the silyl protected allyl-alcohol **468** was treated with freshly distilled methyl chloroformate and pyridine, smoothly affording the desired carbonate **478** in excellent yields.

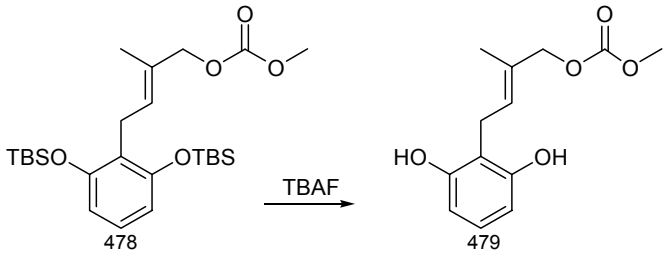


The ^{1}H NMR spectrum for this carbonate is very similar to that of the acetate analogue. Not only does this compound have the same number of protons but the spectra differ only in the position of the signals, and not their multiplicity. The key difference lies in the fact that the methyl group on the carbonate is attached to an oxygen and not to a carbon as in the acetate. Thus, the singlet for the protons H_s is more deshielded, now found at 3.76 ppm. The singlet for the methylene protons, H_n, does not differ too greatly from that of the acetate and is found at 4.49 ppm for this compound. The alkene proton, H_f, couples to the methylene protons H_e, producing a doublet at 5.56 ppm. No long range coupling is observed. A doublet at 3.37 ppm could be assigned to the

protons H_e. Regarding the remaining protons on this compound, the methyl protons, H_l do not display any sign of long range coupling through the double bond and therefore produce a singlet at 1.78 ppm. The protons on the benzene ring are in their usual pattern of a triplet for H_a at 6.92 ppm and a doublet for equivalent protons H_b, at 6.45 ppm. Two large singlets in the upfield region attest to the presence of the silyl protecting groups: these signals are located at 0.99 ppm and 0.23 ppm for protons H_k and H_i respectively. All the carbon signals could be assigned using a CH-correlated spectrum. In the IR spectrum, a strong absorbance at 1751 cm^{-1} is observed as a result of the C=O stretch.

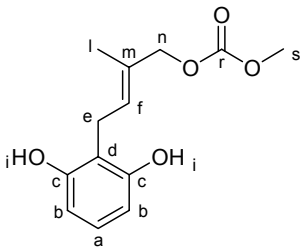
6.1.3.17 Removal of the silyl protecting groups affording *(E)*-4-(2,6-dihydroxyphenyl)-2-methylbut-2-enyl methyl carbonate – 479

Scheme 172



Treatment of the silyl protected compound **478** (Scheme 172) with two equivalents of TBAF (one per silyl group) at 0 °C in THF once again resulted in the desired diol **479** being produced almost immediately. The reaction mixture was then diluted with water and the deprotected compound extracted with ethyl acetate. Normally, it is advisable to slightly acidify the aqueous layer when extracting phenols to ensure that they are protonated and extracted into the organic phase. However, this was avoided in this case as we were concerned about acid hydrolysis of the carbonate moiety. Instead, the aqueous phase was simply extracted with a generous amount of ethyl acetate. Purification of the crude diol proved somewhat more difficult than anticipated. Trace amounts of ethyl acetate always seemed to persist in the viscous oil which constituted the purified product and this may be due to hydrogen bonding participation between the phenolic hydroxyl groups and the ethyl

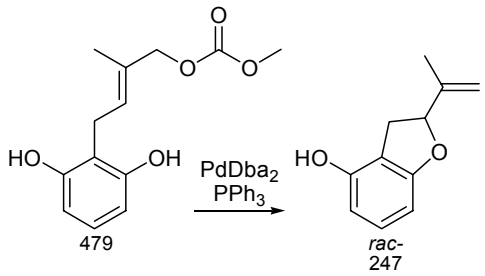
acetate solvent.* The desired diol **479** was obtained in excellent yields using this procedure.



In the ^{1}H NMR spectrum, the two large singlets usually associated with the silyl protecting group are conspicuous by their absence. Instead, a very broad signal in the spectrum over the region 5.80-5.00 ppm attests to the presence of the two equivalent phenoxyl protons, H_i. As for the rest of the ^{1}H NMR spectrum, little has changed. The deshielded singlet for protons H_s at 3.77 ppm attests to the survival of the carbonate group. Interestingly, the carbonate carbon C_r, and the aromatic carbons C_c produce signals with very similar chemical shifts in the ^{13}C NMR spectrum. Fortunately, the larger of the two signals can be assigned to the two equivalent carbons C_c, at 155 ppm, thereby allowing for assignment of the carbonate carbon, C_r to the signal at 156 ppm. In the IR spectrum, a large OH stretch at 3364 cm^{-1} is observed.

6.1.3.18 Synthesis of racemic 2-isopropenyl-2,3-dihydrobenzofuran-4-ol from the carbonate, by Pd π-allyl mediated chemistry - *rac*-247

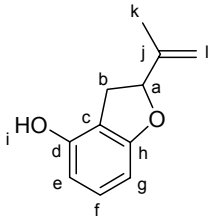
Scheme 173



With the leaving group now modified to the carbonate **479**, we were once again in a position to investigate the Pd π-allyl mediated cyclisation (Scheme 173). Moreover, as was learned previously, Pd^0 in the form of $PdDba_2$ functioned better as a pre-catalyst and since

* This phenomenon has been observed before in work which does not feature as part of this thesis. Purification of Nivirapine by column chromatography produced the desired compound as white crystals hydrogen bonded to ethyl acetate. Subjecting this white powder to heating whilst under vacuum did not reduce the ratio of ethyl acetate to Nivirapine, indicating just how strong this hydrogen bonding interaction can be. The problem could only be overcome by recolumning the material in chloroform.

we wished only to optimise the yield for the reaction at this stage, triphenylphosphine was used as the phosphine ligand as opposed to the more expensive chiral phosphine ligands. In this particular reaction, the carbonate leaving group should immediately be converted into carbon dioxide and methanol and so no base was added to the reaction mixture. Thus, $PdDba_2$ was added to thoroughly degassed DMF forming a wine red solution. Triphenylphosphine was added and as the ligand exchange proceeded, the colour of the solution changed to yellow, as would be expected as the Pd was ligated by the phosphorus ligands. Although only four equivalents of triphenylphosphine are required for every one equivalent of Pd, five equivalents were added in this case in order to ensure that no $PdDba_2$ remained in solution. After approximately 30 minutes, the carbonate was added and the reaction was left to proceed at 80 °C for 18 hours. Pleasingly, TLC analysis of the reaction mixture indicated complete consumption of the starting material. However, a cause for concern was that the only UV active spot on the plate seemed to be the dibenzylidene acetone, previously displaced from the Pd by triphenylphosphine. Fortunately on staining the plate in $KMnO_4$ dip, a new compound was revealed immediately, having a higher R_f than the starting material, and somewhat lower than the Dba. The fact that this compound stained so well with $KMnO_4$ dip was promising as it had been previously discovered in this synthetic sequence that terminal olefins stain very well.* Indeed, purification of this new material by column chromatography afforded the desired 2-isopropenyl-2,3-dihydrobenzofuran-4-ol ***rac*-247** in quantitative yield as clear oil, which was surprisingly poorly UV active on silica TLC.



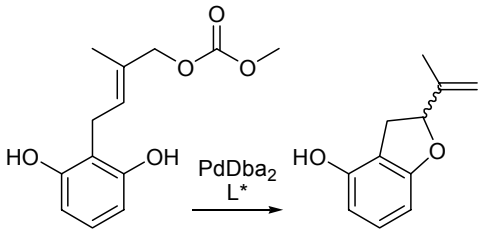
In the ^1H NMR spectrum, the disappearance of the signals associated with the carbonate was immediately apparent, as was the appearance of new signals in the mid-region of the spectrum, clearly indicating the presence of new alkene protons. Since the benzene ring is no longer symmetrical, protons H_e and H_g find themselves in different environments and therefore produce doublets at 6.32 ppm and 6.44 ppm respectively. However, the proton H_f still produces a triplet at 6.99 ppm as perhaps the resolution on the spectrum was not good enough to pick up the more complex double doublet signal one would was expected for this proton. The phenolic proton, H_i, produces a broad flat singlet

* The allylated 1,3-*bis*(methoxymethoxy)benzene stained immediately and exceptionally well using $KMnO_4$ dip.

over the region 5.90-4.30 ppm. Superimposed upon this signal, though clearly distinguishable is the signal for proton H_a, which couples to the methylene protons H_b producing a triplet at 5.21 ppm, as well as the signals for the geminal alkene protons H_l. These geminal protons couple so weakly that their signals appear as singlets, at 5.10 ppm for H_l *trans* to the benzofuran ring system and 4.92 ppm for H_l *cis* to the benzofuran ring system.* The benzylic methylene protons, H_b, adjacent to the stereogenic carbon, C_a, find themselves in different chemical environments and therefore produce two double doublets, at 3.31 ppm and 2.98 ppm. Finally, the methyl protons H_k do not couple to any other protons and therefore produce a singlet at 1.78 ppm. In the ^{13}C NMR spectrum, cyclisation onto the one phenolic oxygen results in a slight downfield shift of the associated carbon, C_h to 161 ppm. In the IR spectrum, a clear OH stretch is observed at 3387 cm^{-1} and a strong C=C stretch is observed at 1607 cm^{-1}.

6.1.3.19 Investigations into various chiral Pd π-allyl mediated cyclisations, leading to the synthesis of (+)-2-isopropenyl-2,3-dihydrobenzofuran-4-ol – (+)-*(S)*-247

Scheme 174



479 (+)-247

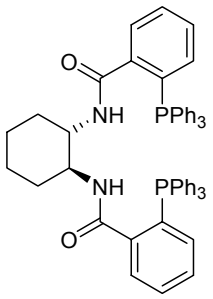
L* = Various chiral phosphine ligands

Having successfully optimised the conditions for the π-allyl Pd cyclisation, we now wished to perform the reaction enantioselectively. Trost has successfully performed similar reactions thereby leading to the synthesis various chroman systems in good enantiomeric excesses.[92] In these reactions, a chiral phosphine ligand would be used in the hope that the Pd-ligand complex will preferentially bind to one face of the substrate, leading to an enantiomerically enriched product. In light of Trost's successes on the chromans which are

* The unambiguous assignment of the two H_l protons was only made possible after obtaining a COSY spectrum for a very similar compound (the phenolic –OH is absent), the discussion of which follows in the next section.

not too dissimilar to our compounds, we initiated our studies using the same ligand, specifically, the *S*,*S*'-Trost ligand **212** (Figure 51), which we had in hand.

Figure 51



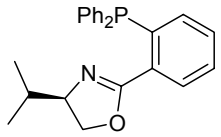
***S*,*S*'-Trost ligand**
212

According to our previously optimised procedure, the reaction was carried out in DMF using $PdDba_2$ as a source of Pd^0 and the Pd-phosphine ligand exchange, using Trost's ligand instead of triphenylphosphine, was allowed to occur before introducing the carbonate. In fact, this new Pd-phosphine catalyst also resulted in a yellow solution as was observed when triphenylphosphine was used as a ligand. In order to ensure that no $PdDba_2$ remained in solution, the Pd was added as 5 mole % of the substrate and the although in theory only twice the amount of the Trost ligand is required to fully complex the Pd,* 12 mole % was actually added. At this point we were uncertain as to whether or not $PdDba_2$ itself could catalyse the reaction. If it could, any remaining $PdDba_2$ would result in the formation of racemic product, compromising the overall enantiomeric excess of the reaction. The reaction was allowed to proceed for 18 hours and the desired product was obtained in 74% yield after column chromatography. In order to determine the enantiomeric excess of the reaction, analysis of the product by chiral HPLC seemed the best method. As a start, the previously synthesised racemic product ***rac*-247** was injected onto a Chiralcel OJ column and after some method development, it was found that 10% isopropyl alcohol in hexane resulted in almost complete separation of the enantiomers. Unfortunately, to our disappointment, similar analysis of our 'chiral' cyclisation (Scheme 174) revealed that we had achieved only a 60% ee, utilising the Trost ligand in DMF.

* The Trost ligand is bidentate

Since we had on hand two other chiral phosphine-based ligands we decided to investigate these in our chiral π-allyl Pd cyclisation. The first of these two ligands, a dihydro-oxazole, known as the Phaltz ligand **480** (Figure 52), differs slightly from the Trost ligand in that although it too is a bidentate ligand, the second coordinating atom is not another phosphorus but rather a nitrogen atom. As an imine, the lone pair of electrons on the nitrogen points almost directly away from the oxazole ring system making them available for coordination by the Pd atom. The stereogenic carbon α to this nitrogen is intended to facilitate a preferred facial binding, analogous to the Trost ligand and therefore impart stereoselectivity to the π-allyl Pd cyclisation.

Figure 52

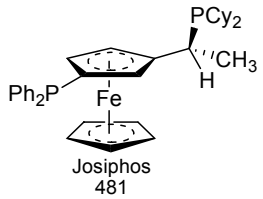


Chiral bidendate dihydrooxazole ligand
480

To this end, when the carbonate **479** was treated with 5 mole % of Pd pre-complexed with 12 mole % of the oxazole ligand **480** in DMF at 80 °C, almost no enantiomeric excess was observed for the reaction, although the racemic product was formed in 80% yield.

The remaining chiral phosphorus ligand that we had in hand was the Josiphos ligand **481** (Figure 53). This ferrocene based ligand is also a bidentate ligand containing two phosphorus atoms available for coordination. One of these is attached to a chiral carbon, thus hopefully imparting stereoselectivity to the intended reaction. Strangely, treatment of our carbonate **479** the with Pd-Josiphos catalyst did not even result in any product forming at all. It was observed however that when the Josiphos was added to $PdDba_2$ in an attempt to preform the desired chiral catalyst, the usual colour change to pale yellow did not occur and in fact, the solution darkened from wine red to black!

Figure 53



Josiphos
481

It was at this point that we decided to pay more attention to our solvent system. The Trost ligand had given us the best enantiomeric excess thus far, albeit only 60% ee. Perhaps this could be improved by changing the conditions. Two likely problems occurred to us at this point: namely that the $PdDba_2$ itself could be a suitable catalyst for the reaction and so if the Pd did not completely reassociate with the chiral Trost ligand, then it would compete with the chiral Trost ligand-Pd complex forming racemic product, compromising the ee's. Moreover, the DMF itself may be a suitable ligand, similarly competing with the chiral catalyst leading to diminished ee's.

As a test reaction, the carbonate **479** was added to a solution of DMF containing $PdDba_2$ and no phosphorus ligands were added. Although this reaction was only performed on a small scale as a test reaction, at 80 °C, and only in the presence of $PdDba_2$ and DMF, the carbonate was rapidly converted to the benzofuran, confirming our suspicions that the $PdDba_2$ was itself a capable catalyst, or that the DMF was a suitable ligand, or both.

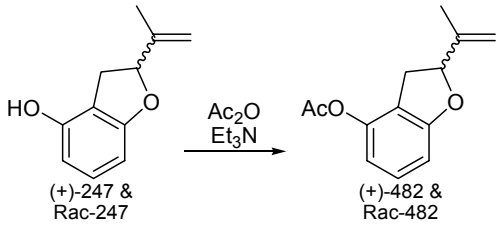
Clearly, a solvent change was required and to this end we decided to switch to dichloromethane, as this particular solvent should not be able to function as a ligand at all. Moreover, a thorough investigation into the work done by Trost revealed that he also added 1 mole of acetic acid for every mole of carbonate to enhance the ee's in the reactions he has reported in the literature.[92] The purpose of the acid is to slow down the process of ring closure by inhibiting the formation of the phenolic anion, as was previously discussed in more detail in the introductory section.

Thus, with this information in hand we tried the Trost ligand once again, using dichloromethane as a solvent. To thoroughly degassed dichloromethane was added 3 mole % $PdDba_2$ which resulted in a wine red solution forming. The addition of

10 mole % of the *S,S'*-Trost ligand* at 25 °C resulted in a colour change to a yellow solution. After 30 minutes, 1 mole equivalent of degassed acetic acid was added followed by the carbonate **479** (Scheme 174) and the reaction was left to proceed at 20-25 °C for 18 hours. Analysis of the reaction mixture by TLC indicated that all the starting material had been consumed and after column chromatography, the desired dihydrobenzofuran was obtained in excellent yield. To our delight, determination of the enantiomeric excess by chiral HPLC presented us with a small problem! The ee of the reaction was so good that the peak corresponding to the minor isomer was so small that it could not be completely resolved from that of the major isomer. At this point, it was clear that our ee had increased to over 85%. Moreover, we now knew that the *S,S'*-Trost ligand afforded the product with a positive specific rotation. An $[\alpha]_D^{19} = +17.3$ was obtained, measured in chloroform, however we could only speculate at this point that the actual stereochemistry for the product was *(S)*-, based upon the chroman work performed by Trost *et al*.[92]

6.1.3.20 Synthesis of racemic and (+)-2-isopropenyl-2,3-dihydrobenzofuran-4-yl acetate - 482

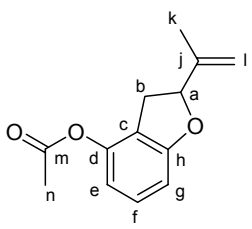
Scheme 175



In order to accurately determine the ee obtained for the chiral cyclisation reaction (Scheme 174), we would need to derivatise our compound in the hope that we could achieve better chiral separation. To this end, we opted for conversion of the remaining phenolic hydroxyl to the corresponding acetate. Of course, for the purposes of HPLC we needed to have both the racemic and chiral materials for analysis. In the event of an enantiomerically pure compound being obtained, only a single peak would be visible on the HPLC

* In theory, only 6 mole % of the Trost ligand is required to completely complex the 3 mole % of the $PdDba_2$. However, we were concerned that our balances could not accurately weigh out the 6.8 mg of $PdDba_2$ which we were using, and so an excess of the chiral Trost ligand was employed to ensure complete complexation. $PdDba_2$ on its own is capable of catalysing the reaction, forming racemic product – leading to diminished ee's.

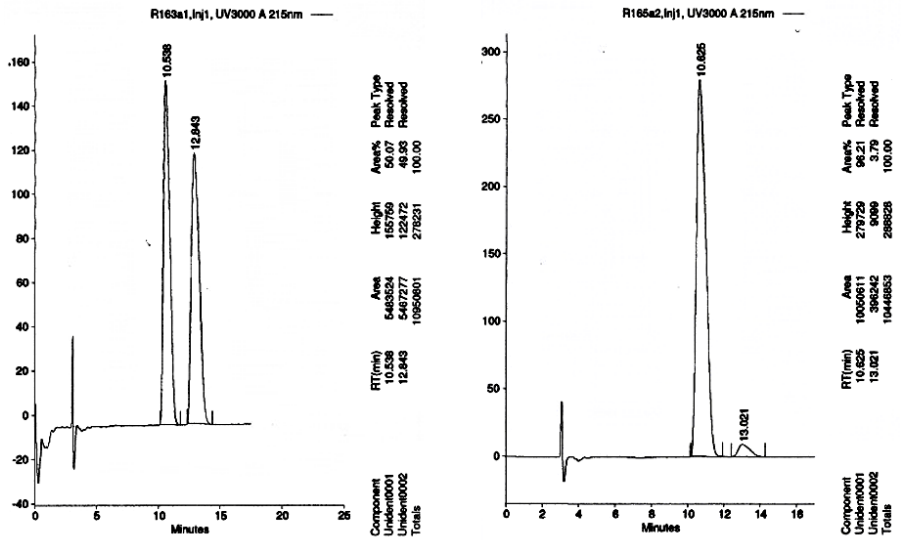
chromatogram. However, without also running a racemic sample for comparative purposes, one could never be certain that in fact the assumed chiral material was not enantiomerically pure and that simply that the two enantiomers were co-eluting as a single peak. Thus, the racemic and (+)-dihydrobenzofurans **247** were separately converted to their acetate derivatives **482** (Scheme 175). This reaction was pleasingly straightforward to accomplish as the phenol rapidly reacted with acetic anhydride in the presence of triethylamine, completely converting to the acetate within 30 minutes. After purification by column chromatography, **(±)-482** and **(+)-482** were obtained in excellent yields.



In the ^{1}H NMR spectrum, the presence of the new singlet at 2.28 ppm confirms that the acetate has indeed formed. This is further attested to by the presence of a carbonyl signal at 168 ppm in the ^{13}C NMR spectrum, corresponding to C_m. As for the remainder of the signals in the ^{1}H NMR spectrum, little has changed in comparison to this compound's precursor with perhaps the exception of the doublet for proton H_e, shifted downfield to 6.69 ppm as a result of the acetate.

As a start for the development of an HPLC method, the racemic acetate **(±)-482** was injected onto the Chiralcel OJ column also using 10% isopropyl alcohol/hexane as a mobile phase. Pleasingly, this initial guess turned out to be exactly the conditions we required. The enantiomers separated completely and the UV absorption was so strong at 215 nM that very little needed to be injected in order to obtain an excellent signal to noise ratio, yet further improving the peak resolution. As one would expect, for the racemic cyclisation reaction there is no preferred facial attack at all, as the two peaks for the racemic product have almost exactly the same areas (Figure 54). However, to our delight, upon injection of the sample cyclised under chiral conditions **(+)-482**, the ratio of the peaks differed dramatically. Although the retention times for each peak in the chiral sample matched those observed for the racemic sample, the ratio of enantiomers, (+) to (-), was 96:4. Clearly, we had achieved a 92% ee in our chiral cyclisation reaction employing the *S,S'*-Trost ligand.

Figure 54

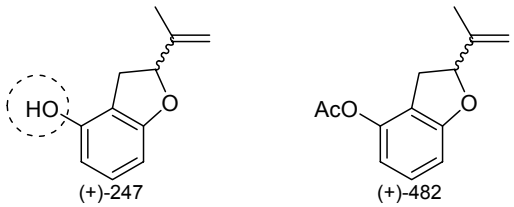


Racemic cyclisation - HPLC trace shows 50:50 ratio of enantiomers

Chiral cyclisation - HPLC trace shows 92% ee

However, at this point we still did not know the exact stereochemistry of our chiral material. We knew that it had a (+)- specific rotation and it was 96% of one enantiomer. On comparison to some of the work done by Trost *et al*. we could hazard a guess that we had formed the *(S)*- enantiomer, as in Trost's chroman work, the *S,S'*-Trost ligand always led to the *(S)*- product. In order to verify this assumption however, we decided to obtain a crystal structure of the chirally cyclised material. This would require some derivatisation as the 2-isopropenyl-2,3-dihydrobenzofuran-4-ol **(+)-247**, obtained directly after the chiral π-allyl Pd cyclisation was an oil, as was its acetate derivative, 2-isopropenyl-2,3-dihydrobenzofuran-4-yl acetate **(+)-482**. Fortunately however, the presence of the unprotected phenol functionality would provide us with a 'handle' for the addition of several groups with the intention of obtaining a crystalline compound (Figure 55).

Figure 55



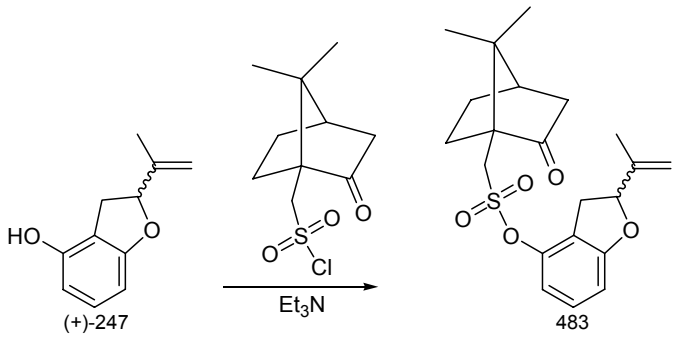
(+)-247
$[\alpha]_D^{19}$=+17°

(+)-482
$[\alpha]_D^{19}$=+25°

92% ee (+)-compounds are both oils - possibly derivitise at phenol to obtain crystalline material

6.1.3.21 Derivatisation of the (+)-dihydrobenzofuran enantiomer to 2-isopropenyl-2,3-dihydrobenzofuran-4-yl-(7,7-dimethyl-2-oxobicyclo-[2.2.1]-heptan-1-yl)-methanesulfonate – 483

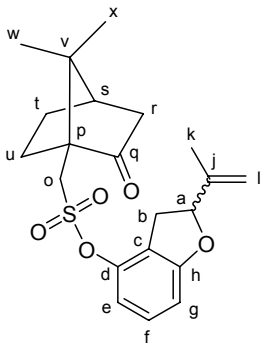
Scheme 176



For the purposes of determining the stereochemistry by crystallography, we needed two things: of course, derivatisation of the chiral dihydrobenzofuran oil must afford a product which is solid and can be crystallised but just as importantly, in order to be absolutely sure of the stereochemistry we needed to introduce another stereogenic carbon of known stereochemistry. This would allow us to unambiguously solve the crystal structure. To this end, we envisaged that the (+)-camphorsulfonyl moiety would serve our purposes nicely. Compounds derivatised using this moiety are usually solid, and the known stereochemistry would allow us to unambiguously solve the crystal structure to reveal the stereochemistry on the dihydrobenzofuran moiety.

Therefore, the chiral dihydrobenzofuran was treated with (+)-camphorsulfonyl chloride and triethylamine (Scheme 176).[*] Within a few hours the reaction had gone to completion and the derivatised dihydrobenzofuran was purified by column chromatography, affording **483** in excellent yield. However, to our dismay, this product stubbornly refused to solidify and despite all efforts, it remained a viscous oil.

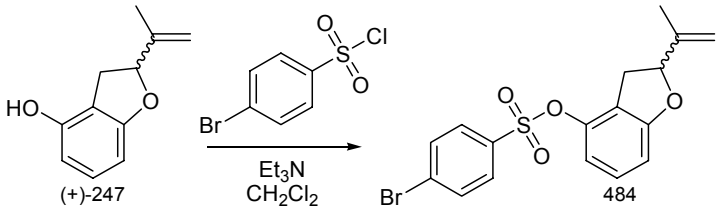
[*] (+)-Camphorsulfonyl chloride was easily prepared from (+)-camphorsulfonic acid and $SOCl_2$.



The ^{1}H NMR spectrum for this compound is obviously rather more complex than previously observed in this series of compounds. Nevertheless, for the most part, the signals associated with the camphor group do not interfere with those of the dihydrofuran moiety. As far as the signals corresponding to the aromatic ring on the benzofuran are concerned, their pattern in the ^{1}H NMR spectrum is largely the same as was observed when an acetate was attached to the phenolic oxygen. Similarly to the acetate group, the sulfonate withdraws electron density deshielding proton H_e so that its doublet is located downfield in the same region as proton H_g. In fact, without further information it is not possible to unambiguously assign these signals in this compound. These two doublets are located at 6.80 ppm and 6.75 ppm. Proton H_f continues to produce a triplet at 7.15 ppm. Proton H_a produces its characteristic triplet at 5.23 ppm as a result of coupling to the methylene protons, H_b, which in turn produce two double doublets at 3.51 ppm and 3.17 ppm. The geminal alkene protons, H_l, couple so weakly that their signals appear as two singlets at 5.09 ppm and 4.92 ppm. Finally, the remaining signal pertaining to the benzofuran moiety is that of the methyl protons, H_k, appearing as a singlet at 1.77 ppm.

6.1.3.22 Derivatisation of the (+)-dihydrobenzofuran enantiomer to 2-isopropenyl-2,3-dihydrobenzofuran-4-yl 4-bromobenzenesulfonate – 484

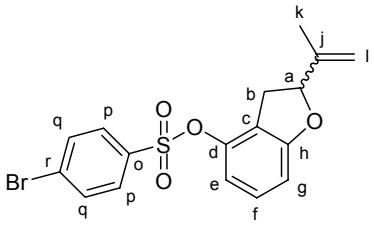
Scheme 177



Having been unable to obtain a crystal structure from the (+)-camphor derivatisation process, we now decided to attempt an alternative derivative. In this case, we hoped that 4-bromobenzene-1-sulfonyl chloride would provide us with the solid we needed. Although this particular derivatising reagent does not contain a known stereogenic carbon as was the case for the (+)-camphorsulfonyl chloride, we would nevertheless still be able to assign the

stereochemistry of the benzofuran in the product **484** due to the presence of a heavy atom, in this case, bromine. The reason for this is because unlike light nuclei which only diffract X-ray radiation, the nuclei of heavy atoms are able to absorb X-rays at certain wavelengths, resulting in an anomalous scattering. Thus the interference pattern will not only depend on the inter-atomic distances (as is the case with light nuclei), but also on their relative positions in space, thus making it possible to determine the absolute stereochemistry of molecules wherein no known stereogenic carbons are present.[121]

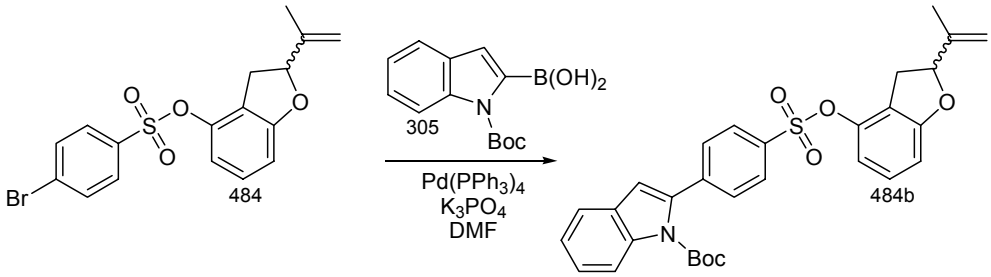
Therefore, the (+)-benzofuran compound **(+)-247** (Scheme 177) was treated with 4-bromobenzene-1-sulfonyl chloride in the presence of triethylamine. Analysis of the reaction by TLC after 18 hours indicated that all the starting material had reacted and so the derivatised benzofuran **484** was isolated and purified by column chromatography. However, once again, a crystal structure was not obtainable as this compound also refused to solidify despite our best efforts. Nevertheless, this derivative was obtained in 78% yield.



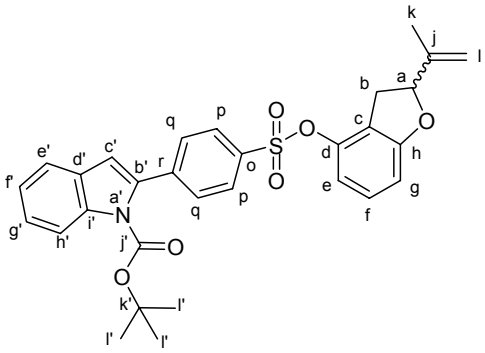
Fortunately, the ^{1}H NMR spectrum of this bromobenzene derivative is rather less complicated than the preceding camphor derivative. In fact, the sole contribution of the bromobenzene moiety is a multiplet in the region 7.66-7.63 ppm for both sets of equivalent protons, H_q and H_p. The remaining signals in the ^{1}H NMR spectrum all pertain to the benzofuran moiety. The pattern is largely the same as for the preceding compounds: Proton H_f produces a triplet at 7.04 ppm and protons H_g and H_e produce doublets at 6.71 ppm and 6.39 ppm, though it is not possible to unambiguously assign these signals. At the stereogenic carbon, proton H_a couples to the methylene protons H_b producing a triplet. However, these protons, being adjacent to the stereogenic carbon couple independently to H_a as well as to each other, producing two double doublets at 3.23 ppm and 2.79 ppm. The geminal alkene protons, H_l, produce two singlets at 5.03 ppm and 4.90 ppm. Finally, the methyl protons, H_k, produce a singlet at 1.69 ppm.

6.1.3.23 Further derivatisation of 2-isopropenyl-2,3-dihydrobenzofuran-4-yl 4-bromobenzenesulfonate to – 484b

Scheme 178



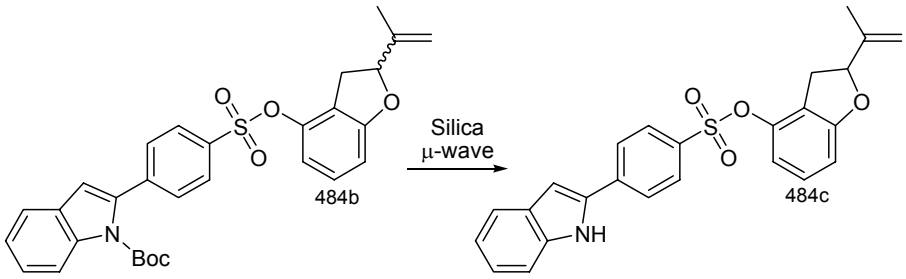
Disappointed at not being able to obtain a crystal structure from derivative **484**, we investigated the possibility of further modifying **484** in the hope of obtaining a solid compound that could be recrystallised. Examination of the structure revealed really just two points on the molecule amenable to further manipulation: the alkene and the aryl halide moiety. For reasons discussed previously, we did not wish to tamper with the chiral isopropenyl functionality and therefore considered the options available for modification of the aryl halide. In the carbazole sections of this thesis we successfully conducted Suzuki couplings of various aryl halides and indole boronic acids – and the products of these reactions were always solids. Therefore, we decided to further derivatise **484** by coupling indole boronic acid **305** using a Suzuki reaction (Scheme 178). However, in contrast to our previous Suzuki reactions which employed a biphasic solvent system consisting of DME and aqueous 2M Na_2CO_3 solution, we opted for the alternative method of 80 °C in DMF, using K_3PO_4 as a base. We once again employed $Pd(PPh_3)_4$ as a catalyst for this reaction. In this way, the rather interesting indolo-furan, coupled by a benzene sulfonyl moiety **484b**, was obtained in 58% yield after 18 hours at 80 °C – unbelievably, as an oil which would not solidify.



This compound, though not particularly useful in terms of obtaining a crystal structure is nevertheless interesting in that it bears components from both parts of this PhD. Astonishingly, no overlap of signals is observed in the ^{1}H NMR spectrum, and in fact, the signals associated with the indole and benzofuran moieties are very similar to the spectra previously obtained for the similar individual compounds. Thus, using NOE and COSY spectra previously obtained for the individual similar compounds, complete assignment of all the ^{1}H NMR signals was made possible. An interesting observation is the separation of the signals for protons H_p and H_q on the linking benzene ring, which previously produced one multiplet in **484**. In compound **484b**, two doublets are observed in the ^{1}H NMR spectrum at 7.90 ppm and 7.60 ppm for H_p and H_q respectively. The signals associated with the benzofuran moiety have hardly changed from **484**, and this is similarly the case for the indole moiety, which produces signals almost analogous to **306**, previously discussed in Chapter 5. Having completely assigned the signals in the ^{1}H NMR spectrum, a CH correlated spectrum allowed for the unambiguous assignment of all the hydrogen-bearing carbons. Analysis of **484b** by high resolution mass spectrometry afforded a mass of 531.1711 amu, in good agreement with the expected value of 531.1716 amu.

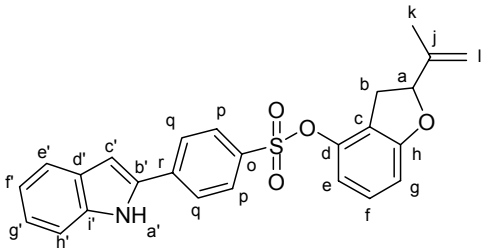
6.1.3.24 Yet further derivatisation, forming 2-isopropenyl-2,3-dihydrobenzofuran-4-yl 4-(1*H*-indol-2-yl)benzenesulfonate – 484c

Scheme 179



With enough **484b** in hand to perform yet one more derivatisation, we decided to remove the Boc protecting group from the indole moiety in the hope that we would *then* form a

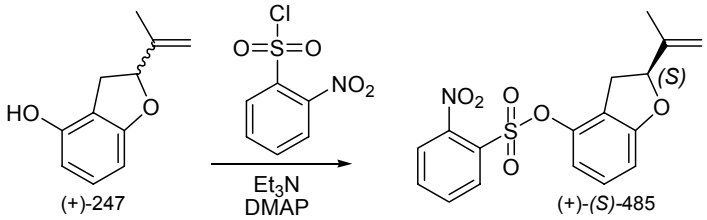
solid for X-ray crystallographic analysis. Therefore, **484b** (Scheme 179) was adsorbed onto silica gel and subjected to bursts of μ-wave radiation successfully cleaving the Boc protecting group in a method which we had used successfully on several of our previous compounds. The product, was purified by column chromatography affording **484c** in 60% yield as a white solid. Recrystallisation of this material was easily achieved from diethyl ether and in the hope of finally being able to confirm the absolute stereochemistry of our benzofuran **(+)-247**, a crystal was selected and analysed by X-ray crystallography, thereby revealing a Pbca space group - **484c** was indeed centrosymmetric and therefore racemic. Evidently, during one of the two derivatisation steps, **484** had racemised. We suspect that during the Suzuki coupling, which employed a Pd^0 catalyst, the isopropenyl benzofuran moiety reformed the Pd π-allyl complex, facilitated by ring opening of the dihydrofuran, followed by ring closing again to reform the benzofuran. However, in the absence of a chiral ligand, the reformation of the benzofuran occurred without any stereochemical control. This result, although frustrating at the time was nevertheless an important one as it revealed that the future planned coupling of the chiral benzofuran **156** and chroman **154** moieties, using a Pd^0 mediated carbonylative coupling to synthesise rotenone, may in fact lead to racemisation of the chiral isopropenyl group. However, so as not to detract from the main thrust of this section, this potential problem, as well as an alternative route are discussed at the end of this chapter in the concluding remarks.



In the ^{1}H NMR spectrum, the presence of a broad deshielded singlet at 8.52 ppm confirms that the Boc group is no longer present. This singlet is produced by the indole NH proton, $H_{a'}$. Fortunately, in the ^{1}H NMR spectrum the only overlapping signals were those for protons $H_{a'}$ and H_f. As was found for this compound's precursor **484b**, the signals for the benzofuran and indole moieties of **484c** are very similar to the ^{1}H NMR spectra obtained for the individual compounds previously synthesised, and so using NOE and COSY spectra previously obtained, completely assigning the ^{1}H NMR spectrum for **484b** was possible. A CH correlated spectrum allowed for the unambiguous assignment of all the hydrogen-bearing carbons.

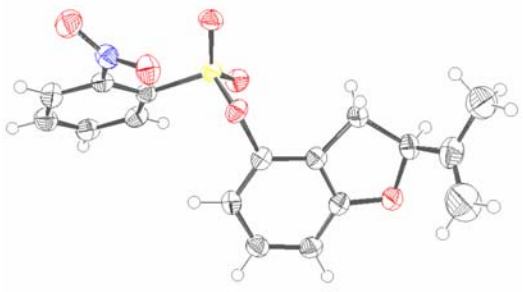
6.1.3.25 Derivatisation of the (+)-dihydrobenzofuran enantiomer to (+)-*(S)*-2-isopropenyl-2,3-dihydrobenzofuran-4-yl-2-nitrobenzenesulfonate – 485

Scheme 180



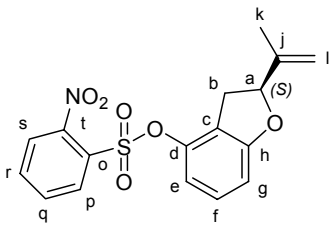
Continuing our pursuit to unambiguously assign the stereochemistry of our chiral compound **(+)-247** by X-ray crystallography, we decided to try a nitrobenzenesulfonate derivative (Scheme 180). Using essentially the same conditions that were employed to prepare the previous two derivatives, the nitrobenzenesulfonate derivative ***(S)*-485** was obtained in excellent yield. Moreover, after purification by column chromatography, evaporation of the solvent finally afforded an off white solid. Nevertheless, the benzofuran ***(S)*-485** seemed unrelenting in its quest not to reveal its stereochemistry as obtaining suitable crystals for crystallography proved quite difficult. Initially, several recrystallisation attempts only afforded a fluffy white powder, unsuitable for analysis by X-ray crystallography. However, with persistence, fine needle-like crystals were eventually obtained. Analysis of one of these crystals by X-ray crystallography revealed that we had indeed obtained the *(S)*- enantiomer as we had expected (Figure 56), consistent with the work done by Trost on his synthesis of several chroman derivatives.[92]

Figure 56



Crystal structure of (+)-*(S)*-2-isopropenyl-2,3-dihydrobenzofuran-4-yl-2-nitrobenzenesulfonate

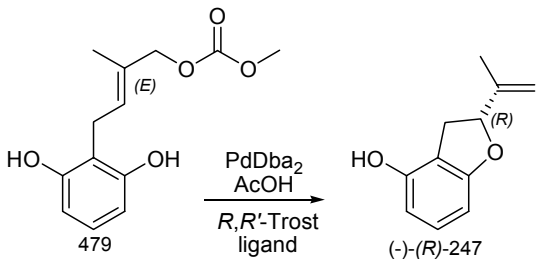
Crystallographic analysis of the benzofuran derivative revealed a chiral P2(1)2(1)2(1) spacegroup with unit cell dimensions: a = 5.74 Å, b = 13.11 Å and c = 22.27 Å. The R−factor for this crystal structure was 3.82%.



In the ^{1}H NMR spectrum, the presence of the nitro group on the nitrobenzene sulfonate significantly deshields all the protons associated with this moiety, and so there is no overlap with any of the protons on the aromatic ring of the benzofuran moiety. The most deshielded proton is H_s, producing a doublet at 8.00 ppm. In the region 7.89-7.81 ppm, there are two overlapping multiplets which are assigned to protons H_p and H_q. Finally, the least deshielded signal associated with this moiety would be H_r, producing a multiplet in the region 7.76-7.66 ppm. Regarding the protons on the benzofuran moiety, H_f once again produces the most deshielded signal - its triplet is located at 7.05 ppm. Protons H_g and H_e produce doublets at 6.73 ppm and 6.55 ppm, respectively. The proton on the stereogenic carbon, H_a couples to methylene protons H_b, producing a triplet at 5.18 ppm. These methylene protons however, being adjacent to this stereogenic carbon produce two double doublets at 3.44 ppm and 3.03 ppm. The geminal alkene protons, H_l, show only the faintest sign of coupling in the ^{1}H NMR spectrum as an expansion of their signals reveals two singlets with very slight deformation of shape. These two signals are located at 5.05 ppm and 4.90 ppm. Finally, the methyl protons, H_k, unable to couple to any other protons produce a singlet at 1.71 ppm. The specific rotation for this compound is $[\alpha]_D^{19}$ = +12.0, measured in chloroform.

6.1.3.26 Synthesis of (-)-*(R)*-2-isopropenyl-2,3-dihydrobenzofuran-4-ol using the *R,R'*-Trost ligand – (-)-*(R)*-247

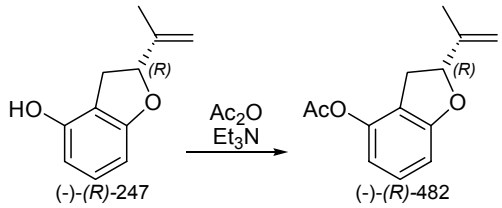
Scheme 181



Having successfully synthesised the *(S)*- benzofuran in excellent enantiomeric excess, and confirmed the stereochemistry by X-ray crystallography we now needed to prove that we could obtain the *(R)*- benzofuran in equally good enantiomeric excess using the *R,R'*-Trost ligand.* To this end, the chiral Pd-Trost ligand catalyst was once again preformed in thoroughly degassed dichloromethane by the addition of just over two equivalents of *R,R'*-Trost ligand per one equivalent of $PdDba_2$ (Scheme 181). As the ligand exchange proceeded, the solution gradually changed colour from wine red to yellow. It was found that for this reaction, 3 mole % of palladium, followed by 8 mole % of the *R,R'*-Trost ligand was adequate to catalyse the reaction to completion. Prior to adding the allyl carbonate, 1 mole equivalent of acetic acid was once again added to slow down the reaction, allowing for better thermodynamic orientation of the chiral Pd-ligand and therefore leading to better enantioselectivity. Finally, the carbonate was added and the reaction was left to proceed for 18 hours at 25 °C. Analysis of the reaction mixture by TLC indicated that all the starting material had reacted. The desired benzofuran ***(R)*-247** was purified by column chromatography and obtained as a clear oil in good yield. Although determination of the enantiomeric excess for this reaction would have to wait until after the conversation to the corresponding acetate, the specific rotation looked promising as it was very close in magnitude to that obtained for the *(S)*- enantiomer ***(S)*-247**, though opposite in sign. For this compound, an $[\alpha]_D^{19} = -18.1$ was obtained.

6.1.3.27 Conversion of (-)-*(R)*-2-isopropenyl-2,3-dihydrobenzofuran-4-ol to the corresponding acetate in order to determine the enantiomeric excess by HPLC – (-)-*(R)*-482

Scheme 182

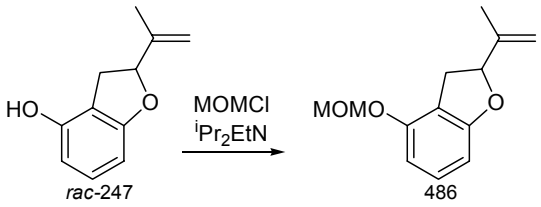


* The observant reader may in fact wonder why on earth we synthesised the *(S)*- benzofuran first anyway, as we actually require the (*R*)- benzofuran in order to synthesise rotenone. The reason for this is quite simply that at the start of the chiral investigations, we only had the *S,S'*-Trost ligand on hand and so it made sense to first investigate the efficacy of the chiral π-allyl Pd cyclisation using this ligand, rather than purchasing new ligand.

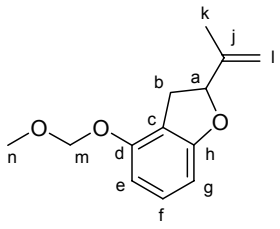
Having performed the chiral cyclisation, determination of the enantiomeric excess for this *(R)*- benzofuran ***(R)*-247** was of vital importance as it is this enantiomer which will be needed as the precursor in the proposed synthesis of rotenone. As was discovered when determining the enantiomeric excess of the *(S)*- benzofuran ***(S)*-247**, conversion of the phenolic hydroxyl group to the corresponding acetate is necessary to completely separate the enantiomers on the Chiralcel OJ chiral column. Thus, using the same methodology as was used previously, the *(R)*- benzofuran was treated with acetic anhydride in the presence of triethylamine, rapidly converting it to the acetate derivative ***(R)*-482** (Scheme 182). Purification by column chromatography afforded the desired compound as a colourless oil in good yield. Finally, determination of the enantiomeric ratio by HPLC using a Chiralcel OJ column and 10% isopropyl alcohol/hexane as a mobile phase resulted in complete resolution of the two enantiomers and pleasingly, a ratio of 96:4 was obtained for the *R*:*S* ratio. This enantiomeric excess of 92% for the *(R)*- benzofuran is analogous to the result obtained for the *(S)*- benzofuran.

6.1.3.28 Attachment of a suitable *ortho* director to (±)-2-isopropenyl-2,3-dihydrobenzofuran-4-ol – 486

Scheme 183



As the final step in the synthesis of the rotenone precursor, the attachment of a suitable *ortho* directing group to the phenolic hydroxyl needed to be demonstrated. Although a variety of *ortho* directing protecting groups could possibly be used, we decided in this case to simply attached a MOM protecting group. To this end, racemic **247** was treated with MOMCl and diisopropylamine affording the **486** in good yield.



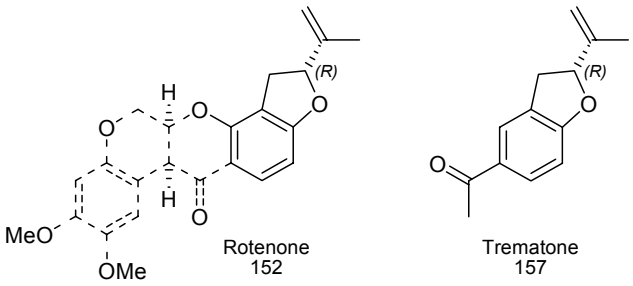
In the ^{1}H NMR spectrum, the appearance of two new singlets confirms that the MOM group is present. Protons H_m produce a deshielded singlet at 5.18 ppm and the methyl protons, H_n, are somewhat upfield at 3.48 ppm. The remaining signals in the ^{1}H NMR spectrum have hardly changed in comparison to the compound's precursor, **247**. In the IR spectrum, the disappearance of the large OH stretch once again confirms that the phenolic hydroxyl has been converted to the MOM ether.

