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The synthesis of aryl-substituted naphthalenes and aromatic phosphorus-containing compounds

Moleele, Simon Sana

2008-03-19T07:55:36Z
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Abstract

This thesis is divided into two parts. Part one presents a novel method for the synthesis of naphthalenes bearing aryl substituents. The novel route starts from three simple and readily available tetralones, α-tetralone, 6-methoxy-α-tetralone and 6,7-dimethoxy-α-tetralone. By means of standard Suzuki coupling methodology and aromatization methods, twelve aryl-substituted naphthalenes were synthesized from the tetralones over five steps in good yields. Some of the aryl-substituted naphthalenes synthesized have shown positive results when tested against malignant cancer cells. Part one also explains how unexpected cyclopropa[*a*]naphthalenes were obtained from 1-aryl-3,4-dihydro-2-naphthaldehydes by treatment with lithium aluminium hydride.

The methodology developed in part one is further explored in part two of the thesis, which describes the synthesis of analogues of [1,1']binaphthalenyl-2,2'-diol. A small library of twelve different biaryl diols was prepared from simple bromo(methoxy)naphthaldehydes that were synthesized in part one. The resultant biaryl diols were used in the design of twenty-two novel phosphite, phosphate, phosphoramidite and phosphoramidate ligands in which the phosphorus atoms are contained in either a nine-or an eight-membered heteroatom ring. However, these ligands are still to be tested in metal-catalyzed hydrogenation reactions.

Acknowledgements

The following people are been acknowledged for their contribution, in one way or another, to the success of this research project.

- My main supervisor, Professor C.B. de Koning: First for offering me an opportunity to work with him and secondly and far more important for being a pillar of strength throughout the project, especially during the write-up stage. Thank you very much Charlie and please keep up the good work.
- My co-supervisor Professor J.P. Michael for his input during the running and the writing-up of the project. Your assistance is highly appreciated Jo.
- Dr W.A.L van Otterlo for showing so much interest in the work that I was doing in the lab and for taking some of our compounds for testing against cancer cells.
- To my dear friend in the School of Chemistry, (Dr) Richard Mampa. First and most importantly for all the nmr analyses done and secondly for all the eye-opening discussions that we had, about both chemistry itself and the other things that matter in life. Richie, you truly are a good listener. Also a big thank you to Dr Manuel Fernandes for the X-ray crystallographic data, Mr Tommie van der Merwe for all the mass spectrometry analyses and Hajierah Davids from the School of Pharmacy for testing our naphthalenes against cancer cells.
- To my entire family members: My father Mr Michael Moleele, my dear mother Mrs Rosinah Senzeni Moleele, my brothers, Masters and Bongani as well as my sisters Christinah, Molebogeng and Stephinah. I have no doubt in my mind that at some point you were wondering what exactly was I doing at varsity for such a long time but still gave me all your unwavering support. I hope and earnestly wish that this thesis answers all your questions. To my beloved fiancée, Mmapule Mashilwane: I know I was never there for you and our son Joti but I am praying that you allow me to present this thesis to you and say "I am sorry, this was the reason". Lastly to my respectable cousin who was forever there for me during my studies, Sello Msiza. *Phathla mbina-komo e thlabane magobejane a ko-Jantjie malela a nga ka bethwa.*

- To the organic chemistry research group, past and present. Thank you very much guys since I have no doubt that at one point or another you played some role, significant or otherwise, in the production of this thesis. Special thanks must go to (Dr) Garreth Morgans for all the friendly chats that we had now and again. I also would like to pass my sincere gratitude to Dr Edwin Mmutlane for all the help he provided me with, especially at the beginning of the research project. How can I forget Dr Sunnyboy Manzini for all the support and encouragement he gave me throughout this research project.
- A big thank you to the reliable store-men of the School of Chemistry: Mr Elias Valoyi and Mr David Moloto.
- The Department of Labour (DoL) for the financial assistance towards this research. Opinions expressed and conclusions arrived at, are those of the author and are not necessarily to be attributed to DoL.
- The Mellon Bursary Scheme and the University of Witwatersrand for financial assistance and the apparatus used in this research project.

Heredity is one thing, but environment
is everything to a human being
Maru: Bessie Head 1997

List of Abbreviations

Ac	acetyl
acac	acetylacetonato
Ar	aryl
AZT	azido-thymidine
BICHEP	2,2'-(dicyclohexylphosphino)-6,6'-dimethyl biphenyl
BIFUP	2,2'-(diphenylphosphino)-4,4'6,6'-*tetrakis*(trifluoromethyl) biphenyl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	[1,1']binaphthalenyl-2,2'-diol
BIPHEMP	2,2'-(diphenylphosphino)-6,6'-dimethyl biphenyl
BPE	1,2-bis(2,5-diakylphospholanyl)ethane
Bn	benzyl
Bu	butyl
CAMP	cyclohexyl-*o*-anisylmethylphosphine
Cat	catalytic
Cy	cyclohexyl
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIOP	1,4-bis(diphenylphosphanyl)-1,4-dideoxy-2,3-*O*-isopropylidene-D-threitol
DIPAMP	1,2'bis[phenyl(-*o*-methoxyphenyl)phosphor]-ethane
DuPHOS	1,2-bis(2,5-dialkylphospholanyl)benzene
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
EI	electro impact
Et	ethyl
EtOAc	ethyl acetate
FAB	fast atom bombardment

FUPMOP	2,2'-(diphenylphosphino)-4,4'6,6'-*tetrakis*(trifluoromethyl)-5,5'dimethoxy biphenyl
h	hour
hυ	light
HRMS	high resolution mass spectrometry
IBX	iodoxybenzoic acid
IR	infrared
LAH	lithium aluminum hydride
LRMS	low resolution mass spectromery
Me	methyl
min	minutes
mp	melting point
MS	mass spectrometry/molecular sieves
nmr	nuclear magnetic resonance
Ph	phenyl
ppm	parts per million
^{i}Pr	isopropyl
RT	room temperature
TBDMS	*tertiary*-butyldimethylsilyl
THF	tetrahydrofuran
TMS	tetramethylsilane

Table of Contents

Abstract i

Acknowledgements ii

List of Abbreviations v

Table of Contents vii

Chapter 1: Introduction 1 2

1.1. Occurrence and toxicity of naphthalene 2

1.2. Some biologically important naphthalenes and naphthoquinones 4

1.3. Naphthalenes and naphthoquinones as ligands for catalysts 7

1.3.1. Cycloaddition reactions *8*

1.3.1.1. Diels-Alder reactions 8

1.3.1.2. Hetero Diels-Alder reactions 10

1.3.1.3. [2+2] Cycloadditions 11

1.3.1.4. Other cycloadditions 12

1.3.2. Aldol Reactions *12*

1.3.2.1. Reactions using BINOL ligands 13

1.3.2.2. Reactions using BINAP ligands 16

1.3.2.3. Reactions using mixed N/O ligands 17

1.3.3. Ene reactions *19*

1.3.4. Allylmetal addition to carbonyl groups *22*

1.3.5. Michael additions *22*

1.4. Origins and aims of this project 25

Chapter 2: Results and Discussion 1 30

2.1 Synthesis of aryl-substituted naphthalenes from α-tetralone 30

2.2 Synthesis of aryl-substituted naphthalenes from 6,7-dimethoxy-α-tetralone 34

2.3 Aromatization of dihydronaphthaldehydes 37

2.4 Synthesis of aryl substituted naphthalenes from 1-bromo-2-naphthaldehyde 39

2.5 Synthesis of aryl substituted naphthalenes from 1-bromo-6-methoxy-2-naphthaldehyde 40

2.6 The synthesis of tetrahydrocyclopropa[a]naphthalenes 42

2.7 Biological activity of aryl-substituted naphthalenes. 45

Preface To Part 2 ..... **51**

Chapter 3: Introduction 2 53

3.1 Bidentate phosphorus ligands 54

3.1.1 Bisphosphines *54*

3.1.1.1 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) 54

3.1.2 1,2'-Bis[(phenyl-o-methoxyphenyl)phosphino]ethane (DIPAMP) *60*

3.1.3 Bisphosphine ligands from the modification of DuPHOS and BPE *62*

3.1.4 Chiral ferrocene-based bisphosphines ... *64*
3.2 Monodentate phosphorus ligands. ... 66
3.2.1 Binaphthol-based monodentate phosphorus ligands ... *67*
3.2.1.1 Binaphthol-based monophosphites. ... 67
3.2.1.2 Binaphthol-based monophosphoramidites. ... 68
3.2.2 Biphenol-based monodentate phosphorus ligands ... *70*
3.2.2.1 Biphenol-based monophosphites. ... 70
3.2.2.2 Biphenol-based monophosphoramidites. ... 71
3.2.3 Tartrate-based monodentate phosphorus ligands ... *72*
3.2.4 TADDOL-based monodentate phosphorus ligands ... *73*
3.2.5 Catechol-based monodentate phosphorus ligands ... *73*
3.3 Aims of this project. ... 74
Chapter 4: Results and Discussion 2 ... **77**
4.1 Suzuki coupling reactions ... 78
4.2 Ullmann coupling reactions ... 81
4.3 Hydrogenolysis of benzyl groups to afford phenols ... 83
4.4 Removal of isopropyl groups to afford naphthols ... 84
4.5 Removal of isopropyl groups to afford phenols ... 85
4.6 Reduction of naphthaldehydes to naphthyl alcohols ... 86
4.7 Syntheses of monodentate phosphorus ligands ... 89
4.7.1 Phosphite and phosphoramidite ligands ... *89*
4.7.1.1 Phosphites containing a nine-membered heterocycle ... 92
4.7.1.2 Phosphites containing an eight-membered heterocycle. ... 94
4.7.1.3 Phosphates containing a nine-membered heterocycle ... 95
4.7.1.4 Phosphoramidites containing a nine-membered heterocycle ... 96
4.7.1.5 Phosphoramidites containing an eight-membered heterocycle ... 98
4.7.1.6 Phosphoramidates containing a nine-membered heterocycle ... 98
4.7.1.7 Phosphoramidates containing an eight-membered heterocycle ... 100
Chapter 5: Conclusion and Future Work ... **100**
Chapter 6: Experimental Procedures To Part One ... **104**
6.1 Synthesis of precursors for Suzuki coupling reactions ... 105
6.1.1 Bromination and formylation of tetralones ... *105*
6.1.1.1 1-Bromo-3,4-dihydro-2-naphthaldehyde (55): ... 105
6.1.1.2 1-Bromo-6,7-dimethoxy-3,4-dihydro-2-naphthaldehyde (86): ... 105
6.1.1.3 6-Methoxy-1-bromo-3,4-dihydro-2-naphthaldehyde (107): ... 106
6.1.2 Syntheses of arylboronic acids ... *107*
6.1.1.1 3,4,5-Trimethoxyphenylboronic acid (56): ... 107
6.1.1.2 1-Naphthylboronic acid (69): ... 107
6.1.1.3 Phenylboronic acid (70): ... 108
6.1.1.4 *o*-Tolylboronic acid (71): ... 108
6.2 Suzuki coupling reactions ... 108
*6.2.1 Suzuki coupling reactions using 1-bromo-3,4-dihydro-2-naphthaldehyde (**55**)* ... *108*
6.2.1.1 1-(3,4,5-Trimethoxyphenyl)-3,4-dihydro-2-naphthaldehyde (72): ... 108