6.1.4 A formal synthesis of trematone and fomannoxin

The recent success in the chiral syntheses of both the *(R)*- and *(S)*- rotenone benzofuran precursors **247** prompted us to investigate other natural products where we could apply this methodology to access either the natural product itself, or to least synthesise a viable chiral precursor to the natural compound. As it turns out, the already synthesised benzofuran rotenone precursor is already very similar in structure to a naturally occurring toxin known as trematone **157** (Figure 57), found in certain plants such as the white snakeroot (*Eupatorium rugosum*). This toxic plant is responsible for the death of animals which graze upon it and initially it produces symptoms known as "trembles" and for this reason the toxin contained in the plant was appropriately named as trematone. The isolation of trematone and a more in depth study of its effects, as well as details pertaining to other compounds similar to trematone has already been covered in the introductory section of this thesis and the interested reader is requested to refer to Chapter 2 for more information.

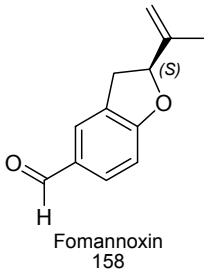
Trematone consists of a dihydrobenzofuran core, chirally substituted with an isopropenyl group in the 2-position, analogous to the benzofuran moiety found in rotenone **152**. In fact, the stereochemistry at the 2-position in trematone is also *(R)*, as is found in rotenone. However, instead of containing the extra oxygen functionality at the 4-position, an acetyl substituent is found at the 5-position in trematone.

Figure 57



In addition, another structurally similar natural product known as fomannoxin **158** (Figure 58), differs from trematone only slightly in that instead of having an acetyl group at the 5-position, this compound has a formyl group. Importantly though, although it bears the same 2-isopropenyl-2,3-dihydrobenzofuran basic structure, the stereochemistry at the 2-position is the opposite to that found in trematone and rotenone.

Figure 58



Fortunately, the synthetic strategy employed for the synthesis of the rotenone precursor allowed us to synthesise both the *(R)*- and *(S)*-2-isopropenyl-2,3-dihydrobenzofuran units in excellent enantiomeric excess, and it was hoped that this same strategy could be employed to access precursors leading to trematone and fomannoxin.

6.1.5 Asymmetric synthesis of the required chiral dihydrobenzofuran - precursors to trematone and fomannoxin

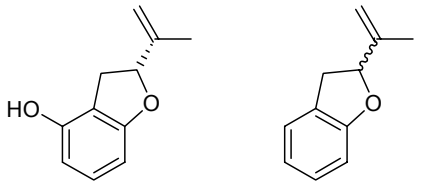
6.1.5.1 Outline of the synthetic strategy

In the introductory section of this thesis (Chapter 2), previous syntheses of trematone and fomannoxin were discussed wherein a chiral resolution procedure was employed to access the chiral dihydrobenzofuran skeletons. The syntheses of both compounds start from 2-

acetylbenzofuran, which is converted over several steps to racemic coumarilic acid. A chiral resolution step at this point using amphetamine afforded the separate enantiomers of coumarilic acid, which was later acetylated. Unfortunately, deacetylation of this compound afforded the chiral 2-isopropenyl-2,3-dihydrobenzofuran compounds in exceptionally poor yields. An improved procedure employing a dehydration step to form the isopropenyl moiety did not greatly improve the yield. Finally, the chiral 2-isopropenyl-2,3-dihydrobenzofuran compounds could then either be acetylated leading to trematone or formylated leading to fomannoxin.[77] Overall however, the use of a chiral resolution step, as well as several poor yielding steps resulted in very low yielding syntheses. For a more detailed description of these syntheses, the interested reader is referred to Chapter 2 in this thesis.

Using our methodology however, we envisaged that we could obtain both the *(R)* and *(S)*-2-isopropenyl-2,3-dihydrobenzofuran compounds **167** (Figure 59) in good yield. This would constitute a formal synthesis of trematone and fomannoxin as the acetylation and formylation steps have previously been accomplished on these compounds.[77]

Figure 59



Rotenone precursor *(R)*-247

Trematone & fomannoxin precursors: *(R)*- & *(S)*-167 resp.

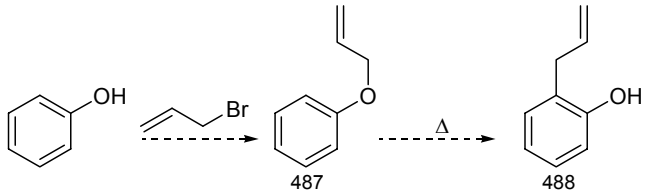
Our strategy to synthesise the appropriate chiral benzofuran would be very similar to that employed previously for the rotenone precursor and so only the parts of the synthesis that differ will be dealt with thoroughly in the following outline. Of course, the major difference between the two syntheses would be the absence of the second phenolic functionality. This however, has rather large implications on the synthesis in that it simplifies it enormously.

One of the major issues in the synthesis of the rotenone precursor was the introduction of the allyl group between the two hydroxyl functionalities, and the issue of appropriate

protection to achieve this. The *ortho* directing protecting groups we required at the start of synthesis to introduce the allyl functionality later proved to be problematic as they could not be removed in the presence of the required acetate or carbonate. On the other hand, initial introduction of protecting groups which would not prove to be problematic later in the synthesis (for example silyl groups) did not work as *ortho* directors for lithiation. Thus, a protecting group switch was required after the allylation step. Fortunately, these steps proved to be high yielding. Nevertheless, the process of removing and replacing protecting groups lengthened the synthesis.

However, the presence of only one phenolic hydroxyl group in the trematone precursor meant that we could easily employ an *O*-allylation forming **487**, and then a Claisen rearrangement would provide us with the correctly allylated material **488**, eliminating the need for *ortho* directing groups and complicated protection strategies (Scheme 184).*

Scheme 184



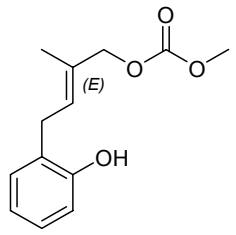
Once the allylated product had been obtained, we could simply proceed directly with the silyl protection and there would be no need for a protecting group switch. From this point of view, the synthesis of the trematone precursor actually looked like it would be shorter than that of the rotenone precursor. In fact, as it turned out, the steps including *O*-allylation followed by a Claisen rearrangement turned out not to be necessary, as the required 2-allylphenol **488** is a commercially available compound, and we had it in hand.

Having wrung out the slight difference in this synthesis as compared to the rotenone precursor, we envisaged that the remainder of the synthesis would be very much the same.

* Incidentally, although not mentioned in the rotenone precursor's section, this procedure of *O*-allylation followed by a Claisen rearrangement was attempted on resorcinol in the hope of similarly obtaining the appropriately substituted 2-allyl resorcinol. However, the route was abandoned as the allylation was inefficient, and the Claisen rearrangement afforded mainly the wrong product – i.e. 4-allylbenzene-1,3-diol.

Of course, our goal was to reach a similar carbonate precursor **489** (Figure 60) in the hope of being able to perform chiral Pd π-allyl mediated cyclisation reactions using the Trost methodology.

Figure 60



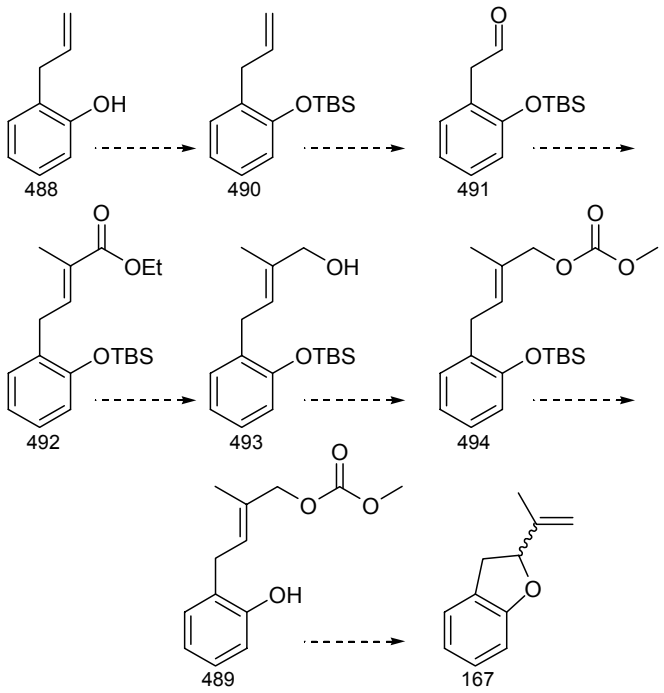
489
Required precursor for
the π-allyl Pd cyclisation

Once again however there were certain key features in the compound that we needed to achieve. For an enantioselective cyclisation, it would be important to have only the *(E)*-allyl carbonate **489**. Any contamination by the *(Z)*- geometrical isomer would lead to diminished ee's. We also needed a strategy whereby the phenolic hydroxyl could be deprotected without affecting the carbonate. Fortunately, for reasons as recently discussed, this seemed like it would be easier to achieve than what was found for the rotenone precursor.

6.1.5.2 A planned synthesis of both the *(R)*- and *(S)*-2-isopropenyl-2,3-dihydrobenzofurans

Starting from readily available 2-allylphenol **488** (Scheme 185), a silyl protection affording **490** followed by ozonolysis to produce **491** should put us in a position to once again perform the Horner-Wadsworth-Emmons reaction which had proven to be so successful in forming only the required *(E)*- alkene in the preceding synthesis of the rotenone precursor. Having completed this reaction and obtained **492**, a reduction yielding **493**, followed by conversion to the carbonate **494** and finally silyl deprotection should furnish the allyl carbonate **489**. Finally, enantioselective π-allyl Pd cyclisations using the Trost ligand should allow us to synthesise either isomer of 2-isopropenyl-2,3-dihydrobenzofuran **167**.

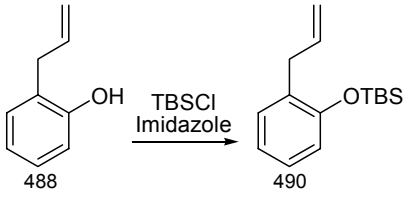
Scheme 185



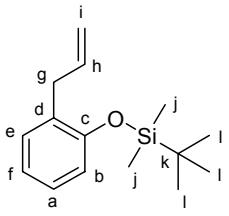
A planned synthesis for the required *(R)*- and *(S)*-benzofurans

6.1.5.3 Synthesis of (2-allylphenoxy)(*tert*-butyl)dimethylsilane – 490

Scheme 186



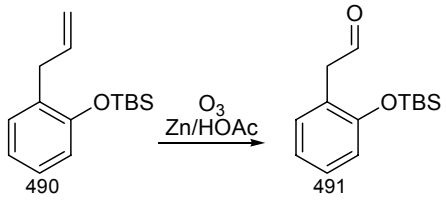
With the knowledge in hand that the silyl protection of allyl phenols is readily accomplished, this first step in the synthetic sequence was immediately carried out on a large scale. Treatment of 5 g of 2-allylphenol with TBSCl and imidazole in acetonitrile resulted in the formation of **490** within 10 hours. Purification of this material proved to be somewhat more tricky than anticipated as this compound was so non-polar that it was virtually unretained on a silica column even when using 1% EtOAc/Hexane as a solvent. Fortunately, the reaction did not produce any side products and so (2-allylphenoxy)(*tert*-butyl)dimethylsilane **490** was still obtained cleanly and in excellent yield.



In the ^{1}H NMR spectrum, the by now all too familiar pattern of signals associated with these compounds was immediately apparent. The obvious differences included the presence of an extra aromatic proton and the integrals for the methyls associated with the silyl were only half the values as observed for the rotenone precursor. The interesting tdd signal for proton H_h, coupling to the methylene protons H_g as well as to each of the alkene protons, H_i was once again present at 6.01 ppm. The methylene protons H_g, coupling to H_h produce a doublet at 3.41 ppm. The alkene protons H_i produce overlapping signals in the region 5.10-5.04 ppm. On the aromatic ring, protons H_e and H_a produce the most deshielded signals, overlapping in the region 7.22-7.06 ppm. Proton H_f, located *para* to the silyloxy group is located slightly upfield at 6.92 ppm and produces a signal which appears as a triplet, even though protons H_e and H_a are not equivalent. The most upfield of the aromatic protons is H_b, this doublet is located at 6.83 ppm. Finally, the methyl protons on the silyl group are located in their typically upfield position. The larger of the two singlets is assigned to protons H_l at 1.05 ppm, and slightly upfield of this, the singlet for protons H_j is found at 0.27 ppm. In the ^{13}C NMR spectrum, the deshielded quaternary carbon located at 153 ppm can be assigned to C_c. On the other extreme, the two equivalent carbons attached to the silicon atom, C_j, are located at -4.1 ppm.

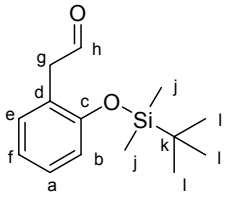
6.1.5.4 Ozonolysis to synthesise 2-(2-(*tert*-butyldimethylsilyloxy)-phenyl)acetaldehyde – 491

Scheme 187



Ozonolysis of the rotenone precursor had proven to be a very successful method to generate the aldehyde functionality and we intended to use it here as well (Scheme 187). Once again, in order to avoid over-oxidation, the starting material was only exposed to ozone for periods of 5 minutes at -85 °C. After each exposure, the residual ozone in the solution was quickly dispersed by bubbling N_2 gas into the solution and the progress of the

reaction was determined by TLC. It was astonishing to note how the absence of one *O*-silyloxy group on the benzene ring decreased the reactivity of this compound. In comparison to the rotenone precursor, this compound **490** required far more exposure time in order to consume almost all the starting material, even though the conditions employed were analogous to that which was used previously. Nevertheless, after several cycles of exposing the material to ozone and progress determination by TLC, the reaction was deemed almost complete and the ozonide was once again reduced using Zn/HOAc. The excess acetic acid employed in this reduction has the ability to begin cleaving the silyl ether. Therefore, it was found to be extremely important to add the excess Zn/HOAc whilst the reaction was still at -85 °C. Once added, the reaction was allowed to slowly warm and at about -30 °C, the reduction proceeded, rapidly converting the ozonide to the aldehyde.[*] At this point, neutralisation of the excess acetic acid was found to be necessary as once the reaction warmed to near room temperature, rapid acid mediated cleavage of the silyl ether began to occur.[†] Although this reaction did prove to be somewhat tricky, after several repetitions these procedures could be carried out without too much difficulty, smoothly affording the aldehyde as a waxy white solid in excellent yield after purification by column chromatography.



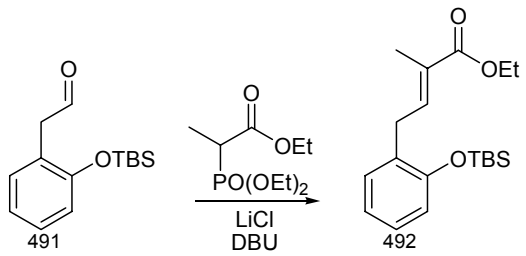
In the ^{1}H NMR spectrum, the appearance of a triplet in the downfield region at 9.70 ppm is a welcome indication that the aldehyde is in place, and this signal can be assigned to the aldehyde proton, H_h, coupling to H_g. The methylene protons, H_g, couple to H_h, resulting in a doublet at 3.64 ppm with a remarkably smaller coupling constant of just 1.89 Hz, as compared to 6.51 Hz when H_h was part of the former alkene. As far as the protons on the aromatic ring are concerned there has been little change. In the ^{13}C NMR spectrum, a deshielded signal at 200 ppm attests to the presence of the carbonyl carbon. In the IR spectrum, a strong C=O absorption is observed at 1732 cm^{-1}.

[*] This was determined by frequently monitoring the reaction by TLC as it slowly warmed. Below this temperature, almost no reduction seemed to have occurred.

[†] Of course, PPh_3 would be a better reductant, but the R_f of the excess PPh_3 is identical to the product. Dimethylsulfide does not reduce the ozonide at all.

6.1.5.5 A Horner-Wadsworth-Emmons reaction to synthesise *(E)*-ethyl 4-(2-(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-enoate – 492

Scheme 188



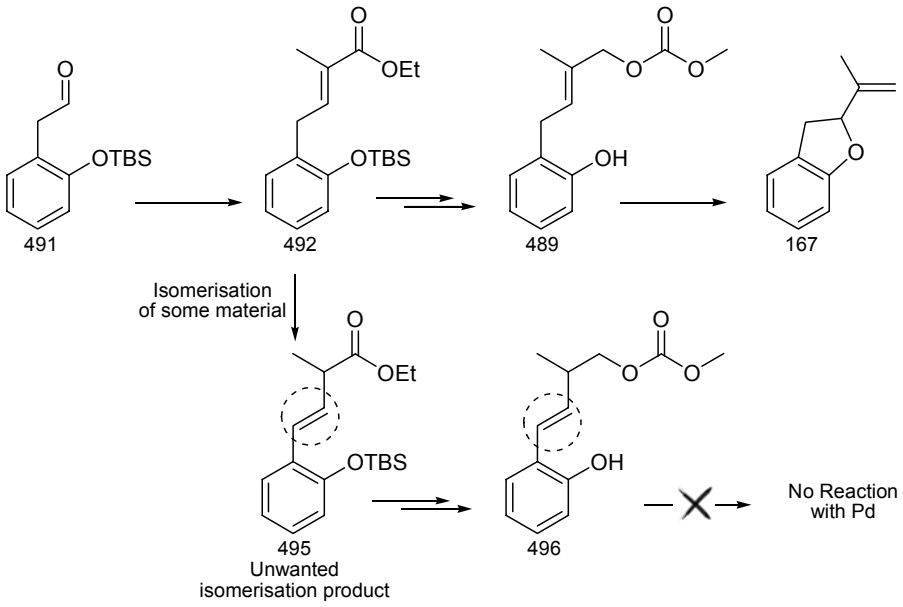
The Horner-Wadsworth-Emmons reaction had proven to be a very successful method for obtaining exclusively the *(E)*- alkene in the synthesis of the rotenone precursor and we envisaged that we would obtain the same result here. Using the same procedure, the ylide was preformed by the addition of DBU to ethyl 2-(diethoxyphosphoryl)propanoate followed by the addition of LiCl. After a few minutes the LiCl dissolved and the aldehyde was slowly added to the ylide solution, resulting in an exothermic reaction.[*] The reaction was left to proceed for 18 hours and as expected, analysis of the reaction mixture after this time indicated a single new compound had formed. However, after purification by column chromatography analysis of the new material by NMR spectroscopy clearly indicated that *more* than one compound present. Careful analysis by TLC only indicated the presence of only one compound suggesting that the impurity had exactly the same R_f as our desired product. At first it was assumed that this impurity was the *(Z)*- alkene and we had formed a mixture of the two alkenes. However, the ^{1}H NMR spectrum was not in agreement with this conclusion. This impurity had a similar spectrum to the desired compound but some signals were puzzling and certainly did not fit the postulation that this impurity was simply the *(Z)*- isomer.

Unfortunately, in order to reveal the nature of this elusive side product, we'll need to jump ahead several reactions in this synthetic sequence Since it was not possible to separate these two compounds, we decided to proceed with the reduction, in the hope that they would then be separable. This was not to be, and in fact, not only were these next two

[*] In fact, this reaction could be quite exothermic on larger scales (masses larger than 1 g) and so a cool water bath was often used as a heat sink.

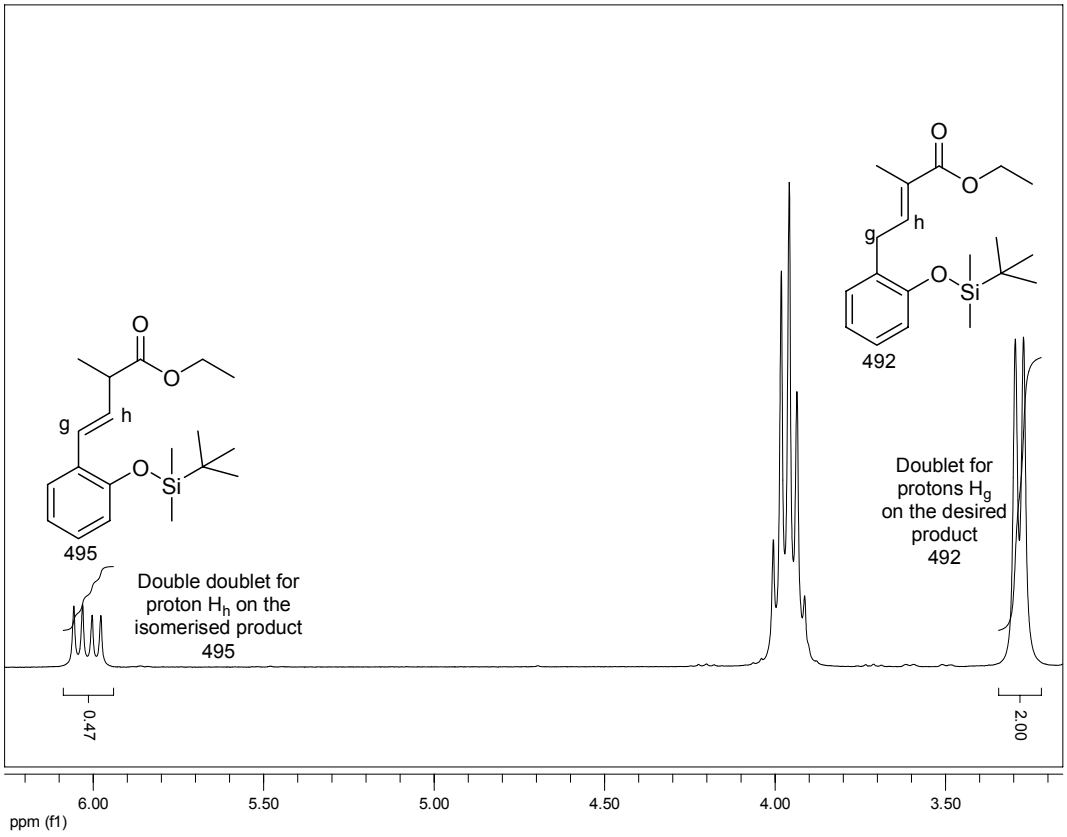
compound inseparable but it appeared that the side product had also reacted with the $LiAlH_4$ and therefore confirmed our suspicions that it was similar in structure to our desired compound. As it turned out, the side product remained completely inseparable through all the subsequent steps leading up to the π-allyl Pd cyclisation. Moreover, it seemingly underwent the same transformations as the desired compound, once again causing us to revisit the idea that it was simply the *(Z)*- alkene. Finally however, having carried this side product through the steps of reduction, addition of the carbonate and silyl deprotection, and all the while the two compounds remained completely inseparable, we set about the π-allyl Pd cyclisation. In this case, as we did for the rotenone precursor, this initial cyclisation was not done using the chiral ligand but rather using triphenylphosphine. Analysis of the reaction at this point indicated that that a new product was forming at higher R_f as expected, but a large portion of the starting material remained unreacted! After purification of these two compounds by column chromatography all was revealed - there was a very good reason as to why it appeared as though some of the starting material had not reacted. The unreacted material was in fact the elusive side product which had also undergone all the preceding transformations but could not undergo the π-allyl Pd reaction for one good reason – the alkene was not where it should have been! During the Horner-Wadsworth-Emmons reaction (Scheme 189), a large portion of the newly formed product **492** had isomerised so that the alkene was now in conjugation with the aromatic ring **495**. Although this new compound would indeed undergo all the subsequent transformations as we observed, the new location of the alkene **496** could not facilitate the formation of the π-allyl-Pd complex, and so it remained unreacted, whereas **489** reacted to form the benzofuran **167**.

Scheme 189



With the knowledge in hand as to the structure of the side product obtained during the Horner-Wadsworth-Emmons reaction, we could now determine the cause of this problem and hopefully, circumvent it by changing the reaction conditions. When this reaction was first performed we obtained only 66% of the desired compound **492** and 33% of the isomerisation product **495**, as determined from a ^{1}H NMR spectrum of the mixture. As can be seen in a portion of the spectrum (Figure 61), the double doublet at 6.02 ppm corresponds to proton H_h on the isomerised product **495** and the doublet at 3.28 ppm corresponds to the methylene protons H_g on the desired product **492**. Given the ratio of the signals, and of course taking into consideration that the signal for the methylene protons H_g actually accounts for two protons, the ratio of the two compounds is approximately 0.5 to 1, or 66% of the desired compound.

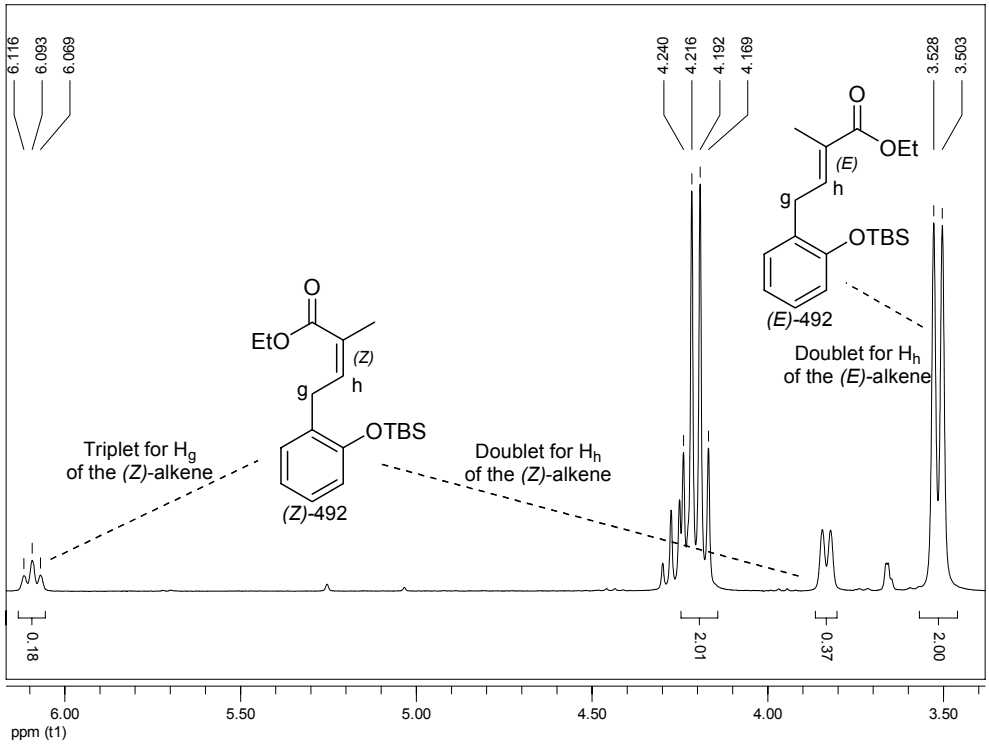
Figure 61



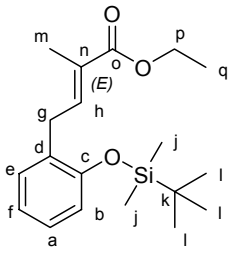
As was mentioned previously, when the Horner-Wadsworth-Emmons reaction was first conducted, the ylide was initially formed and then the aldehyde was slowly added to the ylide solution. It seems reasonable, that given the basic nature of the ylide, and the fact that during the first stages of the addition the ylide would also be in a large excess in comparison to the aldehyde **491**, it is likely that base-induced isomerisation was occurring, assisted by the acidic benzylic protons and driven by the probable thermodynamic preference for conjugation of the double bond with the aromatic ring system, thereby forming **495**. With this knowledge in hand we decided to modify the reaction conditions. To avoid isomerisation of the product **492** the order of addition of the reagents was changed to prevent **492** being exposed to base. To this end, the aldehyde, **491**, the phosphonate and LiCl were all added to the flask already containing acetonitrile. Finally, the base, DBU, was then added very slowly, thereby reacting instantly with the phosphonate, producing the ylide in low enough concentration so that it subsequently reacted immediately with the aldehyde. Moreover, only 0.9 equivalents of DBU was added

to ensure that it was not in excess at the end of the reaction. This modified strategy was employed and the results thereof were gratifying. The double doublet at 6.02 ppm was virtually undetectable – only observable as tiny signals on the baseline if the spectrum was magnified intensely. A rough integration of this signal indicated that the isomerisation product **495** constituted less than 0.2% of the material. However, there was still a price to pay – the presence of a new and poorly resolved triplet at 6.09 ppm had an all too familiar look about it (Figure 62). Upon closer inspection of the ^{1}H NMR spectrum, it was apparent that most of the signals seemed slightly 'contaminated' by smaller, though similar signals. Clearly, as a result of the modified methodology, we had indeed successfully circumvented the formation of the isomerisation product almost entirely, but only to now be plagued with some of the *(Z)*- geometrical isomer ***(Z)*-492** as a contamination product. This of course could have serious implications later on because as discussed previously, a mixture of *(E)*- and *(Z)*- isomers prior to the chiral π-allyl Pd cyclisation would lead to poor enantioselectivity. Fortunately however, the *(Z)*- product only constituted about 16% of the material, and the desired *(E)*- isomer the remaining 84%. Even more fortunately, the prevalence of the *(Z)*- isomer was drastically reduced in the next step. Owing to a slight difference in R_f between the *(E)*- and *(Z)*- geometrical isomers, separation of the unwanted *(Z)*- isomer was made possible.

Figure 62



In summary, using the modified experimental procedure, the desired Horner-Wadsworth-Emmons product ***(E)*-492** could be synthesised in good yield, having a slight contamination of the undesired *(Z)*- geometrical isomer which could be removed in the next step by chromatography.

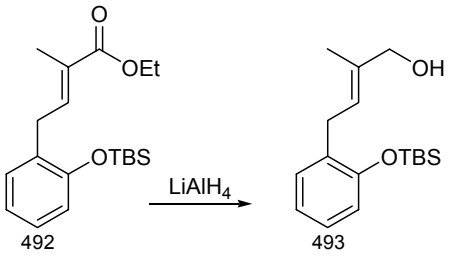


In the ^{1}H NMR spectrum of ***(E)*-492**, the presence of a new singlet at 1.96 ppm, as well as a quartet at 4.20 ppm and a triplet at 1.30 ppm attests to the presence of the ester after the Horner-Wadsworth-Emmons reaction. These signals correspond to protons H_m, H_p and H_q respectively. The two large singlets at 1.04 ppm and 0.28 ppm can be assigned to the *tert*-butyl methyl protons, H_l, and the methyl protons H_j, both of which are associated with the silicon protecting group. The alkene proton, H_h, is drastically shifted downfield in comparison to the allyl precursor **490**. No doubt, extended conjugation into the α,β-unsaturated ester results in deshielding of this proton. Its signal is now located in the region of 7.17-7.08 ppm, overlapping with the aromatic proton, H_a. Slightly upfield of these signals, protons H_e and H_f also produce overlapping signals in the

region 7.02-6.87 ppm. Proton H_b, *ortho* to the silyl ether is the least deshielded of the aromatic protons as its doublet is located at 6.84 ppm. Finally, the benzylic methylene protons, H_g, coupling to H_h produce a doublet at 3.52 ppm. In the ^{13}C NMR spectrum, a quaternary carbon located downfield at 168 ppm attests to the presence of the ester carbonyl, C_o. In the IR spectrum, the ester C=O stretch is located at 1713 cm^{-1}.

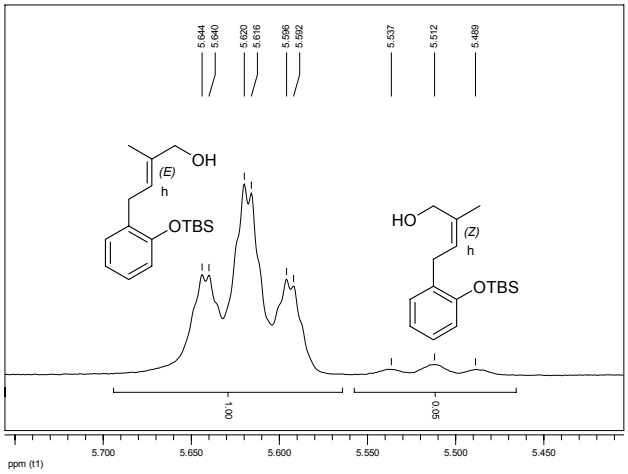
6.1.5.6 Reduction to synthesise *(E)*-4-(2-(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-en-1-ol – 493

Scheme 190

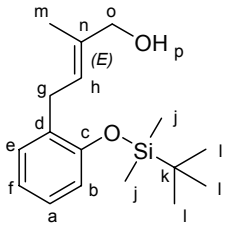


Ploughing along towards the desired carbonate, the reduction of the ester **492** to the alcohol **493** using lithium aluminium hydride in THF at 0 °C proceeded remarkably quickly (Scheme 190). As was learned from this same reaction conducted for the rotenone precursor, performing the reduction at 0 °C and closely monitoring the reaction by TLC is crucial, as extended reaction times cause cleavage of the silyl protecting groups. For the rotenone precursor, bearing two silyl-oxy functional groups on the benzene ring, this reaction took 4-5 hours to complete. However, to our surprise, the absence of one silyl ether on the benzene ring seemed to make a huge difference in the reaction rate. After allowing **492** to react for 1.5 hours, analysis of the reaction by TLC indicated that it was already complete! After workup and purification of the material by column chromatography, the desired alcohol was obtained in the modest yield of 65%. However, on a positive note, the presence of the *(Z)*- geometrical isomer was significantly diminished by the chromatography. By ^1H NMR spectroscopy, it appeared that we now had less than 5% of the *(Z)*- isomer present (Figure 63).

Figure 63



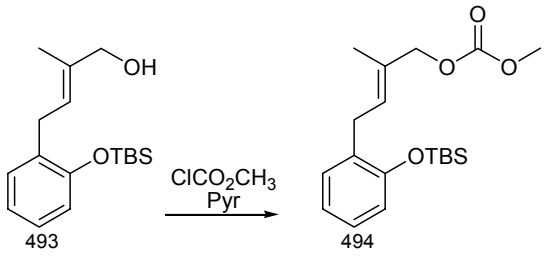
Signals for protons H_h of the *(E)*- and *(Z)*- geometrical isomers



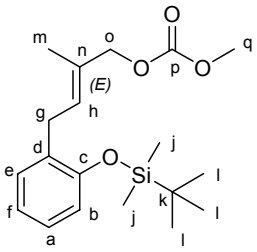
In the ^{1}H NMR spectrum, the disappearance of the two upfield signals associated with the ester is an immediate indication that the reduction has proceeded as planned. A broad singlet at 1.33 ppm attests to the presence of the hydroxyl proton, H_p. In the downfield region, the aromatic protons H_a and H_e have overlapping signals over the range 7.15-7.03 ppm. Proton H_f produces a multiplet over the range 6.91-6.86 ppm. Finally, proton H_b produces a doublet at 6.79 ppm. The reduction of the ester has resulted in an upfield shift of the alkene proton H_h, as electron delocalisation is no longer possible in the absence of the ester. Moreover, weak extended coupling is observed through the double bond. The former carbonyl carbon now bears two equivalent protons, H_o, and the absence of any coupling is evident by the fact that these protons produce a deshielded singlet at 4.05 ppm. Protons, H_g, produce a doublet in the expected benzylic region at 3.37 ppm. Finally, the methyl protons H_m produce a singlet at 1.77 ppm and a slight distortion in the shape of this singlet indicates that these protons may be involved in the extended coupling observed for proton H_h. In the IR spectrum, the hydroxyl group makes up for its reticent appearance in the ^{1}H NMR spectrum by providing a strong OH stretch at 3307 cm^{-1}.

6.1.5.7 Synthesis of *(E)*-4-(2-(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-enyl methyl carbonate – 494

Scheme 191



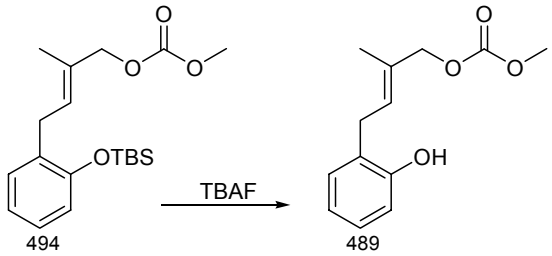
Nearing the final stages of our cyclisation precursor, one of the important functionalities to introduce is the leaving group for the Pd π-allyl complex formation. An acetate is often employed for this purpose but in the preceding rotenone work, it was discovered that the carbonate affords much better yields of the cyclised product. Therefore, the allyl alcohol **493** (Scheme 191) was similarly treated with choromethyl carbonate in the presence of triethylamine, rapidly forming the carbonate **494**. Purification by column chromatography proved uneventful, affording the desired compound in good yield as a clear oil. Interestingly, the desired *(E)*- alkene still had a 5% contamination of the *(Z)*- alkene, as determined by ^{1}H NMR spectroscopy.



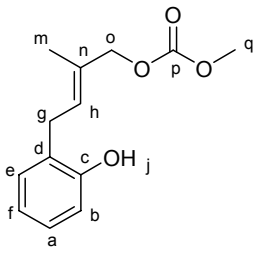
In the ^{1}H NMR spectrum, the entire contribution of the carbonate is to add one singlet, at 3.79 ppm, corresponding to the methyl protons H_q. For the most part the ^{1}H NMR spectrum remains largely similar to the alcohol precursor. An interesting observation is that the alkene proton, H_h, no longer appears to have long range coupling to the methyl protons, H_m. Therefore this signal is a triplet appearing at 5.71 ppm. The singlet for the methyl protons, H_m, appears upfield at 1.77 ppm. In the IR spectrum, the OH stretch is no longer present, and a new C=O stretch is observed at 1750 cm^{-1}.

6.1.5.8 Silyl deprotection affording *(E)*-4-(2-hydroxyphenyl)-2-methylbut-2-enyl methyl carbonate – 489

Scheme 192



As the final step before we could begin our chiral cyclisation investigations, removal of the silyl protecting group was required to provide the phenolic nucleophile. TBAF had previously proven to be a most successful reagent for this purpose and so it was used to remove the silyl functionality on this compound as well. Treatment of the silyl ether **494** with TBAF at 0 °C resulted in complete deprotection of the starting material within a few minutes as determined by TLC analysis (Scheme 192). The workup and extraction of the desired material proved uneventful and **489** was obtained as a clear oil in excellent yield after purification by column chromatography.*

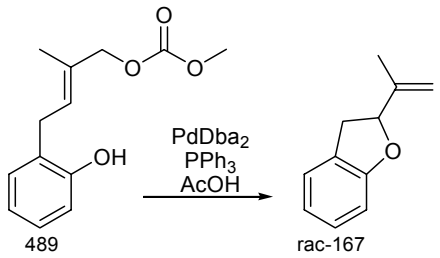


In the ^{1}H NMR spectrum, a new feature was a singlet integrating for one proton at 5.02 ppm. This is produced by the new phenolic hydroxyl proton, H_j. The alkene proton, H_h once again exhibits extended coupling to the methyl protons, H_m, as well as coupling to the methylene protons, H_g. This signal therefore appears as a triplet of doublets at 5.71 ppm. The presence of two deshielded singlets at 3.79 ppm and 4.57 ppm attests to the presence of the required carbonate functionality. These signals are assigned to protons H_q and H_o respectively. Finally, the methyl protons, H_m, produce a singlet at 1.81 ppm and a slight distortion in peak shape confirms some very weak extended coupling to the alkene proton, H_h. In the IR spectrum, a broad OH stretch is observable at 3454 cm^{-1}.

* By ^{1}H NMR spectroscopy, the unwanted *(Z)*- isomer, ***(Z)*-489** still appears to be present in trace amounts (4-5%).

6.1.5.9 Synthesis of racemic 2-isopropenyl-2,3-dihydrobenzofuran by π-allyl Pd chemistry using achiral triphenylphosphine as a ligand source – *rac*-167

Scheme 193

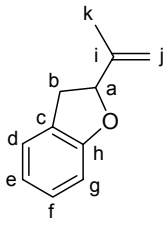


Having finally synthesised the required precursor for the Pd π-allyl mediated cyclisation reaction, we decided to first investigate the methodology using achiral triphenylphosphine as a ligand source (Scheme 193). To this end, the required catalytic system was first preformed by the addition of 5 equivalents of triphenylphosphine to 1 equivalent of $PdDba_2$, at room temperature, in thoroughly degassed dichloromethane. As the ligand exchange proceeded, the colour of the solution gradually changed from wine red to yellow. This process usually took about 10 minutes to complete however, in order to ensure complete exchange of the ligands, the reaction was usually left for 30 minutes. Having prepared the catalytic system, one equivalent of acetic acid was added* followed by the allyl carbonate **489** and the reaction was left to proceed for 18 hours at reflux. In terms of the amount of catalyst required to complete the reaction, it was found that 2-5 mole % of $PdDba_2$ converted all the starting material within a few hours at reflux. In fact, this brings up a very interesting point in terms of the effect of the ligand on the Pd metal. In the rotenone precursor work it was found that when triphenylphosphine was used as a ligand, the reaction did not actually proceed at room temperature in dichloromethane and had to be warmed slightly to the reflux temperature of dichloromethane. However, when the chiral bidentate Trost phosphine ligands were used, the reaction proceeded smoothly and was complete within a few hours at 25 °C. Clearly, the Trost ligand forms a better catalyst

* Of course, the addition of acetic acid is not strictly necessary here as its purpose is to slow down the reaction when using a chiral ligand, leading to better enantioselectivity. However, even though this reaction is not chiral, the acetic acid was added simply to reproduce as close a system as possible to the intended chiral cyclisation reactions.

along with the Pd, lowering the activation energy of the reaction in comparison to the triphenylphosphine-Pd catalytic system.

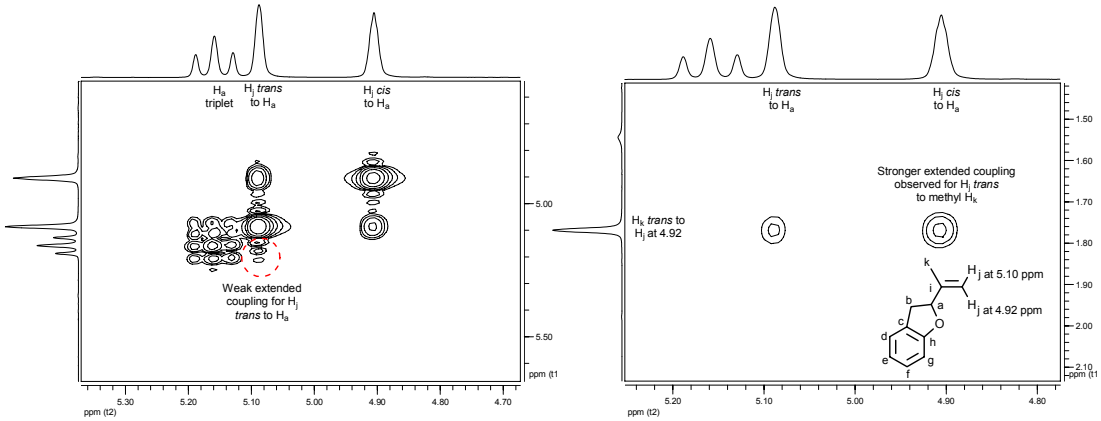
Thus, after refluxing the reaction for 18 hours, analysis of the reaction mixture by TLC indicated that all the starting material had been consumed and that a new product had formed at a higher R_f. Purification of this new compound by column chromatography resulted initially in a pleasant surprise as the clear oil obtained had a wonderfully sweet smelling aroma. This initial pleasant reaction gave way to one of consternation as the realisation dawned that it was currently the high vacuum pump upon which the compound was drying, that was now really getting the most enjoyment from this volatile compound's pleasant aroma! As a result, on this first attempt only a 50% yield was obtained. However, future repetitions of this reaction involved exercising rather more caution when drying the compound under vacuum and the yields of **167** were improved to above 70%.



In the ^{1}H NMR spectrum, the presence of two slightly distorted singlets in the mid-region of the spectrum is a good indication that the reaction has proceeded. These two signals correspond to the weakly coupling geminal alkene protons, H_j. Using a COSY spectrum it was possible to unambiguously assign these two signals appearing at 5.10 ppm and 4.92 ppm. As can be seen in the COSY spectrum (Figure 64), the signal at 5.10 ppm shows some weak extended coupling to proton H_a, which appears as a triplet at 5.17 ppm. This extended coupling is not observed for the alkene proton at 4.92 ppm. This would imply that the singlet at 5.10 ppm is for the alkene proton in a *trans* arrangement to the proton H_a. In agreement with this information is the fact that also observable in the COSY spectrum is the stronger extended coupling of the alkene signal at 4.92 ppm to the methyl protons, H_k. This would imply that the signal at 4.92 ppm is for the alkene proton in a *trans* arrangement to the methyl protons, H_k. As for the remaining protons in the benzofuran system: The methylene protons H_b, adjacent to the stereogenic carbon's proton, H_a, produce two double doublets at 3.34 ppm and 3.05 ppm. Protons H_d and H_f have overlapping signals in the region 7.17-7.09 ppm and protons H_e and H_g also produce overlapping signals in the region 6.86-6.79 ppm. Furthermore, in the COSY spectrum a weak extended coupling can be observed for the most deshielded proton in the spectrum, in

the region 7.17-7.12 ppm to the methylene protons H_b, confirming our assignment of H_d as this deshielded aromatic proton.

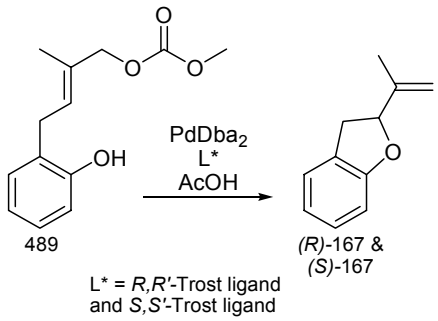
Figure 64



A COSY spectrum allows for unambiguous assignment of the geminal alkene protons

6.1.5.10 Synthesis of *(R)*- and *(S)*-2-isopropenyl-2,3-dihydrobenzofuran by π-allyl Pd chemistry using chiral Trost ligands – (+)-*(R)*-167 and (-)-*(S)*-167

Scheme 194



Having successfully accomplished several achiral cyclisations we now set about synthesising the separate enantiomers of 2-isopropenyl-2,3-dihydrobenzofuran (Scheme 194). To this end, we hoped that the methodology found to be very successful for the rotenone precursor would be just as successful with this compound and provide us with equally good enantiomeric excesses of each isomer. Thus, into thoroughly degassed dichloromethane was placed 2 mole % of $PdDba_2$, followed by 6 mole % of the *S,S'*-Trost ligand. After 30 minutes, the ligand exchange was complete and acetic acid was added to the yellow solution to slow down the desired cyclisation reaction. Once this had been

completed, the allyl carbonate **489** was added and the reaction was left to proceed at 25 °C for 18 hours. After this time, analysis of the reaction mixture indicated that cyclisation had indeed taken place and after purification of the product, ^{1}H NMR analysis indicated that we had formed the benzofuran **167** as desired. However, it was the enantioselectivity of the reaction that was of particular interest to us at this point and therefore we set about optimising the HPLC conditions using the Chiralcel OJ column once again. A mobile phase consisting of 10% isopropyl alcohol/hexane as used previously was found to be far too polar for this benzofuran and after some experimentation, it was found that the isomers could be resolved satisfactorily using 2% isopropyl alcohol/hexane. After several injections of the racemic material in order to ensure repeatability of the HPLC system, the chiral benzofuran was injected. Once both enantiomers had eluted, integration of the peak areas confirmed that this chiral cyclisation had been just as successful as those performed on the rotenone precursor. In this case an enantiomeric ratio of 97:3 was obtained (94% ee). This high ee was not expected as the *(E)*- carbonate ***(E)*-489**,was contaminated with 3-4% of the *(Z)*- carbonate,[*] ***(Z)*-489** which should have produced the opposite enantiomer. It is possible however, that the *(Z)*- isomer does not readily form the Pd π-allyl complex, perhaps due to steric constraints. In support of this theory is the fact that analysis of the reaction after 18 hours indicated a trace amount of starting material still present.

In terms of assigning the absolute stereochemistry, the synthesis of this compound has been accomplished before using chiral resolution, and our specific rotation of $[\alpha]_D^{19}$ = -10.8 (EtOH) was in good agreement with that of $[\alpha]_D$ = -10.4 (EtOH), reported by Kawase *et al*.[71] More importantly, according to this literature, the negative specific rotation indicated that we had synthesised the *(S)*- enantiomer ***(S)*-167**. The synthesis of this enantiomer was therefore consistent with the results obtained in the synthesis of the chiral rotenone precursor, where utilisation of the *S,S'*-Trost ligand afforded the *(S)*- benzofuran, and of course, vice versa for the *R,R'*-Trost ligand.