6.2.1.2 1-(1-Naphthyl)-3,4-dihydro-2-naphthaldehyde (73): 109
6.2.1.3 1-Phenyl-3,4-dihydro-2-naphthaldehyde (74): 110
6.2.1.4 1-(*o*-Tolyl)-3,4-dihydro-2-naphthaldehyde (75): 111
*6.2.2 Suzuki coupling reactions using 1-bromo-6,7-dimethoxy-3,4-dihydro-2-naphthaldehyde (**86**) 112*
6.2.2.1 6,7-Dimethoxy-1-(3,4,5-trimethoxyphenyl)-3,4-dihydro-2-naphthaldehyde (87): 112
6.2.2.2 6,7-Dimethoxy-1-(1-naphthyl)-3,4-dihydro-2-naphthaldehyde (88): 113
6.2.2.3 6,7-Dimethoxy-1-phenyl-3,4-dihydro-2-naphthaldehyde (89): 113
6.2.2.4 6,7-Dimethoxy-1-(*o*-tolyl)-3,4-dihydro-2-naphthaldehyde (90): 114
6.3 Reduction of aldehydes. 115
*6.3.1 [1-(3,4,5-Trimethoxyphenyl)-3,4-dihydronaphthalen-2-yl]methanol (**76**): 115*
*6.3.2 [1-(1-Naphthyl)-3,4-dihydronaphthalen-2-yl]methanol (**77**): 116*
*6.3.3 (1-Phenyl-3,4-dihydronaphthalen-2-yl)methanol (**78**): 116*
*6.3.4 [1-(o-Tolyl)-3,4-dihydronaphthalen-2-yl]methanol (**79**): 117*
*6.3.5 [6,7-Dimethoxy-1-(3,4,5-trimethoxyphenyl)-3,4-dihydronaphthalen-2-yl]methanol (**91**): 118*
*6.3.6 [6,7-Dimethoxy-1-(1-naphthyl)-3,4-dihydronaphthalen-2-yl]methanol (**92**): 118*
*6.3.7 (6,7-Dimethoxy-1-phenyl-3,4-dihydronaphthalen-2-yl)methanol (**93**): 119*
*6.3.8 [6,7-Dimethoxy-1-(o-tolyl)-3,4-dihydronaphthalen-2-yl)methanol (**94**): 120*
6.4 Protection of alcohols as acetates. 120
*6.4.1 [1-(3,4,5-Trimethoxyphenyl)-3,4-dihydronaphthalen-2-yl]methyl acetate (**58**): 120*
*6.4.2 [1-(1-Naphthyl)-3,4-dihydronaphthalen-2-yl]methyl acetate (**80**): 121*
*6.4.3 (1-Phenyl-3,4-dihydronaphthalen-2-yl)methyl acetate (**81**): 122*
*6.4.4 [1-(o-Tolyl)-3,4-dihydronaphthalen-2-yl]methyl acetate (**82**): 123*
*6.4.5 [6,7-Dimethoxy-1-(3,4,5-trimethoxyphenyl)-3,4-dihydronaphthalen-2-yl]methyl acetate (**95**): 123*
*6.4.6 [6,7-Dimethoxy-1-(1-naphthyl)-3,4-dihydronaphthalen-2-yl]methyl acetate (**96**): 124*
*6.4.7 (6,7-Dimethoxy-1-phenyl-3,4-dihydronaphthalen-2-yl)methyl acetate (**97**): 125*
*6.4.8 [6,7-Dimethoxy-1-(o-tolyl)-3,4-dihydronaphthalen-2-yl]methyl acetate (**98**): 125*
6.5 Aromatization reactions. 126
*6.5.1 [1-(3,4,5-Trimethoxyphenyl)naphthalen-2-yl]methyl acetate (**59**): 126*
*6.5.2 [1-(1-Naphthyl)naphthalen-2-yl]methyl acetate (**83**): 127*
*6.5.3 (1-Phenylnaphthalen-2-yl)methyl acetate (**84**): 128*
*6.5.4 [1-(o-Tolyl)naphthalen-2-yl]methyl acetate (**85**): 128*
*6.5.5 [6,7-Dimethoxy-1-(3,4,5-trimethoxyphenyl)naphthalen-2-yl]methyl acetate (**99**): 129*
*6.5.6 [6,7-Dimethoxy-1-(1-naphthyl)naphthalen-2-yl]methyl acetate (**100**): 130*
*6.5.7 (6,7-Dimethoxy-1-phenylnaphthalen-2-yl)methyl acetate (**101**): 130*
*6.5.8 [6,7-Dimethoxy-1-(o-tolyl)naphthalen-2-yl]methyl acetate (**102**): 131*
6.6 Aromatization of bromo(methoxy)naphthaldehydes. 132
*6.6.1 1-Bromo-2-naphthaldehyde (**106**): 132*
*6.6.2 1-Bromo-6-methoxy-2-naphthaldehyde (**108**) 132*
6.7 Coupling reactions using aromatized naphthaldehydes. 133

*6.7.1 Suzuki coupling reactions using 1-bromo-2-naphthaldehyde (**106**)..... 133*
6.7.1.1 1-(3,4,5-Trimethoxyphenyl)-2-naphthaldehyde (109):..... 133
6.7.1.2 1-(1-Naphthyl)-2-naphthaldehyde (110):..... 134
6.7.1.3 1-Phenyl-2-naphthaldehyde (111):..... 135
6.7.1.4 1-(*o*-Tolyl)-2-naphthaldehyde (112):..... 135
*6.7.2 Suzuki coupling reactions using 1-bromo-6-methoxy-2-naphthaldehyde (**108**)..... 136*
6.7.2.1 6-Methoxy-1-(3,4,5-trimethoxyphenyl)-2-naphthaldehyde (117):..... 136
6.7.2.2 6-Methoxy-1-(1-naphthyl)-2-naphthaldehyde (118):..... 137
6.7.2.3 6-Methoxy-1-phenyl-2-naphthaldehyde (119):..... 137
6.7.2.4 6-Methoxy-1-(*o*-tolyl)-2-naphthaldehyde (120):..... 138
6.8 The synthesis of arylnaphthalene alcohols.....139
*6.8.1 [1-(3,4,5-Trimethoxyphenyl)naphthalen-2-yl]methanol (**113**):..... 139*
*6.8.2 [1-(1-Naphthyl)naphthalen-2-yl]methanol (**114**):..... 140*
*6.8.3 (1-Phenylnaphthalen-2-yl)methanol (**115**):..... 140*
*6.8.4 [1-(o-Tolyl)naphthalen-2-yl]methanol (**116**):..... 141*
*6.8.5 [6-Methoxy-1-(3,4,5-trimethoxyphenyl)naphthalen-2-yl]methanol (**121**):..... 142*
*6.8.6 [6-Methoxy-1-(1-naphthyl)naphthalen-2-yl]methanol (**122**):..... 142*
*6.8.7 (6-Methoxy-1-phenylnaphthalen-2-yl)methanol (**123**):..... 143*
*6.8.8 [6-Methoxy-1-(o-tolyl)naphthalen-2-yl]methanol **(124):**..... 144*
6.9 The synthesis of tetrahydrocyclopropa[a]naphthalene. 144
*6.9.1 7b-(3,4,5-Trimethoxyphenyl)-1a,2,3,7b-tetrahydro-1H-cyclopropa-[a]naphthalene (**125**):..... 144*
*6.9.2 7b-Phenyl-1a,2,3,7b-tetrahydro-1H-cyclopropa[a]naphthalene (**130**):... 145*
*6.9.3 7b-(o-Tolyl)-1a,2,3,7b-tetrahydro-1H-cyclopropa[a]naphthalene (**131**):..... 146*
Chapter 7: Experimental Procedures To Part Two..... 147
7.1 Syntheses of arylnaphthaldehydes using Suzuki coupling reaction.....147
*7.1.1 Suzuki coupling reactions using 1-bromo-2-naphthaldehyde (**106**)..... 147*
7.1.1.1 1-(2-Formylphenyl)-2-naphthaldehyde (225):..... 147
7.1.1.2 1-(2-Isopropoxynaphthyl)-2-naphthaldehyde (234):..... 148
7.1.1.3 1-(2-Isopropoxyphenyl)-2-naphthaldehyde (237):..... 149
7.1.1.4 1-(2-Benzyloxyphenyl)-2-naphthaldehyde (240):..... 149
*7.1.2 Suzuki coupling reactions using 1-bromo-6-methoxy-2-naphthaldehyde (**107**)..... 150*
7.1.2.1 1-(2-Formylphenyl)-6-methoxy-2-naphthaldehyde (226):..... 150
7.1.2.2 1-(2-Isopropoxynaphthyl)-6-methoxy-2-naphthaldehyde (235):..... 151
7.1.2.3 1-(2-Isopropoxyphenyl)-6-methoxy-2-naphthaldehyde (238):..... 152
*7.1.3 Suzuki coupling reactions using 1-bromo-6,7-dimethoxy-2-naphthaldehyde (**108**)..... 152*
7.1.3.1 6,7-Dimethoxy-1-(2-formylphenyl)-2-naphthaldehyde (227):..... 152
7.1.3.2 6,7-Dimethoxy-1-(2-isopropoxynaphthyl)-2-naphthaldehyde (236):..... 153
7.1.3.3 6,7-Dimethoxy-1-(2-isopropoxyphenyl)-2-naphthaldehyde (239):..... 154
7.1.3.4 6,7-Dimethoxy-1-(2-benzyloxyphenyl)-2-naphthaldehyde (241):..... 155
7.2 Syntheses of arylnaphthaldehydes using Ullmann coupling reaction.....156
*7.2.1 1-(2-Formylnaphthyl)-2-naphthaldehyde **(231):**..... 156*
*7.2.2 2-(2-Formylphenyl)benzaldehyde **(242):**..... 157*
*7.2.3 1-(2-Formyl-6-methoxy-3,4-dihydronaphthyl)-6-methoxy-3,4-dihydro-2-naphthaldehyde (**243):**..... 157*