Inspired by the success of this reaction, we immediately set about synthesising the opposite *(R)*- enantiomer and, using the same methodology along with the *R,R'*-Trost ligand, were rewarded with a 92% enantiomeric excess of the desired benzofuran ***(R)*-167** as determined

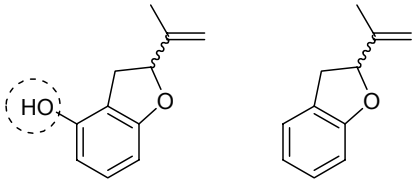
[*] As determined by ^{1}H NMR

by HPLC. The specific rotation of $[\alpha]_D^{19} = +10.3$ (EtOH) obtained for this compound compared well with its enantiomer – though opposite in sign of course. Using this methodology, both enantiomers of **167** were synthesised in excellent yields and good ee.

Finally however, although at this point we were almost convinced about the assignment of our stereochemistry for the *(R)*- and *(S)*- benzofuran molecules, there remained a small amount of uncertainty due to one contributing factor. Our initial assignment of the *(S)*-isomer was based upon the specific rotation as reported by Kawase *et al*. in 1980[71] as well as the fact that this would be consistent with our previous results. However, in 2003, Yamaguchi *et al*. published an article wherein on the first page he reports the specific rotation as being positive for the *(R)*- enantiomer in the first line of a reaction scheme, yet on the same page in the second line of the same scheme reports that it is the *(S)*-enantiomer with the positive specific rotation![70] Therefore, to put aside any doubt regarding the stereochemistry obtained from these reactions, we decided that a crystal structure of one of our enantiomers would be required.

This benzofuran compound **167** exists as a clear oil, similarly to the related rotenone precursor **247**. Unfortunately, unlike the rotenone precursor, the absence of the second free phenolic hydroxyl moiety at the 4-position on the benzofuran drastically reduces the options in terms of derivatising this compound to obtain a solid (Figure 65).

Figure 65

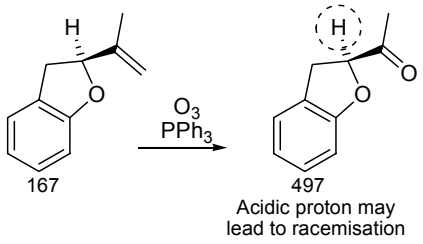


247 167

Derivitisation of the rotenone precursor **247** was easily accomplished by exploiting the free hydroxyl at the 4-position - not possible for the trematone precursor **167**

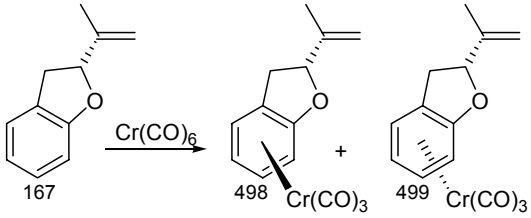
The possibility of converting the alkene **167** to an aldehyde **497** (Scheme 195) by ozonolysis was ruled out as racemisation of the compound may occur as a result of the now acidic proton being located on the stereogenic carbon.

Scheme 195



In light of the fact that we have some experience regarding the synthesis of arene chromium tricarbonyl compounds, it was decided to attempt to convert one of the enantiomers to the arene chromium tricarbonyl complex.* To this end, the *(R)*- benzofuran ***(R)*-167** was reacted with chromium hexacarbonyl forming the arene chromium tricarbonyl compound (Scheme 196). During the formation of the complex, it is possible that the chromium binds to either face of the benzene ring and this was indeed found to be the case as two products were obtained in approximately equal masses, **498** and **499**. Fortunately, separation of the diastereomers was possible by column chromatography and therefore one of the compounds was isolated and recrystallised. As it turns out, the compound selected was the *anti*-diastereomer, **498**.

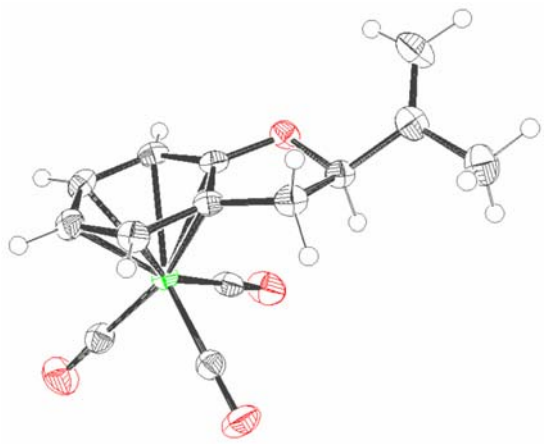
Scheme 196



A crystal structure was obtained, confirming that we had indeed synthesised the *(R)*-benzofuran ***(R)*-167** using the *R,R'*-Trost ligand as we had expected (Figure 66).

* Unfortunately, the time available for experimental work in this PhD had come to an end at this point, and so the synthesis of this arene chromium tricarbonyl complex, as well as obtaining crystals suitable for crystallography was carried out by another PhD student in the same laboratory.

Figure 66

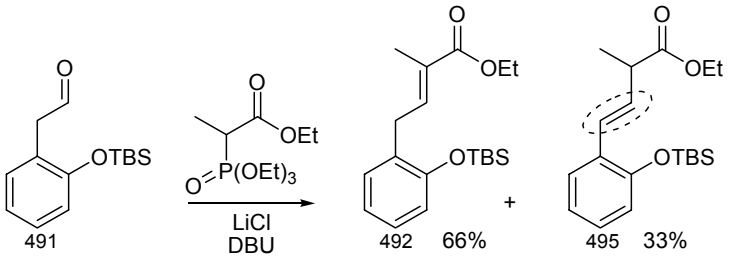


6.2 CONCLUDING REMARKS PERTAINING TO THE ENANTIOSELECTIVE SYNTHESES OF THE BENZOFURAN COMPOUNDS

6.2.1 For both benzofuran precursors - interesting observations noted

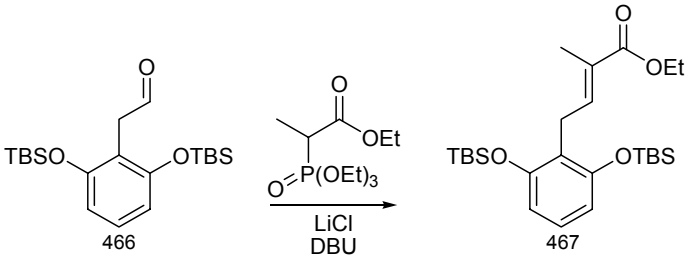
In the synthetic sequences that led to the enantioselective synthesis of both benzofuran precursors, there were several interesting observations that warrant further discussion. Probably the most astonishing result, and completely annoying at the time, was the unexpected isomerisation that occurred during the Horner-Wadsworth-Emmons reaction of **491** *en route* to the trematone benzofuran precursor (Scheme 197). This came as rather a surprise as these conditions were identical to those used for the Horner-Wadsworth-Emmons reaction of **466** *en route* to the rotenone precursor where absolutely no isomerisation was observed (Scheme 198). Structurally, the only difference between the two molecules is the presence of the second silyloxy functionality in the rotenone synthetic sequence.

Scheme 197



Significant isomerisation was observed *en route* to the trematone benzofuran

Scheme 198



No isomerisation was observed *en route* to the rotenone benzofuran

As was previously mentioned, when these reactions were first conducted the ylide was preformed, and then the aldehyde was slowly introduced into the ylide solution. This would mean that as the Horner-Wadsworth-Emmons reaction proceeded, the alkene product (**492** or **467**) would find itself in a basic environment, due to the excess ylide in the

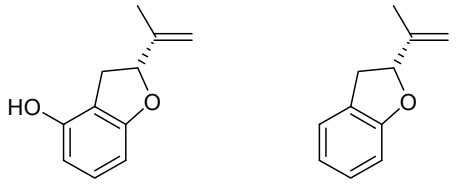
solution especially near the start of the addition. Now for the *bis*-silyloxy aldehyde **466**, this did not pose a problem and the reaction proceeded as planned, producing the desired product. However, for the *mono*-silyloxy aldehyde **491**, this was not the case. No doubt, as this reaction proceeded, the newly formed alkene **492** was in fact affected by the excess ylide which produced a basic environment, facilitating isomerisation due to deprotonation of the benzylic protons, leading to the thermodynamically preferred product **495**. The reason as to why the *bis*-silyloxy compound **466** was not affected by these same conditions may be accounted for by two possible reasons: The first reason may be that simply due to the steric bulk imposed by the two silyloxy groups, deprotonation of the benzylic protons by the ylide was significantly hindered, and isomerisation was therefore not possible. Alternatively, the extra silyloxy functionality may have rendered the benzene ring significantly more electron rich, decreasing the acidity of the benzylic protons which would once again retard deprotonation, and hence inhibit the isomerisation. Fortunately however, this isomerisation problem was overcome by changing the reaction conditions.

Another interesting point of discussion pertains to the π-allyl Pd cyclisations. For both the trematone and rotenone benzofuran precursors, the initial cyclisations were performed using $PdDba_2$ as a source of Pd^0, and triphenylphosphine as the ligand effectively forming $Pd(PPh_3)_4$ as the active catalyst. What is interesting is that for these reactions to proceed, the dichloromethane solvent needed to be warmed to reflux temperature. However, when the chiral bidentate Trost ligands were employed, the reaction required somewhat less activation energy as they proceeded smoothly at temperatures in the region of 25 °C. However, upon repeating one of these chiral cyclisation reactions sometime later in the year when the lab was cooler, *ca.* 16 °C, it was found that the π-allyl Pd cyclisation did not proceed at all, even though the Trost bidentate ligand was being employed. Clearly, at temperatures below 20 °C, there is insufficient energy for the reaction to proceed efficiently. On the other hand, warming the reaction too much also has deleterious effects. A chiral cyclisation on the trematone precursor was attempted using the *R*,*R'*-Trost ligand at 38 °C, and although the reaction proceeded rapidly, the enantioselectivity was slightly poorer than previous attempts, dropping from 94% ee to 88% ee. This observation is consistent with Trost's argument that for better ee's, the reaction needs to be slowed down, or retarded to allow the PdL_2*-substrate complex to equilibrate to the thermodynamically favourable form. If the attack of the phenolic oxygen nucleophile is too rapid, then

equilibration does not proceed properly and a mixture of enantiomers is obtained. The increase in temperature results in an increase in reaction rate, and therefore a drop in enantiomeric excess is observed.

Another interesting point regarding the two chiral benzofurans is that the same enantiomers have opposite specific rotations. For example, if we consider the *(R)*- enantiomers for both compounds (Figure 67), the rotenone precursor **(-)-*(R)*-247**, which contains the extra oxygen functionality has a negative specific rotation, yet the trematone precursor **(-)-*(R)*-167**, differing only in that it is lacking this phenoxyl group at the 4-position, has a positive specific rotation.

Figure 67



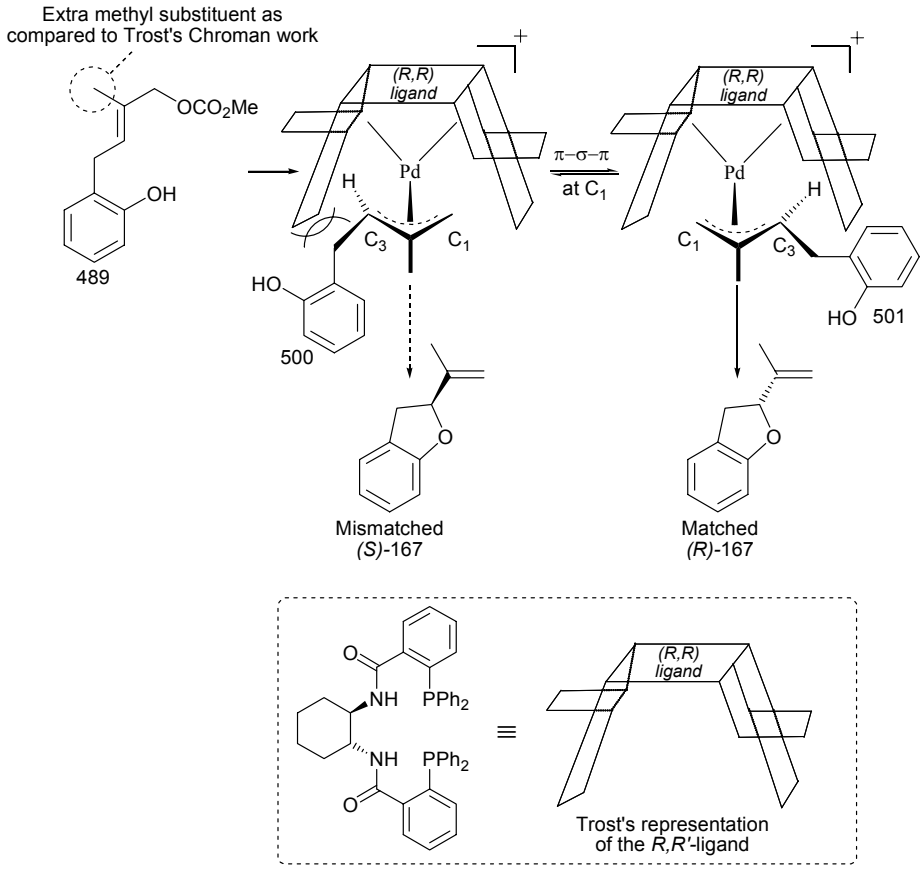
(-)-*(R)*-247
Rotenone precursor

(+)-*(R)*-167
Trematone precursor

Finally, the model proposed by Trost in rationalising the outcome of his chiral cyclisations can similarly be applied to our systems, even though our systems led to 5-membered ring benzofurans which moreover contain an extra methyl substituent, directly affecting the π-allyl-Pd intermediate. As an example (although the model can be applied to all four of the chiral benzofurans synthesised), consider the application of this model using our allyl carbonate **489**, and Trost's representation of the *R,R'*-Trost ligand (Scheme 199): Initially, upon ionization, the chiral π-palladium intermediate **500** is formed to facilitate the departure of the carbonate of **489** from under the right-front flap of the ligand. However, once this has occurred, with the carbonate no longer present, the complex **500** is no longer in the most favourable steric arrangement with respect to the shape of the ligand. The mismatched cyclisation that would result from this arrangement is not favourable and therefore a π-σ-π rearrangement occurs, forming the thermodynamically preferred **501**. Following this, attack of the phenolic hydroxyl occurs from the bottom face, leading to the *(R)*- benzofuran, *(R)*-**167**, in a matched cyclisation process. The alternative argument would similarly apply for the *S,S'*-Trost ligand, leading to the *(S)*- benzofuran, *(S)*-**167**. The π-σ-π rearrangement that occurs immediately after ionisation (**500** to **501**) is very

important and it is for this reason that acetic acid is added to the reaction, decreasing the nucleophilicity of the phenolic hydroxyl, allowing some time for this process to occur. In contrast, if a base is added to the reaction instead of acetic acid, the mismatched cyclisation predominates to an extent (**500** to ***(S)*-167**), leading to the formation of the mismatched enantiomer in a slight excess – but never in good ee.[92]

Scheme 199

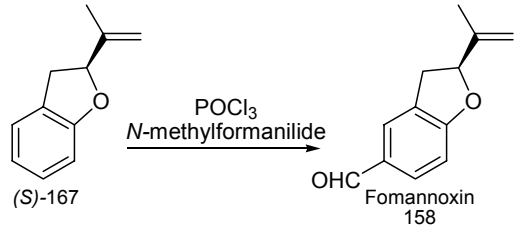


6.2.2 Concluding remarks pertaining to the formal syntheses of trematone and fomannoxin

The synthesis of *(R)*-2-isopropenyl-2,3-dihydrobenzofuran ***(R)*-167** in excellent enantiomeric excess concludes a formal synthesis of trematone **157** and since our strategy also facilitated the synthesis of the opposite *(S)*- enantiomer in equally good enantiomeric excess, we have also completed a formal synthesis of the natural product fomannoxin **158**.

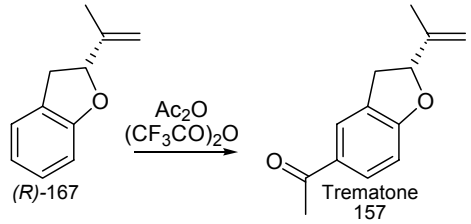
In 1980, Kawase *et al*. published a synthesis of (+)-*(S)*-fomannoxin **158**, employing a chiral resolution step early in the synthesis to finally arrive at *(S)*-2-isopropenyl-2,3-dihydrobenzofuran ***(S)*-167**, although in rather poor yield. Nevertheless, a Vilsmeier formylation of the benzofuran was performed, affording the desired natural product in 19% yield (Scheme 200).

Scheme 200



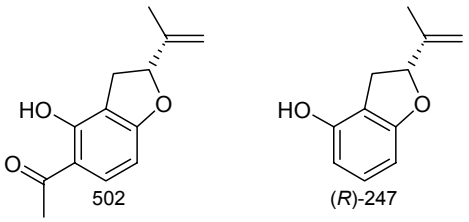
Similarly, a Friedel-Craft acylation has previously been done using the opposite benzofuran enantiomer ***(R)*-167** (Scheme 201), which had been derived using the same chiral resolution procedure. Acylation of *(R)*-2-isopropenyl-2,3-dihydrobenzofuran ***(R)*-167** afforded the natural product, (-)-*(R)*-trematone **157**.

Scheme 201



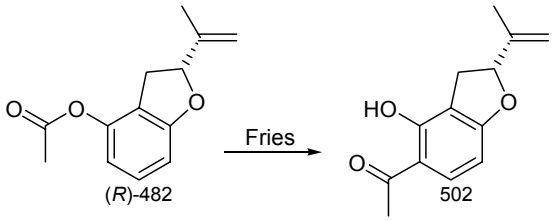
In terms of future work pertaining to these small benzofuran natural products, there is yet another product which we have not discussed in our syntheses thus far, that should be accessible using our strategy. A hydroxyl derivative of trematone, known as hydroxytrematone **502** (Figure 68) has an oxygen substitution pattern which is analogous to our successfully synthesised rotenone benzofuran precursor **247**. In fact, the only difference between our rotenone benzofuran precursor and hydroxytrematone, is the presence of an acetate *ortho* to the phenolic hydroxyl.

Figure 68



Given the fact that we have already chirally synthesised the *O*-acetate version of the rotenone precursor, ***(R)-*** and ***(S)*-482**,* one may envisage that hydroxytrematone might readily be obtained from this compound by employing a Fries rearrangement, converting ***(R)*-482** to *(R)*-hydroxytrematone **502** (Scheme 202).

Scheme 202



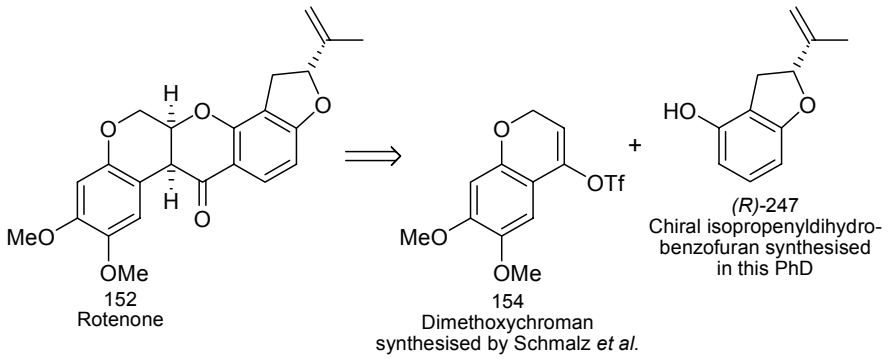
Moreover, there have recently been several articles published in the literature employing photolytic conditions to effect the Fries rearrangement under milder conditions, including publications on photo-Fries work performed on various benzofuran systems.[122-126] Using these conditions, it should be possible to convert our already synthesised *(R)*-2-isopropenyl-2,3-dihydrobenzofuran-4-yl acetate ***(R)*-482** to *(R)*-hydroxytrematone **502**.

6.2.3 Future work to utilise *(R)*-2-isopropenyl-2,3-dihydrobenzofuran-4-ol in the synthesis of rotenone

The chiral synthesis of *(R)*-2-isopropenyl-2,3-dihydrobenzofuran-4-ol **482**, in excellent enantiomeric excess successfully concludes the construction of the two proposed moieties for the synthesis of rotenone (Scheme 203). The other moiety, a dimethoxy chroman **154**, has already been synthesised as part of a collaborative study between ourselves and the group of Professor Schmalz, located at the University of Köln in Germany.

* Synthesis of the *O*-acetate version of the rotenone benzofuran precursors ***(R)*** and ***(S)*-482** was required for better separation of the enantiomers on the Chiralcel OJ HPLC column.

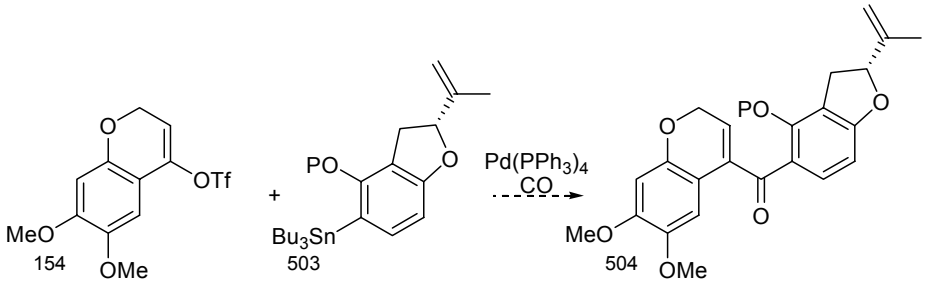
Scheme 203



The two moieties envisaged for the synthesis of rotenone

In linking these two units, a key feature that needs to be born in mind is the introduction of the carbonyl functionality (Scheme 204). In the initial proposed synthesis, a carbonylative coupling was proposed and to this end the chroman moiety would need to be functionalised as the triflate **154**, and the benzofuran moiety would need to be converted to the appropriate tin derivative **503**.

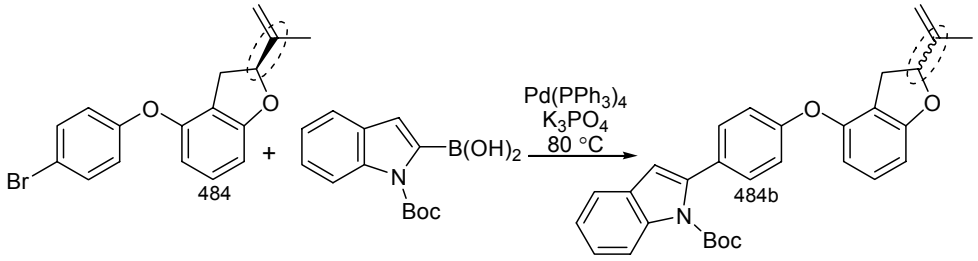
Scheme 204



Conversion of our chiral benzofuran unit to the tin derivative should pose no problem as the presence of the second phenolic hydroxyl group provides a wonderful handle for the introduction a protecting group which could act as an *ortho* director for lithiation, and then treatment with tributyltin chloride should furnish the desired tin adduct. However, it is the Pd mediated carbonylative coupling reaction which follows that is a cause for concern. In the initial planning of the overall synthesis this seemed to be a viable option however, during the course of this PhD, a Suzuki coupling reaction was employed to derivatise the chiral benzofuran **484** (Scheme 205). Unfortunately, as described earlier, although the Suzuki coupling reaction worked, the product **484b** was found to be racemic. We believe that the Suzuki conditions, which employed Pd^0 and high temperatures, may have

facilitated reformation of the Pd π-allyl complex, using the alkene on the isopropenyl functionality and ring opening the dihydrofuran, effectively using the phenolic part of the molecule as a leaving group. The process then reverses, with the phenolic hydroxyl attacking the newly formed Pd π-allyl complex, reforming the benzofuran. However, in the absence of a chiral ligand, the reformation of the benzofuran is not facially selective – leading to racemic product.

Scheme 205

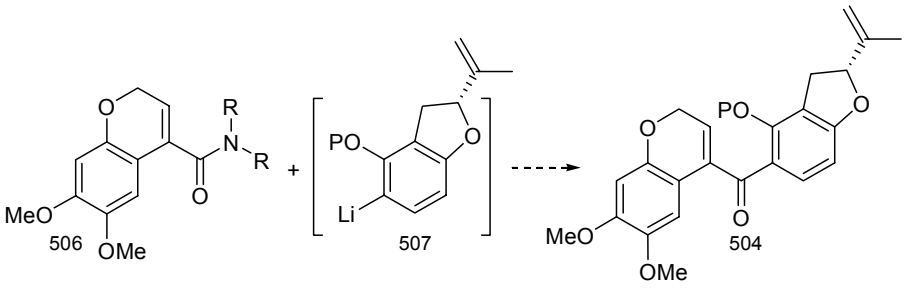


Racemisation of the chiral isopropenyl during a Suzuki coupling does not bode well for a Pd^0 carbonylative coupling

Thus it may be that a Pd catalysed carbonylative coupling to join the two moieties is not the best option as this may also lead to racemisation of the carefully constructed chiral isopropenyl functionality.

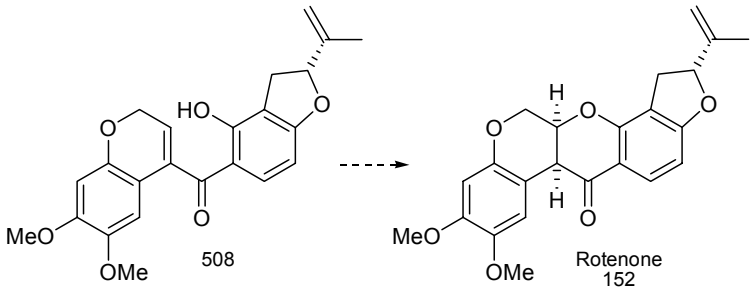
Another strategy for the coupling of the two moieties, proposed by Schmalz *et al*. may be to modify the chroman to incorporate a Weinreb amide **506** (Scheme 206) instead of the triflate, circumventing the need for a carbonylative coupling reaction. This would simplify the benzofuran synthesis as we would no longer require the tin adduct, but could simply lithiate the benzofuran suitably protected with an *ortho* directing group **507** to facilitate addition to the chroman **506**.

Scheme 206



Once the coupling of the two independently synthesised moieties has been achieved, the final steps in the synthesis would be the removal of the protecting group forming **508** (Scheme 207), followed by a chiral Lewis acid assisted Michael addition facilitating ring closure to form the central ring, and rotenone itself **152**.

Scheme 207



Controlling the stereochemistry of the Lewis acid mediated cyclisation would be an area requiring some investigation. It is indeed possible that the cyclisation could be performed without any intentional stereochemical control using for instance aluminium trichloride. Once the ring system is created, epimerisation of the mixture of isomers may be possible to form the single desired enantiomer, driven by the pre-existing stereochemistry of the isopropenyl functional group.

CHAPTER 7 - EXPERIMENTAL

7.1 GENERAL PROCEDURES

7.1.1 Purification of solvents and reagents

Solvents used for chromatographic purposes were distilled before use by means of conventional distillation procedures. Unless otherwise stated, solvents used for reaction purposes were dried over an appropriate drying agent and then distilled under nitrogen gas. Tetrahydrofuran, 1,4-dioxane and diethyl ether were distilled from sodium wire using benzophenone as an indicator. Toluene was distilled from sodium metal lumps. Dichloromethane, dimethylformamide and acetonitrile were distilled from calcium hydride. Pyridine was distilled from potassium hydroxide.

7.1.2 Chromatography

Separation of compounds by column chromatography was performed using Merck silica gel (particle size 0.063-0.200 mm). Thin layer chromatography was performed using Merck silica gel 60 F_{254} coated on aluminium sheets. Compounds on the TLC plates were either viewed under UV light or by dipping the plates into $KMnO_4$ staining solution.

7.1.3 Spectroscopic and physical data

Unless otherwise stated, ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE 300 at 300.132 MHz for ^{1}H and 75.473 for ^{13}C, *J*-values are given in Hz.

Infra-red spectra were recorded using a Bruker IFS-25 Fourier Transform spectrometer or on a Bruker Vector-22 Fourier Transform spectrometer. Measurements were made using either a neat liquid film between sodium chloride plates or using a solution in chloroform in a cell of path length 0.1 mm having sodium chloride windows. The signals are reported on the wavenumber scale (ν /cm^{-1}).

Specific rotations were determined using a Jasco DIP-370 Digital Polarimeter, at the D-line of sodium (589 nm).

Melting points were measured using a Reichart micro hotstage apparatus and are uncorrected.

Mass spectra were recorded on a Kratos MS 9/50, VG 70E MS or a VG 70 SEQ.

Intensity data were collected on a Bruker SMART 1K CCD area detector diffractometer with graphite monochromated Mo Kα radiation (50kV, 30mA). The collection method involved ω-scans of width 0.3°. Data reduction was carried out using the program SAINT+. The crystal structure was solved by direct methods using SHELXTL. Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares calculations based on F2 using SHELXTL. Hydrogen atoms were first located in the difference map then positioned geometrically and allowed to ride on their respective parent atoms. Diagrams and publication material were generated using SHELXTL and PLATON.

7.1.4 High pressure liquid chromatography

High pressure liquid chromatography was performed on a TSP HPLC at flow rates between 0.8 to 1.0 $ml.min^{-1}$ of a mobile phase consisting of isopropyl alcohol and hexane mixtures (see relevant experimental sections). Detection of the analyte was performed using a TSP variable wavelength UV detector at 215 nM. Separation was achieved on a Chiralcel OJ 10μ 250 × 4.6 mm chiral column. All calculations were based on peak area.

7.1.5 Other general procedures

All reactions, unless otherwise stated, were carried out under Ar and the reaction vessels were dried either in an oven or flame-dried whilst under vacuum.

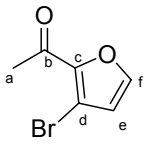
Removal of solvent *in vacuo* refers to removal of the solvent using a rotary evaporator followed by removal of trace amounts of solvent using a high vacuum pump at *ca*. 0.1 mm Hg.

7.2 EXPERIMENTAL WORK PERTAINING TO CHAPTER 4

7.2.1 Towards furostifoline - 18

7.2.1.1 2-Acetyl-3-bromofuran – 82

Into a 100 ml 3-neck round bottom flask, under N_2, fitted with two dropping funnels was placed dichloromethane (15 ml) and the solvent was cooled by means of an ice bath. $AlCl_3$ (1.355 g, 10.16 mmol) was added in one portion and the solution was stirred at 0 °C for 15 min during which time partial dissolution of the $AlCl_3$ took place. A dropping funnel was charged with more dichloromethane (15 ml) and freshly distilled acetyl chloride (0.750 ml, 828 mg, 11.0 mmol). The acetyl chloride solution was then added over a 5 min period to the $AlCl_3$ solution and the reaction was left to proceed at 0 ºC for 30 min. During this time complete dissolution of the $AlCl_3$ occurred. The second dropping funnel was charged with dichloromethane (15 ml) and 3-bromofuran **81** (0.310 ml, 507 mg, 3.45 mmol) and this was added over a 5 min period to the reaction mixture, still at ice bath temperature. The reaction was left to proceed for 20 min and then allowed to warm to rt over a 10 min period. After cooling once again using an ice bath, water (50 ml) was added slowly and then the reaction mixture was decanted to a dropping funnel before being diluted by the addition of dichloromethane (150 ml) and water (200 ml). After thoroughly mixing the phases, the organic layer was separated and the aqueous layer extracted with dichloromethane (3 × 100 ml). The combined organic fractions were washed with saturated $NaHCO_3$ solution (200 ml) followed by brine (200 ml). After drying the organic layer over anhydrous magnesium sulfate the solvent was evaporated *in vacuo*. The crude product was then purified by column chromatography (5% EtOAc/Hexane) followed by distillation (approx 120 ºC, 10 mbar) to afford **82** as a white waxy solid (561 mg, 86%).



δ_H /ppm: 7.50 (1H, d, *J*=1.8 Hz, H_f), 6.63 (d, 1H, *J*=1.7 Hz, H_e), 2.55 (3H, s, H_a). **δ_C ppm:** 186.4 (C_b), 148.3 (C_c), 145.3 (C_f), 117.3 (C_e), 106.9 (C_d), 27.4 (C_a).

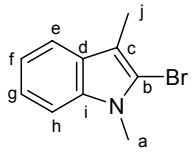
7.2.1.2 2-Bromo-1,3-dimethyl-1*H*-indole – 263

Part 1: Bromination

Into a 2 neck round bottom flask under N_2, fitted with a condenser was placed 3-methylindole **238** (500 mg, 3.81 mmol) followed by dry $CHCl_3$ (20 ml). To the resulting pale yellow solution was added NBS in one portion (814 mg, 4.57 mmol) and the reaction was refluxed under N_2 for 2 hours, by which time analysis of the reaction by TLC indicated that only a trace amount of the starting material remained unreacted. The reaction mixture was filtered and concentrated *in vacuo* affording a dark brown waxy solid.

Part 2 - Methylation

The crude brominated 3-methylindole **267** from part 1 was taken up in THF (20 ml) and cooled to 0 °C using an ice bath. Sodium hydride (183 mg, 4.58 mmol, 60%) was added in one portion and an immediate effervescence of the solution was observed. After stirring under N_2 for 5 min at 0 °C the effervescence subsided and dimethylsulfate (1.44 g, 11.4 mmol, 1.08 ml) was added in one portion and the reaction was left to proceed for 18 h. The reaction was then quenched by the addition of dilute ammonium hydroxide solution and the organic phase was extracted with ethyl acetate (3 × 30 ml) and the combined organic fractions were washed with brine and dried over anhydrous magnesium sulfate. Evaporation of the solvent *in vacuo* afforded the crude product as a brown oil and this was purified by column chromatography affording 2-bromo-1,3-dimethyl-1*H*-indole **263** as a white waxy solid (527 mg, 62% over 2 steps).



δ_H /ppm: 7.47 (1H, d, *J*=7.8 Hz, H_e), 7.22-7.12 (2H, m, Ar-H), 7.11-7.03 (1H, m, Ar-H), 3.65 (3H, s, H_a), 2.26 (3H, s, H_j). **δ_C /ppm:** 136.7 (C_i), 127.7 (C_d), 121.7 (ArCH), 119.3 (ArCH), 118.2 (ArCH), 113.1 (ArC), 110.2 (ArC), 109.0 (ArCH), 31.3 (C_a), 9.9 (C_j). **HRMS**: calcd for $C_{10}H_{10}BrN$ 222.9997 found 222.9993 **M/z:** 222.9993 (100%), 160.0767 (23%), 144.0818 (98%), 128.0525 (21%).

7.2.1.3 *N*-Methyl 2-(2-acetylfuran-3-yl)-3-methylindole – 265

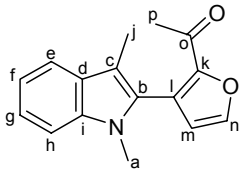
Part 1: Formation of the boronic acid

Into a 2 neck round bottom flask filled with Ar was placed 2-bromo-1,3-dimethyl-1*H*-indole **263** (376 mg, 1.68 mmol) followed by THF (20 ml). The solution was cooled to -78 °C under Ar and then *n*BuLi (1.4 M, 1.43 ml, 2.00 mmol) was added dropwise over a 5 min period. The reaction was left to proceed at -78 °C for 1 h and then was warmed to 0 °C for 10 min. After cooling again to -78 °C, triisopropyl borate (473 mg, 0.580 ml, 2.51 mmol) was added dropwise over a 5 min period and the reaction was left to proceed at -78 °C for 30 min. After this time it was allowed to warm to rt and quenched by the careful addition of water (20 ml). The contents of the flask were transferred to a beaker and diluted with diethyl ether (50 ml) and water (30 ml). Whilst stirring rapidly, HCl solution (1M) was added dropwise until the solution remained acidic. The phases were separated and the aqueous phase extracted with diethyl ether (3 × 30 ml). The combined organic fractions were washed with brine (50 ml) and dried over anhydrous magnesium sulfate. After filtration, the solution was concentrated to approximately 20% of its original volume and then used directly in part 2.

Part 2: Suzuki coupling

A 20 ml 2 neck round bottom flask, fitted with a condenser and a dropping funnel was charged with $Pd(PPh_3)_4$ (255 mg, 0.221 mmol), and the flask was degassed 3 times and refilled with Ar. The dropping funnel was charged with the ethereal solution of boronic acid **264** from part 1 and diluted with DME (10 ml). Whilst gently warming the dropping funnel using hot air, Ar gas was bubbled into the boronic acid solution, thus degassing the solution and driving off the lower boiling ether simultaneously. The solution was concentrated in this manner until a volume of approximately 5 ml was attained and then 2-acetyl-3-bromofuran **82** (212 mg, 1.12 mmol) was added to the solution in the dropping funnel. Degassing was continued without heating for another 1-2 min and the contents of the dropping funnel were subsequently discharged into the flask. The dropping funnel was recharged with 2M aqueous sodium carbonate solution (950 mg, 8.96 mmol in 4.50 ml water), and this solution was similarly degassed for 5 min before being added to the flask. The reaction mixture was refluxed under Ar for 72 h during which time the colour changed from yellow to light brown. The reaction was diluted by the addition of ethyl acetate

(50 ml) and water (50 ml) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 30 ml) and the combined organic fractions were dried over anhydrous magnesium sulfate and filtered. Evaporation of the solvent *in vacuo* afforded the crude product as a brown oil and this was purified by column chromatography (10-20% EtOAc/Hexane) affording the desired compound **265** a pale yellow solid (147 mg, 52%).



δ_h /ppm: 7.69 (1H, d, *J*=1.6 Hz, H_n), 7.60 (1H, d, *J*=7.9 Hz, H_e), 7.36-7.28 (1H, m, ArH), 7.28-7.22 (1H, m, ArH), 7.19-7.10 (1H, m, ArH), 6.58 (1H, d, *J*=1.6 Hz, H_m), 3.57 (3H, s, H_a), 2.30 (3H, s, H_p), 2.22 (3H, s, H_j). **δ_c /ppm:** 186.8 (C_o), 149.6 (ArC), 145.2 (C_n), 137.5 (ArC), 128.0 (ArC), 127.8 (ArC), 123.2 (ArC), 122.3 (ArCH), 119.2 (A-CH), 119.1 (ArCH), 116.0 (C_m), 111.0 (ArC), 109.3 (ArCH), 30.6 (C_a), 26.9 (C_p), 9.5 (C_j). **HRMS**: calcd for $C_{16}H_{15}NO_2$ 253.1103 found 253.1094. **M/z:** 253.1094 (100%), 238.0856 (55%), 210.0905 (21%), 180.0791 (21%), 167.0737 (14%).

7.2.2 Towards the indolocarbazole core

7.2.2.1 2-(1,3-Dimethyl-1*H*-indol-2-yl)-1-methyl-1*H*-indole-3-carbaldehyde – 277

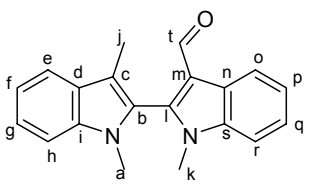
Part 1: Generation of the boronic acid

Into a 2 neck round bottom flask filled with Ar was placed 2-bromo-1,3-dimethyl-1*H*-indole **263** (440 mg, 1.96 mmol) followed by THF (20 ml). The solution was cooled to -78 °C under Ar and then *n*BuLi (1.40 M, 1.70 ml, 2.38 mmol) was added dropwise over a 5 min period. The reaction was left to proceed at -78 °C for 1 h and then was warmed to 0 °C for 10 min. After cooling again to -78 °C, trimethyl borate (927 mg, 8.92 mmol, 1.00 ml) was added dropwise over a 5 min period and the reaction was left to proceed at -78 °C for 30 min. After this time it was allowed to warm to rt and quenched by the careful addition of water (20 ml). The contents of the flask were transferred to a beaker and diluted with diethyl ether (50 ml) and water (30 ml). Whilst stirring rapidly, HCl solution (1M) was added dropwise until the solution remained acidic. The phases were separated and the aqueous phase extracted with diethyl ether (3 × 30 ml). The combined organic fractions were washed with brine (50 ml) and dried over anhydrous magnesium sulfate. After

filtration, the solution was concentrated to approximately 20% of its original volume and then used directly in part 2.

Part 2: Suzuki coupling

A 20 ml 2 neck round bottom flask, fitted with a condenser and a dropping funnel was charged with $Pd(PPh_3)_4$ (226 mg, 0.196 mmol), and the flask was degassed 3 times and refilled with Ar. The dropping funnel was charged with the ethereal solution of boronic acid **264** from part 1 and diluted with DME (10 ml). Whilst gently warming the dropping funnel using hot air, Ar gas was bubbled into the boronic acid solution, thus degassing the solution and driving off the lower boiling ether simultaneously. The solution was concentrated in this manner until a volume of approximately 5 ml was attained and then 2-bromo-1-methyl-1*H*-indole-3-carbaldehyde (358 mg, 1.50 mmol) was added to the solution in the dropping funnel. Degassing was continued without heating for another 1-2 min and the contents of the dropping funnel were subsequently discharged into the flask. The dropping funnel was recharged with 2M aqueous sodium carbonate solution (1.06 g, 10.0 mmol in 5.00 ml water), and this solution was similarly degassed for 5 min before being added to the flask. The reaction mixture was refluxed under Ar for 24 h during which time the colour changed from yellow to light brown. The reaction was diluted by the addition of ethyl acetate (100 ml) and water (100 ml) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 50 ml) and the combined organic fractions were dried over anhydrous magnesium sulfate and filtered. Evaporation of the solvent *in vacuo* afforded the crude product as a brown oil and this was purified by column chromatography (5-10% EtOAc/Hexane) affording the desired compound **277** as a white solid (304 mg, 67%).



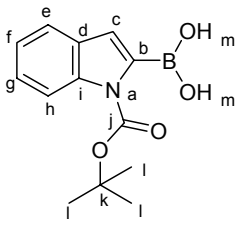
δ_h /ppm: 9.69 (1H, s, H_t), 8.52-8.41 (1H, m, ArH), 7.69 (1H, d, *J*=7.9 Hz, ArH), 7.52-7.33 (5H, m, ArH), 7.29-7.18 (1H, m, ArH), 3.62 (3H, s, H_k), 3.57 (3H, s, H_a), 2.27 (3H, s, H_j). **δ_c /ppm:** 186.7 (C_t), 141.8 (ArC), 138.5 (ArC), 138.4 (ArC), 128.3 (ArC), 125.5 (ArC), 124.8 (ArCH), 124.5 (ArC), 123.9 (2 × ArCH), 122.9 (ArCH), 120.3 (ArCH), 120.0 (ArCH), 118.5 (ArC), 115.8 (ArC), 110.3 (ArCH), 110.1 (ArCH), 31.3 (C_k), 31.2 (C_a), 9.9 (C_j). **HRMS**: calcd for $C_{20}H_{18}N_2O$ 302.1419 found 302.1416. **M/z:** 302.1416 (100%), 285.1403 (48%), 270.1193 (13%), 257.1088 (16%).

7.3 EXPERIMENTAL WORK PERTAINING TO CHAPTER 5

7.3.1 Synthesis of furostifoline - 18

7.3.1.1 1-(*tert*-Butoxycarbonyl)-1*H*-indol-2-yl-2-boronic acid – 305

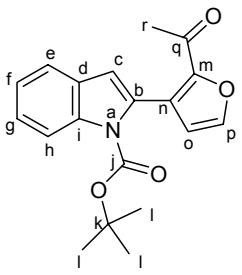
Into a 250 ml 2 neck round bottom flask (oven and flame dried, under Ar) was placed diisopropylamine (4.80 ml, 3.49 g, 34.5 mmol) followed by dry THF (150 ml). The solution was cooled to -78 °C and then *n*BuLi (1.60 M, 21.5 ml, 34.4 mmol) was added dropwise thus forming a pale yellow solution. The reaction was allowed to proceed at -78 °C for 30 min under Ar and then the solution was warmed to 0 °C by means of an ice bath. After cooling once again to -78 °C the boc-indole **304** (5.0 g, 23 mmol) in THF (15 ml) was added dropwise and the lithiation was allowed to proceed for 2 h at -78°C. Trimethyl borate (13.0 ml, 115 mmol, 11.9 g) was then added dropwise and a colour change occurred almost immediately from a yellow solution to almost clear. The reaction mixture was stirred for another 30 min at -78°C before the cooling bath was removed and the solution allowed to warm to rt over 1 h. The reaction mixture was decanted into a beaker and water was added (200 ml) and 2N HCl solution was added carefully and with vigorous stirring until the solution remained acidic, thus hydrolysing the borate ether. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 100 ml). The combined organic fractions were then washed with brine and dried over anhydrous magnesium sulfate. After filtration the solution was concentrated (to *ca* 20 ml) by evaporation of the solvent *in vacuo* and then hexane (100 ml) was added with vigorous stirring resulting in immediate precipitation of the boronic acid. The solid was filtered and washed with cold hexane to afford 1-(*tert*-butoxycarbonyl)-1*H*-indol-2-yl-2-boronic acid **305** as a white solid (4.44 g, 74%).



δ_H /ppm: 8.02 (1H, d, J=8.4 Hz, H_h), 7.60 (1H, d, J=7.6 Hz, H_e), 7.54 (s, 2H, H_m), 7.50 (s, 1H, H_c), 7.38-7.33 (m, 1H, H_g), 7.27-7.23 (m, 1H, H_f), 1.74 (s, 9H, H_l). **δ_C /ppm:** 153.67 (C_j), 138.54 (C_i), 129.96 (C_d), 125.88 (ArCH), 124.78 (ArCH), 123.23 (ArCH), 121.81 (ArCH), 116.41 (C_c), 85.99 (C_k), 28.22 (C_l).

7.3.1.2 *tert*-Butyl 2-(2-acetylfuran-3-yl)-1*H*-indole-1-carboxylate – 306

Into a 2 neck round bottom flask fitted with a dropping funnel and a condenser was placed $Pd(PPh_3)_4$ (1.73 g, 1.50 mmol, 24 mole %) and the reaction vessel was degassed and refilled with Ar gas 5 times. The dropping funnel was charged with DME (28 ml) and 1-(*tert*-butoxycarbonyl)-1*H*-indol-2-yl-2-boronic acid **305** (2.90 g, 11.1 mmol). Ar gas was then bubbled into the dropping funnel by means of a Pasteur pipette and dissolution of the boronic acid occurred almost immediately. During this period of degassing 2-acetyl-3-bromofuran **82** (1.20 g, 6.34 mmol) was added to the dropping funnel and degassing was continued for another 5 min. The solution was then discharged into the reaction vessel and the dropping funnel was recharged with an aqueous Na_2CO_3 solution (2.0 M, 3.3 g, 31 mmol). This solution was similarly degassed for 10 min and then discharged into the reaction vessel. The 2 phase mixture was heated and left to reflux for 3 d. During this time the solution became homogenous and a colour change from yellow to pale brown occurred. The reaction mixture was cooled and decanted into a dropping funnel then diluted with ethyl acetate (200 ml) and water (200 ml). After thoroughly mixing the phases, the organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 × 100 ml). The combined organic fractions were then washed with brine (200 ml) and dried over anhydrous magnesium sulfate. After evaporation of the solvent *in vacuo* the crude material was purified by column chromatography (5-10% EtOAc/Hexane) affording the desired *tert*-butyl 2-(2-acetylfuran-3-yl)-1*H*-indole-1-carboxylate (1.61 g, 78%) **306** as well as a small amount of 2-(2-acetylfuran-3-yl)-1*H*-indole **307**.