7.3 Reduction of aryl-substituted naphthaldehydes 158
*7.3.1 [1-(2-Hydroxymethyl-phenyl)-2-naphthyl]-methanol (**228**):* *158*
*7.3.2 [1-(2-Hydroxymethyl-phenyl)-6-methoxynaphthalen-2-yl]-methanol **(229):*** *159*
*7.3.3 [1-(2-Hydroxymethyl-phenyl)-6,7-dimethoxynaphthalen-2-yl]-methanol **(230):*** *159*
*7.3.4 (2'-Hydroxymethyl-[1,1']binaphthyl-2-yl)-methanol **(232):*** *160*
*7.3.5 (2'-Hydroxymethyl-biphenyl-2-yl)-methanol **(257):*** *161*
*7.3.6 (2'-Hydroxymethyl-6,6',3,4,3',4'-tetrahydro-[1,1']binaphthy-2-yl]-methanol **(258):*** *161*
7.4 Deprotection of isopropyl ethers to afford naphthols 162
*7.4.1 1-(2'-Hydroxynaphthalen-2-yl)-2-naphthaldehyde **(248):*** *162*
*7.4.2 1-(2'-Hydroxynaphthalen-2-yl)-6-methoxy-2-naphthaldehyde **(249):*** *163*
*7.4.3 1-(2'-Hydroxynaphthalen-2-yl)-6,7-dimethoxy-2-naphthaldehyde **(250):*** *164*
7.5 Deprotection of aromatic benzyl ethers 164
*7.5.1 2-(6,7-Dimethoxy-2-methyl-naphthalen-1yl)-phenol **(247):*** *164*
*7.5.2 2-(2-Methyl-naphthalen-1yl)-phenol **(246):*** *165*
7.6 Reduction of aromatic aldehydes 166
*7.6.1 2'-Hydroxymethyl-[1,1']binaphthalenyl-2-ol **(251):*** *166*
*7.6.2 2'-Hydroxymethyl-6'-methoxy-[1,1']binaphthalenyl-2-ol **(252):*** *167*
*7.6.3 2'-Hydroxymethyl-6',7'-dimethoxy-[1,1']binaphthalenyl-2-ol **(253):*** *167*
*7.6.4 2-(2-Hydroxymethyl-naphthalen-1-yl)-phenol **(254):*** *168*
*7.6.5 2-(2-Hydroxymethyl-6-methoxy-naphthalen-1-yl)-phenol **(255):*** *169*
*7.6.6 2-(2-Hydroxymethyl-6,7-dimethoxy-naphthalen-1-yl)-phenol (**256**):* *169*
7.7 Syntheses of phosphite, phosphate, phosphoramidite and phosphoramidate ligands 170
7.7.1 Syntheses of precursors *170*
7.7.1.1 Menthyl phosphodichloridite (233): 170
7.7.1.2 Menthyl phosphodichloridate (271): 171
7.7.1.3 *N*-Phosphodichloridite *bis*-(α-methylbenzyl)amine (276): 171
7.7.1.4 *N*-Phosphodichloridate *bis*-(α-methylbenzyl)amine (281): 172
7.7.2 General procedure for the synthesis of ligands *172*
7.7.2.1 13-{[(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl]oxy}-11,15-dihydrodinaphtho[2,1-*e*:1,2-*g*][1,3,2]dioxaphosphonine (221): 173
7.7.2.2 *N*-(11,15-Dihydrodinaphtho[2,1-*e*:1,2-*g*][1,3,2]dioxaphosphonin-13-yl)-*N*-[(1*R*)-1-phenylethyl]-*N*-[(1*R*)-1-phenylethyl]amine (222): 173
7.7.2.3 13-{[(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl]oxy}-11,15-dihydrodinaphtho[2,1-*e*:1,2-*g*] [1,3,2]dioxaphosphonine 13-oxide (269): 174
7.7.2.4 *N*-(13-Oxido-11,15-dihydrodinaphtho[2,1-*e*:1,2-*g*][1,3,2]dioxaphosphonin-13-yl)-*N*-[(1*R*)-1-phenylethyl]-*N*-[(1*R*)-1-phenylethyl]amine (279): 174
7.7.2.5 7-{[(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl]oxy}-5,9-dihydrodibenzo[*e*,*g*][1,3,2]dioxaphosphonine (266): 175
7.7.2.6 7-{[(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl]oxy}-5,9-dihydrodibenzo[*e*,*g*][1,3,2]dioxaphosphonine 7-oxide (270): 175
7.7.2.7 *N*-(5,9-Dihydrodibenzo[*e*,*g*][1,3,2]dioxaphosphonin-7-yl)-*N*-[(1*R*)-1-phenylethyl]-*N*-[(1*R*)-1-phenylethyl]amine (275): 176
7.7.2.8 *N*-(7-Oxido-5,9-dihydrodibenzo[*e*,*g*][1,3,2]dioxaphosphonin-7-yl)-*N*-[(1*R*)-1-phenylethyl]-*N*-[(1*R*)-1-phenylethyl]amine (280): 176