δ_H /ppm: 8.20 (1H, d, *J*=8.4 Hz, H_h), 7.57 (1H, d, *J*=1.6 Hz, H_p), 7.55 (1H, d, *J*=7.9 Hz, H_e), 7.37-7.31 (1H, m, H_g), 7.27-7.21 (1H, m, H_f), 6.67 (1H, s, H_c), 6.61 (1H, d, *J*=1.6 Hz, H_o), 2.37 (3H, s, H_r), 1.45 (9H, s, H_l). **δ_C /ppm:** 186.8 (C_q), 149.6 (C_j), 148.4 (C_b), 144.1 (C_p), 137.0 (ArC), 130.1 (ArC), 128.7 (ArC), 125.6 (ArC), 124.8 (C_g), 122.8 (C_f), 120.6 (C_h), 115.4 (C_o and C_e), 111.4 (C_c), 85.5 (C_k), 27.67 (C_l), 26.9 (C_r). **ν /cm^{-1}:** 3020 (CH str), 1732 (C=O Amide), 1674 (C=O ketone). **HRMS**: calcd for $C_{19}H_{19}NO_4$ 325.1314 found 325.1296. **M/z:** 325.1296 (18%), 252.0613 (2%), 225.0721 (100%), 210.0575 (8%), 154.0660 (10%). **M.Pt.:** 98-99 °C.

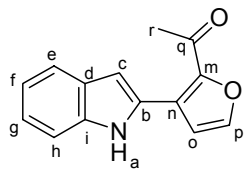
7.3.1.3 2-(2-Acetylfuran-3-yl)-1*H*-indole – 307

Method 1: Using $AlCl_3$

Into a 2 neck round bottom flask under N_2 was placed *tert*-butyl 2-(2-acetylfuran-3-yl)-1*H*-indole-1-carboxylate **306** (925 mg, 2.84 mmol) followed by dichloromethane (70 ml). After the solid had dissolved completely the flask was cooled by means of an ice bath and then $AlCl_3$ (455 mg, 3.41 mmol) was added in one portion. The reaction was allowed to proceed for 2 h at 0 °C during which time the colour of the solution changed to bright red. The reaction was quenched by the careful addition of ice water and the red colour immediately disappeared. The reaction mixture was diluted with more dichloromethane (100 ml) and water (100 ml) and the phases were mixed then separated. The aqueous phase was extracted with dichloromethane (3 × 50 ml) and the combined organic fractions were washed with brine and then dried over anhydrous magnesium sulfate. After filtration and evaporation of the solvent the crude material was purified by column chromatography (5-20% EtOAc/Hexane) to afford the desired product **307** as a bright yellow solid (536 mg, 84%).

Method 2: Using μ-wave and SiO_2

The boc-protected indole **306** (500 mg, 1.54 mmol) was suspended in ethyl acetate (200 ml) and silica was added (200 g). The slurry was concentrated *in vacuo* until a dry off-white powder was obtained. This mixture was then placed into a conventional microwave (500W) for 30 s bursts with 2 min of cooling between each burst. After each burst the adsorbate was mixed to ensure that the reaction progressed evenly through the adsorbate and a small sample was removed for analysis by TLC (a small amount of the silica was placed into ethyl acetate to dissolve the adsorbed material and this was analyzed by TLC). In total, approximately 3 min of microwave heating was required to complete the reaction. As the reaction proceeded, the silica gradually became more yellow in colour. Once the reaction was complete the adsorbed product was purified by column chromatography (5-10% EtOAc/Hexane) affording the product **307** in 83% yield (288 mg) as a bright yellow solid.

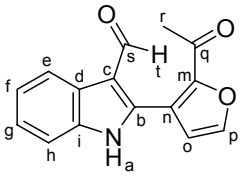


δ_H /ppm: 11.91 (1H, s, H_a), 7.63 (d, 1H, *J*=7.9 Hz, H_e), 7.55 (1H, d, *J*=1.6 Hz, H_p), 7.50 (1H, d, *J*=8.2, H_h), 7.25 (1H, t, *J*=7.1 Hz, H_g), 7.11 (1H, t, *J*=7.4 Hz, H_f), 7.01 (1H, d, *J*=1.6 Hz, H_o), 6.92 (1H, s, H_c) 2.66 (3H, s, H_r). **δ_C /ppm:** 189.7 (C_q), 146.2 (ArC), 145.8 (C_p), 136.2 (ArC), 128.9 (ArC), 128.3 (ArC), 126.9 (ArC), 123.3 (C_g), 120.6 (C_f), 120.0 (C_h), 112.4 (C_e), 111.9 (C_o), 103.4 (C_c), 27.2 (C_r). **ν /cm^{-1}:** 3253 (NH str), 3019 (CH str), 1656 (C=O str). **HRMS**: calcd for $C_{14}H_{11}NO_2$ 225.0790 found 225.0787. **M/z:** 225.0787 (100%), 210.0563 (8%), 196.0784 (11%), 182.0603 (7%), 154.0668 (26%). **M.Pt:** 137-138 °C. **X-ray data:** $C_{14}H_{11}NO_2$; *M*=225.24; Monoclinic; 0.71073 Å; *a*=7.2780(2) Å, *b*=14.3556(3) Å, *c*=10.7002(2) Å, *U*=1102.84(4) Å^3; 173(2) K, space group, P2(1), Z=5;. μ(Mo-Kα)=0.073 mm^{-1} 21862 reflections measured, 5487 unique [R(int)=0.0707] which were used in all calculations. Final R indices [$I>2\sigma(I)$] R_1=0.0400, wR(F^2)=0.0926.

7.3.1.4 Synthesis of 2-(2-acetylfuran-3-yl)-1*H*-indole-3-carbaldehyde – 308

Into a 100 ml 2 neck round bottom flask (dried, under Ar), fitted with a dropping funnel, was placed DMF (1.00 ml, 944 mg, 12.9 mmol) and the flask cooled by means of an ice bath. $POCl_3$ (0.200 ml, 334 mg, 2.18 mmol) was added using a syringe and the reaction was left to proceed for 10 min at 0 °C. By means of the dropping funnel, to the newly formed reagent was added dichloromethane (20 ml) and this solution was allowed to cool to 0 °C for 10 min. The dropping funnel was then charged with 2-(2-acetylfuran-3-yl)-1*H*-indole **307** (320 mg, 1.42 mmol) in dry dichloromethane (30 ml) and this was added dropwise over a period of 5 min. The reaction was left to proceed for another 5 min and analysis of the reaction mixture by TLC indicated that all starting material had been converted to the Vilsmeier salt (only a highly UV active spot on the baseline if the TLC was run in 40% EtOAc/Hexane). Ice cold water was immediately added (40 ml) and the reaction mixture was transferred to a beaker. Dichloromethane was added (150 ml) followed by water (100 ml) and the 2 phase mixture was stirred vigorously. By means of gentle heating the mixture was warmed to the boiling point of the dichloromethane and then 2M NaOH solution was slowly added until the pH of the solution remained slightly basic. The organic phase was then separated and the aqueous phase extracted with dichloromethane (3 × 100 ml). The combined organic fractions were washed with brine (100 ml) and dried over anhydrous magnesium sulfate. Evaporation of the solvent afforded

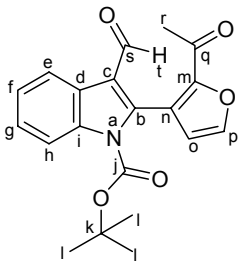
the crude product **308** as a dark brown solid. Purification by column chromatography (40% EtOAc/Hexane) removed most of the impurities however complete purification was not possible even after a second column. Recrystallisation of the material (ethyl acetate/hexane mixtures) afforded the desired compound 2-(2-acetylfuran-3-yl)-1*H*-indole-3-carbaldehyde as pure (247 mg) however by TLC it was clear that large amounts of the product **308** were still in the mother liquor. ^{1}H NMR spectral data were then collected using the pure material and then the pure and impure fractions were recombined and used in the next reaction.



δ_H /ppm: 12.68 (1H, s, H_a), 10.50 (1H, s, H_t), 8.29 (1H, d, *J*=7.3 Hz, H_e), 7.67 (1H, d, *J*=1.8 Hz, H_p), 7.59 (1H, d, *J*=1.8 Hz, H_o), 7.51 (1H, dd, *J*=1.3 and 6.9 Hz, H_h), 7.40-7.27 (2H, overlapping m's, H_f and H_g), 2.70 (3H, s, H_r).

7.3.1.5 *tert*-Butyl 2-(2-acetylfuran-3-yl)-3-formyl-1*H*-indole-1-carboxylate – 309

The crude **308** (assume 1.42 mmol) was taken up in dry THF (40 ml) and Boc_2O was added in one portion (0.500 ml, 475 mg, 2.18 mmol) followed by DMAP (23 mg, 0.19 mmol). The reaction was left to proceed under Ar for 5 h at rt. Water was then added (50 ml) and the reaction mixture was diluted with ethyl acetate (100 ml). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 × 100 ml). The combined organic fractions were washed with brine (200 ml) and dried over anhydrous magnesium sulfate. After filtration and evaporation of the solvent *in vacuo* the crude material was purified by column chromatography (20-30% EtOAc/Hexane) followed by recrystallisation from ethyl acetate/hexane mixtures to afford the desired *tert*-butyl 2-(2-acetylfuran-3-yl)-3-formyl-1*H*-indole-1-carboxylate **309** (397 mg, 79% over the 2 steps starting from **307**) as a pale yellow solid.



δ_H /ppm: 9.82 (1H, s, H_t), 8.37-8.34 (1H, m, H_e), 8.20-8.17 (1H, m, H_h), 7.68 (1H, d, *J*=1.7 Hz, H_p), 7.45-7.35 (2H, overlapping m's, H_f and H_g), 6.72 (1H, d, *J*=1.7 Hz, H_o), 2.45 (3H, s, H_r), 1.45 (9H, s, H_l). **δ_C /ppm:** 186.9 (C_q), 186.7 (C_s), 149.6 (C_j), 148.9 (ArC), 144.5 (ArCH), 140.0 (ArC), 136.4 (ArC), 126.2 (ArCH), 125.4 (ArC), 124.7 (ArCH), 121.9 (C_e), 121.0 (ArC), 120.2 (ArC), 116.4 (ArCH), 115.24 (C_h), 85.13 (C_k), 27.62 (C_l), 26.62 (C_r). **ν /cm^{-1}:** 2981 (CH str), 1747 (C=O str), 1672 (C=O str). **HRMS**: calcd for $C_{20}H_{19}NO_5$ 353.1263 found 353.1270. **M/z:** 353.1269 (2%), 310.1058 (42%), 254.0449 (29%), 224.0700 (26%), 210.0588 (100%), 154.0595 (5%). **M.Pt:** 151-153 °C

7.3.1.6 *tert*-Butyl 2*a*-methyl-1,2,2*a*,10*c*-tetrahydro-6*H*-cyclobuta[*c*]furo[3,2-*a*]carbazole-6-carboxylate – 312

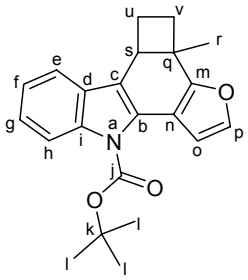
Part 1: Preparation of the ylide

Into a 250 ml 2 neck round bottomed flask under Ar was placed methyl triphenylphosphonium bromide (3.00g, 8.40 mmol) followed by dry diethyl ether (150 ml). The phosphonium salt was not soluble in this solvent and so formed a white suspension. The solution was cooled to 0 °C under Ar and then *n*BuLi (6.0 ml, 8.40 mmol, 1.4M) was added dropwise over a period of 5 min. The solution rapidly changed colour to yellow as the *n*BuLi was added however a white solid remained insoluble in the solution (LiBr). After the addition of the *n*BuLi the solution was stirred at 0 °C for 30 min and then warmed to rt for 30 min. Stirring was stopped and the insoluble LiBr salt allowed to settle to the bottom of the flask.

Part 2: Addition of the Ylide – formation of the diene

Into a 250 ml 2 neck round bottom flask, fitted with a dropping funnel was placed *tert*-butyl 2-(2-acetylfuran-3-yl)-3-formyl-1*H*-indole-1-carboxylate **309** (300 mg, 0.849 mmol) followed by diethyl ether (50 ml). The ylide as prepared in Part A above was transferred by cannula into the dropping funnel. The contents of the round bottom flask were cooled to 0 ºC under Ar and then the ylide was added in small portions (*ca*. 5-10 ml) until the formation of the diene was complete (as determined by monitoring the reaction by TLC). Without delay, the reaction was quenched by the addition of water (50 ml) and the mixture was diluted by the addition of ethyl acetate (100 ml). After thoroughly mixing the phases

the organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 × 50 ml). The combined organic fractions were collected, washed with brine (100 ml) and then dried over anhydrous magnesium sulfate. Without delay, the crude material was adsorbed onto silica and purified by column chromatography (5% EtOAc/Hexane). The diene, now suspended in the ethyl acetate/hexane solvent was then was concentrated *in vacuo* to 20% of its original volume and then toluene was added (100 ml) and the solution once again concentrated to 20% of its original volume. Toluene was added once again (100 ml) and the solution was concentrated *in vacuo* to approximately 10 ml. In this way the lower boiling solvents were essentially removed and replaced by toluene without ever fully concentrating the diene. The solution was then degassed *in vacuo* and Grubbs II catalyst (72 mg, 0.085 mmol) was added. After 3 h, analysis of the reaction mixture by TLC indicated that nothing appeared to be happening and so the solution was heated to 80 °C for 18 h. Analysis of the reaction mixture by TLC still indicated that only starting material was present and so another addition of Grubbs II catalyst was made (72 mg, 0.085 mmol) and the reaction was left to proceed at 80 °C for another 5 h. Analysis by TLC indicated no change and so the mixture was adsorbed onto silica gel and purified by column chromatography (5% EtOAc/Hexane) affording the unreacted diene as a clear oil (152 mg, 51% from dicarbonyl **309**). However, as soon as this oil was finally concentrated on the high vacuum it rapidly changed colour from clear to opaque and became waxy. After subjecting the wax for 3 h at rt under high vacuum the material was columned once again (5% EtOAc/Hexane) affording **312** (82 mg, 28%, calculated from the dicarbonyl **309**) as a white waxy solid.

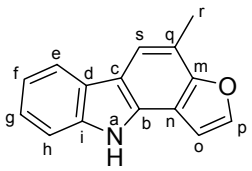


δ_H /ppm: 7.98-7.92 (1H, m, H_h), 7.32 (1H, d, *J*=1.9 Hz, H_p), 7.31-7.28 (1H, m, H_e), 7.21-7.15 (2H, overlapping m's, H_f and H_g), 7.01 (1H, d, *J*=1.9 Hz, H_o), 3.66 (1H, t, *J*=7.5 Hz, H_s), 2.66-2.58 (1H, m, H_u or H_v), 2.46-2.36 (1H, m, H_v or H_u), 2.32-2.15 (2H, overlapping m's, H_v or H_u), 1.72 (9H, s, H_l), 1.54 (3H, s, H_r). **$\delta_{C\ /ppm:}$** 159.15 (C_j), 150.5 (ArC), 140.7 (C_p), 136.2 (ArC), 130.5 (ArC), 128.5 (ArC), 123.0 (ArCH), 122.7 (ArCH), 117.6 (ArCH), 116.0 (ArC), 115.4 (ArCH), 111.8 (ArC), 109.8 (ArCH), 84.0 (C_k), 39.7 (C_s), 39.7 (C_q), 35.8 (C_v), 23.2 (C_r), 26.2 (C_u). **ν /cm^{-1}:** 2958 (CH str), 1739 (C=O str). **HRMS**: calcd for $C_{22}H_{23}NO_3$ 349.1678

found 349.1684. **M/z:** 349.1684 (16%), 321.1417 (5%), 265.0700 (100%), 248.1058 (4%), 221.0841 (55%).

7.3.1.7 Furostifoline – 18

To a mixture containing mainly **312** and a small amount (as determined by NMR) of *tert*-butyl 4-methyl-10*H*-furo[3,2-*a*]carbazole-10-carboxylate **311**, was added dichloromethane (5 ml) followed by $AlCl_3$ (33.0 mg, 0.248 mmol). The reaction was left to proceed under Ar at 0 °C for 1 h and then ice cold water (5 ml) was added in one portion. The reaction mixture was transferred to a separating funnel and diluted with dichloromethane (10 ml) and water (10 ml). After thoroughly mixing the phases, the organic phase was separated and the aqueous phase was extracted with dichloromethane (3 × 10 ml). The combined organic fractions were then washed with brine (50 ml), separated and dried over anhydrous magnesium sulfate. After filtration and evaporation of the solvent *in vacuo* the crude material was purified by column chromatography affording a trace amount of furostifoline[12,39] **18** (10 mg, 5% from the dicarbonyl - **309**).



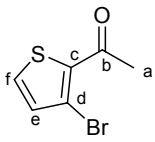
δ_H /ppm: 8.24 (1H, brs, H_a), 8.04 (1H, d, *J*=7.8 Hz, H_e), 7.77 (1H, s, H_s), 7.71 (1H, d, *J*=2.1 Hz, H_p), 7.47 (1H, d, *J*=8.0 Hz, H_h), 7.39-7.33 (1H, m, H_g), 7.26-7.21 (1H, m, H_f), 6.98 (1H, d, *J*=2.1 Hz, H_o), 2.66 (3H, s, H_r).

7.3.2 Synthesis of thiofurostifoline 314

7.3.2.1 2-Acetyl-3-bromothiophene – 318

Into a 100 ml 3 neck round bottom flask (dry, under Ar) was placed dichloromethane (15 ml) and the solvent was cooled using an ice bath before $AlCl_3$ (2.45 g, 18.4 mmol) was added. Partial dissolution of the $AlCl_3$ was observed. A dropping funnel was charged with freshly distilled acetyl chloride (1.34 ml, 1.48 g, 19.6 mmol) in dichloromethane (15 ml) and this added over a 10 min period to the $AlCl_3$ suspension. After about 30 min of stirring at 0 °C most of the $AlCl_3$ had dissolved. A second dropping funnel was charged with 3-bromothiophene **319** (0.574 ml, 1.00 g, 6.13 mmol) in dichloromethane (15 ml) and this was added to the reaction mixture over a 10 min period. The reaction was left to proceed at 0 °C for 30 min and then warmed slowly to rt over about another 1 h. Then reaction

mixture was cooled to 0 °C once again and water (40 ml) was added carefully. After transferring to a separating funnel the reaction mixture was diluted with more dichloromethane (150 ml) and another portion of water (150 ml) was added. After thoroughly mixing the phases, the organic phase was separated and the aqueous phase was extracted with dichloromethane (3 × 100 ml). The combined organic extracts were washed with saturated $NaHCO_3$ (100 ml), then brine (100 ml) and finally dried over anhydrous magnesium sulfate. Evaporation of the solvent and purification by column chromatography (5% EtOAc/Hexane) followed by bulb-bulb distillation (130 °C at 10 mbar) afforded the desired compound **318** as a white waxy solid (1.23 g, 98%).

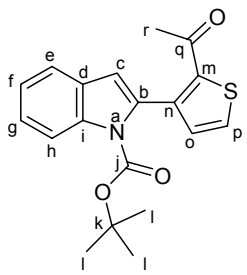


δ_H /ppm: 7.52 (1H, d, *J*=5.2 Hz, H_f), 7.11 (1H, d, *J*=5.2 Hz, H_e), 2.70 (3H, s, H_a). **δ_C /ppm:** 190.1 (C_b), 139.1 (C_c), 133.6 (C_f), 132.2 (C_e), 114.3 (C_d), 29.6 (C_a). **ν /cm^{-1}:** 1658 (C=O str), 1492, 1405, 1359. **HRMS**: calcd for C_6H_5BrOS 203.9244 found 203.9251. **M/z:** 203.9251 (57%), 188.9018 (99%), 81.9268 (22%). **M.Pt.:** 28-31 °C.

7.3.2.2 *tert*-Butyl 2-(2-acetylthiophen-3-yl)-1*H*-indole-1-carboxylate – 321

Into 50 ml 2 neck round bottom flask fitted with a dropping funnel and a condenser, was placed $Pd(PPh_3)_4$ (1.12 g, 0.969 mmol, 20 mole %) followed by 1-(*tert*-butoxycarbonyl)-1*H*-indol-2-yl-2-boronic acid **305** (1.90 g, 7.28 mmol) and the flask was degassed and refilled with Ar 5 times. The dropping funnel was then fitted with a Pasteur pipette attached to an Ar line to act as a bubbler for the purposes of degassing the subsequent solvents. DME (12 ml) was added to the dropping funnel followed by 2-acetyl-3-bromothiophene **318** (1.00 g, 4.88 mmol) and the mixture was degassed for 10 min by gently bubbling Ar through the solution. This solution was then added to the flask in one portion and the dropping funnel was charged with an aqueous Na_2CO_3 solution (2.00 M, 2.59 g, 24.5 mmol). This solution was similarly degassed before being added to the flask in one portion. The reaction mixture was then heated to reflux and after about 1 h the solution became homogenous and was pale orange in colour. The mixture was heated at reflux for 72 h during which time a colour change was observed from pale orange to light brown. Analysis of the reaction mixture indicated that the reaction had consumed nearly all of the thiophene and that the desired compound had formed as well as some of the deprotected analogue. After cooling, the reaction mixture was diluted with ethyl acetate (50 ml), water

was added (50 ml) and the 2 phases were thoroughly mixed. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 50 ml). The combined organic fractions were washed with brine (100 ml) and dried over anhydrous magnesium sulfate. After removal of the solvent *in vacuo* the crude mixture was taken up in THF (50 ml) and treated with Boc_2O (2.20 ml, 2.09 g, 9.58 mmol) and DMAP (90 mg, 0.74 mmol) for 2 h, thus converting trace amounts of the deprotected indole **322** back to the desired compound **321** (the unreacted 2-acetyl-3-bromothiophene and **322** have almost identical R_f values and so for purification purposes it is desirable to reprotect the indole). The reaction mixture was then diluted with ethyl acetate (50 ml) and water (50 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 50 ml). The combined organic fractions were washed with brine (100 ml) and dried over anhydrous magnesium sulfate. Evaporation of the solvent *in vacuo* and purification by column chromatography (5-10% EtOAc/Hexane) afforded the desired *tert*-butyl 2-(2-acetylthiophen-3-yl)-1*H*-indole-1-carboxylate **321** (1.299 g, 78%), as a pale yellow solid.



δ_H /ppm: 8.29 (1H, d, *J*=8.3 Hz, H_h), 7.57-7.53 (2H, overlapping d's, H_e and H_p), 7.39-7.33 (1H, m, H_g), 7.29-7.24 (1H, m, H_f), 7.07 (1H, d, *J*=5.0 Hz, H_o), 6.58 (1H, s, H_c), 2.19 (3H, s, H_r), 1.34 (9H, s, H_l). **δ_C /ppm:** 191.0 (C_q), 149.5 (C_j), 141.3 (ArC), 138.3 (ArC), 136.7 (ArC), 132.4 (ArC), 132.0 (ArCH), 130.4 (ArCH), 128.7 (ArC), 124.8 (ArCH), 123.0 (ArCH), 120.5 (ArCH), 115.6 (ArCH), 111.0 (ArCH), 83.5 (C_k), 28.0 (C_r), 27.5 (C_l). **ν /cm^{-1}:** 1733 (C=O str), 1656 (C=O str), 1453, 1369, 1333. **HRMS**: calcd for $C_{19}H_{19}NO_3S$ 341.1086 found 341.1057. **M/z:** 341.1057 (27%), 241.0544 (100%), 226.0280 (16%). **M.Pt.:** 92-94 °C.

7.3.2.3 2-(2-Acetyl-3-thienyl)-1*H*-indole – 322

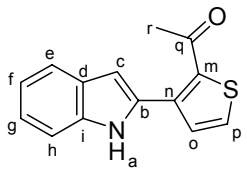
Procedure 1: using $AlCl_3$

Into a dry 100 ml round bottom flask under Ar was placed *tert*-butyl 2-(2-acetylthiophen-3-yl)-1*H*-indole-1-carboxylate **321** (1.00 g, 2.93 mmol) followed by dry dichloromethane (50 ml). The solution was cooled by means of an ice bath and then $AlCl_3$ (508 mg, 3.81 mmol) was added in one portion. A colour change from pale yellow to bright red occurred over a period of 15 min. The reaction was left to proceed at 0 °C for 1 h and then

was quenched by the careful addition of water (50 ml). The reaction mixture was then diluted with dichloromethane (100 ml) and water (100 ml) and the phases were thoroughly mixed. The organic phase was separated and the aqueous phase extracted with dichloromethane (3 × 50 ml). The combined organic fractions were washed with brine (100 ml) and after separation, dried over anhydrous magnesium sulfate. Evaporation of the solvent *in vacuo* and purification by column chromatography (5-10% EtOAc/Hexane) afforded the desired product **322** as a bright yellow solid (612 mg, 87%).

Procedure 2: Using SiO_2 and µ-wave

Into a 250 ml round bottom flask was placed *tert*-butyl 2-(2-acetylthiophen-3-yl)-1*H*-indole-1-carboxylate **321** (3.329 g, 9.750 mmol) followed by ethyl acetate (150 ml) and silica gel (150 g). The solvent was removed *in vacuo* thus adsorbing the compound onto the silica gel and trace amounts of solvent were removed under vacuum for 1 h. The adsorbate was then placed into a conventional microwave (500W) for 30 s bursts with 2 min of cooling between each burst. After each burst the adsorbate was mixed to ensure that the reaction progressed evenly through the adsorbate and a small sample was removed for analysis by TLC (a small amount of the silica was placed in ethyl acetate to dissolve the adsorbed material and this was analyzed by TLC). As the reaction progressed the silica gel changed colour from off white to bright yellow. In this particular case, 7 × 45 s bursts were required to complete the reaction. Once the reaction was complete the adsorbed product was loaded onto a column and purified by column chromatography (5-10% EtOAc/Hexane). Evaporation of volatiles *in vacuo* afforded the desired product **322** as a bright yellow solid (2.335 g, 99%).



δ_H /ppm: 12.31 (1H, s, H_a), 7.70 (1H, d, *J*=5.3 Hz, H_p), 7.64 (1H, d, *J*=8.0 Hz, H_e), 7.54 (1H, d, *J*=5.3 Hz, H_o), 7.51 (1H, d, *J*=8.2 Hz, H_h), 7.28-7.22 (1H, m, H_g), 7.12 (1H, t, *J*=7.4, Hz, H_f), 6.97 (1H, d, *J*=1.1 Hz, H_c), 2.72 (3H, s, H_r). **δ_C /ppm:** 192.1 (C_q), 138.7 (ArC), 136.0 (ArC), 133.0 (ArC), 132.4 (ArC), 131.0 (ArCH), 130.7 (ArCH), 128.1 (ArC), 123.3 (ArCH), 120.7 (ArCH), 120.1 (ArCH), 112.1 (ArCH), 103.9 (ArCH), 30.4 (C_r). **ν /cm^{-1}:** 3178 (NH str), 1645 (C=O str), 1537, 1488, 1377, 1220. **HRMS**: calcd for $C_{14}H_{11}NOS$ 241.0561 found 241.0564. **M/z:** 241.0564 (100%), 226.0348 (26%), 198.0396 (12%), 171.0254 (10%), 68.9952 (1%). **M.Pt.:** 102-104 °C.

7.3.2.4 *tert*-Butyl 2-(2-acetylthiophen-3-yl)-3-formyl-1*H*-indole-1-carboxylate – 317, as well as *tert*-butyl 2-(2-(1-(*tert*-butoxycarbonyloxy)vinyl)-thiophen-3-yl)-3-formyl-1*H*-indole-1-carboxylate - 324.

Part 1: Formylation

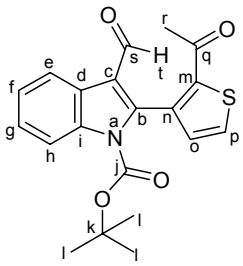
Into a 250 ml 2 neck round bottom flask fitted with a dropping funnel (dried and under Ar) was placed DMF (5.80 ml, 5.48 g, 74.9 mmol). The flask was then cooled by means of an ice bath and $POCl_3$ (1.15 ml, 1.92 g, 12.5 mmol) was added drop wise. The formation of the salt was allowed to proceed for 30 min under Ar at 0 °C. The dropping funnel was charged with dichloromethane (100 ml) and this was added over a 10 min period to dilute the newly formed reagent. This solution was left to cool to 0 °C for another 15 min. Meanwhile the dropping funnel was once again charged with dichloromethane (50 ml) and the indole **322** (2.15 g, 8.91 mmol). This yellow solution was then added dropwise over a period of 5-10 min to the flask still at 0 °C and it was observed that the yellow colour immediately disappeared as **322** reacted with the iminium salt. After the addition was complete the reaction was carefully monitored by TLC (*ca.* every 5 min) and after about 15 min all of the starting material had been converted to the salt (only a highly UV active spot on the baseline if the TLC was run in 40% EtOAc/Hexane). The reaction was then immediately quenched by the careful addition of cold water (50 ml) and transferred to a 500 ml beaker. Dichloromethane (100 ml) was added to dilute the mixture followed by water (100 ml). By means of gentle heating and vigorous stirring the 2-phase mixture was brought to a gentle boil (dichloromethane boiling) and 1N NaOH solution was slowly added until the pH of the solution remained slightly basic. The organic phase was then separated and the aqueous phase extracted with dichloromethane (3 × 80 ml). The combined organic fractions were washed with brine, separated and dried over anhydrous magnesium sulfate for 30 min. Filtration and evaporation of the solvent afforded the crude 2-(2-acetylthiophen-3-yl)-1*H*-indole-3-carbaldehyde **323** as a dark red solid. This was then Boc protected (Part 2) without further purification.

Part 2: Boc protection

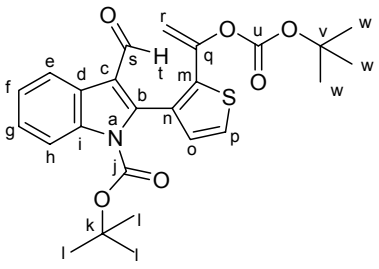
The crude material **323** from Part 1 (assume 8.91 mmol) was taken up in dry THF (200 ml) and transferred to a dry 250 ml round bottom flask containing Ar. To the flask at rt was added Boc_2O (3.30 ml, 3.14 g, 14.4 mmol) and DMAP (0.122 g, 0.998 mmol). The

reaction was left to proceed for 18 h under Ar and then transferred to a separating funnel. Water (200 ml) was added followed by ethyl acetate (200 ml) and after vigorous shaking the organic phase was separated. The aqueous phase was extracted with ethyl acetate (3 × 100 ml) and the combined organic fractions were washed with brine, separated and dried over anhydrous magnesium sulfate. After filtration and evaporation of the solvent *in vacuo* the crude product was obtained as a brown solid. Column chromatography (20-40% EtOAc/Hexane) followed by recrystallisation from ethyl acetate/hexane afforded the desired compound **317** as an off-white solid (1.64 g, 50% over 2 steps) and the excess Boc reagent had further trapped the enolate version of this compound **324**, isolated as a white solid (1.46 g, 35%). Total conversion for both products starting from **322** is 85% yield.

For 317



δ_H /ppm: 9.65 (1H, s, H_t); 8.36 (1H, d, *J*=7.2 Hz; H_e); 8.25 (1H, d, *J*=8.3 Hz, H_h); 7.68 (1H, d, *J*=5.0 Hz, H_p); 7.48-7.38 (2H, overlapping triplets, H_f and H_g); 7.20 (1H, d, *J*=5.0 Hz, H_o); 2.31 (3H, s, H_r); 1.37 (9H, s, H_l). **δ_C /ppm:** 189.4 (C_q), 186.6 (C_s), 148.8 (C_j), 143.0 (ArC), 141.7 (ArC), 136.3 (ArC), 134.1 (ArC), 132.3 (C_o), 130.6 (C_p), 126.2 (ArCH), 125.4 (ArC), 124.8 (ArCH), 121.9 (C_e), 120.4 (ArC), 115.3 (C_h), 85.0 (C_k), 28.4 (C_r), 27.5 (C_l). **ν /cm^{-1}:** 1745 (C=O str), 1669 (C=O str), 1454, 1318. **HRMS**: calcd for $C_{20}H_{19}NO_4S$ 369.1035 found 369.1029. **M/z:** 369.1029 (10%), 340.1137 (13%), 326.0904 (22%), 269.0488 (17%), 240.0530 (72%), 226.0354 (100%). **M.Pt.:** 139-140 °C



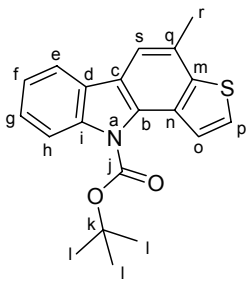
For 324

δ_H /ppm: 9.67 (1H, s, H_t), 8.37-8.34 (1H, m, H_e), 8.31-8.28 (1H, m, H_h), 7.44-7.37 (2H, overlapping m's, H_f and H_g), 7.33 (1H, d, *J*=5.2 Hz, H_p), 7.01 (1H, d, *J*=5.1 Hz, H_o), 5.18 (1H, d, *J*=2.8 Hz, $H_{r\ trans\ to\ O}$), 5.01 (1H, d, *J*=2.8 Hz, $H_{r\ cis\ to\ O}$), 1.36 (9H, s, H_l), 1.14 (9H, s, H_w).

7.3.2.5 *tert*-Butyl 4-methyl-10*H*-thieno[3,2-*a*]carbazole-10-carboxylate – 315

Into a 50 ml 2 neck round bottom flask (oven dried, under Ar) was placed $MePPh_3Br$ (2.90 g, 8.12 mmol) followed by dry diethyl ether (30 ml). The white suspension was cooled to -10 ºC and then *n*BuLi (1.4 M, 5.8 ml, 8.1 mmol) was added dropwise, thus forming a yellow solution. The solution was allowed to warm to rt and stirred for another 1.5 h. Stirring was stopped and the white salt was allowed to settle, leaving a yellow solution. Into a separate 100 ml round bottom flask fitted with a dropping funnel (oven dried, under Ar) was placed the dicarbonyl **317** (300 mg, 0.812 mmol) followed by dry diethyl ether (60 ml) and the solution was cooled to 0 ºC by means of an ice bath. The ylide solution from the first flask was transferred by cannula into the second flask containing the dicarbonyl **317** in diethyl ether over a 10 min period. The reaction mixture was stirred for 30 min at 0 ºC and then quenched by the addition of water (60 ml). The diethyl ether layer was separated, washed successively with water (2 × 100 ml) and then brine (100 ml). After drying the diethyl ether layer with magnesium sulfate, the crude intermediate diene was adsorbed onto silica gel and purified hastily by column chromatography. The diene **316**, now suspended in ethyl acetate/hexane was then concentrated by removing 80% of the solvent mixture *in vacuo* and then toluene was added (150 ml) and the mixture was again concentrated *in vacuo* to about 20% of its original volume. Toluene (150 ml) was added once again and the volume was reduced *in vacuo* to 20 cm^3, thus removing most of the ethyl acetate/hexane without ever fully concentrating the diene (which is unstable when neat). The solution was transferred to a 50 ml round bottom flask, degassed several times *in vacuo* and then Grubbs II catalyst was added (50 mg, 0.059 mmol). After degassing once more the flask was covered in aluminium foil and the reaction was allowed to proceed under Ar at rt for 3 h. Analysis of the reaction mixture by TLC indicated that not all of the diene had reacted and so a further quantity of Grubbs II catalyst was added (30 mg, 0.035 mmol) and the reaction mixture was degassed

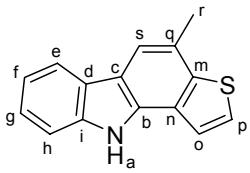
again and left for 18 h. The solvent was then removed *in vacuo* and the crude material purified by column chromatography to afford the desired product **315** as a white solid (109 mg, 40% over 2 steps).



δ_H /ppm: 8.16 (1H, d, *J*=5.7 Hz, H_p), 8.14 (1H, d, *J*=8.1 Hz, H_h), 7.95 (1H, d, *J*=7.4 Hz, H_e), 7.70 (1H, s, H_s), 7.47 (1H, d, *J*=5.7 Hz, H_o), 7.42 (1H, t, *J*=7.2 Hz, H_g), 7.33 (1H, t, *J*=7.5 Hz, H_f), 2.67 (3H, s, H_r), 1.76 (9H, s, H_l). **δ_C /ppm:** 151.2 (C_j), 141.2 (ArC), 138.5 (ArC), 132.2 (ArC), 127.7 (ArC), 127.2 (ArC), 126.3 (ArC), 126.0 (ArCH), 125.9 (ArCH), 123.9 (ArCH), 123.3 (ArC), 122.9 (ArCH), 119.1 (ArCH), 115.8 (ArCH), 115.7 (ArCH), 84.2 (C_k), 28.3 (C_l), 20.5 (C_r). **ν /cm^{-1}:** 1732 (C=O str), 1471, 1316, 1365, 1154. **HRMS**: calcd for $C_{20}H_{19}NO_2S$ 337.1136 found 337.1138. **M/z:** 337.1138 (39%), 281.0452 (96%), 237.0562 (100%), 118.0261 (6%). **M.Pt.:** 111-115 °C.

7.3.2.6 Thiofurostifoline – 314

The boc-carbazole **315** (93 mg, 0.28 mmol) was dissolved in dry dichloromethane (15 ml) and treated at rt with TFA (0.63 ml, 93 mg, 0.82 mmol). After 1 h, analysis of the reaction by TLC indicated that no reaction was taking place and so the solution was heated to reflux and the stopper removed from the 2 neck round bottom flask (Ar blowing through) to simultaneously concentrate the solution (to *ca.* 1-2 ml). Another addition of TFA was made (0.63 ml, 93 mg, 0.82 mmol) and after 1 h of reacting at rt the reaction was complete. The reaction was diluted with dichloromethane (30 ml) and washed with water (50 ml). The water layer was extracted with dichloromethane (2 × 50 ml) and the combined organic extracts were washed with brine (100 ml) before being dried over anhydrous magnesium sulfate. Purification of the indole was achieved by means of column chromatography (10-20% EtOAc/Hexane) to afford thiofurostifoline **314** as a white solid (47.7 mg, 72 %).



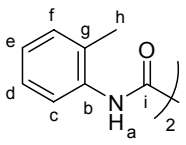
δ_H /ppm: 8.39 (1H, s, H_a), 8.08 (1H, d, *J*=7.8 Hz, H_e), 7.84 (1H, s, H_s), 7.63 (1H, d, *J*=5.5 Hz, H_p), 7.54 (1H, d, *J*=5.5 Hz, H_o), 7.50 (1H, d, *J*=8.2 Hz, H_h), 7.40 (1H, t, *J*=7.5 Hz, H_g), 7.27 (1H, t, *J*=7.05 Hz, H_f), 2.71 (3H, s, H_r). **δ_C /ppm:** 139.2 (ArC), 138.5

(ArC), 132.9 (ArC), 125.3 (ArCH), 124.8 (ArCH), 124.0 (ArC), 123.9 (ArC), 123.3 (ArC), 119.9 (ArCH), 119.8 (ArCH), 119.7 (ArCH), 119.5 (ArC), 116.8 (ArCH), 110.9 (ArCH), 20.5 (C_r). **ν /cm^{-1}:** 3413 (NH str), 1452, 1249, 738. **HRMS**: calcd for $C_{15}H_{11}NS$ 237.0612 found 237.0606. **M/z:** 237.0606 (100%), 204.0828 (5%), 191.0779 (3%), 118.5317 (17%). **M.Pt.:** 189-191 °C.

7.3.3 Synthesis of the indolocarbazole core - 341

7.3.3.1 Oxalyl-*o*-toluidide – 336

Into a 100 ml round bottom flask fitted with a dropping funnel (oven dried and under Ar) was placed distilled *o*-toluidine (2.00 ml, 2.01 g, 18.7 mmol) followed by dry THF (30 ml) and $NaHCO_3$ (3.50 g, 41.7 mmol). The dropping funnel was charged with oxalyl chloride (0.80 ml, 1.2 g; 9.5 mmol) in THF (30 ml). The oxalyl chloride solution was added to the stirred suspension at rt over a period of 5 min and a white precipitate formed immediately. This precipitate was filtered and washed with water affording **336** in quantitative yield (2.50 g). Further purification was not necessary as the compound was deemed to be pure by NMR analysis.

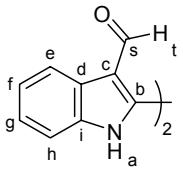


δ_H /ppm: 9.37 (2H, s, H_a), 8.09 (2H, d, *J*=8.1 Hz, H_c), 7.31-7.24 (4H, m, H_f and H_d), 7.17-7.12 (2H, m, *J*=7.4 Hz, H_e), 2.39 (6H, s, H_e). **δ_C /ppm:** 157.7 (C_i), 134.4 (C_b), 130.7 (ArCH), 128.5 (C_g), 127.0 (ArCH), 125.8 (ArCH), 121.3 (ArCH), 17.45 (C_h).

7.3.3.2 2,2'-Biindolyl-3,3'-dicarboxaldehyde – 338

Into a 10 ml 2 neck round bottom flask fitted with a dropping funnel (dried, under Ar) was placed DMF (1.0 ml; 0.94 g, 13 mmol) and the flask was cooled in an ice bath. $POCl_3$ (0.27 ml, 0.44 g, 2.9 mmol) was added slowly and after 10 min of stirring at 0°C, the *bis*-indole **337** (300 mg; 1.29 mmol) in DMF (2 ml) was added dropwise. The reaction was left to proceed at 0°C for 10 min and then at rt for 1 h before being quenched by the addition of cold water (2 ml). The reaction mixture was transferred to a conical flask. Sodium hydroxide solution (550 mg, 13.7 mmol, in 3 ml water) was added and the mixture was briefly boiled whilst stirring vigorously. The precipitate was filtered and washed with

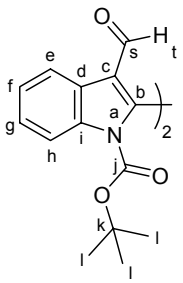
water. After drying for 18 h in a dessicator the desired compound **338** was obtained in 80% yield (297 mg) as a white solid.



δ_H /ppm: 14.93 (2H, s, H_a), 10.34 (2H, s, H_t), 8.01 (2H, d, *J*=7.5 Hz, H_e), 7.69 (2H, d, *J*=8.1 Hz, H_h), 7.46-7.36 (4H, m, H_f and H_g). **δ_C /ppm:** 184.6 (C_s), 135.3 (ArC), 134.4 (ArC), 130.2 (ArC), 125.3 (ArCH), 123.7 (ArCH), 117.5 (ArCH), 113.6 (ArCH), 112.6 (ArC).

7.3.3.3 *N,N'*-Di-*tert*-butylcarboxylate-2,2'-biindolyl-3,3'-dicarboxaldehyde – 339

Into a 50 ml flame dried round bottom flask was placed **338** (200 mg, 0.694 mmol) followed by dry THF (20 ml) thus forming an insoluble suspension. Boc_2O (0.500 ml, 475 mg, 2.18 mmol) was added in one portion followed by DMAP (21 mg, 0.17 mmol). The reaction was left to proceed under Ar for 10 min during which time the solution became homogeneous and TLC analysis of the reaction mixture indicated that the reaction was complete. The solvent was evaporated and the crude material purified by column chromatography (20% EtOAc/Hexane) affording *N,N'*-di-*tert*-butyldicarboxylate-2,2'-biindolyl-3,3'-dicarboxaldehyde **339** as a white crystalline material (301 mg, 89%).

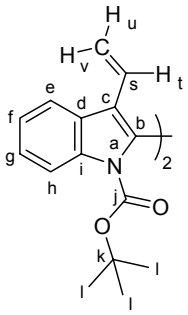


δ_H /ppm: 9.83 (2H, s; H_t); 8.44 (1H, d; *J*=7.4 Hz; H_e); 8.33 (2H, d; *J*=8.2 Hz; H_h); 7.55-7.50 (2H; m, H_g); 7.49-7.44 (2H, m, H_f); 1.26 (18H, s; H_l). **δ_C /ppm:** 186.1 (C_s), 148.6 (C_j), 136.7 (ArC), 136.2 (ArC), 127.3 (ArCH), 125.3 (ArCH), 125.1 (ArC), 123.4 (ArC), 122.3 (ArCH), 115.5 (ArCH), 86.1 (C_k), 27.6 (C_l). **ν /cm^{-1}:** 1746 (C=O str), 1677 (C=O str), 1346, 1316, 1141, 1093. **HRMS**: calcd for $C_{28}H_{28}N_2O_6$ 488.1947 found 488.1916. **M/z:** 488.1916 (40%), 359.1399 (27%), 303.0759 (85%), 288.0859 (78%), 259.0828 (100%), 232.0962 (24%). **M.Pt.:** Decomposition at 170 °C

7.3.3.5 *N,N'*-Di-*tert*-butylcarboxylate-2,2'-biindolyl-3,3'-divinyl – 340

Into a 50 ml 2 neck oven dried flask, fitted with a dropping funnel, was placed $MePPh_3Br$ (533 mg, 1.49 mmol) and the contents of the flask were blanketed with Ar. THF (10 ml) was added forming a white suspension and after cooling to -50 °C, *n*BuLi (1.2 M, 1.2 ml,

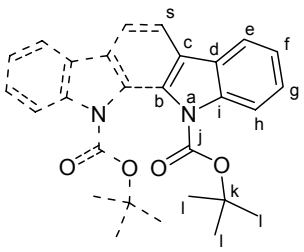
1.4 mmol) was added resulting in a yellow solution with a white suspension. The reaction was allowed to proceed under Ar for 30 min at -50 °C and was then warmed to 0 °C for 10 min. The reaction was again cooled to -30 °C and the *bis*-indole **339** (300 mg, 0.614 mmol), in THF (15 ml) was added dropwise over 5 min. The reaction was left to proceed for 18 h at 0 °C before pouring the reaction mixture onto water/crushed ice (20 ml). The crude diene was extracted into ethyl acetate and rapidly purified by column chromatography (5% EtOAc/Hexane) affording the slightly impure product **340** (326 mg, 106% - impure as shown by NMR) as a pale yellow oil which was only stable if kept below 5 °C.



δ_H /ppm: 8.40 (2H, d, *J*=8.3 Hz, H_h), 7.92 (2H, d, *J*=7.6 Hz, H_e), 7.44-7.38 (2H, m, H_g), 7.36-7.30 (2H, m, H_f), 6.46 (2H, dd, *J*=18.0 and 11.6 Hz, H_t), 5.74 (2H, dd, *J*=18.0, 1.1 Hz, H_v), 5.26 (2H, dd, J=11.6 and 1.1 Hz, H_u), 1.14 (18H, s, H_l).

7.3.3.6 Di(*tert*-butyl) indolo[2,3-*a*]carbazole-11,12-dicarboxylate – 341

Into a 2 neck round bottom flask fitted with a condenser (oven dried and under Ar) was placed the diene **340** (assume 0.614 mmol) dissolved in toluene (60 ml). To the solution was added Grubbs II catalyst (26 mg, 0.031 mmol) and the solution was vacuum degassed before being covered by an Ar atmosphere. The solution was heated to 80 °C for 20 h and then analysis of the reaction mixture by TLC indicated that not all the diene had reacted. More Grubbs II catalyst was added (14 mg, 0.016 mmol) and the reaction was left to proceed at 80 ºC for another 4 h. The solvent was then evaporated *in vacuo* and the crude material purified by column chromatography (5-10% EtOAc/Hexane). Recrystallisation from an ethyl acetate/hexane mixture afforded the desired compound **341** as white crystals (178 mg, 64%, or 74% if the recovered starting material is taken into account).



δ_h /ppm: 8.27 (2H, d, *J*=7.9 Hz, H_h), 8.04-8.01 (4H, overlapping d and s, H_h and H_s), 7.51-7.46 (2H, m, H_g), 7.41-7.36 (2H, m, H_f), 1.63 (18H, s, H_l). **δ_c /ppm:** 151.4 (C_j), 139.8 (ArC), 128.1 (ArC), 127.3 (ArC), 126.9 (ArCH), 123.2 (ArCH), 119.5 (ArCH), 116.3 (ArC), 115.4 (ArCH), 84.2 (C_k), 28.3 (C_l). **ν /cm^{-1}:** 2980, 1728 (C=O str), 1334, 1295, 1152. **HRMS**: calcd for $C_{28}H_{28}N_2O_4$ 456.2049 found 456.2011. **M/z:** 456.2011 (28%), 300.0854 (64%), 256.0996 (100%), 237.0562 (6%). **M.Pt.:** Decomposition at 230 °C. **X-ray data:** $C_{28}H_{28}N_2O_4$; *M*=456.52; monoclinic; 0.71073 Å; *a*=17.031(3) Å, *b*=7.8425(15) Å, *c*=18.690(4) Å, *U*=2420.1(8) Å^3; 293(2) K, space group, p2(1)/n, Z=4;. μ(Mo-Kα)=0.084 mm^{-1} 15515 reflections measured, 5820 unique [R(int)=0.0605] which were used in all calculations. Final R indices [$I>2\sigma(I)$] R_1=0.0547, w$R(F^2)$=0.1340.