7.7.2.9 3-{[(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl]oxy}-1,5-dihydronaphtho[2,1-*f*][2,4,3]benzodioxaphosphonine (262): ... 176
7.7.2.10 3-{[(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl]oxy}-1,5-dihydronaphtho[2,1-*f*][2,4,3]benzodioxaphosphonine-3-oxide (268): ... 177
7.7.2.11 *N*-(1,5-Dihydronaphtho[2,1-*f*][2,4,3]benzodioxaphosphonin-3-yl)-*N*-[(1*R*)-1-phenylethyl]-*N*-[(1*R*)-1-phenylethyl]amine (272): ... 177
7.7.2.12 *N*-(3-Oxido-1,5-dihydronaphtho[2,1-*f*][2,4,3]benzodioxaphosphonin-3-yl)-*N*-[(1*R*)-1-phenylethyl]-*N*-[(1*R*)-1-phenylethyl]amine (277): ... 177
7.7.2.13 3-{[(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl]oxy}-1,5-dihydronaphtho[2,1-*f*][2,4,3]benzodioxaphosphonin-9-ylmethyl ether (263): ... 178
7.7.2.14 *N*-(9-Methoxy-1,5-dihydronaphtho[2,1-*f*][2,4,3]benzodioxaphosphonin-3-yl)-*N*-[(1*R*)-1-phenylethyl]-*N*-[(1*R*)-1-phenylethyl]amine (273): ... 178
7.7.2.15 *N*-(9-Methoxy-3-oxido-1,5-dihydronaphtho[2,1-*f*][2,4,3]benzodioxaphosphonin-3-yl)-*N*-[(1*R*)-1-phenylethyl]-*N*-[(1*R*)-1-phenylethyl]amine (278): ... 179
7.7.2.16 3-{[(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl]oxy}-1,5-dihydronaphtho[2,1-*f*][2,4,3]benzodioxaphosphonin-9-yl methyl ether (264): ... 179
7.7.2.17 *N*-(9,10-Dimethoxy-1,5-dihydronaphtho[2,1-*f*][2,4,3] benzodioxaphosphonin-3-yl)-*N*-[(1*R*)-1-phenylethyl]-*N*-[(1*R*)-1-phenylethyl]amine (274): ... 180
7.7.2.18 13-{[(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl]oxy}-2,7-dimethoxy-9,10,11,15,16,17-hexahydrodinaphtho[2,1-*e*:1,2-*g*][1,3,2] dioxaphosphonine (265): 180
7.7.2.19 2-{[(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl]oxy}-4*H*-naphtho[2,1-*e*][1,3,2]benzodioxaphosphocin-8-yl methyl ether (267): ... 181
7.7.2.20 12-{[(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl]oxy}-14*H*-dinaphtho[2,1-*d*:1,2-*f*][1,3,2]dioxaphosphocine (223): ... 181
7.7.2.21 *N*-(14*H*-Dinaphtho[2,1-*d*:1,2-*f*][1,3,2]dioxaphosphocin-12-yl)-*N*-[(1*R*)-1-phenylethyl]-*N*-[(1*R*)-1-phenylethyl]amine (224): ... 181
7.7.2.22 *N*-(14*H*-Dinaphtho-12-oxido-[2,1-*d*:1,2-*f*][1,3,2]dioxaphosphocin-12-yl)-*N*-[(1*R*)-1-phenylethyl]-*N*-[(1*R*)-1-phenylethyl]amine (282): ... 182

References ... 183

Appendices ... 199

Appendix 1: Selected ^{1}H , ^{13}C and ^{31}P nmr spectra ... 199

Appendix 2: Crystal structure solution and refinement of 7b-(3,4,5-trimethoxyphenyl)-1a,2,3,7b-tetrahydro-1H-cyclopropa[a]naphthalene (125) ... 225

PART ONE

Synthesis of aryl-substituted naphthalenes

Chapter 1: Introduction 1

The biaryl axis is the central building block in a large number of natural products of differing structure, biological activity and biosynthetic origin. Examples include polyketides, terpenes, lignans, coumarins, flavonoids, tannins, peptides and alkaloids.[1] Because of their interesting properties, not only as pharmaceutically active natural products, but also as chiral reagents,[2] in crown ethers,[3] as chiral host molecules for inclusion compounds,[4] as the basis of chiral phases for chromatography,[5] as flexible 'spacers' between two halves of a molecule[6,7] and as chiral liquid crystals,[8] natural and unnatural biaryls constitute attractive synthetic goals. Many of these important biaryls contain a naphthalene or naphthoquinone skeleton[9] and hence the introduction of this thesis is aimed at highlighting the importance and uses of naphthalenes and naphthoquinones that bear aryl substituents.

1.1. Occurrence and toxicity of naphthalene

Naphthalene, discovered in 1819 by Garden,[10] is a natural constituent of coal tar and crude oil, which are major contributors to its presence in the environment. They contain up to 11% and 1.3% of the chemical, respectively.[11] Forest fires also contribute to the presence of naphthalene in the environment, as the chemical is a natural combustion product of wood.[12]

Naphthalene has been measured in a wide variety of workplaces for many years. Exposure to naphthalene has been extensively measured in Germany. Samples collected between 1991 and 1995 were found predominantly from wood manufacturing (50%), construction (16%) and metal-working and machine construction (12%). Ninety-five per cent of the available 183 measurements from 94 factories were within the analytical limit of detection (1.0 mg/m^3 for 2 h sampling time). Only in the manufacture of repellents and perfumed disinfectants were concentrations above the limit of detection.[13] Naphthalene is the most abundant component of creosote vapour and constitutes 10~16 wt% of creosote oils.[14]

Naphthalene has been identified in the USA by the Environmental Protection Agency and the Agency for the Toxic Substances and Disease Registry as one of the most commonly found substances at hazardous waste sites on the 'National Priorities List'. It also features in the Canadian Priority List of hazardous substances.[15] The general population is exposed to naphthalene principally by inhalation of ambient and indoor air, with naphthalene-containing moth-repellents and tobacco smoke as the main contributors. Another source is the use of kerosene heaters.[16] Much lower exposure to naphthalene may occur from ingestion of drinking water and/or food. Estimated exposure from drinking water (assuming a water concentration of 0.001-2.0 μg/L naphthalene and water consumption of 2 L per day) is 0.002-4.0 μg per day.[17]

The major toxicological responses reported in humans from acute exposure to naphthalene have been haemolytic anaemia and cataracts.[18] Poisoning from naphthalene has been accidental or suicidal and occurs as a result of either inhalation of fumes containing naphthalene or by ingestion of mothballs.[19] In 1990, 2400 cases of accidental naphthalene ingestion were reported to 72 poison control centres in the USA.[20]

Naphthalene causes cataracts in rats,[21] rabbits[22] and mice.[23] Yamauchi *et al*.[24] reported that daily administration of oral doses of 1 g/kg naphthalene to male Wistar rats resulted in increase in levels of serum and liver lipid peroxides, suggesting enhanced lipid peroxidation. Male albino rats were administered 1 g/kg naphthalene orally in refined groundnut oil daily for 10 days. Biochemical alterations in the liver, kidney and eye were evaluated. Significant changes were observed only in the liver, including increased liver weight, lipid peroxidation and aniline hydroxylase activity.[25]

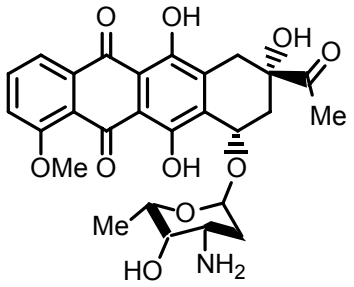
Exposure to naphthalene has also been associated with reproductive and developmental problems. Sensorineural hearing loss was reported in an infant with neonatal hyperbilirubinaemia from haemolysis due to glucose-6-phosphate dehydrogenase deficiency and naphthalene exposure. The baby had normal hearing at 13 days of age, but had developed profound bilateral hearing loss by seven months of age. On the day of admittance to hospital, the infant had been dressed in clothes and placed on a blanket that

had all been stored in naphthalene mothballs for five years.[26] Melzer-Lange and Walsh-Kelly reported naphthalene-induced haemolysis in a black female infant deficient in glucose-6-phosphate dehydrogenase.[27] Fourteen of 24 children identified as having glucose-6-phosphatase deficiency were diagnosed with haemolysis associated with exposure to naphthalene-containing moth-repellents.[28]

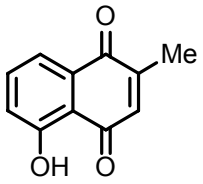
In CD-1 mice given 300 mg/kg naphthalene per day by gavage on gestation days 7~14, material lethality was increased, material gain was decreased and the average number of live offspring per litter was increased. There was no concomitant increased in the number of dead pups, suggesting that the smaller litter size was due to early embryonic resorption. In a study of the role of biotransformation on the rodent *in vitro* preimplementation embryotoxicity of naphthalene, no effects were observed in the absence of a rat S9 activation system in the culture medium. In the presence of the S9 system, naphthalene caused concentration-dependent embryolethality. This result indicates that the enbryotocicity of naphthalene is dependent on activation to reactivate metabolites.

1.2. Some biologically important naphthalenes and naphthoquinones

As illustrated above, naphthalene can have toxic effects. However, a range of natural products possessing naphthalene and naphthoquinone skeletons exhibit totally different biological activities. For example many naphthoquinones or derivatives are active as antibiotics, are cytototoxic, (like daunomycin **1**) or are weakly antiviral.[29] Even simple compounds such as plumbagin **2** proved to be highly effective and selective as enzyme inhibitors.

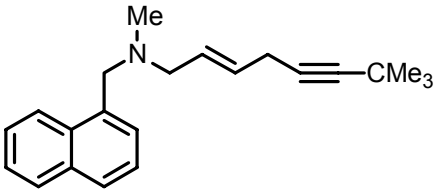


1



2

Other examples include terbinafine **3**, an antidermatophytic (antifungal) agent which has selective action in the inhibition of squalene epoxidation.[30] Ergosterol is an essential component of fungal membranes, so a deficiency in its production brought about by **3** creates a serious problem for fungi. Mammalian cell membranes are not as efficiently inhibited by terbinafine, integrating for the useful selective toxicity of this agent. The original substance for this fungal class was discovered during screening, and a derivative generating program eventually led to **3**.[31]