7.3.4 Off the beaten track

7.3.4.1 *tert*-Butyl 4-(*tert*-butoxycarbonyloxy)-10*H*-thieno[3,2-*a*]carbazole-10-carboxylate - 326

Part 1: Wittig reaction

Done in the absence of sunlight and with minimal lighting:

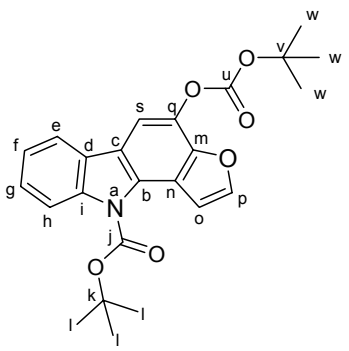
Into a 2 neck round bottom (dried and containing Ar) was placed methyltriphenylphosphonium bromide (630 mg, 1.76 mmol) followed by dry diethyl ether (35 ml), thus forming a white suspension. This suspension was cooled to -10 °C by means of an acetone-ice bath and *n*BuLi (1.60 M, 1.10 ml, 1.76 mmol) was added dropwise by means of a syringe. Upon addition of the *n*BuLi, the reaction mixture became yellow in colour however a white solid still remained (LiBr). After 45 min of stirring at -10 to 0 °C the solution containing the ylide was allowed to stand for 10 min to allow the insoluble salt to settle onto the bottom of the flask. In the meantime, another dry reaction vessel was prepared by fitting a dropping funnel to a 2 neck round bottom flask. After drying this apparatus in the oven and flame drying under vacuum, the vessel was filled with Ar and the indolo-thiophene **324** (200 mg, 0.441 mmol) was added to the flask, followed by dry diethyl ether (35 ml). The solution containing the ylide was cannulated into the dropping funnel and the reaction vessel was cooled to -10 °C using an acetone-ice bath. The ylide was then added dropwise and the progress of the reaction was regularly monitored by TLC

analysis. Once the stating material had been consumed the addition of the ylide was ceased and the reaction rapidly quenched by the addition of ice cold water. The reaction mixture was diluted with ethyl acetate (100 ml) and water (50 ml) and after thoroughly mixing the phases, the organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 × 50 ml). The combined organic fractions were washed with brine (100 ml) and finally dried over anhydrous magnesium sulfate. After filtration, most of the solvent was removed *in vacuo* and then silica gel was added forming a slurry. The remainder of the solvent was removed and the crude material rapidly purified by column chromatography (2% EtOAc/Hexane). Once the chromatography was complete, the solvent was not removed for fear of the diene **325** being unstable in its neat form. Rather, approximately 80% of the solvent was removed and then toluene (100 ml) was added, and the solution was once again concentrated to just 20% of its original volume. This process of adding toluene and concentrating the solution was repeated 3 times thus driving off the lower boiling solvents and leaving the diene suspended in about 10 ml of toluene only.

Part 2: Metathesis reaction

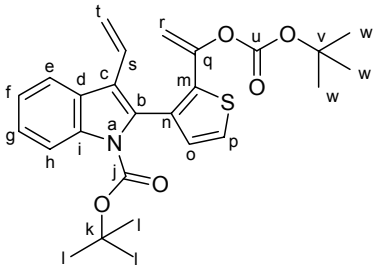
Done in the absence of sunlight and with minimal lighting:

The diene **325** in toluene (assume 0.441 mmol) from part 1 was transferred into a dry 2 neck round bottom flask and thoroughly degassed by means of bubbling Ar into the solution using a Pasteur pipette. Hoveyda catalyst (14 mg, 0.022 mmol, 5 mole %) was added in one portion and the reaction mixture was heated to 80 °C under Ar for 5 h. After this time, analysis of the reaction mixture indicated that a new product was forming however, some of the starting diene still seemed to be present. Thus, another addition of Hoveyda catalyst was made (14 mg, 0.022 mmol) and the reaction was heated to 80 °C for 18 h. After this time, although it appeared that some diene still remained, the reaction was concentrated *in vacuo* and purified by column chromatography affording the desired carbazole in a poor yield (17 mg, 9%) as well as some of the recovered diene **325** (41 mg).



Spectral data for **326**:

δ_H /ppm: 8.17-8.14 (2H, overlapping d's, H_p and H_h), 8.00 (1H, d, *J*=7.5 Hz, H_e), 7.83 (1H, s, H_s), 7.51 (1H, d, *J*=5.7 Hz, H_o), 7.46 (1H, t, *J*=7.7 Hz, H_g), 7.38 (1H, t, *J*=7.4 Hz, H_f), 1.78 (9H, s, H_w), 1.48 (9H, s, H_l).



Spectral data for recovered **325**:

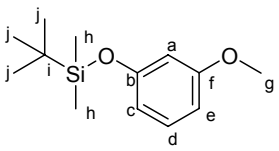
δ_H /ppm: 8.36 (1H, d, *J*=8.2 Hz, H_h), 7.87 (1H, d, *J*=7.7 Hz, H_e), 7.39-7.34 (1H, m, H_g), 7.32-7.26 (2H, overlapping signals, H_f and H_p), 6.92 (1H, d, *J*=5.1 Hz, H_o), 6.46 (1H, dd, J=18.0 Hz and 11.7 Hz, H_s), 5.71 (1H, d, *J*=17.9 Hz, H_t *trans* to H_s), 5.26 (1H, d, *J*=11.8 Hz, H_t *cis* to H_s), 5.05 (1H, d, *J*=2.6 Hz, H_r *trans* to O), 4.91 (1H, d, *J*=2.5 Hz, H_r *cis* to O), 1.32 (9H, s, H_l), 1.24 (9H, s, H_w).

7.4 EXPERIMENTAL WORK PERTAINING TO CHAPTER 6

7.4.1 Towards the rotenone precursor

7.4.1.1 *tert*-Butyl(3-methoxyphenoxy)dimethylsilane – 460

Into a 100 ml 2 neck round bottom flask containing Ar was placed 3-methoxyphenol **459** (500 mg, 4.03 mmol) followed by acetonitrile (50 ml). To the flask was added imidazole (350 mg, 5.14 mmol) in one portion followed by TBSCl (800 mg, 5.31 mmol). The reaction was left to proceed under Ar at rt for 18 h during which time a white precipitate formed. Analysis of the reaction mixture by TLC indicated that the reaction had gone to completion and the solvent was removed *in vacuo*, during which time the white precipitate dissolved into the resultant viscous oil. To this oil was added ethyl acetate (50 ml) and the white precipitate immediately formed again. Upon the addition of water (50 ml), this white precipitate rapidly dissolved into the aqueous layer. After thoroughly mixing the phases, the organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 × 30 ml). The combined organic fractions were dried over anhydrous magnesium sulfate and filtered. Evaporation of the solvent *in vacuo* followed column chromatography (5% EtOAc/Hexane) afforded the desired compound **460** as a clear oil (850 mg, 88%).

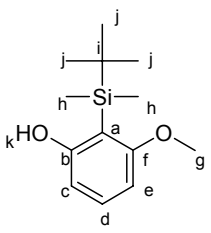


δ_H /ppm:. 7.14 (1H, t, *J*=8.1 Hz, H_d), 6.55 (1H, dd, *J*=8.0 and 2.0 Hz, ArH), 6.50-6.44 (2H, overlapping signals, 2 × ArH), 3.80 (3H, s, H_g), 1.03 (9H, s, H_j), 0.24 (6H, s, H_h). **δ_C /ppm:** 160.7 (C_f), 156.8 (C_b), 129.6 (C_d), 112.5 (ArCH), 106.8 (ArCH), 106.3 (ArCH), 55.1 (C_g), 25.7 (C_j), 18.2 (C_i), -4.4 (C_h).

7.4.1.2 Attempted synthesis of (2-allyl-3-methoxyphenoxy)(*tert*-butyl)dimethylsilane, resulting in the synthesis of 2-(*tert*-butyldimethylsilyl)-3-methoxyphenol - 461

Into a 2 neck round bottom flask containing Ar was placed *tert*-butyl(3-methoxyphenoxy)dimethylsilane **460** (700 mg, 2.94 mmol) followed by THF (50 ml). The solution was cooled to -30 °C and *n*BuLi was added dropwise over a 10 min period. The reaction was left to proceed under Ar at -30 °C for another 45 min and then allyl bromide (769 mg, 6.36 mmol, 55.0 ml) was added dropwise over a 5 min period. The reaction was

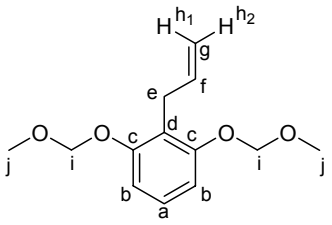
left to proceed at -30 °C for 90 min and was finally quenched by the addition of water (20 ml). The mixture was diluted with ethyl acetate (100 ml) and water (100 ml) and the phases were thoroughly mixed then separated. The aqueous phase was extracted with ethyl acetate (3 × 50 ml) and the combined organic fractions were washed with brine (100 ml), separated and dried over anhydrous magnesium sulfate. After filtration, the solvent was removed *in vacuo* and the crude oil purified by column chromatography (10 % EtOAc/Hexane) affording unexpectedly 2-(*tert*-butyldimethylsilyl)-3-methoxyphenol **461** in poor yield (98 mg, 14%).



δ_H /ppm:. 7.20 (1H, t, *J*=8.1 Hz, H_d), 6.44 (1H, d, *J*=8.2 Hz, H_e), 6.37 (1H, d, *J*=8.0 Hz, H_c), 5.03 (1H, s, H_k), 3.74 (3H, s, H_g), 0.94 (9H, s, H_j), 0.38 (6H, s, H_h). **δ_C /ppm:** 165.9 (C_f), 162.0 (C_b), 131.4 (C_d), 109.9 (C_a), 108.6 (ArCH), 102.5 (ArCH), 54.8 (C_g), 26.9 (C_j), 18.3 (C_i), -1.9 (C_h).

7.4.1.3 2-Allyl-1,3-*bis*(methoxymethoxy)benzene – 463

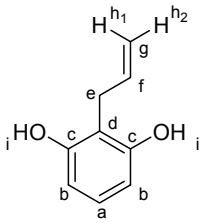
Into a dry 2 neck 250 ml round bottomed flask, fitted with a dropping funnel and under Ar was placed dry THF (170 ml) followed by 1,3-*bis*(methoxymethoxy)benzene **462** (4.00 g, 20.18 mmol). The solution was cooled to 0 °C and the dropping funnel was charged with *n*BuLi (1.40 M, 17.0 ml, 24.0 mmol). The *n*BuLi was added dropwise over a period of 10 min thus forming a yellow solution which was stirred at 0 °C for another 90 min. During this time the yellow colour intensified and eventually turned slightly orange. The dropping funnel was then charged with allyl bromide (3.50 ml, 40.0 mmol) in THF (10 ml) and this solution was added dropwise to the reaction mixture over a period of 10 min, with a resulting colour change from orange to clear. The reaction was left to proceed at 0 °C for another 60 min and then allowed to warm to rt and left for 18 h during which time the colour of the solution changed to orange once again. The reaction mixture was transferred to a separating funnel and diluted with ethyl acetate (100 ml) and water (100 ml). After mixing the organic phase was separated and the aqueous phase was extracted once with ethyl acetate. The combined organic fractions were washed with brine and then dried over anhydrous magnesium sulfate. After filtration and evaporation of the solvent *in vacuo* the crude oil was purified by column chromatography (2% EtOAc/Hexane) affording the desired compound **463** as a clear oil (3.74 g, 78%).



δ_H /ppm: 7.09 (1H, t, *J*=8.3 Hz, H_a), 6.77 (2H, d, *J*=8.3 Hz, H_b), 5.96 (1H, tdd, *J*=6.1 Hz, 10.0 Hz and 16.2 Hz, H_f), 5.17 (4H, s, H_i), 5.01-4.91 (2H, overlapping signals, H_{h1} and H_{h2}), 3.48-3.46 (8H, overlapping d and s, H_e and H_j). **δ_C /ppm:** 155.8 (C_c), 136.7 (C_f), 127.1 (C_a), 118.3 (C_d), 114.1 (C_g), 107.9 (C_b), 94.4 (C_i), 55.9 (C_j), 27.6 (C_e). **ν /cm^{-1}:** 2901, 1596, 1471, 1154, 1041. **HRMS**: calcd for $C_{13}H_{18}O_4$ 238.1205 found 238.1216. **M/z:** 238.1216 (25%), 174.0687 (6%), 161.0575 (34%), 147.0454 (10%).

7.4.1.4 2-Allylbenzene-1,3-diol – 464

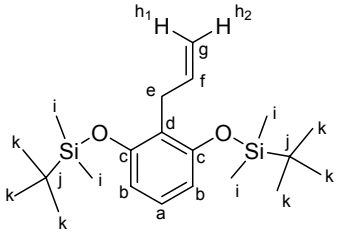
Into a 250 ml flask fitted with a condenser was placed 2-allyl-1,3-*bis*(methoxymethoxy)benzene **463** (4.20 g, 17.6 mmol) followed by THF (100 ml) and methanol (50 ml). The solution was acidified slightly by the addition of 3 drops of 32% HCl solution and then heated to reflux for 18 h. Analysis of the reaction mixture by TLC indicated that nearly all the starting material had been consumed however a significant amount of the mono-protected molecule was present as well as some of the desired completely deprotected species. Another addition of acid was made (5 drops) and the solution was refluxed for another 18 h. Analysis of the reaction mixture by TLC indicated that only a trace amount of the mono-protected molecule remained. The solvent was evaporated *in vacuo* affording a clear oil. Removal of trace amounts of water was achieved by dissolving the crude material in ethyl acetate and adding magnesium sulfate. After filtration, the solvent was removed *in vacuo* affording the crude product which was purified by column chromatography (10% EtOAc/Hexane) affording the desired diol **464** as a clear oil in quantitative yield (2.97 g).



δ_H /ppm: 6.97 (1H, t, *J*=8.1 Hz, H_a), 6.43 (2H, d, *J*=8.1 Hz, H_b), 6.02 (1H, tdd, *J*=6.0 Hz, 10.1 Hz and 16.1 Hz, H_f), 5.41 (2H, s, H_i), 5.20-5.11 (2H, overlapping signals, H_{h1} and H_{h2}), 3.50-3.48 (2H, m, H_e). **δ_C /ppm:** 155.0 (C_c), 135.9 (C_f), 127.6 (C_a), 115.9 (C_g), 112.1 (C_d), 108.2 (C_b), 27.5 (C_e). **ν /cm^{-1}:** 3413, 1614, 1465, 1294. **HRMS**: calcd for $C_9H_{10}O_2$ 150.0681 found 150.0694. **M/z:** 150.0694 (100%), 135.0457 (30%), 123.0475 (20%), 107.0453 (18%), 103.0523 (8%).

7.4.1.5 2-Allyl-1,3-*bis*(*tert*-butyldimethylsilyloxy)-benzene – 465

Into a dry 2 neck flask containing was placed the diol **464** (2.40 g, 16.0 mmol) followed by dry acetonitrile (180 ml). Imidazole was added in one portion (3.26 g, 47.9 mmol) followed by TBSCl (6.02 g, 39.9 mmol), which was also added in one portion. The reaction was left to proceed under Ar at rt for 18 h during which time some of the imidazole hydrochloride precipitated from solution. Analysis of the reaction mixture by TLC indicated that all of the starting material had reacted. The acetonitrile was evaporated affording an oil containing the imidazole hydrochloride as a white precipitate. The crude mixture taken up into ethyl acetate (150 ml) and water was added (150 ml) facilitating dissolution of the imidazole hydrochloride salt into the aqueous phase upon mixing. After allowing the phases to separate the organic phase was separated and the aqueous phase was extracted with ethyl acetate (2 × 100 ml). The organic phases were combined and washed with brine (200 ml), then separated and dried over anhydrous magnesium sulfate. After filtration and evaporation of the solvent *in vacuo*, the crude product was obtained as a clear oil. This was purified by column chromatography (2% EtOAc/Hexane) affording the desired silylated compound **465** as a clear oil (4.79 g, 79%).

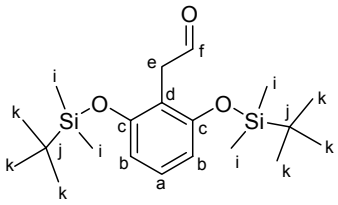


δ_H /ppm: 6.93 (1H, t, *J*=8.2 Hz, H_a), 6.45 (2H, d, *J*=8.1 Hz, H_b), 5.93 (1H, tdd, *J*=5.9 Hz, 9.4 Hz, and 17.8 Hz, H_f), 4.94-4.88 (2H, overlapping signals, H_{h1} and H_{h2}), 3.39 (2H, d, *J*=5.8 Hz, H_e), 1.01 (18H, s, H_k), 0.23 (12H, s, H_j). **δ_C /ppm:** 154.8 (C_c), 136.8 (C_f), 126.3 (C_a), 121.6 (C_d), 114.0 (C_g), 111.5 (C_b), 28.4 (C_e), 25.9 (C_k), 18.3 (C_j), -4.1 (C_i). **ν /cm^{-1}:** 2931 (CH str), 1588, 1465, 1259. **HRMS**: calcd for $C_{21}H_{38}O_2Si_2$ 378.2410 found 378.2414. **M/z:** 378.2414 (8%), 321.1720 (64%), 293.1399 (10%), 279.1541 (15%), 256.2368 (62%), 149.0200 (48%).

7.4.1.6 2-(2,6-*bis*(*tert*-butyldimethylsilyloxy)-phenyl)acetaldehyde – 466

Into a 3 neck round bottom flask was placed the alkene **465** (4.40 g, 11.6 mmol) followed by dry dichloromethane (180 ml). Whilst bubbling N_2 gas into the solution, the flask was immersed into an acetone bath cooled to -80 °C. After allowing to cool for several min and maintaining a temperature between -80 °C to -70 °C, ozone gas was bubbled into the

solution. During the addition of the ozone the N_2 bubbler was removed from the solution and left to blow gently above the level of the dichloromethane. After 5 min of ozonolysis, the ozone bubbler was removed from the solution and the N_2 bubbler was once again placed beneath the level of dichloromethane in order to quickly purge excess ozone from the solution. Analysis of the reaction mixture by TLC indicated that a significant amount of starting material had been consumed and that the ozonide was forming. Whilst maintaining the temperature of the bath around -75 °C, the solution was once again treated with ozone gas for another 5 min, in an analogous procedure to above. This procedure was continued until analysis of the reaction mixture by TLC showed only a trace amount of starting material to be present. The reaction mixture was then warmed to -10 °C and a large excess of acetic acid was added (ca. 10 ml) followed by an excess of Zn powder (added in small portions every 10 min until all the ozonide was reduced to the aldehyde). The reaction mixture was then filtered, washed twice with saturated sodium bicarbonate solution, and then finally washed once with brine before being dried over anhydrous magnesium sulfate. After filtration and evaporation of the solvent *in vacuo* the crude product was purified by column chromatography (2% EtOAc/Hexane) affording **466** as an oil at rt (3.92 g, 89%), or a waxy solid at 0-5 °C.

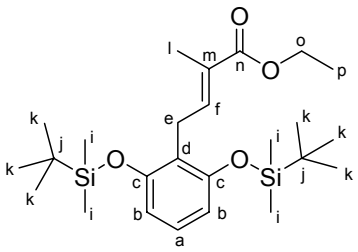


δ_H /ppm: 9.61 (1H, s, H_f), 7.03 (1H, t, *J*=8.2 Hz, H_a), 6.51 (2H, d, *J*=8.2 Hz, H_b), 3.65 (2H, d, *J*=1.5 Hz, H_e), 0.98 (18H, s, H_k), 0.23 (12H, s, H_i). **δ_C /ppm:** 200.8 (C_f), 155.3 (C_c), 127.8 (C_a), 115.0 (C_d), 111.4 (C_b), 39.4 (C_e), 25.7 (C_k), 18.2 (C_j), -4.2 (C_i). **ν /cm^{-1}:** 2859 (CH str), 1729 (C=O str), 1589, 1465, 1259. **HRMS**: calcd for $C_{20}H_{36}O_3Si_2$ 380.2203 found 380.2213. **M/z:** 380.2213 (2%), 365.1962 (5%), 323.1448 (100%), 265.0726 (9%), 237.0270 (6%), 115.0918 (11%).

7.4.1.7 *(E)*-Ethyl-4-(2,6-*bis*(*tert*-butyl-dimethylsilyloxy)phenyl)-2-methylbut-2-enoate – 467

Into a dry 2 neck round bottom flask fitted with a dropping funnel, containing Ar, was placed LiCl (510 mg, 12.0 mmol) followed by dry acetonitrile (8 ml). Ethyl 2-(diethoxyphosphoryl)propanoate (1.70 ml, 1.89 g, 7.93 mmol) was added in one portion and then whilst cooling the reaction mixture in a bath at 5 °C, DBU (1.25 ml, 1.27 g, 8.34 mmol) was added dropwise over a period of 5 min. During the addition, dissolution of

the LiCl salt occurred thus forming a clear homogeneous solution. After 15 min of stirring at 5 °C, 2-(2,6-*bis*(*tert*-butyldimethylsilyloxy)phenyl)acetaldehyde **466** (2.00 g, 5.25 mmol) in acetonitrile (2 ml) was added dropwise over a period of 10 min and the reaction was left to proceed for 18 h during which time a colour change occurred from clear to pale yellow. The reaction mixture was transferred to a separating funnel and diluted with ethyl acetate (150 ml) and water (150 ml). After mixing the phases the organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 × 100 ml). The combined organic fractions were then washed with brine (250 ml) and dried over anhydrous magnesium sulfate. After filtration and evaporation of the volatiles *in vacuo*, the crude oil was purified by column chromatography to afford *(E)*-ethyl 4-(2,6-*bis*(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-enoate **467** as a clear oil (2.10 g, 86%).

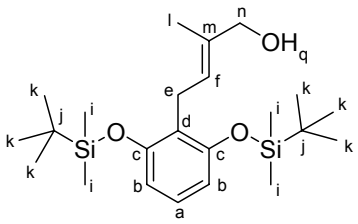


δ_H /ppm: 6.94 (1H, t, *J*=8.2 Hz, H_a), 6.81 (1H, *t*, J=6.0 Hz, H_f), 6.46 (2H, d, *J*=8.2 Hz, H_b), 4.14 (2H, q, *J*=7.1 Hz, H_o), 3.49 (2H, d, *J*=6.3 Hz, H_e), 1.92 (3H, s, H_l), 1.23 (3H, t, *J*=7.1 Hz, H_p), 0.98 (18H, s, H_k), 0.24 (12H, s, H_i). **δ_C /ppm:** 168.6 (C_n), 155.3 (C_c), 142.8 (C_f), 127.4 (C_d), 127.0 (C_a), 121.6 (C_m), 111.9 (C_b), 60.5 (C_o), 26.2 (C_k), 24.5 (C_e), 18.7 (C_j), 14.7 (C_p), 13.1 (C_l), -3.7 (C_i). **ν /cm^{-1}:** 2931 (CH str), 1712 (C=O), 1648, 1588, 1465, 1248. **HRMS**: calcd for $C_{25}H_{44}O_4Si_2$ 464.2778 found 464.2502. **M/z:** 464.2784 (10%), 449.2502 (3%), 407.2110 (100%), 379.1805 (7%), 361.1726 (5%), 218.9856 (10%).

7.4.1.8 *(E)*-4-(2,6-*Bis*(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-en-1-ol – 468

Into a 2 neck flask containing Ar was placed the ester **467** (643 mg, 1.38 mmol) followed by dry THF (10 ml). The solution was cooled to 0 °C by means of an ice bath and then $LiAlH_4$ (68.0 mg, 1.79 mmol) was added resulting in effervescence of the solution. The reaction was then left to proceed at 0 °C under Ar but was closely monitored by means of TLC every 20 min. After approximately 3 h all the starting material had been consumed. Ice cold water was added in small portions (50 ml) and the reaction mixture was diluted with ethyl acetate (50 ml). Upon mixing of the 2 phases an emulsion formed and this was broken by the addition of a small amount of 1M HCl solution. The phases were separated

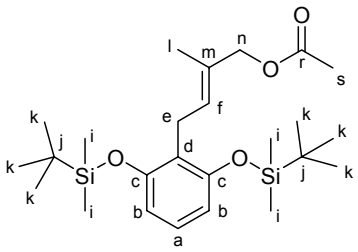
and the aqueous phase was extracted with ethyl acetate (2 × 50 ml). The combined organic phases were filtered through celite and then washed once with brine (100 ml). After separation, the organic phase was dried over anhydrous magnesium sulfate, filtered and evaporated affording the crude product as a pale yellow oil. After purification by column chromatography (2-5% EtOAc/Hexane) the desired alcohol **468** was obtained as a viscous clear oil (451 mg, 77%).



δ_H /ppm: 6.91 (1H, t, *J*=8.2 Hz, H_a), 6.45 (2H, d, *J*=8.1 Hz, H_b), 5.46 (1H, t, *J*=5.6 Hz, H_f), 3.96 (2H, s, H_n), 3.37 (2H, d, *J*=5.9 Hz, H_e), 2.17 (1H, s, H_q), 1.78 (3H, s, H_l), 0.99 (18H, s, H_k), 0.23 (12H, s, H_i). **δ_C /ppm:** 154.7 (C_c), 134.1 (C_m), 126.2 (C_f), 126.1 (C_a), 122.8 (C_d), 111.7 (C_b), 69.2 (C_n), 25.7 (C_k), 23.0 (C_e), 18.3 (C_j), 14.0 (C_l), -4.1 (C_i). **ν /cm^{-1}:** 3331, 2930, 1587, 1463, 1362, 1244, 1177, 1064, 913, 828, 732, 685. **HRMS**: calcd for $C_{23}H_{42}O_3Si_2$ 422.2672 found 422.2655. **M/z:** 422.2655 (15%), 365.1943 (100%), 347.1858 (12%), 309.1293 (15%), 273.1638 (5%), 218.9856 (11%).

7.4.1.9 *(E)*-4-(2,6-*Bis*(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-enyl acetate – 469

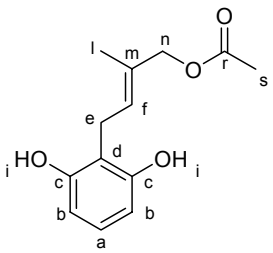
Into a 100 ml 2 neck round bottom flask was placed the alcohol **468** (1.86 g, 4.40 mmol) followed by dry THF (75 ml). To the clear solution was added triethylamine (813 mg, 8.04 mmol, 1.20 ml), DMAP (54 mg, 0.44 mmol) and finally acetic anhydride (702 mg, 6.88 mmol, 0.65 ml). The reaction was left to proceed under Ar for 4 h at rt after which analysis of the reaction mixture by TLC indicated that all of the starting material had been consumed. The reaction mixture was then transferred to a separating funnel containing ice cold water (200 ml) and ethyl acetate (200 ml) was added. After thoroughly mixing the phases, the organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 × 100 ml). The combined organic fractions were washed with brine (200 ml) and dried over anhydrous magnesium sulfate. After filtration and evaporation of the solvent *in vacuo* the crude material was purified by column chromatography (2-5% EtOAc/Hexane) to afford the desired ester **469** as a clear oil (1.57 g, 77%).



δ_H /ppm: 6.91 (1H, t, *J*=8.1 Hz, H_a), 6.45 (2H, d, *J*=8.1 Hz, H_b), 5.52 (1H, t, *J*=5.8 Hz, H_f), 4.42 (2H, s, H_n), 3.37 (2H, d, *J*=6.0 Hz, H_e), 2.04 (3H, s, H_s), 1.75 (3H, s, H_l), 0.99 (18H, s, H_k), 0.23 (12H, s, H_i). **δ_C /ppm:** 171.0 (C_r), 154.8 (C_c), 129.3 (C_f), 129.1 (C_m), 126.2 (C_a), 122.5 (C_d), 111.6 (C_b), 70.2 (C_n), 25.8 (C_k), 23.1 (C_e), 21.0 (C_s), 18.3 (C_j), 14.4 (C_l), -4.1 (C_i). **ν /cm^{-1}:** 2887 (CH str), 1744 (C=O), 1588, 1464, 1245. **HRMS**: calcd for $C_{25}H_{44}O_4Si_2$ 464.2778 found 464.2785. **M/z:** 464.2785 (1%), 407.2011 (100%), 347.1888 (23%), 273.1677 (14%), 233.0572 (8%).

7.4.1.10 *(E)*-4-(2,6-Dihydroxyphenyl)-2-methylbut-2-enyl acetate – 470

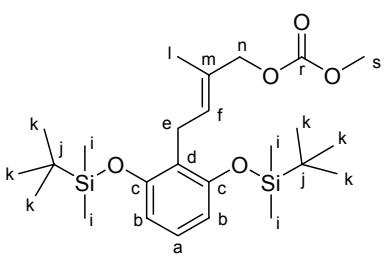
Into a dry 50 ml round bottom flask containing Ar was placed *(E)*-4-(2,6-*bis*(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-enyl acetate **469** (100 mg, 0.215 mmol) followed by dry THF (20 ml). The reaction mixture was cooled to 0 °C by means of an ice bath and then TBAF (1.00M, 0.44 ml, 0.44 mmol) was added in 1 portion and the reaction was left to proceed at 0 °C for 10 min. Analysis of the reaction mixture at this time indicated that all of the starting material had reacted. The reaction mixture was transferred to a separating funnel and diluted with ethyl acetate (100 ml) and water (100 ml). After thoroughly mixing the phases, the organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 × 100 ml). The combined organic fractions were washed with brine (200 ml) and dried over anhydrous magnesium sulfate. After evaporation of the solvent *in vacuo*, the crude oil was purified by column chromatography (20-30% EtOAc/Hexane) affording the desired diol **470** as a clear oil (44.7 mg, 88%).



δ_H /ppm: 6.91 (1H, t, *J*=8.1, Hz, H_a), 6.38 (2H, d, *J*=8.1 Hz, H_b), 6.20-5.00 (2H, brs, H_i), 5.60 (1H, t, *J*=6.6 Hz, H_f), 4.47 (2H, s, H_n), 3.45 (2H, d, J=7.0 Hz, H_e), 2.07 (3H, s, H_s), 1.83 (3H, s, H_l). **δ_C /ppm:** 171.7 (C_r), 155.0 (C_c), 131.2 (C_f), 127.2 (ArC), 127.2 (ArC), 113.4 (C_d), 108.0 (C_b), 70.3 (C_n), 22.0 (C_e), 21.0 (C_s), 14.0 (C_l). **HRMS**: calcd for $C_{13}H_{16}O_4$ 236.1049 found 236.1028. **M/z:** 236.1028 (2%), 176.0848 (42%), 161.0601 (100%), 147.0481 (6%), 123.0463 (14%).

7.4.1.11 *(E)*-4-(2,6-*bis*(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-enyl methyl carbonate – 478

Into a dry 2 neck round bottom flask containing Ar was placed the alcohol **468** (1.00 g, 2.37 mmol) followed by dry dichloromethane (20 ml). The flask was placed into a cooling bath (approx 5 °C) and pyridine (0.80 ml, 0.78 g, 9.9 mmol) was added in one portion. Methyl chloroformate (0.38 ml, 0.46 g, 4.9 mmol) was then added dropwise over a period of about 2 min and the reaction was left to proceed for 5 min before the cooling bath was removed. After allowing the reaction to proceed at rt for another 30 min, water was carefully added (20 ml) and the mixture was decanted into a separating funnel. The mixture was diluted with dichloromethane (50 ml) and water (50 ml). After thoroughly mixing the phases, the organic phase was separated and the aqueous phase was extracted once with dichloromethane (50 ml). the combined organic fractions were then washed with HCl solution (0.2N, 2 × 50 ml), once with water (50 ml) and finally once with brine (100 ml). After drying over anhydrous magnesium sulfate volatiles were removed *in vacuo* and the crude oil was purified by column chromatography (5% EtOAc/Hexane) affording the desired carbonate **478** as a clear oil (0.933 g, 82%).

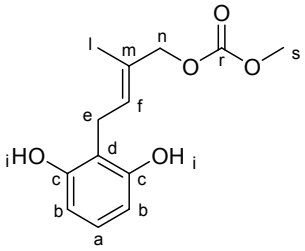


δ_H /ppm: 6.92 (1H, t, *J*=8.1 Hz, H_a), 6.45 (2H, d, *J*=8.1 Hz, H_b), 5.56 (1H, t, *J*=5.7 Hz, H_f), 4.49 (2H, s, H_n), 3.76 (3H, s, H_s), 3.37 (2H, d, *J*=5.9 Hz, H_e), 1.78 (3H, s, H_l), 0.99 (18H, s, H_k), 0.23 (12H, s, H_i). **δ_C /ppm:** 155.8 (C_r), 154.8 (C_c), 130.3 (C_f), 128.8 (C_m), 126.2 (C_a), 122.3 (C_d), 111.6 (C_b), 73.9 (C_n), 54.6 (C_s), 25.8 (C_k), 23.1 (C_e), 18.3 (C_j), 14.2 (C_l), -4.1 (C_i). **ν /cm^{-1}:** 2959 (CH str), 1751 (C=O str), 1588, 1464, 1261, 1068. **HRMS**: calcd for $C_{25}H_{44}O_5Si_2$ 480.2727 found 480.2720. **M/z:** 480.2720 (2%), 423.2000 (77%), 405.2622 (20%), 379.2153 (69%), 347.1747 (30%), 291.1276 (5%), 233.0630 (11%), 215.0906 (4%).

7.4.1.12 *(E)*-4-(2,6-Dihydroxyphenyl)-2-methylbut-2-enyl methyl carbonate – 479

Into a 100 ml round bottom flask containing Ar was placed the *bis*-silyl carbonate **478** (300 mg, 0.624 mmol) followed by dry THF (50 ml). The solution was cooled to 0 °C

under Ar and TBAF (1M, 1.24 ml, 1.24 mmol) was added in one portion. The reaction was left to proceed for 5 min during which time the colour changed to deep purple. Water was added (50 ml), and the mixture was diluted with ethyl acetate (100 ml). After thoroughly mixing the phases, the organic phase was separated and the aqueous phase was thoroughly extracted with ethyl acetate (5 × 30 ml). The combined organic fractions were washed with brine (50 ml) and dried over anhydrous magnesium sulfate. After filtration, the solvent was removed *in vacuo* and the crude oil purified by column chromatography affording the desired product **479** as a clear oil containing some ethyl acetate (as determined by NMR) which could not be removed under vacuum (169 mg).



δ_H /ppm: 6.90 (1H, t, *J*=8.1 Hz, H_a), 6.37 (2H, d, *J*=8.1 Hz, H_b), 5.63 (1H, t, *J*=6.8 Hz, H_f), 5.80-5.00 (2H, br s, H_i), 4.52 (2H, s, H_n), 3.77 (3H, s, H_s), 3.44 (2H, d, *J*=7.1 Hz, H_e), 1.84 (3H, s, H_l). **δ_C /ppm:** 155.9 (C_r), 154.9 (C_c), 130.6 (C_m), 128.0 (C_f), 127.2 (C_a), 113.4 (C_d), 108.0 (C_b), 73.7 (C_n), 54.8 (C_s), 22.0 (C_e), 13.8 (C_l). **ν /cm^{-1}:** 3364 (OH str), 2959 (CH str), 1699 (C=O), 1615, 1471. **HRMS**: calcd for $C_{13}H_{16}O_5$ 252.0998 found 252.1015. **M/z:** 252.1015 (2%), 176.0842 (40%), 161.0514 (84%), 142.1580 (26%), 123.0439 (11%).

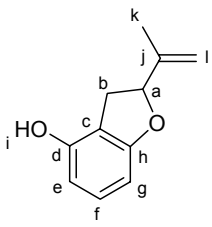
7.4.1.13 Racemic 2-isopropenyl-2,3-dihydrobenzofuran-4-ol – *rac*-247

From the acetate – 470

A dry 2 neck round bottom flask containing Ar was charged with THF (10 ml) followed by triethylamine (0.15 ml, 0.11 g, 1.1 mmol) and $Pd(PPh_3)_4$ (112 mg, 0.0969 mmol, 10 mole %). The solution was immediately degassed by bubbling Ar into the solution for 5 min using a Pasteur pipette. The allyl acetate **470** was added (231 mg, 0.978 mmol) and the solution was stirred at rt for 18 h. Analysis of the reaction after this time indicated that no reaction had taken place and so $PdDba_2$ was added (50 mg, 0.087 mmol, 9 mole %) followed by triphenylphosphine (95 mg, 0.36 mmol). The reaction was stirred for another 18 h and then concentrated *in vacuo*. Purification of the crude material by column chromatography (10-20% EtOAc/Hexane) afforded the desired racemic benzofuran **247** as a clear oil (38 mg, 22%).

From the carbonate – 479

Into a dry 5 ml 2 neck round bottom flask, fitted with a condenser and containing Ar was placed dichloromethane (2 ml). This solvent was degassed for 3 min by bubbling Ar into the solvent by means of a Pasteur. $PdDba_2$ (2.0 mg, 0.0035 mmol) was then added in one portion forming a violet solution. The solution was once again degassed for 1 min and then triphenylphosphine (4.7 mg, 0.018 mmol) was added against a flow of Ar. The solution gradually changed colour as the ligands exchanged and after 15 min the solution was yellow. Degassed acetic acid (15 µl, 16 mg, 0.26 mmol) was added in one portion and the solution was stirred under Ar at rt for another 5 min. Finally, the carbonate **479** (50.0 mg, 0.198 mmol) was introduced to the reaction mixture through the sidearm against a flow of Ar and the reaction was left to proceed at reflux for 18 h. Analysis of the reaction mixture after this time by TLC indicated that all the starting material had been consumed. The reaction mixture was then transferred to a round bottom flask and the crude material adsorbed directly onto silica gel *in vacuo* and purified by column chromatography (10-20% EtOAc/Hexane), affording the racemic benzofuran **247** as a clear oil (28.1 mg, 81%).



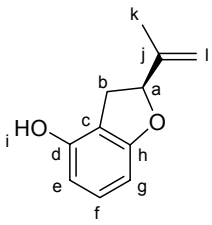
δ_H /ppm: 6.99 (1H, t, *J*=8.0 Hz, H_f), 6.44 (1H, d, *J*=7.9 Hz, H_g), 6.32 (1H, d, *J*=8.0 Hz, H_e), 6.00-4.30 (1H, brs, H_i), 5.21 (1H, t, *J*=8.8 Hz, H_a), 5.10 (1H, s, $H_{l\ trans}$), 4.92 (1H, s, $H_{l\ cis}$), 3.31 (1H, dd, *J*=9.7 Hz and 15.3 Hz, H_b), 2.98 (1H, dd, *J*=8.0 Hz and 15.3 Hz, H_b), 1.78 (3H, s, H_k). **δ_C /ppm:** 161.4 (C_h), 152.4 (C_d), 143.8 (C_j), 129.1 (C_f), 112.2 (C_c), 112.1 (C_l), 107.7 (C_e), 102.2 (C_g), 86.1 (C_a), 31.7 (C_b), 17.1 (C_k). **ν /cm^{-1}:** 3387 (OH str), 2976 (CH str), 1607, 1464. **HRMS**: calcd for $C_{11}H_{12}O_2$ 176.0837 found 176.0820. **M/z:** 176.0820 (45%), 161.0581 (100%), 145.0627 (33%), 117.0724 (7%), 115.0549 (10%).

7.4.1.14 (+)-*(S)*-2-isopropenyl-2,3-dihydrobenzofuran-4-ol – (+)-*(S)*-247

Into a dry 2 neck round bottom flask containing Ar was placed dichloromethane (2.5 ml) followed by $PdDba_2$ (6.8 mg, 0.012 mmol, 3 mole %), thus forming a deep red solution. The solution was degassed for 3 min by bubbling Ar directly into the solution by means of a Pasteur pipette. The *S,S'*-Trost ligand (28.0 mg, 0.0405 mmol, 10 mole %) was then added in one portion against a gentle flow of Ar and a colour change occurred over a 15

min period from deep red to light yellow. The reaction was left to stir at rt for another 10 min and then degassed acetic acid was added in one portion (25 µl, 26 mg, 0.44 mmol) and after 5 min of stirring, the allyl carbonate **479** was added in one portion (100 mg, 0.396 mmol). The reaction was left to proceed at rt for 18 h under Ar and it was observed that the colour of the solution changed to a more pale yellow during this time. The reaction mixture was then concentrated *in vacuo* and the crude material adsorbed onto silica gel and purified by column chromatography affording 2-isopropenyl-2,3-dihydrobenzofuran-4-ol (65.3 mg, 94%, 92% ee). The ee was determined by conversion to the acetate **(+)-*(S)*-482** and then analysis by HPLC since the enantiomers of **247** do not resolve well by HPLC using our Chiralcel OJ column.

NB: Room temperature refers to 20-25 °C, as below 16 °C the reaction proceeds exceptionally slowly and above 35 °C, the ee's are compromised due to the rate increase.



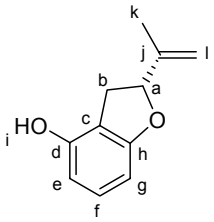
δ_H /ppm: 6.99 (1H, t, *J*=8.0 Hz, H_f), 6.44 (1H, d, *J*=7.9 Hz, H_g), 6.32 (1H, d, *J*=8.0 Hz, H_e), 6.00-4.30 (1H, brs, H_i), 5.21 (1H, t, *J*=8.8 Hz, H_a), 5.10 (1H, s, $H_{l\ trans}$), 4.92 (1H, s, $H_{l\ cis}$), 3.31 (1H, dd, *J*=9.7 Hz and 15.3 Hz, H_b), 2.98 (1H, dd, *J*=8.0 Hz and 15.3 Hz, H_b), 1.78 (3H, s, H_k). **δ_C /ppm:** 161.4 (C_h), 152.4 (C_d), 143.8 (C_j), 129.1 (C_f), 112.2 (C_c), 112.1 (C_l), 107.7 (C_e), 102.2 (C_g), 86.1 (C_a), 31.7 (C_b), 17.1 (C_k). **ν /cm^{-1}:** 3387 (OH str), 2976 (CH str), 1607, 1464. **HRMS**: calcd for $C_{11}H_{12}O_2$ 176.0837 found 176.0820. **M/z:** 176.0820 (45%), 161.0581 (100%), 145.0627 (33%), 117.0724 (7%), 115.0549 (10%). **$[\alpha]_D^{19}$** = +17.3.

7.4.1.15 (-)-*(R)*-2-isopropenyl-2,3-dihydrobenzofuran-4-ol – *(R)*-247

Into a dry 2 neck round bottom flask containing Ar was placed dichloromethane (5 ml) followed by $PdDba_2$ (6.0 mg, 0.010 mmol, 3 mole %), forming a wine red solution. The solution was degassed for 3 min by bubbling Ar directly into the solution by means of a Pasteur pipette and then the *R,R'*-Trost ligand (20.0 mg, 0.0290 mmol, 8 mole %) was then added in one portion against a gentle flow of Ar. A colour change occurred over a 15 min period from deep purple to a light yellow colour as the ligand exchange occurred. The reaction was left to stir at rt for another 10 min and then degassed acetic acid (22 µl, 23 mg, 0.38 mmol) was added in one portion. After 5 min of stirring, the allyl carbonate

479 was added in one portion (90.0 mg, 0.357 mmol) and the reaction was left to proceed at rt for 18 h. After this time, it was observed that the colour of the solution had changed to a more pale yellow. The reaction mixture was then concentrated *in vacuo* and the crude material adsorbed onto silica gel and purified by column chromatography (10-20% EtOAc/Hexane) affording (-)-*(R)*-2-isopropenyl-2,3-dihydrobenzofuran-4-ol (50.5 mg, 80%, 92% ee). The ee was determined by conversion to the acetate **(-)-*(R)*-482** and then analysis by HPLC since the enantiomers of **247** do not resolve well by HPLC using our Chiralcel OJ column.

NB: Room temperature refers to 20-25 °C, as below 16 °C the reaction proceeds exceptionally slowly and above 35 °C, the ee's are compromised due to the rate increase.

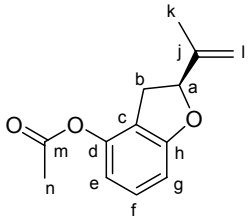


δ_H /ppm: 6.99 (1H, t, *J*=8.0 Hz, H_f), 6.44 (1H, d, *J*=7.9 Hz, H_g), 6.32 (1H, d, *J*=8.0 Hz, H_e), 6.00-4.30 (1H, brs, H_i), 5.21 (1H, t, *J*=8.8 Hz, H_a), 5.10 (1H, s, $H_{l\ trans}$), 4.92 (1H, s, $H_{l\ cis}$), 3.31 (1H, dd, *J*=9.7 Hz and 15.3 Hz, H_b), 2.98 (1H, dd, *J*=8.0 Hz and 15.3 Hz, H_b), 1.78 (3H, s, H_k). **δ_C /ppm:** 161.4 (C_h), 152.4 (C_d), 143.8 (C_j), 129.1 (C_f), 112.2 (C_c), 112.1 (C_l), 107.7 (C_e), 102.2 (C_g), 86.1 (C_a), 31.7 (C_b), 17.1 (C_k). **ν /cm^{-1}:** 3387 (OH str), 2976 (CH str), 1607, 1464. **HRMS**: calcd for $C_{11}H_{12}O_2$ 176.0837 found 176.0820. **M/z:** 176.0820 (45%), 161.0581 (100%), 145.0627 (33%), 117.0724 (7%), 115.0549 (10%). **$[\alpha]_D^{19}$** = -18.1 ($CHCl_3$).

7.4.1.16 (+)-*(S)*-2-isopropenyl-2,3-dihydrobenzofuran-4-yl acetate – (+)-*(S)*-482

Into a 2 neck round bottom flask containing Ar was placed 2-isopropenyl-2,3-dihydrobenzofuran-4-ol (+)-***(S)*-247** (25.0 mg, 0.142 mmol) followed by dichloromethane (1.5 ml). To the solution was added Et_3N (39 µl, 28 mg, 0.28 mmol) followed by DMAP (5.0 mg, 0.015 mmol) and acetic anhydride (18 µl, 19 mg, 0.19 mmol). The reaction was left to proceed at rt for 18 h and after this time analysis of the reaction mixture indicated that all of the starting material had reacted. The solvent was evaporated *in vacuo* and the crude material adsorbed onto silica gel and purified by column chromatography (10% EtOAc/Hexane) affording the desired acetate **(+)-*(S)*-482** as a clear oil (30.0 mg, 97%). Analysis of the acetate by chiral HPLC (Chiralcel OJ 10µ 250 × 4.6 mm, 10% isopropyl alcohol/hexane) revealed 92% ee of **(+)-*(S)*-482**.

(Although not described here, the acetylation of racemic **(±)-247** was similarly carried out, forming **(±)-482** and this racemic material was used to confirm that the HPLC methodology was indeed completely separating the enantiomers of **482**).

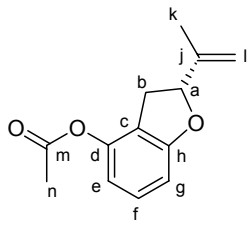


δ_H /ppm: 7.12 (1H, t, *J*=8.0 Hz, H_f), 6.69 (1H, d, *J*=8.0 Hz, H_e), 6.57 (1H, d, *J*=8.1 Hz, H_g), 5.20 (1H, t, *J*=8.8 Hz, H_a), 5.08 (1H, s, H_l), 4.91 (1H, s, H_l), 3.23 (1H, dd, *J*=9.6 Hz and 15.7 Hz, H_b), 2.93 (1H, dd, *J*=8.1 Hz and 15.7 Hz, H_b), 2.28 (3H, s, H_n), 1.76 (3H, s, H_k). **δ_C /ppm:** 168.4 (C_m), 161.3 (C_h), 147.3 (C_d), 143.6 (C_j), 129.0 (C_f), 119.3 (C_c), 113.4 (C_g), 112.4 (C_l), 107.0 (C_e), 86.2 (C_a), 32.7 (C_b), 20.9 (C_n), 17.1 (C_k). **ν /cm^{-1}:** 2920 (CH str), 1767 (C=O str). **HRMS**: calcd for $C_{13}H_{14}O_3$ 218.0943 found 218.0945. **M/z:** 218.0945 (24%), 176.0804 (30%), 161.0628 (100%). **$[\alpha]_D^{19}$** = +25.0 ($CHCl_3$).

7.4.1.17 (-)-*(R)*-2-isopropenyl-2,3-dihydrobenzofuran-4-yl acetate – (-)-*(R)*-482

Into a 2 neck round bottom flask containing Ar was placed **(-)-*(R)*-247** (48.2 mg, 0.274 mmol) followed by dichloromethane (5 ml). To the solution was added Et_3N (77 µl, 56 mg, 0.55 mmol) followed by DMAP (5 mg, 0.014 mmol) and acetic anhydride (34 µl, 37 mg, 0.36 mmol). The reaction was left to proceed for 18 h at rt and thereafter analysis of the reaction mixture indicated that all of the starting material had been consumed. The solvent was evaporated *in vacuo* and the crude material adsorbed onto silica gel and purified by column chromatography (10% EtOAc/Hexane) affording the desired acetate **(-)-*(R)*-482** as a clear oil (59.0 mg, 99%). Analysis of the acetate by chiral HPLC (Chiralcel OJ 10µ 250 × 4.6 mm, 10% isopropyl alcohol/hexane) revealed 92% ee of **(-)-*(R)*-482**.

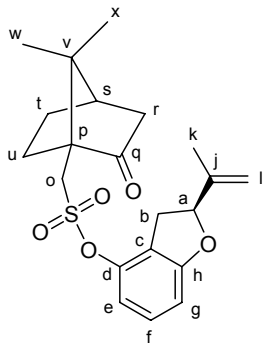
(Although not described here, the acetylation of racemic **(±)-247** was similarly carried out, forming **(±)-482** and this racemic material was used to confirm that the HPLC methodology was indeed completely separating the enantiomers of **482**).



δ_H /ppm: 7.12 (1H, t, *J*=8.0 Hz, H_f), 6.69 (1H, d, *J*=8.0 Hz, H_e), 6.57 (1H, d, *J*=8.1 Hz, H_g), 5.20 (1H, t, *J*=8.8 Hz, H_a), 5.08 (1H, s, H_l), 4.91 (1H, s, H_l), 3.23 (1H, dd, *J*=9.6 Hz and 15.7 Hz, H_b), 2.93 (1H, dd, *J*=8.1 Hz and 15.7 Hz, H_b), 2.28 (3H, s, H_n), 1.76 (3H, s, H_k). **δ_C /ppm:** 168.4 (C_m), 161.3 (C_h), 147.3 (C_d), 143.6 (C_j), 129.0 (C_f), 119.3 (C_c), 113.4 (C_g), 112.4 (C_l), 107.0 (C_e), 86.2 (C_a), 32.7 (C_b), 20.9 (C_n), 17.1 (C_k). **ν /cm^{-1}:** 2920 (CH str), 1767 (C=O str). **HRMS**: calcd for $C_{13}H_{14}O_3$ 218.0943 found 218.0945. **M/z:** 218.0945 (24%), 176.0804 (30%), 161.0628 (100%). **$[\alpha]_D^{19}$** = -25.8 ($CHCl_3$).

7.4.1.18 *(S)*-2-Isopropenyl-2,3-dihydrobenzofuran-4-yl ((1*S*,4*R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonate – 483

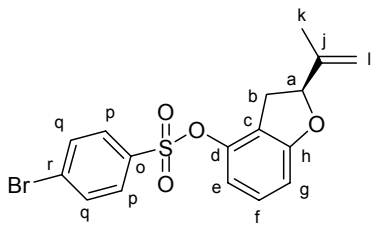
Into a 2 neck round bottom flask containing Ar was placed *(S)*-2-isopropenyl-2,3-dihydrobenzofuran-4-ol **(+)-*(S)*-247** (65 mg, 0.37 mmol) followed by dry dichloromethane (3 ml). To the solution was added triethylamine (110 µl, 80.1 mg, 0.792 mmol) followed by (+)-(1*S*)-camphor-10-sulfonyl chloride (231 mg, 0.921 mmol). The reaction was left to proceed for 18 h at rt under Ar. The solvent was removed *in vacuo* and the crude oil was purified by column chromatography affording the desired product **483** as a clear oil (116 mg, 81%).



δ_H /ppm: 7.15 (1H, t, *J*=8.2 Hz, H_f), 6.80 (1H, d, *J*=8.2 Hz, H_g), 6.75 (1H, d, *J*=8.1 Hz, H_e), 5.23 (1H, t, *J*=8.8 Hz, H_a), 5.09 (1H, s, H_l), 4.92 (1H, s, H_l), 3.85 (1H, d, *J*=15.0 Hz, H_o), 3.51 (1H, dd, *J*=16.1 Hz and 9.6 Hz, H_b), 3.23 (1H, d, *J*=15.0 Hz, H_o), 3.17 (1H, dd, *J*=16.2 Hz and 8.0 Hz, H_b), 2.62-2.48 (1H, m, H_r), 2.47-2.32 (1H, m, H_s), 2.20-1.88 (3H, m, 3 × C*H*), 1.83-1.65 (1H, m, C*H*), 1.77 (3H, s, H_k), 1.52-1.39 (1H, m, C*H*), 1.17 (3H, s, CH_3), 0.92 (3H, s, CH_3). **δ_C /ppm:** 213.9 (C_q), 161.7 (C_h), 145.6 (ArC), 143.3 (ArC), 129.4 (C_f), 120.6 (ArC), 113.8 (C_g), 112.5 (C_l), 108.2 (C_e), 86.4 (C_a), 58.1 (C_p), 48.1 (C_o), 47.9 (C_v), 42.8 (C_s), 42.4 (CH_2), 32.9 (C_b), 26.8 (CH_2), 25.1 (CH_2), 19.9 (CH_3), 19.7 (CH_3), 17.1 (C_k). **HRMS**: calcd for $C_{21}H_{26}O_5S$ 390.1501 found 390.1488. **M/z**: 390.1488 (60%), 263.9871 (8%), 215.0728 (100%), 176.0817 (46%), 161.0609 (53%), 151.1110 (76%), 123.1160 (79%).

7.1.4.19 *(S)*-2-isopropenyl-2,3-dihydrobenzofuran-4-yl 4-bromobenzene-sulfonate – (484)

Into a 2 neck round bottom flask containing Ar was placed *(S)*-2-isopropenyl-2,3-dihydrobenzofuran-4-ol **(+)-*(S)*-247** (71 mg, 0.40 mmol) followed by dry dichloromethane (10 ml). Triethylamine (112 µl, 81.3 mg, 0.804 mmol) was added in one portion followed by *p*-bromobenzenesulfonyl chloride (153 mg, 0.600 mmol). The reaction was left to proceed under Ar at rt for 18 h and then analysis of the reaction mixture by TLC indicated that the reaction was complete. The solvent was evaporated *in vacuo* and the crude material was purified by column chromatography (10% EtOAc/Hexane) affording a clear oil **484** (123 mg, 78%).

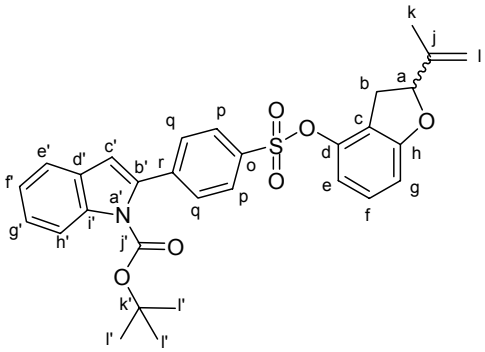


δ_H /ppm:. 7.66-7.63 (4H, m, $H_{q,p}$), 7.04 (1H, t, *J*=8.1 Hz, H_f), 6.71 (1H, d, *J*=8.0 Hz, H_g), 6.39 (1H, d, *J*=8.2 Hz, H_e), 5.13 (1H, t, *J*=8.7 Hz, H_a), 5.03 (1H, s, H_l), 4.90 (1H, s, H_l), 3.23 (1H, dd, *J*=16.1 Hz and 9.6 Hz, H_b), 2.79 (1H, dd, *J*=16.1 Hz and 7.8 Hz, H_b), 1.69 (3H, s, H_k). **δ_C /ppm:** 161.6 (C_h), 145.9 (ArC), 143.2 (ArC), 134.7 (ArC), 132.6 (2 × ArCH), 129.9 (2 × ArCH), 129.7 (C_r), 129.2 (C_f), 120.6 (C_c), 114.0 (C_e), 112.5 (C_l), 108.4 (C_g), 86.3 (C_a), 32.5 (C_b), 17.0 (C_k). **HRMS**: calcd for $C_{17}H_{15}BrO_4S$ 393.9874 found 393.9876. **M/z**: 393.9876 (57%), 395.9875 (60%), 378.9626 (30%), 380.9630 (29%), 175.0783 (100%), 159.0836 (58%).

7.1.1.20 *tert*-Butyl 2-(4-(2-isopropenyl-2,3-dihydrobenzofuran-4-yloxysulfonyl)phenyl)-1*H*-indole-1-carboxylate – 484b

Into a 2 neck round bottom flask was placed $Pd(PPh_3)_4$ (50 mg, 0.043 mmol, 20 mole %) followed by 1-(*tert*-butoxycarbonyl)-1*H*-indol-2-ylboronic acid **305** (80 mg, 0.31 mmol) and 2-isopropenyl-2,3-dihydrobenzofuran-4-yl 4-bromobenzenesulfonate **484** (83 mg, 0.21 mmol). Tripotassium phosphate (120 mg, 0.565 mmol) was finally added in one portion and the slurry in the flask was degassed several times by the freeze-thaw process. The reaction was then left to proceed under Ar at 80 °C for 18 h. Analysis of the reaction mixture by TLC indicated that a new product had formed and so the reaction mixture was

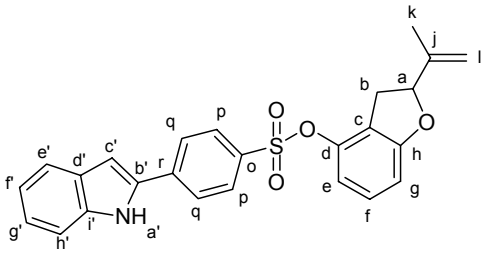
diluted with ethyl acetate (20 ml) and water (20 ml). After thoroughly mixing the phases the organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 x 20 ml). The combined organic fractions were dried over anhydrous magnesium sulfate and filtered. After evaporation of the solvent *in vacuo* the crude material was purified by column chromatography (10% EtOAc/Hexane) affording the product **484b** as a clear oil (65 mg, 58%).



δ_H /ppm:. 8.19 (1H, d, *J*=8.3 Hz, $H_{h'}$), 7.90 (2H, d, *J*=8.3 Hz, H_p), 7.60 (2H, d, *J*=8.3 Hz, H_q), 7.59 (1H, d, *J*=7.7 Hz, $H_{e'}$), 7.38 (1H, t, *J*=7.6 Hz, $H_{g'}$), 7.28 (1H, t, *J*=7.6 Hz, $H_{f'}$), 7.04 (1H, t, *J*=8.1 Hz, H_f), 6.71 (1H, d, *J*=8.0 Hz, H_g), 6.67 (1H, s, $H_{c'}$), 6.50 (1H, d, J=8.2 Hz, H_e), 5.15 (1H, t, *J*=8.7 Hz, H_a), 5.04 (1H, s, H_l), 4.89 (1H, s, H_l), 3.24 (1H, dd, *J*=16.1 Hz and 9.6 Hz, H_b), 2.92 (1H, dd, *J*=16.1 Hz and 8.0 Hz, H_b), 1.70 (3H, s, H_k), 1.39 (9H, s, $H_{l'}$). **δ_C /ppm:** 161.6 (C_h), 149.8 ($C_{j'}$), 146.0 (ArC), 143.3 (ArC), 140.9 (ArC), 138.0 (ArC), 137.8 (ArC), 134.5 (ArC), 129.1 (C_q), 128.9 (ArC), 127.9 (C_p), 125.3 ($C_{g'}$), 123.3 ($C_{f'}$), 120.9 ($C_{e'}$), 120.7 (C_c), 115.4 ($C_{h'}$), 114.1 (C_e), 112.5 (C_l), 112.1 ($C_{C'}$), 108.2 (C_g), 86.3 (C_a), 84.4 ($C_{k'}$), 32.5 (C_b), 27.7 ($C_{l'}$), 17.04 (C_k). **HRMS**: calcd for $C_{30}H_{29}NO_6S$ 531.1716 found 531.1711. **M/z**: 531.1711 (24%), 431.1235 (54%), 416.0954 (19%), 367.1519 (22%), 192.0808 (84%).

7.4.1.21 (±)-2-Isopropenyl-2,3-dihydrobenzofuran-4-yl 4-(1*H*-indol-2-yl)benzenesulfonate – 484c

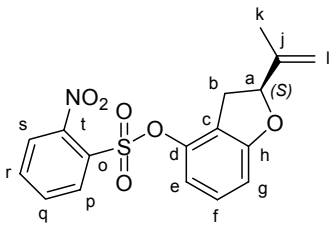
Into a round bottom flask was placed the Boc protected indolo-benzofuran compound **484b** (58 mg, 0.11 mmol) followed by ethyl acetate thus forming a pale yellow solution. Silica was added (approx 2 g) and the solvent was removed *in vacuo* forming an off-white dry adsorbate. The adsorbate was heated in a conventional μ-wave oven (500 Watt) for 20 sec and then the adsorbate was agitated and a sample of the adsorbate was analysed by TLC to monitor the progress of the reaction. The process was repeated until all the starting material had reacted. The product was then eluted off the silica (10% EtOAc/Hexane) affording **484c** as a white solid (28 mg, 60%). Recrystallisation was achieved from diethyl ether and X-ray analysis of the crystal structure revealed a racemic space group.



δ_H /ppm: 8.52 (1H, s, $H_{a'}$), 7.87 (2H, d, *J*=8.3 Hz, H_p), 7.77 (2H, d, *J*=8.1 Hz, H_q), 7.67 (1H, d, *J*=7.8 Hz, $H_{e'}$), 7.43 (1H, d, *J*=8.1 Hz, $H_{h'}$), 7.26 (1H, t, *J*=7.4 Hz, $H_{g'}$), 7.16 (1H, t, *J*=7.4 Hz, $H_{f'}$), 7.02 (1H, t, *J*=8.2 Hz, H_f), 7.00 (1H, s, $H_{c'}$), 6.70 (1H, d, *J*=8.0 Hz, H_g), 6.44 (1H, d, *J*=8.2 Hz, H_e), 5.10 (1H, t, *J*=8.63 Hz, H_a), 4.99 (1H, s, H_l), 4.84 (1H, s, H_l), 3.23 (1H, dd, *J*=16.0 Hz and 9.6 Hz, H_b), 2.83 (1H, dd, *J*=16.1 Hz and 7.8 Hz, H_b), 1.63 (3H, s, H_k). **δ_C /ppm:** 161.6 (C_h), 146.0 (ArC), 143.2 (ArC), 138.1 (ArC), 137.5 (ArC), 135.1 (ArC), 133.7 (ArC), 129.3 (C_p), 129.1 (C_f), 128.9 (ArC), 125.1 (C_q), 123.9 ($C_{g'}$), 121.3 ($C_{e'}$), 120.9 ($C_{f'}$), 120.7 (C_c), 114.2 (C_e), 112.4 (C_l), 111.3 ($C_{h'}$), 108.3 (C_g), 103.1 ($C_{c'}$), 86.3 (C_a), 32.5 (C_b), 17.0 (C_k). **HRMS**: calcd for $C_{25}H_{21}NO_4S$ 431.1191 found 431.1180. **M/z:** 431.1180 (48%), 367.1457 (11%), 208.0792 (8%), 192.0827 (100%), 165.0732 (11%). **X-ray data:** $C_{25}H_{21}NO_4S$; *M*=431.49; orthorhombic; 0.71073 Å; *a*=16.9709(11) Å, *b*=7.3848(5) Å, *c*=33.108(2) Å, *U*=4149.3(5) $Å^3$; 173(2) K, space group, Pbca, Z=8;. μ(Mo-Kα)=0.073 mm^{-1} 35345 reflections measured, 5005 unique [R(int)= 0.0955] which were used in all calculations. Final R indices [$I>2\sigma(I)$] R_1=0.0654, wR(F^2)= 0.1735.

7.4.1.22 (+)-*(S)*-2-isopropenyl-2,3-dihydrobenzofuran-4-yl-2-nitrobenzenesulfonate – 485

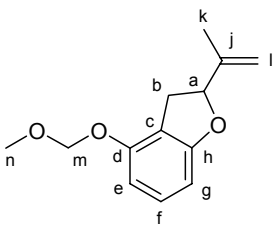
Into a 2 neck round bottom flask was placed the chiral benzofuran **(+)-*(S)*-247** (28.0 mg, 0.159 mmol) followed by dry dichloromethane (5 ml). To the solution, at rt was added triethylamine (42 µl, 30 mg, 0.30 mmol) followed by 2-nitrobenzenesulfonyl chloride (43.0 mg, 0.194 mmol). The solution was stirred at rt for 18 h under Ar after which time analysis of the reaction mixture by TLC indicated that all the starting material had been consumed and a new product had formed. The reaction mixture was concentrated *in vacuo* and the crude material was purified by column chromatography (20% EtOAc/Hexane) affording the desired compound **485** as a white solid (45.9 mg, 80%). Recrystallisation of this compound from diethyl ether afforded white needle-like crystals, suitable for crystal structure analysis.



δ_h /ppm: 8.00 (1H, d, *J*=7.8 Hz, H_s), 7.89-7.81 (2H, m, H_p and H_q), 7.76-7.66 (1H, m, H_r), 7.05 (1H, t, *J*=8.1 Hz, H_f), 6.73 (1H, d, *J*=8.0 Hz, H_g), 6.55 (1H, d, *J*=8.3 Hz, H_e), 5.18 (1H, t, *J*=8.7 Hz, H_a), 5.05 (1H, s, H_l), 4.90 (1H, s, H_l), 3.44 (1H, dd, *J*=16.3 Hz and 9.6 Hz, H_b), 3.03 (1H, dd, *J*=16.3 Hz and 7.9 Hz, H_b), 1.71 (3H, s, H_k). **δ_c /ppm:** 161.8 (C_h), 145.6 (C_d) 143.2 (C_j), 135.4 (ArCH), 132.03 (ArCH), 132.00 (ArCH) 129.3 (C_f) 128.9 (C_t), 124.9 (ArCH), 120.8 (C_c), 113.9 (C_e) 112.6 (C_l), 108.7 (C_g), 86.5 (C_a), 32.7 (C_b) 17.0 (C_k). **ν /cm^{-1}:** 2923 (CH str), 1654 (C=C), 1594 (NO str). **HRMS**: calcd for $C_{17}H_{15}NO_6S$ 361.0620 found 361.0627. **M/z:** 361.0627 (100%), 346.0342 (41%), 264.9931 (8%), 213.9929 (7%), 175.0756 (70%), 159.0790 (83%). **X-ray data:** $C_{17}H_{15}NO_6S$; *M*=361.36; orthorhombic; 0.71073 Å; *a*=5.7422(8)Å, *b*=13.106(2)Å, *c*=22.274(3)Å, *U*=1676.3(4) Å^3; 173(2) K, space group, P2(1)2(1)2(1), Z=4;. μ(Mo-Kα)=0.073 mm^{-1} 13907 reflections measured, 4041 unique [R(int)=0.0355] which were used in all calculations. Final R indices [$I>2\sigma(I)$] R_1=0.0382, wR(F^2)=0.0916. **$[\alpha]_D^{20}$** = +12.0 ($CHCl_3$).

7.4.1.23 (±)-4-(methoxymethoxy)-2-isopropenyl-2,3-dihydrobenzofuran – 486

Into a 2 neck round bottom flask was placed racemic 2-isopropenyl-2,3-dihydrobenzofuran-4-ol ***rac*-247** (70 mg, 0.40 mmol) followed by dry dichloromethane (3 ml). To the solution was added diisopropylamine (140 ml, 104 mg, 0.804 mmol) followed by MOMCl (37 ml, 40 mg, 0.50 mmol). The reaction was left to proceed under Ar at rt for 2 h after which time analysis of the reaction mixture by TLC indicated that only a trace of the starting material remained and a new compound had formed with a higher Rf. The reaction was quenched by the addition of dilute ammonia solution (5 ml) and the organic phase was diluted with dichloromethane (10 ml). The phases were separated and the aqueous phase was extracted with dichloromethane (3 × 5 ml). The combined organic fractions were dried over anhydrous magnesium sulfate and filtered. Evaporation of the solvent *in vacuo* afforded an oil constituting the crude product which was purified by column chromatography (5-10% EtOAc/Hexane) affording **486** as a clear oil (60 mg, 68%).

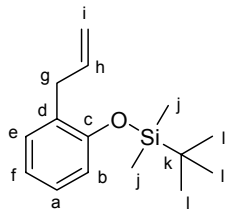


δ_H /ppm:. 7.06 (1H, t, *J*=8.1 Hz, H_f), 6.59 (1H, d, *J*=8.3 Hz, H_g), 6.50 (1H, d, *J*=8.0 Hz, H_e), 5.19 (1H, t, *J*=8.8 Hz, H_d), 5.18 (2H, s, H_m), 5.09 (1H, s, H_l), 4.90 (1H, s, H_l), 3.48 (3H, s, H_n), 3.33 (1H, dd, *J*=15.7 Hz and 9.6 Hz, H_b), 2.99 (1H, dd, *J*=15.7 Hz and 8.13 Hz. H_b), 1.78 (3H, s, H_k). **δ_C /ppm:** 161.2 (C_h), 154.0 (C_d), 144.0 (C_j), 129.1 (C_f), 114.7 (C_c), 111.9 (C_l), 106.5 (ArCH), 103.4 (ArCH), 94.4 (C_m), 86.1 (C_a), 56.1 (C_n), 32.3 (C_b), 17.2 (C_k). **ν /cm^{-1}:** 2952 (CH str), 1609, 1489, 1463. **HRMS**: calcd for $C_{13}H_{16}O_3$ 220.1099 found 220.1100. **M/z**: 220.1010 (100%), 205.0859 (15%), 188.0837 (30%), 175.0765 (68%), 161.0596 (49%).

7.4.2 Formal syntheses of fomannoxin and trematone

7.4.2.1 (2-Allylphenoxy)(*tert*-butyl)dimethylsilane – 490

Into a 250 ml round bottom flask containing Ar was added at rt acetonitrile (200 ml) followed by 2-allylphenol **488** (4.90 ml, 5.04 g, 37.5 mmol). Imidazole (3.05 g, 44.8 mmol) was then added in one portion followed by TBSCl (6.75 g, 44.8 mmol), also added in one portion. The solution was stirred at rt under Ar for 18 h during which time imidazole hydrochloride precipitated from solution. Analysis of the reaction mixture indicated that all the starting material had reacted and so the solvent was removed *in vacuo*. As the crude mixture concentrated to an oil the precipitate became solubilised. Ethyl acetate (200 ml) was added in one portion resulting in immediate precipitation of the imidazole hydrochloride salt once again. Water was added (200 ml) and after vigorous shaking the salt dissolved into the aqueous layer. The phases were separated and the aqueous phase was extracted with ethyl acetate (3 × 100 ml). The combined organic fractions were washed with brine (200 ml) and dried over anhydrous magnesium sulfate. After filtration, the solvent was removed *in vacuo* affording an orange oil which was purified by column chromatography (2% EtOAc/Hexane), affording the desired product **490** as a clear oil (8.36 g, 90%).

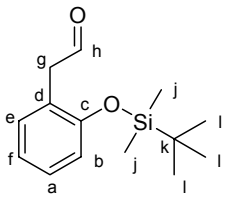


δ_H /ppm:. 7.22-7.06 (2H, overlapping signals, H_e and H_a), 6.92 (1H, t, *J*=7.4 Hz, H_f), 6.83 (1H, d, *J*=8.0 Hz, H_b), 6.01 (1H, tdd, *J*=19.3 Hz, 9.4 Hz and 6.6 Hz, H_h), 5.10-5.04 (2H, overlapping signals, H_i), 3.41 (2H, d, *J*=6.5 Hz, H_g), 1.05 (9H, s, H_l), 0.27 (6H, s, H_j). **δ_C /ppm:** 153.4 (C_c), 137.1 (C_h), 130.7 (C_d), 130.1 (ArCH), 127.0 (ArCH), 121.1 (ArCH), 118.4 (ArCH), 115.4 (C_i), 34.4 (C_g), 25.8 (C_l), 18.3 (C_k), -4.1 (C_j). **ν /cm^{-1}:** 3077, 2958, 1600, 1491, 1266, 936. **HRMS**: calcd for $C_{15}H_{24}OSi$ 248.1596 found 248.1597. **M/z:** 248.1597 (7%), 191.0902 (100%), 163.0522 (25%), 151.0456 (13%), 135.0247 (5%), 115.0546 (5%).

7.4.2.2 2-(2-(*tert*-Butyldimethylsilyloxy)phenyl)acetaldehyde – 491

Into a 3 neck round bottom flask fitted with 2 glass bubbling tubes was placed dichloromethane (150 ml) followed by (2-allylphenoxy)(*tert*-butyl)dimethylsilane **490** (3.50 g, 14.1 mmol). The reaction mixture was cooled to -85 °C whilst bubbling a steady

stream of N_2 into the solution using one of the bubbling tubes. Once the reaction mixture had cooled, the N_2 bubbling tube was removed from beneath the surface of the reaction mixture and the ozone bubbling tube was immersed into the reaction mixture. Ozone was thus introduced into the reaction mixture at -85 °C for a period of 10 min and then the ozone tube was removed and the N_2 tube immersed into the reaction mixture to rapidly expel any residual ozone in the solution. The reaction mixture was then analysed by TLC to determine the extent of the reaction and it was found that the reaction was only approximately 30% complete. This process of introducing the ozone for 10 min at -85 °C followed by TLC analysis was repeated until all the starting material had been consumed. Acetic acid (15.0 ml, 15.8 g, 262 mmol) was then added followed immediately by zinc powder (2.00 g, 30.6 mmol). Analysis of the reaction mixture by TLC indicated that the ozonide was not reducing at -80 °C however once the slurry warmed to about -30 °C the ozonide rapidly reduced to the aldehyde. The reaction mixture was rapidly filtered, and whilst maintaining the solution below 0 °C to avoid cleavage of the silyl protecting groups, the acetic acid was neutralised by the careful addition of aqueous sodium bicarbonate solution. The organic phase was separated and the aqueous phase extracted with dichloromethane (3 × 100 ml). The combined organic fraction were dried over anhydrous magnesium sulfate and filtered. Evaporation of the solvent *in vacuo* afforded the crude product as murky oil which was purified by column chromatography (2-5% EtOAc/Hexane), affording desired aldehyde **491** as an oil at rt or a waxy solid at refrigeration temperatures (3.13 g, 89%).



δ_H /ppm:. 9.70 (1H, t, *J*=2.1 Hz, H_h), 7.24-7.10 (2H, m, H_e and H_a), 6.95 (1H, t, *J*=7.4 Hz, H_f), 6.88 (1H, d, *J*=8.1 Hz, H_b), 3.64 (2H, d, *J*=1.9 Hz, H_g), 1.00 (9H, s, H_l), 0.26 (6H, s, H_j). **δ_C /ppm:** 200.0 (C_h), 154.1 (C_c), 131.5 (ArCH), 128.7 (ArCH), 123.7 (C_d), 121.4 (ArCH), 118.4 (ArCH), 45.6 (C_g), 25.7 (C_l), 18.2 (C_k), -4.2 (C_j). **ν /cm^{-1}:** 2956 (CH str), 1732 (C=O), 1584, 1495. **HRMS**: calcd for $C_{14}H_{22}O_2Si$ 250.1389 found 250.1394. **M/z:** 250.1394 (1%), 209.0593 (28%), 193.0632 (100%), 179.0537 (49%), 149.0382 (15%).

7.4.2.3 *(E)*-Ethyl 4-(2-(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-enoate – 492

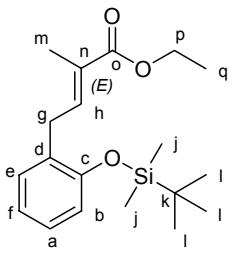
Poor procedure: Producing a mixture of 492 and 495

Into a 2 neck round bottom flask containing Ar was placed acetonitrile (20 ml) followed by ethyl 2-(diethoxyphosphoryl)propanoate (3.33 g, 14.0 mmol, 3.00 ml), LiCl (760 mg, 17.9 mmol) and finally DBU (2.44 g, 16.0 mmol, 2.40 ml). The solution was stirred for 10 min during which time all the LiCl dissolved, thus forming a clear solution. A solution of 2-(2-(*tert*-butyldimethylsilyloxy)phenyl)acetaldehyde **491** (2.64 g, 10.5 mmol) in acetonitrile (10 ml) was then added dropwise over a 10 min period and a slightly exotherm was observed during the addition. The reaction was left to proceed for 18 h at rt during which time the colour of the solution changed to pale yellow. Analysis of the reaction mixture after this time indicated that the starting material had been consumed and so ice cold water was added (100 ml) followed by ethyl acetate (200 ml). After thoroughly mixing the phases, the organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 × 100 ml). The combined organic fractions were washed with brine (100 ml) then dried over anhydrous magnesium sulfate. After filtration, the solvent was removed *in vacuo* and the crude yellow oil was purified by column chromatography affording what appeared to be a single compound by TLC. However, ^{1}H NMR analysis revealed that at least 2 compounds were present as a mixture. It was later determined that the mixture consisted of the desired product, **492**, as well as its isomer, **495** in the ratio 1:0.5 (2.70 g, 77% combined). Under these basic reaction conditions, **492** once formed, readily isomerises to **495**.

Optimised procedure: Producing 492 only

Into a 2 neck round bottom flask containing Ar was placed 2-(2-(*tert*-butyldimethylsilyloxy)phenyl)acetaldehyde **491** (2.60 g, 10.4 mmol) followed by acetonitrile (150 ml). To the solution was added ethyl 2-(diethoxyphosphoryl)propanoate (2.05 ml, 2.28 g, 9.56 mmol) and LiCl (1.05 g, 24.8 mmol). Whilst stirring under Ar, the solution was cooled to 0 °C and then DBU (1.41 ml, 1.44 g, 9.43 mmol) in acetonitrile (20 ml) was added dropwise over a 20 min period. The reaction was left to proceed for another 1 h and then water was added (150 ml) followed by ethyl acetate (300 ml). After thoroughly mixing the phases, the organic phase was separated and then aqueous phase

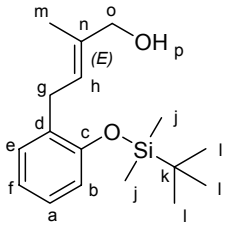
was extracted with ethyl acetate (3 × 50 ml). The combined organic fractions were dried over anhydrous magnesium sulfate and filtered. Evaporation of the solvent *in vacuo* afforded a yellow oil which was purified by column chromatography (5% EtOAc/Hexane) affording the desired *(E)*- alkene ***(E)*-492** as a clear oil (2.35 g, 68% if based upon the aldehyde, or 75% if based upon the limiting DBU), containing trace amounts of the *(Z)*-alkene ***(Z)*-492** (as determined by ^{1}H NMR).



δ_H /ppm: 7.17-7.08 (2H, overlapping signals, H_h and H_a), 7.02-6.87 (2H, overlapping signals, H_e and H_f), 6.84 (1H, d, *J*=8.1 Hz, H_b), 4.20 (2H, q, *J*=7.1 Hz, H_p), 3.52 (2H, d, *J*=7.3 Hz, H_g), 1.96 (3H, s, H_m), 1.30 (3H, t, *J*=7.1 Hz, H_q), 1.04 (9H, s, H_l), 0.28 (6H, s, H_j). **δ_C /ppm:** 168.1 (C_o), 153.5 (C_c), 140.4 (C_h), 130.0 (C_e), 129.7 (C_n), 128.2 (C_d), 127.4 (C_a), 121.2 (C_f), 118.4 (C_b), 60.4 (C_p), 29.7 (C_g), 25.8 (C_l), 18.3 (C_k), 14.3 (C_q), 12.5 (C_m), -4.1 (C_j). **ν /cm^{-1}:** 2859 (CH str), 1713 (C=O), 1495. **HRMS**: calcd for $C_{19}H_{30}O_3Si$ 334.1964 found 334.1947. **M/z:** 334.1947 (3%), 289.1639 (12%), 277.1237 (100%), 264.9920 (6%), 231.0825 (45%), 193.0693 (17%), 161.0462 (9%).

7.4.2.4 *(E)*-4-(2-(*tert*-Butyldimethylsilyloxy)phenyl)-2-methylbut-2-en-1-ol – 493

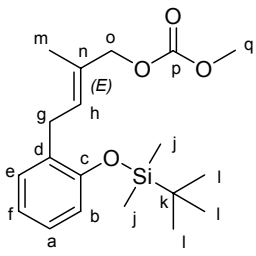
Into a 2 neck round bottomed flask containing Ar was placed the ester **492** (1.90 g, 5.68 mmol) followed by dry THF (30 ml). The reaction mixture was cooled to 0 °C and then $LiAlH_4$ (280 mg, 7.38 mmol) was added in one portion. The reaction was then stirred under Ar at 0 °C and monitored every 20 min by TLC to observe the progress of the reaction. After 1.5 h, the reaction appeared to have gone to completion and ice cold water (50 ml) was carefully added. The reaction mixture was diluted with ethyl acetate (50 ml) and after thoroughly mixing the phases, the organic phase was separated. The aqueous phase was extracted with ethyl acetate (3 × 30 ml) and then the combined organic fractions were washed with brine (100 ml) and finally dried over anhydrous magnesium sulfate. After filtration, the solvent was removed *in vacuo* affording the crude product as an off white oil. Purification by column chromatography (10% EtOAc/Hexane) afforded the desired alcohol **493** as a clear oil (1.08 g, 65%).



δ_H /ppm: 7.15-7.03 (2H, overlapping signals, H_a and H_e), 6.91-6.86 (1H, m, H_f), 6.79 (1H, d, *J*=7.9 Hz, H_b), 5.62 (1H, td, *J*=7.2 Hz and 1.2 Hz, H_h), 4.05 (2H, s, H_o), 3.37 (2H, d, *J*=7.1 Hz, H_g), 1.77 (3H, s, H_m), 1.33 (1H, br s, H_p), 1.02 (9H, s, H_l), 0.25 (6H, s, H_j). **δ_C /ppm:** 153.4 (C_c), 135.6 (C_n), 131.4 (C_d), 129.7 (C_e), 126.9 (C_a), 124.6 (C_h), 121.1 (C_f), 118.4 (C_b), 69.0 (C_o), 28.3 (C_g), 25.8 (C_l), 18.3 (C_k), 13.8 (C_m), -4.1 (C_j). **ν /cm^{-1}:** 3307 (OH str), 2858 (CH str), 1599, 1489. **HRMS**: calcd for $C_{17}H_{28}O_2Si$ 292.1859 found 292.1845. **M/z:** 292.1845 (10%), 235.1124 (82%), 217.1073 (89%), 195.0884 (29%), 177.0759 (77%), 143.0834 (28%).

7.4.2.5 *(E)*-4-(2-(*tert*-Butyldimethylsilyloxy)phenyl)-2-methylbut-2-enyl methyl carbonate – 494

Into a 2 neck round bottomed flask containing dichloromethane (50 ml) was placed the alcohol **493** (2.20 g, 7.52 mmol) thus forming a clear solution. Pyridine (2.40 ml, 2.35 g, 29.7 mmol) was added followed by methyl chloroformate (1.20 ml, 1.47 g, 15.5 mmol). The reaction was left to proceed under Ar at rt for 18 h and after this time analysis of the reaction mixture by TLC indicated that all the starting material had reacted. Water (20 ml) was added and the reaction mixture was then further diluted by the addition of dichloromethane (50 ml) and more water (50 ml). The phases were thoroughly mixed and after separation, the aqueous phase was extracted with dichloromethane (3 × 100 ml). The combined organic fractions were washed dilute HCl (0.01N, 2 × 100 ml), then water (1 × 100 ml) and finally with brine (1 × 100 ml). The organic phase, now free of pyridine, was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The resulting crude oil was purified by column chromatography (5% EtOAc/Hexane) affording the desired carbonate **494** as a clear viscous oil (2.04 g, 77%).

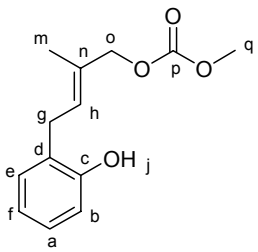


δ_H /ppm: 7.11-7.06 (2H, overlapping signals, H_a and H_e), 6.88 (1H, t, *J*=7.4 Hz, H_f), 6.79 (1H, d, *J*=8.0 Hz, H_b), 5.71 (1H, t, *J*=7.1 Hz, H_h), 4.57 (2H, s, H_o), 3.79 (3H, s, H_q), 3.38 (2H, d, *J*=7.2 Hz, H_g), 1.77 (3H, s, H_m), 1.01 (9H, s, H_l), 0.24 (6H, s, H_j). **δ_C /ppm:** 155.8 (C_p), 153.4 (C_c), 130.8 (C_n), 130.4 (C_d), 129.6 (C_e), 128.6 (C_h), 127.0 (C_a), 121.1 (ArCH), 118.4 (ArCH), 73.7 (C_o), 54.7 (C_q), 28.4

(C_g), 25.8 (C_l), 18.3 (C_k), 13.9 (C_m), -4.1 (C_j). **ν /cm^{-1}:** 2859 (CH str), 1750 (C=O str), 1491. **HRMS**: calcd for $C_{19}H_{30}O_4Si$ 350.1913 found 350.1921. **M/z:** 350.1921 (2%), 293.1217 (57%), 275.1833 (34%), 249.1278 (37%), 217.1051 (96%), 177.0738 (38%), 161.0418 (31%), 133.0328 (91%).

7.4.2.6 *(E)*-4-(2-Hydroxyphenyl)-2-methylbut-2-enyl methyl carbonate – 489

Into a 250 ml round bottom flask containing Ar was placed dry THF (120 ml) followed by the silyl ether **494** (1.80 g, 5.14 mmol). The solution was cooled to 0 °C by means of an ice bath and then TBAF (5.20 ml, 5.20 mmol, 1M solution in THF) was added in one portion. The reaction was left to proceed for 5 min at 0 °C under Ar after which time analysis of the reaction mixture by TLC indicated that all the starting material had reacted. The reaction mixture was transferred to a separating funnel and diluted with water (150 ml) and ethyl acetate (200 ml). After vigorously mixing the phases, the organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 × 100 ml). The combined organic fractions were washed with brine and dried over anhydrous magnesium sulfate. After evaporation of the solvent *in vacuo* the resulting crude oil was purified by column chromatography affording the desired phenol **489** as a viscous clear oil (1.19 g, 98%).



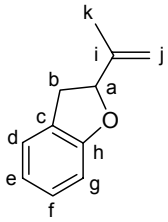
δ_H /ppm: 7.11-7.07 (2H, overlapping signals, H_e and H_a), 6.89-6.75 (2H, overlapping signals, H_f and H_b), 5.71 (1H, dt, *J*=7.2 Hz and 1.1 Hz, H_h), 5.02 (1H, s, H_j), 4.57 (2H, s, H_o), 3.79 (3H, s, H_q), 3.41 (2H, d, *J*=7.3 Hz, H_g), 1.81 (3H, s, H_m). **δ_C /ppm:** 155.8 (C_p), 153.7 (C_c), 131.2 (ArC), 129.9 (ArCH), 127.7 (C_h), 127.5 (ArCH), 126.2 (C_d), 120.9 (C_f), 115.4 (C_b), 73.4 (C_o), 54.8 (C_q), 28.6 (C_g), 13.9 (C_m). **ν /cm^{-1}:** 3454 (OH str), 2958 (CH str), 1722 (C=O str), 1594, 1456. **HRMS**: calcd for $C_{13}H_{16}O_4$ 236.1049 found 236.1033. **M/z:** 236.1033 (2%), 196.0753 (4%), 160.0849 (67%), 145.0621 (100%), 127.0507 (7%), 120.0571 (59%), 107.0510 (20%).

7.4.2.7 Racemic 2-isopropenyl-2,3-dihydrobenzofuran from a mixture of 489 and 496 – *rac*-167 and recovery of 496

Into a 10 ml 2 neck round bottom flask, fitted with a condenser was placed dichloromethane (6 ml) followed by $PdDba_2$ (2.4 mg, 0.0042 mmol, 2 mole %). The dark

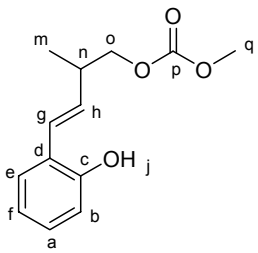
red solution thus formed was degassed for 5 min by bubbling Ar gas into the solution using a pipette. After this time, triphenylphosphine (5.5 mg, 0.021 mmol, 10 mole %) was added in one portion and over a period of 15 min the colour of the solution changed from dark purple to light orange as the phosphorus ligand exchanged with the Dba. Acetic acid (15 µl, 16 mg, 0.26 mmol) was added in one portion and the solution was stirred at rt under Ar for 5 min. Finally, the mixture of compounds consisting of **489** and its isomer **496** (50 mg total mass, ∴31 mg, 0.13 mmol of **489** and 19 mg, 0.080 mmol of **496** – determined by NMR) was added in one portion. The reaction was heated to reflux for 5 h under Ar. Analysis of the reaction mixture after this time indicated that a new product had formed and that some material remained at the original R_f of the starting material. The solvent was removed *in vacuo* and the crude mixture purified by column chromatography (10% EtOAc/Hexane) affording the desired benzofuran ***rac*-167** as a clear volatile oil (12 mg, 58%) as well as the contaminant **496** which could not undergo the Pd π-allyl mediated cyclisation and so was recovered unreacted (18 mg, 95% recovery).

For ***rac*-167**:



δ_H /ppm: 7.17-7.09 (2H, overlapping signals, H_d and H_f), 6.86-6.79 (2H, overlapping signals, H_e and H_g), 5.17 (1H, t, *J*=8.9 Hz, H_a), 5.10 (1H, s, H_j *cis* to H_k), 4.92 (1H, s, H_j *trans* to H_k), 3.34 (1H, dd, *J*=15.6 Hz and 9.5 Hz, H_b), 3.05 (1H, dd, *J*=15.6 Hz and 8.2 Hz, H_b), 1.78 (1H, s, H_k). **δ_C /ppm:** 159.7 (C_h), 144.0 (C_i), 128.0 (C_f), 126.6 (C_c), 124.8 (C_d), 120.3 (C_g), 112.0 (C_j), 109.2 (C_e), 85.6 (C_a), 34.7 (C_b), 17.2 (C_k). **HRMS**: calcd for $C_{11}H_{12}O$ 160.0888 found 160.0888. **M/z:** 160.0888 (80%), 145.0637 (100%), 127.0459 (15%), 115.0533 (10%), 91.0514 (17%).

For recovered **496**:

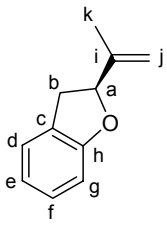


δ_H /ppm: 7.30 (1H, dd, *J*=7.6 and 0.9 Hz, H_i), 7.10 (1H, dt, *J*=8.0 Hz and 1.4 Hz, H_k), 6.88 (1H, t, *J*=7.2 Hz, H_j), 6.79 (1H, d, *J*=8.0 Hz, H_l), 6.65 (1H, d, *J*=16.1 Hz, H_g), 6.08 (1H, dd, *J*=16.1 and 7.7 Hz, H_f), 5.28 (1H, s, H_n), 4.13 (2H, ddd, *J*=25.5 Hz, 10.5 Hz and 6.7 Hz, H_c), 3.77 (3H, s, H_a), 2.75 (1H, td, *J*=13.7 and 6.8 Hz, H_d), 1.16 (3H, d, *J*=6.8 Hz, H_e). **δ_C /ppm:** 156.0 (C_b), 152.7 (C_m), 133.4 (C_f), 128.4 (C_k), 127.5 (C_i), 125.2 (C_g), 124.4 (C_h), 120.8 (C_j), 115.9 (C_l), 71.9 (C_c), 54.8 (C_a), 37.2 (C_d), 16.7

(C_e). **ν /cm^{-1}:** 3428 (OH str), 2961 (CH str), 1725 (C=O str), 1454. **HRMS**: calcd for $C_{13}H_{16}O_4$ 236.1049 found 236.1047. **M/z:** 236.1047 (1%), 219.9711 (8%), 160.0873 (44%), 145.0672 (100%), 115.0560 (8%), 107.0490 (17%).

7.4.2.8 (-)-*(S)*-2-isopropenyl-2,3-dihydrobenzofuran – (-)-*(S)*-167

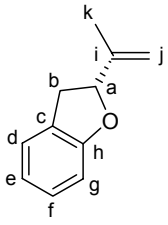
Into a 2 neck round bottomed flask thoroughly degassed with Ar was placed $PdDba_2$ (2.5 mg, 0.0043 mmol, 2 mole %) followed by dry dichloromethane (5 ml), thus forming a wine red solution. The solution was degassed by bubbling Ar into the solution for 5 min using a Pasteur pipette. The *S*,*S'*-Trost ligand (9.0 mg, 0.013 mmol, 6 mole %) was then added to the degassed solution and over a period of 15 min the colour of the solution changed from wine-red to yellow due to ligand exchange. The solution was stirred for another 15 min and then degassed acetic acid (13 µl, 14 mg, 0.23 mmol) was added. The solution was stirred for 2 min and then finally *(E)*-4-(2-hydroxyphenyl)-2-methylbut-2-enyl methyl carbonate **489** (50.0 mg, 0.212 mmol) was added and the reaction was left to proceed under Ar at rt for 18 h. Analysis of the reaction mixture by TLC after this time indicated that all the starting material had reacted and so the solvent was removed *in vacuo* and the crude material purified by column chromatography (10% EtOAc/Hexane) affording the desired chiral benzofuran **(-)-*(S)*-167** (25.0 mg, 74%) and 94% ee as determined by chiral HPLC (Chiralcel OJ 10µ 250 × 4.6 mm, 2% isopropyl alcohol/hexane).



δ_H /ppm: 7.17-7.09 (2H, overlapping signals, H_d and H_f), 6.86-6.79 (2H, overlapping signals, H_e and H_g), 5.17 (1H, t, *J*=8.9 Hz, H_a), 5.10 (1H, s, H_j *cis* to H_k), 4.92 (1H, s, H_j *trans* to H_k), 3.34 (1H, dd, *J*=15.6 Hz and 9.5 Hz, H_b), 3.05 (1H, dd, *J*=15.6 Hz and 8.2 Hz, H_b), 1.78 (1H, s, H_k). **δ_C /ppm:** 159.7 (C_h), 144.0 (C_i), 128.0 (C_f), 126.6 (C_c), 124.8 (C_d), 120.3 (C_g), 112.0 (C_j), 109.2 (C_e), 85.6 (C_a), 34.7 (C_b), 17.2 (C_k). **HRMS**: calcd for $C_{11}H_{12}O$ 160.0888 found 160.0888. **M/z:** 160.0888 (80%), 145.0637 (100%), 127.0459 (15%), 115.0533 (10%), 91.0514 (17%). **$[\alpha]_D^{19}$** = -10.8 (EtOH).

7.4.2.9 (+)-*(R)*-2-isopropenyl-2,3-dihydrobenzofuran – (+)-*(R)*-167

A dry 2 neck round bottom flask containing Ar was charged with dichloromethane (10 ml) followed by $PdDba_2$ (5.0 mg, 0.0087 mmol, 2 mole %), thus forming a wine-red solution. The solution was thoroughly degassed by bubbling Ar into the solution for 5 min and then the *R,R'*-Trost ligand (18.0 mg, 0.0261 mmol, 6 mole %) was added. The solution was stirred at rt under Ar for 30 min during which time the colour gradually changed from wine-red to yellow as the ligand exchange occurred. Degassed acetic acid (25 µl, 26 mg, 0.44 mmol) was added, and after 5 min of stirring, the allyl carbonate **489** (100 mg, 0.423 mmol) was added. The reaction was left to proceed for 18 h at rt under Ar during which time it was observed that the yellow colour had faded somewhat. Analysis of the reaction mixture by TLC indicated that a new product had formed and so the reaction mixture was concentrated *in vacuo*. Purification by column chromatography afforded the desired benzofuran **(+)-*(R)*-167** (66.6 mg, 98%) and 92 % ee as determined by chiral HPLC (Chiralcel OJ 10µ 250 × 4.6 mm, 2% isopropyl alcohol/hexane).



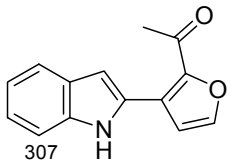
δ_H /ppm: 7.17-7.09 (2H, overlapping signals, H_d and H_f), 6.86-6.79 (2H, overlapping signals, H_e and H_g), 5.17 (1H, t, *J*=8.9 Hz, H_a), 5.10 (1H, s, H_j *cis* to H_k), 4.92 (1H, s, H_j *trans* to H_k), 3.34 (1H, dd, *J*=15.6 Hz and 9.5 Hz, H_b), 3.05 (1H, dd, *J*=15.6 Hz and 8.2 Hz, H_b), 1.78 (1H, s, H_k). **δ_C /ppm:** 159.7 (C_h), 144.0 (C_i), 128.0 (C_f), 126.6 (C_c), 124.8 (C_d), 120.3 (C_g), 112.0 (C_j), 109.2 (C_e), 85.6 (C_a), 34.7 (C_b), 17.2 (C_k). **HRMS**: calcd for $C_{11}H_{12}O$ 160.0888 found 160.0888. **M/z:** 160.0888 (80%), 145.0637 (100%), 127.0459 (15%), 115.0533 (10%), 91.0514 (17%). **$[\alpha]_D^{19}$** = +10.3 (EtOH).

CHAPTER 8 – APPENDICES

8.1 APPENDIX I – X-RAY CRYSTALLOGRAPHICAL DATA

Intensity data were collected on a Bruker SMART 1K CCD area detector diffractometer with graphite monochromated Mo K_α radiation (50kV, 30mA). The collection method involved ω-scans of width 0.3°. Data reduction was carried out using the program *SAINT+*. The crystal structure was solved by direct methods using *SHELXTL*. Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares calculations based on F^2 using *SHELXTL*. Hydrogen atoms were first located in the difference map then positioned geometrically and allowed to ride on their respective parent atoms. Diagrams and publication material were generated using SHELXTL and PLATON.

8.1.1 X-Ray crystallographical data for 2-(2-acetylfuran-3-yl)-1*H*-indole – 307



307

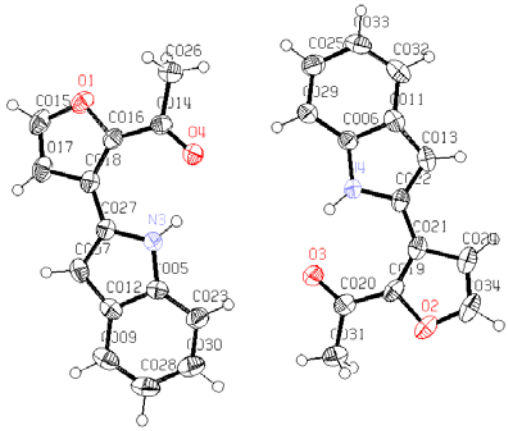


Table 1. Crystal data and structure refinement for **307**.

Identification code	**307**
Empirical formula	C11.20 H8.80 N0.80 O1.60
Formula weight	180.19
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)

Unit cell dimensions	a = 7.2780(2) Å α= 90°. b = 14.3556(3) Å β= 99.4330(10)°. c = 10.7002(2) Å γ= 90°.
Volume	1102.84(4) $Å^3$
Z	5
Density (calculated)	1.357 Mg/m^3
Absorption coefficient	0.092 mm^{-1}
F(000)	472
Crystal size	0.35 x 0.23 x 0.14 mm^3
Theta range for data collection	1.93 to 28.34°.
Index ranges	-9<=h<=9, -19<=k<=19, -14<=l<=14
Reflections collected	21862
Independent reflections	5487 [R(int) = 0.0707]
Completeness to theta = 28.34°	99.7 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5487 / 1 / 309
Goodness-of-fit on F^2	0.975
Final R indices [I>2sigma(I)]	R1 = 0.0400, wR2 = 0.0926
R indices (all data)	R1 = 0.0609, wR2 = 0.1011
Absolute structure parameter	1.5(9)
Largest diff. peak and hole	0.153 and -0.171 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **307**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(3)	3234(2)	2824(1)	2303(1)	40(1)
O(4)	8787(2)	4173(1)	4910(1)	40(1)
O(2)	-1523(2)	2220(1)	1757(1)	43(1)
O(1)	13546(2)	4770(1)	5498(1)	40(1)
C(005)	7690(2)	4652(1)	1213(2)	31(1)
C(006)	4337(2)	2427(1)	6035(2)	32(1)
C(007)	10589(3)	5256(1)	1233(2)	36(1)
N(3)	8717(2)	4542(1)	2398(1)	31(1)
C(009)	8092(3)	5300(1)	-817(2)	44(1)
N(4)	3339(2)	2470(1)	4831(1)	32(1)
C(011)	3169(3)	2010(1)	6815(2)	35(1)
C(012)	8848(3)	5099(1)	457(2)	34(1)
C(013)	1441(3)	1828(1)	6032(2)	37(1)
C(014)	10364(3)	4342(1)	5458(2)	33(1)
C(015)	14689(3)	5089(2)	4712(2)	45(1)
C(016)	11818(2)	4657(1)	4771(2)	32(1)
C(017)	13771(3)	5183(1)	3531(2)	43(1)
C(018)	11891(2)	4896(1)	3528(2)	32(1)
C(019)	222(2)	2341(1)	2476(2)	35(1)
C(020)	1642(3)	2677(1)	1775(2)	35(1)
C(021)	163(2)	2104(1)	3721(2)	34(1)
C(022)	1578(2)	2116(1)	4827(2)	33(1)
C(023)	5871(3)	4395(1)	748(2)	40(1)
C(024)	-1736(3)	1837(1)	3742(2)	44(1)
C(025)	6766(3)	2591(2)	7770(2)	46(1)
C(026)	10874(3)	4251(1)	6865(2)	44(1)
C(027)	10475(2)	4908(1)	2419(2)	31(1)
C(028)	6296(3)	5051(1)	-1272(2)	48(1)
C(029)	6129(3)	2719(1)	6500(2)	38(1)
C(030)	5191(3)	4602(2)	-492(2)	48(1)

C(031)	1072(3)	2842(1)	387(2)	43(1)
C(032)	3883(3)	1894(1)	8109(2)	42(1)
C(033)	5660(3)	2180(2)	8565(2)	45(1)
C(034)	-2651(3)	1925(2)	2563(2)	50(1)

Table 3. Bond lengths [Å] and angles [°] for **307**.

O(3)-C(020)	1.221(2)
O(4)-C(014)	1.224(2)
O(2)-C(034)	1.353(3)
O(2)-C(019)	1.383(2)
O(1)-C(015)	1.356(3)
O(1)-C(016)	1.376(2)
C(005)-N(3)	1.371(2)
C(005)-C(023)	1.386(3)
C(005)-C(012)	1.414(2)
C(006)-N(4)	1.372(2)
C(006)-C(029)	1.383(3)
C(006)-C(011)	1.418(2)
C(007)-C(027)	1.378(2)
C(007)-C(012)	1.414(3)
C(007)-H(007)	0.9500
N(3)-C(027)	1.380(2)
N(3)-H(008)	0.8800
C(009)-C(028)	1.366(3)
C(009)-C(012)	1.414(3)
C(009)-H(009)	0.9500
N(4)-C(022)	1.378(2)
N(4)-H(010)	0.8800
C(011)-C(032)	1.407(3)
C(011)-C(013)	1.417(3)
C(013)-C(022)	1.373(3)
C(013)-H(013)	0.9500
C(014)-C(016)	1.456(3)
C(014)-C(026)	1.496(3)
C(015)-C(017)	1.336(3)
C(015)-H(015)	0.9500
C(016)-C(018)	1.383(3)
C(017)-C(018)	1.428(2)
C(017)-H(017)	0.9500
C(018)-C(027)	1.439(2)
C(019)-C(021)	1.383(3)
C(019)-C(020)	1.455(3)
C(020)-C(031)	1.494(3)
C(021)-C(022)	1.436(3)
C(021)-C(024)	1.438(3)
C(023)-C(030)	1.370(3)
C(023)-H(023)	0.9500
C(024)-C(034)	1.333(3)
C(024)-H(024)	0.9500
C(025)-C(029)	1.374(3)
C(025)-C(033)	1.394(3)
C(025)-H(025)	0.9500
C(026)-H(02A)	0.9800
C(026)-H(02B)	0.9800
C(026)-H(02C)	0.9800
C(028)-C(030)	1.407(3)
C(028)-H(028)	0.9500
C(029)-H(029)	0.9500

C(030)-H(030)	0.9500
C(031)-H(03A)	0.9800
C(031)-H(03B)	0.9800
C(031)-H(03C)	0.9800
C(032)-C(033)	1.368(3)
C(032)-H(032)	0.9500
C(033)-H(033)	0.9500
C(034)-H(034)	0.9500
C(034)-O(2)-C(019)	106.42(16)
C(015)-O(1)-C(016)	106.62(15)
N(3)-C(005)-C(023)	130.13(17)
N(3)-C(005)-C(012)	107.23(16)
C(023)-C(005)-C(012)	122.64(17)
N(4)-C(006)-C(029)	130.33(17)
N(4)-C(006)-C(011)	107.19(16)
C(029)-C(006)-C(011)	122.47(18)
C(027)-C(007)-C(012)	107.45(16)
C(027)-C(007)-H(007)	126.3
C(012)-C(007)-H(007)	126.3
C(005)-N(3)-C(027)	109.52(14)
C(005)-N(3)-H(008)	125.2
C(027)-N(3)-H(008)	125.2
C(028)-C(009)-C(012)	119.27(19)
C(028)-C(009)-H(009)	120.4
C(012)-C(009)-H(009)	120.4
C(006)-N(4)-C(022)	109.56(15)
C(006)-N(4)-H(010)	125.2
C(022)-N(4)-H(010)	125.2
C(032)-C(011)-C(013)	135.16(18)
C(032)-C(011)-C(006)	118.00(18)
C(013)-C(011)-C(006)	106.82(16)
C(005)-C(012)-C(009)	118.04(18)
C(005)-C(012)-C(007)	107.24(16)
C(009)-C(012)-C(007)	134.72(18)
C(022)-C(013)-C(011)	107.80(16)
C(022)-C(013)-H(013)	126.1
C(011)-C(013)-H(013)	126.1
O(4)-C(014)-C(016)	121.45(16)
O(4)-C(014)-C(026)	121.53(17)
C(016)-C(014)-C(026)	117.01(16)
C(017)-C(015)-O(1)	110.99(17)
C(017)-C(015)-H(015)	124.5
O(1)-C(015)-H(015)	124.5
O(1)-C(016)-C(018)	109.79(16)
O(1)-C(016)-C(014)	115.08(15)
C(018)-C(016)-C(014)	135.11(17)
C(015)-C(017)-C(018)	107.69(18)
C(015)-C(017)-H(017)	126.2
C(018)-C(017)-H(017)	126.2
C(016)-C(018)-C(017)	104.89(17)
C(016)-C(018)-C(027)	131.37(16)
C(017)-C(018)-C(027)	123.71(16)
O(2)-C(019)-C(021)	109.53(16)
O(2)-C(019)-C(020)	114.85(17)
C(021)-C(019)-C(020)	135.62(17)
O(3)-C(020)-C(019)	121.31(18)
O(3)-C(020)-C(031)	121.35(18)
C(019)-C(020)-C(031)	117.34(17)
C(019)-C(021)-C(022)	131.29(16)

C(019)-C(021)-C(024)	105.21(17)
C(022)-C(021)-C(024)	123.49(18)
C(013)-C(022)-N(4)	108.62(17)
C(013)-C(022)-C(021)	128.13(17)
N(4)-C(022)-C(021)	123.20(16)
C(030)-C(023)-C(005)	117.5(2)
C(030)-C(023)-H(023)	121.2
C(005)-C(023)-H(023)	121.2
C(034)-C(024)-C(021)	107.01(19)
C(034)-C(024)-H(024)	126.5
C(021)-C(024)-H(024)	126.5
C(029)-C(025)-C(033)	121.7(2)
C(029)-C(025)-H(025)	119.1
C(033)-C(025)-H(025)	119.1
C(014)-C(026)-H(02A)	109.5
C(014)-C(026)-H(02B)	109.5
H(02A)-C(026)-H(02B)	109.5
C(014)-C(026)-H(02C)	109.5
H(02A)-C(026)-H(02C)	109.5
H(02B)-C(026)-H(02C)	109.5
C(007)-C(027)-N(3)	108.56(16)
C(007)-C(027)-C(018)	128.36(16)
N(3)-C(027)-C(018)	123.08(15)
C(009)-C(028)-C(030)	121.0(2)
C(009)-C(028)-H(028)	119.5
C(030)-C(028)-H(028)	119.5
C(025)-C(029)-C(006)	117.41(19)
C(025)-C(029)-H(029)	121.3
C(006)-C(029)-H(029)	121.3
C(023)-C(030)-C(028)	121.5(2)
C(023)-C(030)-H(030)	119.2
C(028)-C(030)-H(030)	119.2
C(020)-C(031)-H(03A)	109.5
C(020)-C(031)-H(03B)	109.5
H(03A)-C(031)-H(03B)	109.5
C(020)-C(031)-H(03C)	109.5
H(03A)-C(031)-H(03C)	109.5
H(03B)-C(031)-H(03C)	109.5
C(033)-C(032)-C(011)	119.35(19)
C(033)-C(032)-H(032)	120.3
C(011)-C(032)-H(032)	120.3
C(032)-C(033)-C(025)	121.07(19)
C(032)-C(033)-H(033)	119.5
C(025)-C(033)-H(033)	119.5
C(024)-C(034)-O(2)	111.83(17)
C(024)-C(034)-H(034)	124.1
O(2)-C(034)-H(034)	124.1

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for **307**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(3)	30(1)	55(1)	35(1)	2(1)	4(1)	0(1)
O(4)	30(1)	53(1)	38(1)	7(1)	5(1)	-2(1)
O(2)	27(1)	46(1)	52(1)	-7(1)	-3(1)	1(1)
O(1)	27(1)	47(1)	44(1)	-5(1)	1(1)	4(1)
C(005)	38(1)	27(1)	28(1)	-2(1)	5(1)	4(1)

C(006)	34(1)	29(1)	32(1)	4(1)	4(1)	1(1)
C(007)	40(1)	32(1)	41(1)	-2(1)	17(1)	-3(1)
N(3)	32(1)	33(1)	29(1)	1(1)	6(1)	-3(1)
C(009)	68(2)	34(1)	31(1)	1(1)	12(1)	4(1)
N(4)	28(1)	36(1)	33(1)	4(1)	6(1)	-5(1)
C(011)	40(1)	29(1)	39(1)	0(1)	15(1)	3(1)
C(012)	46(1)	27(1)	31(1)	-1(1)	12(1)	4(1)
C(013)	36(1)	31(1)	47(1)	2(1)	18(1)	-1(1)
C(014)	33(1)	32(1)	31(1)	0(1)	2(1)	5(1)
C(015)	25(1)	54(1)	57(1)	-11(1)	6(1)	-1(1)
C(016)	26(1)	32(1)	38(1)	-2(1)	1(1)	2(1)
C(017)	29(1)	48(1)	53(1)	-8(1)	15(1)	-2(1)
C(018)	29(1)	30(1)	39(1)	-5(1)	10(1)	2(1)
C(019)	24(1)	32(1)	46(1)	-8(1)	-1(1)	3(1)
C(020)	32(1)	31(1)	40(1)	-3(1)	4(1)	6(1)
C(021)	28(1)	27(1)	47(1)	-4(1)	8(1)	3(1)
C(022)	28(1)	27(1)	45(1)	-3(1)	9(1)	-1(1)
C(023)	40(1)	40(1)	38(1)	-3(1)	0(1)	-2(1)
C(024)	29(1)	41(1)	62(1)	-4(1)	10(1)	-4(1)
C(025)	49(1)	47(1)	39(1)	2(1)	-2(1)	-8(1)
C(026)	49(1)	45(1)	35(1)	1(1)	4(1)	2(1)
C(027)	29(1)	30(1)	36(1)	-5(1)	8(1)	0(1)
C(028)	68(2)	45(1)	30(1)	0(1)	1(1)	7(1)
C(029)	40(1)	41(1)	34(1)	6(1)	5(1)	-5(1)
C(030)	52(1)	48(1)	40(1)	-6(1)	-7(1)	2(1)
C(031)	43(1)	44(1)	38(1)	-5(1)	0(1)	5(1)
C(032)	60(1)	34(1)	36(1)	5(1)	20(1)	6(1)
C(033)	65(1)	43(1)	27(1)	1(1)	5(1)	2(1)
C(034)	24(1)	50(1)	74(2)	-9(1)	4(1)	-1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **307**.

	x	y	z	U(eq)
H(007)	11643	5547	983	44
H(008)	8316	4278	3045	37
H(009)	8825	5605	-1351	53
H(010)	3758	2691	4164	39
H(013)	376	1556	6294	44
H(015)	15972	5228	4967	54
H(017)	14277	5401	2821	51
H(023)	5124	4086	1269	48
H(024)	-2242	1635	4461	52
H(025)	7990	2787	8115	55
H(02A)	9756	4107	7229	65
H(02B)	11415	4838	7221	65
H(02C)	11785	3748	7067	65
H(028)	5784	5183	-2129	58
H(029)	6891	2998	5963	46
H(030)	3945	4438	-832	58
H(03A)	2153	3050	23	64
H(03B)	103	3323	253	64
H(03C)	585	2263	-25	64
H(032)	3139	1619	8661	50
H(033)	6149	2096	9437	55
H(034)	-3940	1796	2318	59

Table 6. Torsion angles [°] for **307**.

C(023)-C(005)-N(3)-C(027)	179.89(18)
C(012)-C(005)-N(3)-C(027)	0.38(18)
C(029)-C(006)-N(4)-C(022)	-178.21(19)
C(011)-C(006)-N(4)-C(022)	1.18(18)
N(4)-C(006)-C(011)-C(032)	-179.58(15)
C(029)-C(006)-C(011)-C(032)	-0.1(3)
N(4)-C(006)-C(011)-C(013)	-1.11(18)
C(029)-C(006)-C(011)-C(013)	178.34(17)
N(3)-C(005)-C(012)-C(009)	-179.45(15)
C(023)-C(005)-C(012)-C(009)	1.0(2)
N(3)-C(005)-C(012)-C(007)	-0.38(17)
C(023)-C(005)-C(012)-C(007)	-179.93(17)
C(028)-C(009)-C(012)-C(005)	-0.6(3)
C(028)-C(009)-C(012)-C(007)	-179.32(19)
C(027)-C(007)-C(012)-C(005)	0.24(18)
C(027)-C(007)-C(012)-C(009)	179.09(19)
C(032)-C(011)-C(013)-C(022)	178.72(19)
C(006)-C(011)-C(013)-C(022)	0.63(19)
C(016)-O(1)-C(015)-C(017)	0.0(2)
C(015)-O(1)-C(016)-C(018)	0.7(2)
C(015)-O(1)-C(016)-C(014)	-178.18(16)
O(4)-C(014)-C(016)-O(1)	-176.53(16)
C(026)-C(014)-C(016)-O(1)	4.5(2)
O(4)-C(014)-C(016)-C(018)	5.0(3)
C(026)-C(014)-C(016)-C(018)	-173.9(2)
O(1)-C(015)-C(017)-C(018)	-0.7(2)
O(1)-C(016)-C(018)-C(017)	-1.1(2)
C(014)-C(016)-C(018)-C(017)	177.45(19)
O(1)-C(016)-C(018)-C(027)	-179.23(16)
C(014)-C(016)-C(018)-C(027)	-0.7(4)
C(015)-C(017)-C(018)-C(016)	1.1(2)
C(015)-C(017)-C(018)-C(027)	179.43(17)
C(034)-O(2)-C(019)-C(021)	1.0(2)
C(034)-O(2)-C(019)-C(020)	-178.99(16)
O(2)-C(019)-C(020)-O(3)	179.00(16)
C(021)-C(019)-C(020)-O(3)	-0.9(3)
O(2)-C(019)-C(020)-C(031)	-0.4(2)
C(021)-C(019)-C(020)-C(031)	179.6(2)
O(2)-C(019)-C(021)-C(022)	-179.31(17)
C(020)-C(019)-C(021)-C(022)	0.6(4)
O(2)-C(019)-C(021)-C(024)	-0.7(2)
C(020)-C(019)-C(021)-C(024)	179.3(2)
C(011)-C(013)-C(022)-N(4)	0.1(2)
C(011)-C(013)-C(022)-C(021)	-177.52(16)
C(006)-N(4)-C(022)-C(013)	-0.80(19)
C(006)-N(4)-C(022)-C(021)	176.94(16)
C(019)-C(021)-C(022)-C(013)	-176.75(19)
C(024)-C(021)-C(022)-C(013)	4.8(3)
C(019)-C(021)-C(022)-N(4)	6.0(3)
C(024)-C(021)-C(022)-N(4)	-172.45(17)
N(3)-C(005)-C(023)-C(030)	179.55(18)
C(012)-C(005)-C(023)-C(030)	-1.0(3)
C(019)-C(021)-C(024)-C(034)	0.1(2)
C(022)-C(021)-C(024)-C(034)	178.90(17)
C(012)-C(007)-C(027)-N(3)	-0.01(19)
C(012)-C(007)-C(027)-C(018)	179.43(16)
C(005)-N(3)-C(027)-C(007)	-0.23(19)

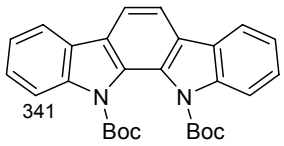
C(005)-N(3)-C(027)-C(018)	-179.71(15)
C(016)-C(018)-C(027)-C(007)	171.77(19)
C(017)-C(018)-C(027)-C(007)	-6.1(3)
C(016)-C(018)-C(027)-N(3)	-8.9(3)
C(017)-C(018)-C(027)-N(3)	173.25(17)
C(012)-C(009)-C(028)-C(030)	0.2(3)
C(033)-C(025)-C(029)-C(006)	0.2(3)
N(4)-C(006)-C(029)-C(025)	179.45(18)
C(011)-C(006)-C(029)-C(025)	0.1(3)
C(005)-C(023)-C(030)-C(028)	0.6(3)
C(009)-C(028)-C(030)-C(023)	-0.2(3)
C(013)-C(011)-C(032)-C(033)	-178.1(2)
C(006)-C(011)-C(032)-C(033)	-0.2(3)
C(011)-C(032)-C(033)-C(025)	0.5(3)
C(029)-C(025)-C(033)-C(032)	-0.5(3)
C(021)-C(024)-C(034)-O(2)	0.5(2)
C(019)-O(2)-C(034)-C(024)	-0.9(2)

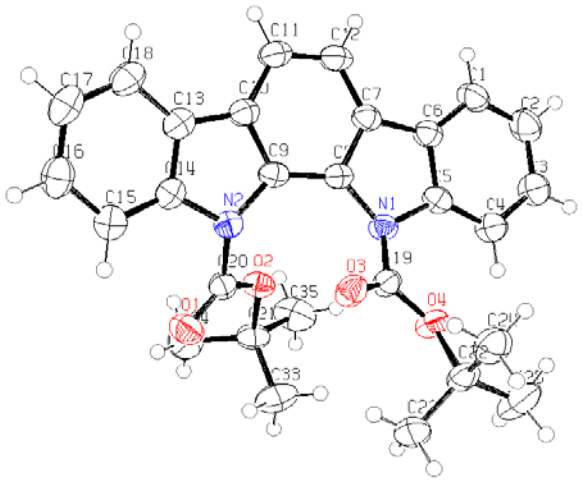
Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for **307** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)

8.1.2 X-Ray crystallographical data for d(*tert*-butyl) indolo[2,3-*a*]carbazole-11,12-dicarboxylate – 341





Empirical formula	C28 H28 N2 O4
Formula weight	456.52
Temperature	293(2) K
Wavelength	0.71073 A
Crystal system, space group	monoclinic, p2(1)/n
Unit cell dimensions	a = 17.031(3) A alpha = 90 deg. b = 7.8425(15) A beta = 104.196(3) deg. c = 18.690(4) A gamma = 90 deg.
Volume	2420.1(8) A^3
Z, Calculated density	4, 1.253 Mg/m^3
Absorption coefficient	0.084 mm^-1
F(000)	968
Crystal size	0.42 x 0.20 x 0.09 mm
Theta range for data collection	1.45 to 28.00 deg.
Limiting indices	-22<=h<=22, -10<=k<=9, -17<=l<=24
Reflections collected / unique	15515 / 5820 [R(int) = 0.0605]
Completeness to theta = 28.00	99.5 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5820 / 0 / 336
Goodness-of-fit on F^2	0.963
Final R indices [I>2sigma(I)]	R1 = 0.0547, wR2 = 0.1340
R indices (all data)	R1 = 0.1298, wR2 = 0.1711
Extinction coefficient	0.0065(11)
Largest diff. peak and hole	0.261 and -0.273 e.A^-3

Crystal data and structure refinement for **341**.
Identification code **341**

Empirical formula	C28 H28 N2 O4

Formula weight	456.52
Temperature	293(2) K
Wavelength	0.71073 A
Crystal system, space group	monoclinic, P2(1)/n
Unit cell dimensions	a = 17.031(3) A alpha = 90 deg.
	b = 7.8425(15) A beta = 104.196(3) deg.
	c = 18.690(4) A gamma = 90 deg.
Volume	2420.1(8) A^3
Z, Calculated density	4, 1.253 Mg/m^3
Absorption coefficient	0.084 mm^-1
F(000)	968
Crystal size	0.42 x 0.20 x 0.09 mm
Theta range for data collection	1.45 to 28.00 deg.
Limiting indices	-22<=h<=22, -10<=k<=9, -17<=l<=24
Reflections collected / unique	15515 / 5820 [R(int) = 0.0605]
Completeness to theta = 28.00	99.5 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5820 / 0 / 336
Goodness-of-fit on F^2	0.963
Final R indices [I>2sigma(I)]	R1 = 0.0547, wR2 = 0.1340
R indices (all data)	R1 = 0.1298, wR2 = 0.1711
Extinction coefficient	0.0065(11)
Largest diff. peak and hole	0.261 and -0.273 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **341**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(24)	6567(2)	3683(3)	1264(2)	60(1)
C(23)	6256(2)	6446(4)	581(1)	57(1)
C(25)	7439(2)	6226(5)	1673(2)	74(1)
C(34)	3633(2)	11109(3)	1227(2)	60(1)
C(33)	4884(2)	9914(3)	936(2)	58(1)
C(35)	4847(2)	10467(4)	2240(1)	63(1)
O(2)	4089(1)	8201(2)	1611(1)	37(1)
O(1)	3378(1)	7762(2)	421(1)	46(1)
N(1)	5158(1)	5712(2)	2483(1)	34(1)
O(3)	4920(1)	5038(2)	1258(1)	43(1)
O(4)	6128(1)	6150(2)	1871(1)	41(1)
N(2)	3330(1)	5828(2)	1328(1)	33(1)
C(20)	3604(1)	7341(3)	1058(1)	34(1)
C(9)	3613(1)	5192(3)	2056(1)	33(1)
C(8)	4380(1)	5167(3)	2547(1)	32(1)
C(19)	5373(1)	5578(3)	1806(1)	35(1)
C(10)	2971(1)	4358(3)	2260(1)	35(1)
C(15)	1989(1)	5506(3)	369(1)	42(1)
C(12)	3788(1)	3783(3)	3471(1)	42(1)
C(5)	5710(1)	5467(3)	3189(1)	35(1)
C(6)	5283(1)	4731(3)	3669(1)	37(1)
C(4)	6530(1)	5832(3)	3432(1)	43(1)
C(13)	2284(1)	4361(3)	1621(1)	38(1)
C(7)	4448(1)	4517(3)	3263(1)	36(1)
C(14)	2518(1)	5263(3)	1057(1)	35(1)
C(22)	6589(1)	5602(3)	1319(1)	43(1)
C(3)	6914(2)	5430(3)	4153(1)	48(1)
C(11)	3058(1)	3664(3)	2967(1)	42(1)
C(18)	1510(1)	3672(3)	1501(1)	47(1)
C(21)	4365(1)	9965(3)	1483(1)	40(1)
C(16)	1219(1)	4805(3)	267(2)	50(1)

C(1)	5681(2)	4342(3)	4393(1)	48(1)
C(17)	981(1)	3903(3)	818(2)	51(1)
C(2)	6498(2)	4692(3)	4627(1)	53(1)

Table 3. Bond lengths [A] and angles [deg] for **341**.

C(24)-C(22)	1.508(3)
C(24)-H(24A)	0.9600
C(24)-H(24B)	0.9600
C(24)-H(24C)	0.9600
C(23)-C(22)	1.510(3)
C(23)-H(23A)	0.9600
C(23)-H(23B)	0.9600
C(23)-H(23C)	0.9600
C(25)-C(22)	1.518(3)
C(25)-H(25A)	0.9600
C(25)-H(25B)	0.9600
C(25)-H(25C)	0.9600
C(34)-C(21)	1.515(3)
C(34)-H(34A)	0.9600
C(34)-H(34B)	0.9600
C(34)-H(34C)	0.9600
C(33)-C(21)	1.505(3)
C(33)-H(33A)	0.9600
C(33)-H(33B)	0.9600
C(33)-H(33C)	0.9600
C(35)-C(21)	1.505(3)
C(35)-H(35A)	0.9600
C(35)-H(35B)	0.9600
C(35)-H(35C)	0.9600
O(2)-C(20)	1.336(2)
O(2)-C(21)	1.500(2)
O(1)-C(20)	1.204(2)
N(1)-C(19)	1.405(3)
N(1)-C(8)	1.425(3)
N(1)-C(5)	1.432(3)
O(3)-C(19)	1.198(2)
O(4)-C(19)	1.339(2)
O(4)-C(22)	1.504(3)
N(2)-C(20)	1.413(3)
N(2)-C(9)	1.417(3)
N(2)-C(14)	1.422(3)
C(9)-C(8)	1.402(3)
C(9)-C(10)	1.406(3)
C(8)-C(7)	1.408(3)
C(10)-C(11)	1.403(3)
C(10)-C(13)	1.452(3)
C(15)-C(14)	1.390(3)
C(15)-C(16)	1.391(3)
C(15)-H(15)	0.9300
C(12)-C(11)	1.368(3)
C(12)-C(7)	1.400(3)
C(12)-H(12)	0.9300
C(5)-C(4)	1.390(3)
C(5)-C(6)	1.409(3)
C(6)-C(1)	1.390(3)
C(6)-C(7)	1.449(3)
C(4)-C(3)	1.382(3)
C(4)-H(4)	0.9300

C(13)-C(18)	1.392(3)
C(13)-C(14)	1.404(3)
C(3)-C(2)	1.389(3)
C(3)-H(3)	0.9300
C(11)-H(11)	0.9300
C(18)-C(17)	1.381(3)
C(18)-H(18)	0.9300
C(16)-C(17)	1.390(4)
C(16)-H(16)	0.9300
C(1)-C(2)	1.380(3)
C(1)-H(1)	0.9300
C(17)-H(17)	0.9300
C(2)-H(2)	0.9300
C(22)-C(24)-H(24A)	109.5
C(22)-C(24)-H(24B)	109.5
H(24A)-C(24)-H(24B)	109.5
C(22)-C(24)-H(24C)	109.5
H(24A)-C(24)-H(24C)	109.5
H(24B)-C(24)-H(24C)	109.5
C(22)-C(23)-H(23A)	109.5
C(22)-C(23)-H(23B)	109.5
H(23A)-C(23)-H(23B)	109.5
C(22)-C(23)-H(23C)	109.5
H(23A)-C(23)-H(23C)	109.5
H(23B)-C(23)-H(23C)	109.5
C(22)-C(25)-H(25A)	109.5
C(22)-C(25)-H(25B)	109.5
H(25A)-C(25)-H(25B)	109.5
C(22)-C(25)-H(25C)	109.5
H(25A)-C(25)-H(25C)	109.5
H(25B)-C(25)-H(25C)	109.5
C(21)-C(34)-H(34A)	109.5
C(21)-C(34)-H(34B)	109.5
H(34A)-C(34)-H(34B)	109.5
C(21)-C(34)-H(34C)	109.5
H(34A)-C(34)-H(34C)	109.5
H(34B)-C(34)-H(34C)	109.5
C(21)-C(33)-H(33A)	109.5
C(21)-C(33)-H(33B)	109.5
H(33A)-C(33)-H(33B)	109.5
C(21)-C(33)-H(33C)	109.5
H(33A)-C(33)-H(33C)	109.5
H(33B)-C(33)-H(33C)	109.5
C(21)-C(35)-H(35A)	109.5
C(21)-C(35)-H(35B)	109.5
H(35A)-C(35)-H(35B)	109.5
C(21)-C(35)-H(35C)	109.5
H(35A)-C(35)-H(35C)	109.5
H(35B)-C(35)-H(35C)	109.5
C(20)-O(2)-C(21)	119.99(16)
C(19)-N(1)-C(8)	120.43(17)
C(19)-N(1)-C(5)	124.28(17)
C(8)-N(1)-C(5)	107.17(16)
C(19)-O(4)-C(22)	119.52(16)
C(20)-N(2)-C(9)	125.00(17)
C(20)-N(2)-C(14)	120.82(17)
C(9)-N(2)-C(14)	107.72(17)
O(1)-C(20)-O(2)	127.8(2)
O(1)-C(20)-N(2)	122.00(19)

O(2)-C(20)-N(2)	110.06(17)
C(8)-C(9)-C(10)	118.54(19)
C(8)-C(9)-N(2)	132.66(19)
C(10)-C(9)-N(2)	108.66(18)
C(9)-C(8)-C(7)	118.25(19)
C(9)-C(8)-N(1)	132.62(19)
C(7)-C(8)-N(1)	109.12(18)
O(3)-C(19)-O(4)	126.87(19)
O(3)-C(19)-N(1)	122.71(19)
O(4)-C(19)-N(1)	110.42(18)
C(11)-C(10)-C(9)	121.8(2)
C(11)-C(10)-C(13)	130.8(2)
C(9)-C(10)-C(13)	107.38(18)
C(14)-C(15)-C(16)	116.6(2)
C(14)-C(15)-H(15)	121.7
C(16)-C(15)-H(15)	121.7
C(11)-C(12)-C(7)	119.5(2)
C(11)-C(12)-H(12)	120.3
C(7)-C(12)-H(12)	120.3
C(4)-C(5)-C(6)	120.7(2)
C(4)-C(5)-N(1)	130.8(2)
C(6)-C(5)-N(1)	108.50(17)
C(1)-C(6)-C(5)	120.3(2)
C(1)-C(6)-C(7)	131.8(2)
C(5)-C(6)-C(7)	107.87(18)
C(3)-C(4)-C(5)	118.0(2)
C(3)-C(4)-H(4)	121.0
C(5)-C(4)-H(4)	121.0
C(18)-C(13)-C(14)	120.4(2)
C(18)-C(13)-C(10)	132.2(2)
C(14)-C(13)-C(10)	107.41(18)
C(12)-C(7)-C(8)	121.9(2)
C(12)-C(7)-C(6)	130.8(2)
C(8)-C(7)-C(6)	107.26(19)
C(15)-C(14)-C(13)	121.6(2)
C(15)-C(14)-N(2)	129.7(2)
C(13)-C(14)-N(2)	108.62(18)
O(4)-C(22)-C(24)	108.82(18)
O(4)-C(22)-C(23)	111.06(18)
C(24)-C(22)-C(23)	112.2(2)
O(4)-C(22)-C(25)	102.20(18)
C(24)-C(22)-C(25)	110.9(2)
C(23)-C(22)-C(25)	111.2(2)
C(4)-C(3)-C(2)	121.6(2)
C(4)-C(3)-H(3)	119.2
C(2)-C(3)-H(3)	119.2
C(12)-C(11)-C(10)	119.4(2)
C(12)-C(11)-H(11)	120.3
C(10)-C(11)-H(11)	120.3
C(17)-C(18)-C(13)	118.4(2)
C(17)-C(18)-H(18)	120.8
C(13)-C(18)-H(18)	120.8
O(2)-C(21)-C(33)	110.11(18)
O(2)-C(21)-C(35)	102.13(17)
C(33)-C(21)-C(35)	111.7(2)
O(2)-C(21)-C(34)	109.29(18)
C(33)-C(21)-C(34)	112.1(2)
C(35)-C(21)-C(34)	111.0(2)
C(17)-C(16)-C(15)	122.4(2)

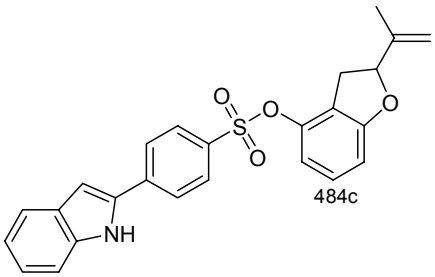
C(17)-C(16)-H(16)	118.8
C(15)-C(16)-H(16)	118.8
C(2)-C(1)-C(6)	118.5(2)
C(2)-C(1)-H(1)	120.7
C(6)-C(1)-H(1)	120.7
C(18)-C(17)-C(16)	120.6(2)
C(18)-C(17)-H(17)	119.7
C(16)-C(17)-H(17)	119.7
C(1)-C(2)-C(3)	120.9(2)
C(1)-C(2)-H(2)	119.6
C(3)-C(2)-H(2)	119.6

Symmetry transformations used to generate equivalent atoms:

Anisotropic displacement parameters (A^2 x 10^3) for **341**. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
C(24)	62(2)	58(2)	68(2)	3(2)	35(2)	13(1)
C(23)	60(2)	76(2)	44(1)	9(1)	28(1)	14(1)
C(25)	47(2)	113(3)	68(2)	-18(2)	29(2)	-20(2)
C(34)	62(2)	40(2)	78(2)	-2(1)	21(2)	5(1)
C(33)	68(2)	46(2)	71(2)	-5(1)	39(2)	-14(1)
C(35)	85(2)	48(2)	51(2)	-8(1)	9(2)	-25(2)
O(2)	45(1)	33(1)	34(1)	0(1)	12(1)	-6(1)
O(1)	52(1)	49(1)	34(1)	6(1)	6(1)	-4(1)
N(1)	35(1)	39(1)	28(1)	0(1)	9(1)	-4(1)
O(3)	35(1)	60(1)	35(1)	-8(1)	10(1)	-2(1)
O(4)	38(1)	52(1)	37(1)	-6(1)	17(1)	-8(1)
N(2)	34(1)	33(1)	33(1)	-1(1)	11(1)	-1(1)
C(20)	34(1)	36(1)	31(1)	-1(1)	10(1)	3(1)
C(9)	40(1)	29(1)	32(1)	-1(1)	14(1)	1(1)
C(8)	37(1)	29(1)	33(1)	0(1)	14(1)	-1(1)
C(19)	31(1)	39(1)	35(1)	-1(1)	11(1)	-1(1)
C(10)	38(1)	30(1)	41(1)	1(1)	16(1)	1(1)
C(15)	43(1)	42(1)	41(1)	-7(1)	9(1)	1(1)
C(12)	51(1)	39(1)	42(1)	7(1)	23(1)	2(1)
C(5)	43(1)	34(1)	29(1)	-2(1)	8(1)	0(1)
C(6)	42(1)	37(1)	34(1)	2(1)	12(1)	2(1)
C(4)	42(1)	49(1)	38(1)	-3(1)	9(1)	-7(1)
C(13)	38(1)	32(1)	45(1)	-5(1)	14(1)	-1(1)
C(7)	43(1)	34(1)	35(1)	2(1)	15(1)	4(1)
C(14)	34(1)	33(1)	39(1)	-7(1)	11(1)	1(1)
C(22)	38(1)	55(2)	39(1)	-4(1)	19(1)	1(1)
C(3)	46(1)	56(2)	38(1)	-5(1)	2(1)	-6(1)
C(11)	44(1)	38(1)	49(1)	4(1)	23(1)	-2(1)
C(18)	42(1)	39(1)	61(2)	-6(1)	18(1)	-5(1)
C(21)	51(1)	29(1)	43(1)	0(1)	18(1)	-6(1)
C(16)	42(1)	54(2)	51(2)	-14(1)	3(1)	1(1)
C(1)	55(2)	53(2)	36(1)	9(1)	13(1)	5(1)
C(17)	37(1)	51(2)	66(2)	-15(1)	12(1)	-6(1)
C(2)	57(2)	63(2)	35(1)	1(1)	6(1)	7(1)

8.1.3 X-Ray crystallographical data for 2-isopropenyl-2,3-dihydrobenzofuran-4-yl 4-(1*H*-indol-2-yl)benzenesulfonate – 484c



484c

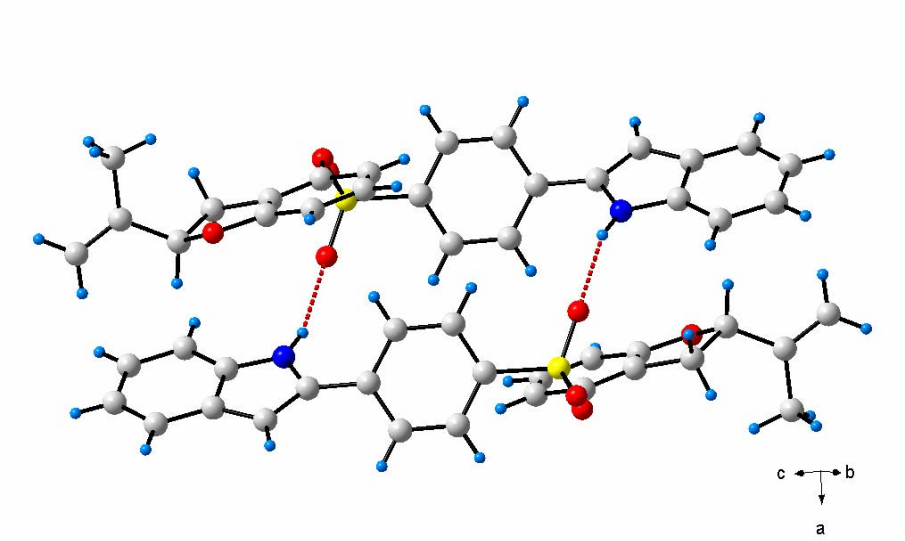


Table 1. Crystal data and structure refinement for **484c**.

Identification code	**484c**	
Empirical formula	C25 H21 N O4 S	
Formula weight	431.49	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pbca	
Unit cell dimensions	a = 16.9709(11) Å	α= 90°.
	b = 7.3848(5) Å	β= 90°.
	c = 33.108(2) Å	γ= 90°.
Volume	4149.3(5) Å^3	
Z	8	
Density (calculated)	1.381 Mg/m^3	
Absorption coefficient	0.189 mm^{-1}	
F(000)	1808	
Crystal size	0.29 x 0.19 x 0.02 mm^3	
Theta range for data collection	1.23 to 27.99°.	
Index ranges	-22<=h<=22, -9<=k<=9, -37<=l<=43	
Reflections collected	35345	
Independent reflections	5005 [R(int) = 0.0955]	
Completeness to theta = 27.99°	100.0 %	
Absorption correction	Semi-empirical from equivalents	

Max. and min. transmission	0.9962 and 0.9471
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5005 / 291 / 280
Goodness-of-fit on F^2	1.004
Final R indices [I>2sigma(I)]	R1 = 0.0654, wR2 = 0.1735
R indices (all data)	R1 = 0.1167, wR2 = 0.2110
Largest diff. peak and hole	0.925 and -0.573 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **484c**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	8821(2)	-1154(5)	-1421(1)	46(1)
C(3)	9191(3)	-3720(5)	-1768(1)	48(1)
C(4)	8836(3)	-4322(5)	-1360(1)	49(1)
C(5)	8695(2)	-2550(4)	-1147(1)	38(1)
C(6)	8461(2)	-2121(4)	-761(1)	32(1)
C(7)	8365(2)	-337(4)	-641(1)	35(1)
C(8)	8504(2)	1024(5)	-920(1)	43(1)
C(9)	8724(2)	646(5)	-1314(1)	47(1)
C(10)	8842(3)	-4597(5)	-2131(1)	59(1)
C(11)	9296(6)	-5417(8)	-2391(2)	122(2)
C(12)	7985(4)	-4593(11)	-2173(2)	144(3)
C(17)	8872(2)	-2659(4)	195(1)	25(1)
C(18)	8173(2)	-2397(4)	403(1)	30(1)
C(19)	8117(2)	-1033(4)	683(1)	30(1)
C(20)	8761(2)	121(4)	754(1)	26(1)
C(21)	9470(2)	-211(4)	552(1)	28(1)
C(22)	9531(2)	-1597(4)	276(1)	27(1)
C(23)	8700(2)	1628(4)	1037(1)	30(1)
C(24)	8321(2)	1744(5)	1402(1)	35(1)
C(25)	8479(2)	3483(4)	1563(1)	34(1)
C(26)	8294(2)	4351(5)	1926(1)	45(1)
C(27)	8560(2)	6086(5)	1990(1)	50(1)
C(28)	8999(2)	7003(5)	1699(1)	46(1)
C(29)	9198(2)	6183(4)	1337(1)	39(1)
C(30)	8943(2)	4406(4)	1278(1)	31(1)
N(1)	9082(2)	3243(3)	964(1)	33(1)
O(2)	9019(2)	-1743(3)	-1797(1)	64(1)
O(13)	8265(1)	-3568(3)	-500(1)	32(1)
O(15)	9658(1)	-4252(3)	-382(1)	30(1)
O(16)	8587(1)	-5958(3)	-51(1)	36(1)
S(14)	8908(1)	-4289(1)	-188(1)	27(1)

Table 3. Bond lengths [Å] and angles [°] for **484c**.

C(1)-O(2)	1.362(5)
C(1)-C(9)	1.386(5)
C(1)-C(5)	1.389(5)
C(3)-C(10)	1.487(5)
C(3)-O(2)	1.492(4)
C(3)-C(4)	1.546(5)
C(3)-H(3)	1.0000
C(4)-C(5)	1.505(5)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(5)-C(6)	1.375(5)
C(6)-C(7)	1.386(4)

C(6)-O(13)	1.414(4)
C(7)-C(8)	1.385(5)
C(7)-H(7)	0.9500
C(8)-C(9)	1.386(6)
C(8)-H(8)	0.9500
C(9)-H(9)	0.9500
C(10)-C(11)	1.305(8)
C(10)-C(12)	1.461(8)
C(11)-H(11A)	0.9500
C(11)-H(11B)	0.9500
C(12)-H(12A)	0.9800
C(12)-H(12B)	0.9800
C(12)-H(12C)	0.9800
C(17)-C(18)	1.386(4)
C(17)-C(22)	1.391(4)
C(17)-S(14)	1.748(3)
C(18)-C(19)	1.374(4)
C(18)-H(18)	0.9500
C(19)-C(20)	1.405(4)
C(19)-H(19)	0.9500
C(20)-C(21)	1.397(4)
C(20)-C(23)	1.459(4)
C(21)-C(22)	1.377(4)
C(21)-H(21)	0.9500
C(22)-H(22)	0.9500
C(23)-C(24)	1.371(4)
C(23)-N(1)	1.379(4)
C(24)-C(25)	1.416(5)
C(24)-H(24)	0.9500
C(25)-C(26)	1.399(5)
C(25)-C(30)	1.404(5)
C(26)-C(27)	1.375(5)
C(26)-H(26)	0.9500
C(27)-C(28)	1.394(6)
C(27)-H(27)	0.9500
C(28)-C(29)	1.383(5)
C(28)-H(28)	0.9500
C(29)-C(30)	1.395(5)
C(29)-H(29)	0.9500
C(30)-N(1)	1.370(4)
N(1)-H(1)	0.8800
O(13)-S(14)	1.596(2)
O(15)-S(14)	1.427(2)
O(16)-S(14)	1.422(2)
O(2)-C(1)-C(9)	124.7(3)
O(2)-C(1)-C(5)	113.5(3)
C(9)-C(1)-C(5)	121.8(4)
C(10)-C(3)-O(2)	107.2(3)
C(10)-C(3)-C(4)	115.1(4)
O(2)-C(3)-C(4)	105.2(3)
C(10)-C(3)-H(3)	109.7
O(2)-C(3)-H(3)	109.7
C(4)-C(3)-H(3)	109.7
C(5)-C(4)-C(3)	102.8(3)
C(5)-C(4)-H(4A)	111.2
C(3)-C(4)-H(4A)	111.2
C(5)-C(4)-H(4B)	111.2
C(3)-C(4)-H(4B)	111.2
H(4A)-C(4)-H(4B)	109.1

C(6)-C(5)-C(1)	118.6(3)
C(6)-C(5)-C(4)	132.9(3)
C(1)-C(5)-C(4)	108.4(3)
C(5)-C(6)-C(7)	121.4(3)
C(5)-C(6)-O(13)	117.5(3)
C(7)-C(6)-O(13)	121.0(3)
C(8)-C(7)-C(6)	118.5(3)
C(8)-C(7)-H(7)	120.7
C(6)-C(7)-H(7)	120.7
C(7)-C(8)-C(9)	121.8(3)
C(7)-C(8)-H(8)	119.1
C(9)-C(8)-H(8)	119.1
C(1)-C(9)-C(8)	117.8(3)
C(1)-C(9)-H(9)	121.1
C(8)-C(9)-H(9)	121.1
C(11)-C(10)-C(12)	121.7(6)
C(11)-C(10)-C(3)	119.9(5)
C(12)-C(10)-C(3)	118.3(5)
C(10)-C(11)-H(11A)	120.0
C(10)-C(11)-H(11B)	120.0
H(11A)-C(11)-H(11B)	120.0
C(10)-C(12)-H(12A)	109.5
C(10)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
C(10)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
C(18)-C(17)-C(22)	120.9(3)
C(18)-C(17)-S(14)	119.0(2)
C(22)-C(17)-S(14)	120.0(2)
C(19)-C(18)-C(17)	119.8(3)
C(19)-C(18)-H(18)	120.1
C(17)-C(18)-H(18)	120.1
C(18)-C(19)-C(20)	120.2(3)
C(18)-C(19)-H(19)	119.9
C(20)-C(19)-H(19)	119.9
C(21)-C(20)-C(19)	119.0(3)
C(21)-C(20)-C(23)	120.1(3)
C(19)-C(20)-C(23)	120.9(3)
C(22)-C(21)-C(20)	120.8(3)
C(22)-C(21)-H(21)	119.6
C(20)-C(21)-H(21)	119.6
C(21)-C(22)-C(17)	119.2(3)
C(21)-C(22)-H(22)	120.4
C(17)-C(22)-H(22)	120.4
C(24)-C(23)-N(1)	108.7(3)
C(24)-C(23)-C(20)	130.3(3)
N(1)-C(23)-C(20)	121.0(3)
C(23)-C(24)-C(25)	107.4(3)
C(23)-C(24)-H(24)	126.3
C(25)-C(24)-H(24)	126.3
C(26)-C(25)-C(30)	118.7(3)
C(26)-C(25)-C(24)	134.2(3)
C(30)-C(25)-C(24)	107.1(3)
C(27)-C(26)-C(25)	119.0(4)
C(27)-C(26)-H(26)	120.5
C(25)-C(26)-H(26)	120.5
C(26)-C(27)-C(28)	121.5(3)
C(26)-C(27)-H(27)	119.3

C(28)-C(27)-H(27)	119.3
C(29)-C(28)-C(27)	121.0(4)
C(29)-C(28)-H(28)	119.5
C(27)-C(28)-H(28)	119.5
C(28)-C(29)-C(30)	117.3(3)
C(28)-C(29)-H(29)	121.4
C(30)-C(29)-H(29)	121.4
N(1)-C(30)-C(29)	130.0(3)
N(1)-C(30)-C(25)	107.5(3)
C(29)-C(30)-C(25)	122.5(3)
C(30)-N(1)-C(23)	109.2(3)
C(30)-N(1)-H(1)	125.4
C(23)-N(1)-H(1)	125.4
C(1)-O(2)-C(3)	107.5(3)
C(6)-O(13)-S(14)	119.21(18)
O(16)-S(14)-O(15)	120.14(13)
O(16)-S(14)-O(13)	103.57(13)
O(15)-S(14)-O(13)	108.11(12)
O(16)-S(14)-C(17)	110.65(14)
O(15)-S(14)-C(17)	110.14(13)
O(13)-S(14)-C(17)	102.52(13)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for **484c**. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	70(3)	28(2)	41(2)	4(1)	1(2)	-2(2)
C(3)	65(2)	37(2)	42(2)	3(1)	-3(2)	3(2)
C(4)	82(3)	28(2)	38(2)	1(1)	0(2)	-1(2)
C(5)	50(2)	25(2)	38(2)	0(1)	-6(2)	-4(1)
C(6)	27(2)	27(1)	40(2)	5(1)	-7(1)	0(1)
C(7)	27(2)	34(2)	44(2)	-4(1)	-2(1)	5(1)
C(8)	46(2)	24(2)	58(2)	1(1)	-7(2)	7(1)
C(9)	63(2)	24(2)	53(2)	8(2)	1(2)	-1(2)
C(10)	96(3)	41(2)	40(2)	11(2)	-27(2)	-11(2)
C(11)	232(7)	80(4)	54(3)	-21(3)	-33(4)	44(5)
C(12)	109(3)	192(8)	131(5)	99(5)	-71(4)	-74(4)
C(17)	27(1)	20(1)	28(1)	0(1)	1(1)	-1(1)
C(18)	26(1)	27(2)	38(2)	2(1)	3(1)	-4(1)
C(19)	24(1)	30(2)	35(2)	3(1)	7(1)	0(1)
C(20)	26(1)	25(1)	27(2)	5(1)	2(1)	4(1)
C(21)	23(1)	26(2)	36(2)	0(1)	1(1)	-3(1)
C(22)	24(1)	25(2)	32(2)	0(1)	2(1)	1(1)
C(23)	28(2)	27(1)	35(2)	3(1)	2(1)	2(1)
C(24)	37(2)	32(2)	35(2)	1(1)	6(1)	2(1)
C(25)	35(2)	32(2)	34(2)	-1(1)	1(1)	9(1)
C(26)	51(2)	50(2)	35(2)	-6(2)	6(2)	6(2)
C(27)	59(2)	48(2)	43(2)	-17(2)	-1(2)	14(2)
C(28)	59(2)	27(2)	51(2)	-8(1)	-12(2)	11(2)
C(29)	48(2)	28(2)	41(2)	2(1)	-7(2)	5(1)
C(30)	37(2)	25(1)	31(2)	1(1)	-3(1)	7(1)
N(1)	41(2)	27(1)	30(1)	-1(1)	6(1)	0(1)
O(2)	119(3)	28(1)	43(1)	6(1)	13(2)	-5(2)
O(13)	28(1)	32(1)	37(1)	5(1)	-5(1)	-6(1)
O(15)	30(1)	30(1)	31(1)	0(1)	2(1)	2(1)
O(16)	48(1)	23(1)	37(1)	1(1)	2(1)	-7(1)
S(14)	30(1)	21(1)	29(1)	0(1)	0(1)	-2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **484c**.

	x	y	z	U(eq)
H(3)	9774	-3918	-1766	57
H(4A)	8337	-4994	-1399	59
H(4B)	9209	-5092	-1207	59
H(7)	8208	-54	-373	42
H(8)	8448	2251	-838	51
H(9)	8805	1589	-1504	56
H(11A)	9071	-6032	-2615	146
H(11B)	9852	-5400	-2356	146
H(12A)	7749	-3923	-1948	216
H(12B)	7790	-5842	-2172	216
H(12C)	7840	-4010	-2429	216
H(18)	7733	-3158	351	36
H(19)	7642	-870	831	35
H(21)	9915	530	607	34
H(22)	10016	-1825	142	32
H(24)	8010	826	1524	42
H(26)	7988	3751	2126	55
H(27)	8443	6673	2238	60
H(28)	9165	8211	1749	55
H(29)	9496	6803	1138	47
H(1)	9369	3488	750	39

Table 6. Torsion angles [°] for **484c**.

C(10)-C(3)-C(4)-C(5)	-132.7(4)
O(2)-C(3)-C(4)-C(5)	-14.9(4)
O(2)-C(1)-C(5)-C(6)	-177.4(3)
C(9)-C(1)-C(5)-C(6)	0.5(6)
O(2)-C(1)-C(5)-C(4)	1.1(5)
C(9)-C(1)-C(5)-C(4)	179.0(4)
C(3)-C(4)-C(5)-C(6)	-172.9(4)
C(3)-C(4)-C(5)-C(1)	9.0(4)
C(1)-C(5)-C(6)-C(7)	-1.3(5)
C(4)-C(5)-C(6)-C(7)	-179.3(4)
C(1)-C(5)-C(6)-O(13)	174.2(3)
C(4)-C(5)-C(6)-O(13)	-3.8(6)
C(5)-C(6)-C(7)-C(8)	0.6(5)
O(13)-C(6)-C(7)-C(8)	-174.8(3)
C(6)-C(7)-C(8)-C(9)	0.9(5)
O(2)-C(1)-C(9)-C(8)	178.5(4)
C(5)-C(1)-C(9)-C(8)	0.9(6)
C(7)-C(8)-C(9)-C(1)	-1.6(6)
O(2)-C(3)-C(10)-C(11)	117.3(5)
C(4)-C(3)-C(10)-C(11)	-126.1(5)
O(2)-C(3)-C(10)-C(12)	-65.9(5)
C(4)-C(3)-C(10)-C(12)	50.8(6)
C(22)-C(17)-C(18)-C(19)	2.2(5)
S(14)-C(17)-C(18)-C(19)	-175.2(2)
C(17)-C(18)-C(19)-C(20)	1.5(5)
C(18)-C(19)-C(20)-C(21)	-3.9(4)
C(18)-C(19)-C(20)-C(23)	177.1(3)
C(19)-C(20)-C(21)-C(22)	2.8(4)
C(23)-C(20)-C(21)-C(22)	-178.2(3)
C(20)-C(21)-C(22)-C(17)	0.8(4)
C(18)-C(17)-C(22)-C(21)	-3.3(5)

S(14)-C(17)-C(22)-C(21)	174.1(2)
C(21)-C(20)-C(23)-C(24)	-140.7(3)
C(19)-C(20)-C(23)-C(24)	38.2(5)
C(21)-C(20)-C(23)-N(1)	36.8(4)
C(19)-C(20)-C(23)-N(1)	-144.3(3)
N(1)-C(23)-C(24)-C(25)	-0.6(4)
C(20)-C(23)-C(24)-C(25)	177.2(3)
C(23)-C(24)-C(25)-C(26)	-176.3(4)
C(23)-C(24)-C(25)-C(30)	1.5(4)
C(30)-C(25)-C(26)-C(27)	1.1(5)
C(24)-C(25)-C(26)-C(27)	178.7(4)
C(25)-C(26)-C(27)-C(28)	1.0(6)
C(26)-C(27)-C(28)-C(29)	-1.5(6)
C(27)-C(28)-C(29)-C(30)	-0.2(5)
C(28)-C(29)-C(30)-N(1)	-176.5(3)
C(28)-C(29)-C(30)-C(25)	2.3(5)
C(26)-C(25)-C(30)-N(1)	176.3(3)
C(24)-C(25)-C(30)-N(1)	-1.9(4)
C(26)-C(25)-C(30)-C(29)	-2.8(5)
C(24)-C(25)-C(30)-C(29)	179.0(3)
C(29)-C(30)-N(1)-C(23)	-179.4(3)
C(25)-C(30)-N(1)-C(23)	1.6(4)
C(24)-C(23)-N(1)-C(30)	-0.7(4)
C(20)-C(23)-N(1)-C(30)	-178.7(3)
C(9)-C(1)-O(2)-C(3)	170.9(4)
C(5)-C(1)-O(2)-C(3)	-11.2(5)
C(10)-C(3)-O(2)-C(1)	139.3(4)
C(4)-C(3)-O(2)-C(1)	16.2(4)
C(5)-C(6)-O(13)-S(14)	97.6(3)
C(7)-C(6)-O(13)-S(14)	-86.9(3)
C(6)-O(13)-S(14)-O(16)	-166.7(2)
C(6)-O(13)-S(14)-O(15)	-38.2(2)
C(6)-O(13)-S(14)-C(17)	78.1(2)
C(18)-C(17)-S(14)-O(16)	-49.0(3)
C(22)-C(17)-S(14)-O(16)	133.5(3)
C(18)-C(17)-S(14)-O(15)	175.8(2)
C(22)-C(17)-S(14)-O(15)	-1.7(3)
C(18)-C(17)-S(14)-O(13)	60.9(3)
C(22)-C(17)-S(14)-O(13)	-116.6(2)

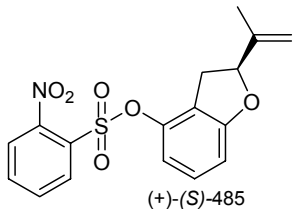
Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for **484c** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1)...O(15)#1	0.88	2.13	2.973(3)	161.1

Symmetry transformations used to generate equivalent atoms:
#1 -x+2,-y,-z

8.1.4 X-Ray crystallographical data for (+)-*(S)*-2-isopropylidene-2,3-dihydrobenzofuran-4-yl-2-nitrobenzenesulfonate - 485



(+)-*(S)*-485

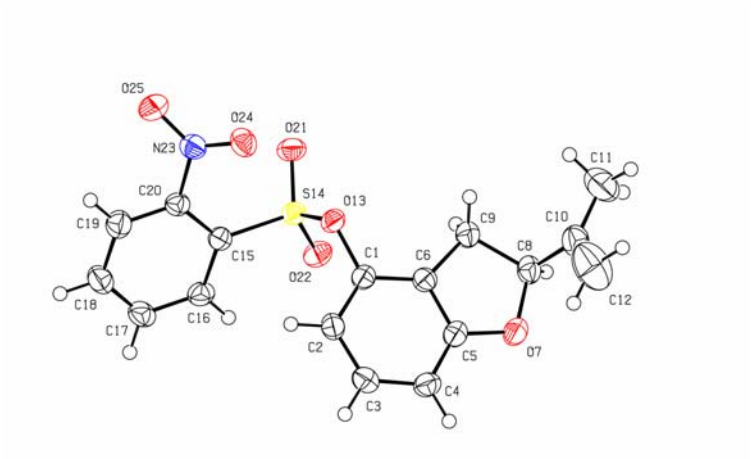


Table 1. Crystal data and structure refinement for **485**.

Identification code	**485**	
Empirical formula	C17 H15 N O6 S	
Formula weight	361.36	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 5.7422(8) Å	α= 90°.
	b = 13.106(2) Å	β= 90°.
	c = 22.274(3) Å	γ= 90°.
Volume	1676.3(4) $Å^3$	
Z	4	
Density (calculated)	1.432 Mg/m^3	
Absorption coefficient	0.227 mm^{-1}	
F(000)	752	
Crystal size	0.48 x 0.12 x 0.12 mm^3	
Theta range for data collection	1.80 to 28.00°.	
Index ranges	-7<=h<=7, -17<=k<=17, -21<=l<=29	
Reflections collected	13907	
Independent reflections	4041 [R(int) = 0.0355]	
Completeness to theta = 28.00°	100.0 %	
Absorption correction	None	
Max. and min. transmission	0.9733 and 0.8988	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4041 / 0 / 227	
Goodness-of-fit on F^2	1.038	
Final R indices [I>2sigma(I)]	R1 = 0.0382, wR2 = 0.0916	

R indices (all data)	R1 = 0.0502, wR2 = 0.0974
Absolute structure parameter	0.00(7)
Largest diff. peak and hole	0.358 and -0.338 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **485**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	4330(4)	9448(2)	5428(1)	29(1)
C(2)	6046(4)	8729(2)	5310(1)	33(1)
C(3)	6096(4)	8282(2)	4740(1)	35(1)
C(4)	4500(4)	8541(2)	4294(1)	35(1)
C(5)	2832(4)	9263(2)	4439(1)	33(1)
C(6)	2701(4)	9726(1)	5002(1)	30(1)
C(8)	-237(4)	10386(2)	4358(1)	35(1)
C(9)	686(4)	10452(2)	5017(1)	36(1)
C(10)	-8(5)	11378(2)	4022(1)	48(1)
C(11)	-1595(9)	12178(2)	4201(2)	84(1)
C(12)	1514(7)	11493(3)	3580(2)	85(1)
C(15)	5253(4)	8672(2)	6892(1)	27(1)
C(16)	5171(4)	7610(2)	6827(1)	34(1)
C(17)	6765(5)	7000(2)	7131(1)	37(1)
C(18)	8380(5)	7417(2)	7516(1)	40(1)
C(19)	8462(4)	8470(2)	7591(1)	38(1)
C(20)	6941(4)	9089(2)	7282(1)	29(1)
O(7)	1104(3)	9584(1)	4057(1)	43(1)
O(13)	4249(3)	9954(1)	5995(1)	31(1)
O(21)	2248(3)	10161(1)	6942(1)	37(1)
O(22)	1360(3)	8674(1)	6297(1)	36(1)
O(24)	6994(3)	10754(1)	6929(1)	39(1)
O(25)	7824(3)	10487(1)	7871(1)	45(1)
S(14)	3006(1)	9380(1)	6541(1)	28(1)
N(23)	7244(3)	10196(1)	7367(1)	33(1)

Table 3. Bond lengths [Å] and angles [°] for **485**.

C(1)-C(6)	1.382(3)
C(1)-C(2)	1.388(3)
C(1)-O(13)	1.427(2)
C(2)-C(3)	1.398(3)
C(2)-H(2)	0.9500
C(3)-C(4)	1.393(3)
C(3)-H(3)	0.9500
C(4)-C(5)	1.385(3)
C(4)-H(4)	0.9500
C(5)-O(7)	1.374(3)
C(5)-C(6)	1.394(3)
C(6)-C(9)	1.498(3)
C(8)-O(7)	1.467(3)
C(8)-C(10)	1.506(3)
C(8)-C(9)	1.562(3)
C(8)-H(8)	1.0000
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(12)	1.325(4)
C(10)-C(11)	1.445(4)
C(11)-H(11A)	0.9800

C(11)-H(11B)	0.9800
C(11)-H(11C)	0.9800
C(12)-H(12A)	0.9500
C(12)-H(12B)	0.9500
C(15)-C(16)	1.400(3)
C(15)-C(20)	1.411(3)
C(15)-S(14)	1.772(2)
C(16)-C(17)	1.393(3)
C(16)-H(16)	0.9500
C(17)-C(18)	1.377(4)
C(17)-H(17)	0.9500
C(18)-C(19)	1.392(3)
C(18)-H(18)	0.9500
C(19)-C(20)	1.376(3)
C(19)-H(19)	0.9500
C(20)-N(23)	1.474(3)
O(13)-S(14)	1.5970(15)
O(21)-S(14)	1.4266(15)
O(22)-S(14)	1.4304(15)
O(24)-N(23)	1.227(2)
O(25)-N(23)	1.230(2)
C(6)-C(1)-C(2)	121.91(18)
C(6)-C(1)-O(13)	117.59(18)
C(2)-C(1)-O(13)	120.46(17)
C(1)-C(2)-C(3)	118.14(19)
C(1)-C(2)-H(2)	120.9
C(3)-C(2)-H(2)	120.9
C(4)-C(3)-C(2)	122.1(2)
C(4)-C(3)-H(3)	119.0
C(2)-C(3)-H(3)	119.0
C(5)-C(4)-C(3)	117.09(19)
C(5)-C(4)-H(4)	121.5
C(3)-C(4)-H(4)	121.5
O(7)-C(5)-C(4)	124.34(18)
O(7)-C(5)-C(6)	112.66(18)
C(4)-C(5)-C(6)	122.99(19)
C(1)-C(6)-C(5)	117.77(19)
C(1)-C(6)-C(9)	132.47(19)
C(5)-C(6)-C(9)	109.76(18)
O(7)-C(8)-C(10)	110.27(19)
O(7)-C(8)-C(9)	106.92(17)
C(10)-C(8)-C(9)	112.93(19)
O(7)-C(8)-H(8)	108.9
C(10)-C(8)-H(8)	108.9
C(9)-C(8)-H(8)	108.9
C(6)-C(9)-C(8)	101.92(17)
C(6)-C(9)-H(9A)	111.4
C(8)-C(9)-H(9A)	111.4
C(6)-C(9)-H(9B)	111.4
C(8)-C(9)-H(9B)	111.4
H(9A)-C(9)-H(9B)	109.2
C(12)-C(10)-C(11)	122.6(3)
C(12)-C(10)-C(8)	121.6(3)
C(11)-C(10)-C(8)	115.7(3)
C(10)-C(11)-H(11A)	109.5
C(10)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	109.5
C(10)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11C)	109.5

H(11B)-C(11)-H(11C)	109.5
C(10)-C(12)-H(12A)	120.0
C(10)-C(12)-H(12B)	120.0
H(12A)-C(12)-H(12B)	120.0
C(16)-C(15)-C(20)	118.18(19)
C(16)-C(15)-S(14)	116.72(17)
C(20)-C(15)-S(14)	124.72(15)
C(17)-C(16)-C(15)	119.9(2)
C(17)-C(16)-H(16)	120.1
C(15)-C(16)-H(16)	120.1
C(18)-C(17)-C(16)	121.2(2)
C(18)-C(17)-H(17)	119.4
C(16)-C(17)-H(17)	119.4
C(17)-C(18)-C(19)	119.5(2)
C(17)-C(18)-H(18)	120.3
C(19)-C(18)-H(18)	120.3
C(20)-C(19)-C(18)	120.2(2)
C(20)-C(19)-H(19)	119.9
C(18)-C(19)-H(19)	119.9
C(19)-C(20)-C(15)	121.07(19)
C(19)-C(20)-N(23)	116.13(19)
C(15)-C(20)-N(23)	122.76(18)
C(5)-O(7)-C(8)	108.34(15)
C(1)-O(13)-S(14)	117.98(12)
O(21)-S(14)-O(22)	120.05(10)
O(21)-S(14)-O(13)	106.02(9)
O(22)-S(14)-O(13)	108.14(9)
O(21)-S(14)-C(15)	108.69(10)
O(22)-S(14)-C(15)	108.03(9)
O(13)-S(14)-C(15)	104.91(9)
O(24)-N(23)-O(25)	124.84(17)
O(24)-N(23)-C(20)	118.08(16)
O(25)-N(23)-C(20)	117.02(17)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for **485**. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	33(1)	26(1)	27(1)	1(1)	-2(1)	-5(1)
C(2)	33(1)	31(1)	34(1)	3(1)	-5(1)	2(1)
C(3)	36(1)	32(1)	39(1)	1(1)	3(1)	4(1)
C(4)	40(1)	35(1)	31(1)	-5(1)	2(1)	1(1)
C(5)	35(1)	35(1)	29(1)	0(1)	-3(1)	-2(1)
C(6)	32(1)	27(1)	30(1)	1(1)	0(1)	-1(1)
C(8)	30(1)	39(1)	37(1)	2(1)	-7(1)	2(1)
C(9)	35(1)	39(1)	33(1)	-2(1)	-4(1)	7(1)
C(10)	60(2)	40(1)	44(1)	7(1)	-9(1)	-1(1)
C(11)	128(3)	60(2)	63(2)	8(2)	6(2)	42(2)
C(12)	77(2)	77(2)	101(3)	40(2)	21(2)	2(2)
C(15)	30(1)	27(1)	25(1)	2(1)	4(1)	1(1)
C(16)	44(1)	28(1)	29(1)	-1(1)	2(1)	-4(1)
C(17)	49(1)	27(1)	36(1)	5(1)	7(1)	3(1)
C(18)	45(1)	36(1)	39(1)	7(1)	3(1)	9(1)
C(19)	38(1)	39(1)	37(1)	1(1)	-5(1)	0(1)
C(20)	31(1)	28(1)	28(1)	-1(1)	4(1)	0(1)
O(7)	45(1)	54(1)	31(1)	-7(1)	-9(1)	13(1)

O(13)	41(1)	27(1)	26(1)	-1(1)	-4(1)	-3(1)
O(21)	34(1)	39(1)	39(1)	-13(1)	-1(1)	5(1)
O(22)	34(1)	37(1)	37(1)	-7(1)	-3(1)	-7(1)
O(24)	40(1)	30(1)	47(1)	5(1)	-8(1)	-2(1)
O(25)	50(1)	43(1)	42(1)	-12(1)	-9(1)	-1(1)
S(14)	27(1)	29(1)	29(1)	-4(1)	-1(1)	-1(1)
N(23)	29(1)	30(1)	40(1)	-4(1)	-2(1)	0(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **485**.

	x	y	z	U(eq)
H(2)	7155	8546	5607	40
H(3)	7255	7786	4654	43
H(4)	4553	8235	3908	42
H(8)	-1915	10183	4366	42
H(9A)	1198	11152	5118	43
H(9B)	-512	10229	5308	43
H(11A)	-1294	12791	3962	126
H(11B)	-1366	12333	4628	126
H(11C)	-3202	11951	4136	126
H(12A)	1591	12120	3367	102
H(12B)	2528	10948	3476	102
H(16)	4030	7307	6574	40
H(17)	6736	6282	7073	45
H(18)	9431	6989	7729	48
H(19)	9571	8764	7857	45

Table 6. Torsion angles [°] for **485**.

C(6)-C(1)-C(2)-C(3)	-0.1(3)
O(13)-C(1)-C(2)-C(3)	-177.81(19)
C(1)-C(2)-C(3)-C(4)	0.4(3)
C(2)-C(3)-C(4)-C(5)	-0.3(3)
C(3)-C(4)-C(5)-O(7)	-178.4(2)
C(3)-C(4)-C(5)-C(6)	0.0(3)
C(2)-C(1)-C(6)-C(5)	-0.2(3)
O(13)-C(1)-C(6)-C(5)	177.52(18)
C(2)-C(1)-C(6)-C(9)	178.7(2)
O(13)-C(1)-C(6)-C(9)	-3.5(3)
O(7)-C(5)-C(6)-C(1)	178.86(18)
C(4)-C(5)-C(6)-C(1)	0.3(3)
O(7)-C(5)-C(6)-C(9)	-0.3(3)
C(4)-C(5)-C(6)-C(9)	-178.9(2)
C(1)-C(6)-C(9)-C(8)	177.5(2)
C(5)-C(6)-C(9)-C(8)	-3.5(2)
O(7)-C(8)-C(9)-C(6)	5.9(2)
C(10)-C(8)-C(9)-C(6)	-115.6(2)
O(7)-C(8)-C(10)-C(12)	-9.9(4)
C(9)-C(8)-C(10)-C(12)	109.6(3)
O(7)-C(8)-C(10)-C(11)	168.3(3)
C(9)-C(8)-C(10)-C(11)	-72.2(3)
C(20)-C(15)-C(16)-C(17)	-1.4(3)
S(14)-C(15)-C(16)-C(17)	-174.66(16)
C(15)-C(16)-C(17)-C(18)	2.4(3)
C(16)-C(17)-C(18)-C(19)	-1.6(4)
C(17)-C(18)-C(19)-C(20)	-0.1(3)

C(18)-C(19)-C(20)-C(15)	1.0(3)
C(18)-C(19)-C(20)-N(23)	-176.9(2)
C(16)-C(15)-C(20)-C(19)	-0.2(3)
S(14)-C(15)-C(20)-C(19)	172.41(16)
C(16)-C(15)-C(20)-N(23)	177.53(19)
S(14)-C(15)-C(20)-N(23)	-9.8(3)
C(4)-C(5)-O(7)-C(8)	-177.1(2)
C(6)-C(5)-O(7)-C(8)	4.4(2)
C(10)-C(8)-O(7)-C(5)	116.7(2)
C(9)-C(8)-O(7)-C(5)	-6.4(2)
C(6)-C(1)-O(13)-S(14)	99.38(19)
C(2)-C(1)-O(13)-S(14)	-82.8(2)
C(1)-O(13)-S(14)-O(21)	-154.86(15)
C(1)-O(13)-S(14)-O(22)	-24.89(17)
C(1)-O(13)-S(14)-C(15)	90.22(16)
C(16)-C(15)-S(14)-O(21)	137.51(17)
C(20)-C(15)-S(14)-O(21)	-35.2(2)
C(16)-C(15)-S(14)-O(22)	5.75(19)
C(20)-C(15)-S(14)-O(22)	-166.98(17)
C(16)-C(15)-S(14)-O(13)	-109.44(16)
C(20)-C(15)-S(14)-O(13)	77.84(18)
C(19)-C(20)-N(23)-O(24)	141.0(2)
C(15)-C(20)-N(23)-O(24)	-36.9(3)
C(19)-C(20)-N(23)-O(25)	-36.2(3)
C(15)-C(20)-N(23)-O(25)	146.0(2)

Symmetry transformations used to generate equivalent atoms:

8.2 APPENDIX II – PAPERS PUBLISHED

The two papers which follow cover almost all the work already discussed in this thesis. The first paper covers the topic relating to the carbazole alkaloids and the second paper covers the topic relating to the benzofuran compounds.

8.2.1 Paper 1 - Metathesis reactions for the synthesis of ring-fused carbazoles

S. C. Pelly, C. J. Parkinson, W. A. L. van Otterlo, and C. B. de Koning*, *J. Org. Chem.*, 2005, **70**, 10474.

Abstract

The metathesis reaction is used as a key step for the synthesis of the indolo[2,3-*a*]carbazole core of rebeccamycin and the sulfur analog of furostifoline. Using the same methodology for the attempted synthesis of furostifoline, we unexpectedly formed *tert*-butyl-2a-methyl-1,2,2a,10ctetrahydro-6*H*-cyclobuta[*c*]furo[3,2-*a*]carbazole-6-carboxylate from the unstable diene, *tert*-butyl-2-(2-isopropenyl-3-furyl)-3-vinyl-1*H*-indole-1-carboxylate, presumably via a spontaneous π_8 electrocyclization reaction.

8.2.2 Paper 2 - Stereoselective syntheses of the 2-isopropenyl-2,3-dihydrobenzofuran nucleus. Potential chiral building blocks for the syntheses of tremetone, 4-hydroxytremetone and rotenone

S. C. Pelly, S. Govender, M. A. Fernandes, H.-G. Schmalz, and C. B. de Koning*, *J. Org. Chem.*, 2007, **72**, 2857.

Abstract

The first enantioselective synthesis of the 2-isopropenyl-2,3-dihydrobenzofuran skeleton of tremetone and hydroxytremetone from (*E*)-4-(2-hydroxyphenyl)-2-methyl-2-butenyl methyl carbonate and (*E*)-4-(2,6-dihydroxyphenyl)-2-methyl-2-butenyl methyl carbonate, respectively, is described. The key step is a catalytic palladium-mediated reaction in the presence of the chiral Trost ligand.

CHAPTER 9 –REFERENCES

1 G. P. Moss, P. A. S. Smith, and D. Tavernier, *Pure Appl. Chem.*, 1995, **67**, 1309.

2 C. Graebe and C. Glazer, *Ber. Dtsch. Chem. Ges.*, 1872, **5**, 12.

3 D. P. Chakraborty, B. K. Barman, and P. K. Bose, *Tetrahedron*, 1965, **21**, 681.

4 H.-J. Knölker, *Curr. Org. Synth.*, 2004, **1**, 309.

5 H.-J. Knölker and K. R. Reddy, *Chem. Rev.*, 2002, **102**, 4303.

6 M. Fiebig, J. M. Pezzuto, D. D. Soejarto, and A. D. Kinghorn, *Phytochemistry*, 1985, **24**, 3041.

7 B. K. Chowdhury and C. Saha, *Phytochemistry*, 1998, **48**, 363.

8 H. Furukawa, C. Ito, Y. Thoyama, M. Omura, and I. Kajiura, *Chem. Pharm. Bull.*, 1993, **41**, 2096.

9 D. P. Chakraborty, K. C. Das, and B. K. Chowdhury, *J. Org. Chem.*, 1971, **36**, 725.

10 B. S. Joshi, V. N. Kamat, D. H. Gawad, and T. R. Govindachari, *Phytochemistry*, 1972, **11**, 2065.

11 H.-J. Knölker, M. Bauermeister, P. Jorn-Bernd, D. Blaser, and R. Boese, *Tetrahedron*, 1993, **49**, 841.

12 H. Furukawa and C. Ito, *Chem. Pharm. Bull.*, 1990, **38**, 1548.

13 G. Timári, T. Soos, G. Hajos, A. Messmer, J. Nacsa, and J. Molnar, *J. Bioorg. Med. Chem. Lett.*, 1996, **6**, 2831.

14 G. Timári, T. Soos, and G. Hajos, *Synth. Commun.*, 1997, **29**, 3959.

15 H.-J. Knölker, M. P. Krahl, and K. R. Reddy, *Heterocycles*, 2004, **63**, 2393.

16 S. Goodwin, A. F. Smith, and E. C. Horning, *J. Am. Chem. Soc.*, 1959, **81**, 1903.

17 L. K. Dalton, S. Demerac, B. C. Elmes, J. W. Loder, J. M. Swan, and T. Teitei, *Aust. J. Chem.*, 1967, **20**, 2715.

18 V. K. Kansal, R. Sundaramoorthi, Das, B. C., and Potier, P., *Tetrahedron Letters*, 1985, **26**, 4933.

19 S. Omura, Y. Iwai, A. Hirano, A. Nakagawa, J. Awaya, H. Tsuchiya, Y. Takahashi, and R. Matsuma, *J. Antibiot.*, 1977, **30**, 275.

20 N. Funato, H. Takayanagi, Y. Konda, Y. Toda, and Y. Harigaya, *Tetrahedron Lett.*, 1994, **35**, 1251.

21 M. Trudell, S. Lifer, Y. Tan, M. Martin, L. Deng, P. Skolnick, and J. Cook, *J. Med. Chem.*, 1990, **33**, 2412.

22 M. Trudell, A. Basile, H. Shannon, P. Skolnick, and J. Cook, *J. Med. Chem.*, 1987, **30**, 456.

23 T. Yasuzawa, T. Lida, M. Yoshida, N. Hirayama, M. Takahashi, K. Shirahata, and H. Sano, *J Antibiot (Tokyo)*, 1986, **39**, 1072.

24 Y. Matsuda, S. Nakanishi, K. Nagasawa, K. Iwahasho, and H. Kase, *Biochem. J.*, 1988, **256**, 75.

25 P. Hoehn-Thierry, O. Ghisalba, T. Moerker, and H. Peter, *J. Antibiot.*, 1995, **48**, 300.

26 P. J. Scheuer and R. B. Kinnel, *J. Org. Chem.*, 1992, **57**, 6327.

27 D. E. Nettleton, T. W. Doyle, B. Kirshnan, G. K. Matsumoto, and J. Clardy, *Tetrahedron Lett.*, 1985, **26**, 4011.

28 Y. Yamashita, N. Fujii, C. Murkata, T. Ashizawa, M. Okabe, and H. Nakano, *Biochemistry*, 1992, **31**, 12069.

29 K. S. Lam, D. R. Schroeder, J. A. Veitch, J. A. Matson, and S. Forenza, *J. Antibiot.*, 1991, **44**, 934.

30 S. Tanaka, M. Ohkubo, K. Kojiri, and H. Suda, *J. Antibiot.*, 1992, **45**, 1797.

31 H. Arakawa, T. Iguchi, T. Yoshinari, K. Kojiri, H. Suda, and A. Okura, *Jpn. J. Cancer Res.*, 1993, **84**, 574.

32 A. Giannis, A. Huwe, and R. Mazitschek, *Angew. Chem. Int. Ed.*, 2003, **42**, 2122.

33 J. A. Endicott, M. E. M. Noble, L. N. Johnson, A. Lawrie, P. Tunnah, and N. R. Brown, *Nat. Struct. Biol.*, 1997, **4**, 796.

34 E. Meggers, H. Bregman, and D. Williams, *Synthesis*, 2005, 1521.

35 E. Meggers, H. Bregman, D. Williams, G. Atilla, and P. Carrol, *J. Am. Chem. Soc.*, 2004, **126**, 13594.

36 E. Meggers, L. Zhang, and P. Carrol, *Org. Lett.*, 2004, **6**, 521.

37 E. Meggers, H. Bregman, and P. J. Carroll, *J. Am. Chem. Soc.*, 2006, **128**, 877.

38 E. Wong and C. M. Giandomenico, *Chem. Rev.*, 1999, **99**, 2451.

39 H.-J. Knölker and W. Fröhner, *Tetrahedron Lett.*, 1996, **37**, 9183.

40 H.-J. Knölker and W. Fröhner, *Synthesis*, 2000, 2131.

41 E. Beccalli, F. Clerici, and A. Marchesini, *Tetrahedron*, 1998, **54**, 11675.

42 S. Hibino, H. Hagiwara, T. Choshi, H. Fujimoto, and E. Sugino, *Chem. Pharm. Bull.*, 1998, **46**, 1948.

43 S. Hibino, H. Hagiwara, T. Choshi, J. Nobuhiro, and H. Fujimoto, *Chem. Pharm. Bull.*, 2001, **49**, 881.

44 G. Timári, T. Soós, and G. Hajós, *Tetrahedron Lett.*, 1999, **40**, 8607.

45 T. Sakamoto, Y. Kondo, S. Iwashita, T. Nagano, and H. Yamanaka, *Chem. Pharm. Bull.*, 1988, **36**, 1305.

46 A. Yasuhara, N. Suzuki, and T. Sakamoto, *Chem. Pharm. Bull.*, 2002, **50**, 143.

47 M. L. Tomlinson, R. J. Brunton, F. K. Drayson, and S. G. P. Plant, *J. Am. Chem. Soc.*, 1956, 4783.

48 R. J. Sundberg, 'Indoles', Academic Press Limited, London, 1996.

49 E. M. Beccalli, A. Marchesini, and T. Pilati, *Tetrahedron*, 1993, **49**, 4741.

50 C. A. Merlic and D. M. McInnes, *Tetrahedron Lett.*, 1997, **38**, 7661.

51 J. Bergman and L. Venemalm, *J. Org. Chem.*, 1992, **57**, 2495.

52 C. H. Hill, W. Harris, E. Keech, and P. Malsher, *Tetrahedron Lett.*, 1993, **34**, 8361.

53 S. J. Danishefsky, J. T. Link, and S. Raghavan, *J. Am. Chem. Soc.*, 1995, **117**, 552.

54 R. J. Anderson, R. G. Berlinck, R. Britton, E. Piers, L. Lim, M. Roberge, and R. Moreira da Roche, *J. Org. Chem.*, 1998, **63**, 9850.

55 M. M. Faul, L. L. Winneroski, and C. A. Krumrich, *J. Org. Chem.*, 1998, **63**, 6053.

56 M. M. Faul, L. L. Winneroski, and C. A. Krumrich, *Tetrahedron Lett.*, 1999, **40**, 1109.

57 D. E. Ray, 'Pesticides derived from plants and other organisms.' ed. W. J. Hayes and E. R. Laws, Academic Press, New York, 1991.

58 F. B. LaForge, *J. Am. Chem. Soc.*, 1932, **54**, 3377.

59 G. Büchi, L. Crombie, P. J. Godin, J. S. Kaltenbronn, and K. S. Siddalingaiah, *J. Chem. Soc.*, 1961, 2843.

60 S. Lai, J. Orchison, and D. Whiting, *Tetrahedron*, 1989, **45**, 5895.

61 F. B. LaForge, H. L. Haller, and L. E. Smith, *Chem. Rev.*, 1933, **12**, 181.

62 D. M. Wood, H. Alsahaf, P. Streete, P. I. Dargan, and A. L. Jones, *Critical Care*, 2005, **9**, R280.

63 A. R. De Wilde, A. Heyndrickx, and D. Carton, *J. Forensic Sci.*, 1986, **31**, 1492.

64 E. A. Holland, *Trans. R. Soc. Trop. Med. Hyg.*, 1938, **32**, 293.

65 J. T. Greenamyre, R. Betarbet, T. B. Sherer, G. MacKenzie, M. Garcia-Osuna, and A. V. Panov, *Nature Neuroscience*, 2000, **3**, 1301.

66 D. Sames and S. Pastine, *Org. Lett.*, 2003, **5**, 4053.

67 P. Anzeveno, *J. Org. Chem.*, 1979, **44**, 2578.

68 M. Hirotani, J. O'Reilly, and D. Donnelly, *Tetrahedron Lett.*, 1977, **7**, 651.

69 F. Bohlmann, J. Jakupovic, A. Schuster, R. M. King, and H. Robinson, *Phytochemistry*, 1982, **21**, 161.

70 S. Yamaguchi, S. Muro, M. Kobayashi, M. Miyazawa, and Y. Hirai, *J. Org. Chem.*, 2003, **68**, 6274.

71 Y. Kawase, S. Yamaguchi, O. Inoue, M. Sannomiya, and K. Kawabe, *Chem. Lett.*, 1980, **12**, 1581.

72 J. I. DeGraw, D. M. Bowen, and W. A. Bonner, *Tetrahedron*, 1963, **19**, 19.

73 R. Shriner and J. Anderson, *J. Am. Chem. Soc.*, 1939, **61**, 2705.

74 R. Stoermer, C. Chydenius, and E. Schinn, *Ber. Dtsch. Chem. Ges.*, 1924, **57**, 72.

75 D. M. Bowen, J. I. DeGraw, V. R. Shah, and W. A. Bonner, *J. Med. Chem.*, 1963, **6**, 315.

76 J. Nickl, *Chem. Ber.*, 1958, **91**, 553.

77 Y. Kawase, S. Yamaguchi, Y. Kondo, and K. Shimokawa, *Chem. Lett.*, 1978, 253.

78 Y. Kawase, S. Yamaguchi, Y. Kondo, K. Shimokawa, O. Inoue, and M. Sannomiya, *Bull. Chem. Soc. Jpn.*, 1982, **55**, 2500.

79 T. Hosokawa, K. Maeda, K. Koga, and I. Moritani, *Tetrahedron Lett.*, 1973, 739.

80 T. Hosokawa, S. Yamashita, S.-I. Murahashi, and A. Sonoda, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 3662.

81 T. Hosokawa, T. Uno, S. Inui, and S.-I. Murahashi, *J. Am. Chem. Soc.*, 1981, **103**, 2318.

82 T. Hosokawa, C. Okuda, and S.-I. Murahashi, *J. Org. Chem.*, 1985, **50**, 1282.

83 Y. Uozumi, K. Kato, and T. Hayashi, *J. Am. Chem. Soc.*, 1997, **119**, 5063.

84 G. Consiglio and R. Waymouth, *Chem. Rev.*, 1989, **89**, 257.

85 K. B. Sharpless and H. Becker, *Angew. Chem. Intl. Ed.*, 1996, **35**, 448.

86 J. Tsuji, 'Palladium reagents and catalysts', John Wiley & Sons, New York, 1995.

87 B. Söderberg, *Coordination Chemistry Reviews*, 2003, **241**, 147.

88 B. Trost and M. Crawley, *Chem. Rev.*, 2003, **103**.

89 B. Trost and D. Toste, *J. Am. Chem. Soc.*, 1998, **120**, 9074.

90 K. Achiwa and E. Mizuguchi, *Chem. Pharm. Bull.*, 1997, **45**, 1209.

91 D. Sinou, J.-R. Labrosse, C. Poncet, and P. Lhoste, *Tetrahedron: Asymmetry*, 1999, **10**, 1069.

92 B. M. Trost, H. C. Shen, L. Dong, J.-P. Surivet, and C. Sylvain, *J. Am. Chem. Soc.*, 2004, **126**, 11966.

93 W. J. Faller, M. E. Thomsen, and M. J. Mattina, *J. Am. Chem. Soc.*, 1971, **93**, 2642.

94 C. B. de Koning, J. Michael, and A. Rousseau, *J. Chem. Soc., Perkin Trans. 1*, 2000, 787.

95 V. Sniekus, M. P. Sibi, and J. W. Dankwardt, *J. Org. Chem.*, 1986, **51**, 271.

96 C. de Koning, J. Michael, and A. Rousseau, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1705.

97 A. Tanaka, J. Koyanagi, K. Yamamoto, and K. Nakayama, *J. Heterocyclic Chem.*, 1995, **32**, 1289.

98 M. Somei, S. Sayama, K. Naka, and F. Yamada, *Heterocycles*, 1988, **27**, 1585.

99 M. Smith, 'Organic Synthesis', ed. J. Speer and J. Morriss, McGraw-Hill Inc., Singapore, 1994.

100 W. C. Still and C. Gennart, *Tetrahedron Lett.*, 1983, **24**, 4405.

101 E. Negishi, S. Liou, C. Xu, and S. Huo, *Org. Lett.*, 2002, **4**, 261.

102 J. Clayden, N. Greeves, S. Warren, and P. Wothers, 'Organic chemistry', Oxford university press, Oxford, 2001.

103 A. Fürstner, *Angew. Chem. Intl. Ed.*, 2000, **39**, 3012.

104 A. Fürstner, O. R. Thiel, H.-J. Schanz, and S. P. Nolan, *J. Org. Chem.*, 2000, **65**, 2204.

105 R. H. Grubbs, A. K. Chatterjee, J. P. Morgan, and M. Scholl, *J. Am. Chem. Soc.*, 2000, **122**, 3783.

106 E. Vazquez, I. W. Davies, and J. F. Payack, *J. Org. Chem.*, 2002, **67**, 7551.

107 S. Blechert, S. Randl, and S. J. Connon, *Chem. Commun.*, 2001, 1796–1797.

108 A. H. Hoveyda, J. S. Kingsbury, J. P. A. Harrity, and P. J. Bonitatebus, *J. Am. Chem. Soc.*, 1999, **121**, 791.

109 W. Madelung, *Ber.*, 1912, **45**, 1128.

110 W. Madelung, *Ann. Chem.*, 1914, **405**, 58.

111 J. Bergman, E. Koch, and B. Pelcman, *Tetrahedron*, 1995, **51**, 5631.

112 J. M. Concellón, H. Rodríguez-Solla, E. Bardales, and M. Huerta, *Eur. J. Org. Chem.*, 2003, 1775.

113 P. L. Coe and C. E. Scriven, *J. Chem. Soc., Perkin Trans. 1*, 1986, 475.

114 A. Lanver, 'Studien zur übergangsmetallvermittelten Synthese von bioaktiven carbocyclischen Nucleosiden und von Rotenoiden', Ph.D., der Universität zu Köln, Köln, 2005.

115 A. Katritzky, O. Meth-Cohn, and C. Rees, 'Comprehensive organic functional group transformations', ed. S. Roberts, Cambridge University Press, Cambridge, 1995.

116 B. Trost and I. Flemming, 'Comprehensive organic synthesis', Pergamon Press, Oxford, 1993.

117 C. A. Townsend, S. G. Davis, S. B. Christensen, J. C. Link, and C. P. Lewis, *J. Am. Chem. Soc.*, 1981, **103**, 6885.

118 C. A. Townsend, T. L. Graybill, E. G. Casillas, and K. Pal, *J. Am. Chem. Soc.*, 1999, **121**, 7729.

119 B. M. Trost and G. M. Schroeder, *J. Org. Chem.*, 2000, **65**, 1569.

120 B. M. Trost, H. C. Shen, L. Dong, and J.-P. Surivet, *J. Am. Chem. Soc.*, 2003, **125**, 9276.

121 G.-Q. Lin, Y.-M. Li, and A. S. C. Chan, 'Principles and applications of asymmetric synthesis', John Wiley & Sons, New York, 2001.

122 K. K. Park, S.-H. Kim, and J. W. Park, *J. Photochem. Photobiol., A: Chem.*, 2004, **163**, 241.

123 K. K. Park, H. J. Lee, E. H. Kim, and S. K. Kang, *J. Photochem. Photobiol., A: Chem.*, 2003, **159**, 17.

124 P. Magnus and C. Lescop, *Tetrahedron Lett.*, 2001, **42**, 7193.

125 V. Ramamurthy, K. Pitchumani, M. Warrier, C. Cui, and R. G. Weiss, *Tetrahedron Lett.*, 1996, **37**, 6251.

126 V. T. Ramakrishnan and K. Sriraghavan, *Tetrahedron*, 2003, **59**, 1791.