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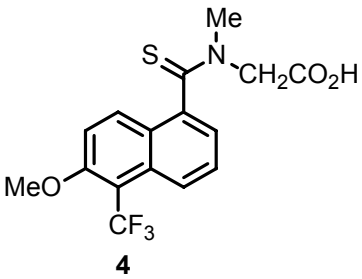
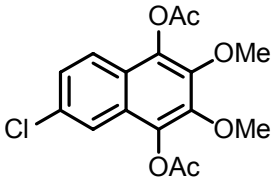


4

The complex thioamide tolrestat **4** is an inhibitor of aldose reductase. This enzyme catalyzes the reduction of glucose to sorbitol. The enzyme is not very active, but in diabetic individuals where blood glucose levels can spike to quite high levels in tissues where insulin is not required for glucose uptake (nerve, kidney, retina and lens), sorbitol is formed by the action of aldose reductase and contributes to diabetic complications. Very prominent amongst these are eye problems (diabetic retinopathy). Tolrestat is intended for oral administration to prevent this condition.[32]

The hydroquinone derivative lonapalene **5** is used topically for the treatment of the skin disease psoriasis in place of classical treatments such as coal tar, anthralin, and cortical steroids. These suffer from the defects of staining the skin and/or causing atrophy. Lonapalene inhibits 5-lipoxygenase *in vitro* and is believed to exert its effects by blocking leucotriene formation *in vivo*.[33]



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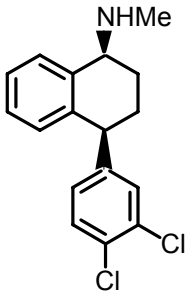
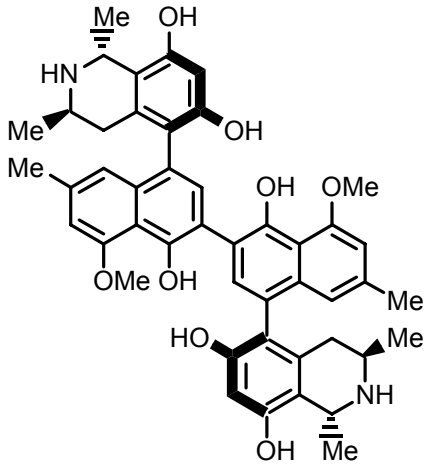


6

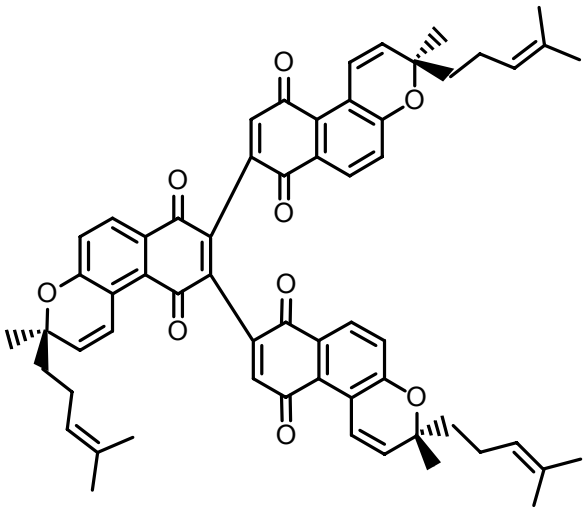
Some biologically active naphthalene derivatives (tetralins) have lost aromaticity in one of the fused rings. An example thereof is sertraline **6**, which possesses nonsedative antidepressant activity. At subtherapeutic doses it potentiates the action of a subthreshold dose of morphine in analgesia. This effect is mediated through serotonin and adrenergic neurones and therefore satisfies the stated goals of the program by possessing antidepressant activity by a pharmacological mechanism different to the classical agents[34] (which appear to inhibit norepinephrine uptake at certain receptors).

Many other naturally occurring naphthalenes and naphthoquinones possess a biaryl linkage that appears to be an important feature governing the biological activity of these natural products. This biaryl linkage is important as it introduces atropisomerism into some of these compounds due to restricted rotation along the biaryl axis. Examples of such compounds include the michellamines[35] (e.g. michellamine A, **7**), which are naphthylisoquinoline alkaloids showing antiviral activity against AZT-resistant HIV strains.[36]



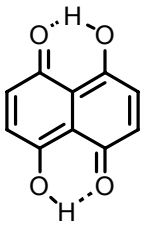
7

Another natural naphthoquinone that exhibits atropisomerism is conocurvone **8**, the isomeric mixture of which showed high anti-HIV activity in a variety of *in vitro* tests conducted by the US National Cancer Institute.[37] This physiological property is dependent on the trimeric nature of the compound as the anti-HIV activity is completely absent in the naturally occurring monomer.[38]



8

Apart from their biological activities, naphthalenes and naphthoquinones are useful as dyes.[39] Dyes derived from naphthazarin **9** or diaminonaphthoquinone **10** are industrially important as they are used as colouring agents in a variety of applications.[40] An example of a commercially available dye is CI Disperse Blue 20 **11**.



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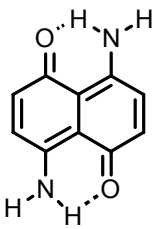

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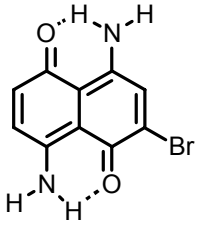


11

1.3. Naphthalenes and naphthoquinones as ligands for catalysts

Apart from their interesting biological activities, naphthalene compounds with aryl substituents find application as chiral reagents as a result of either a stereogenic axis or

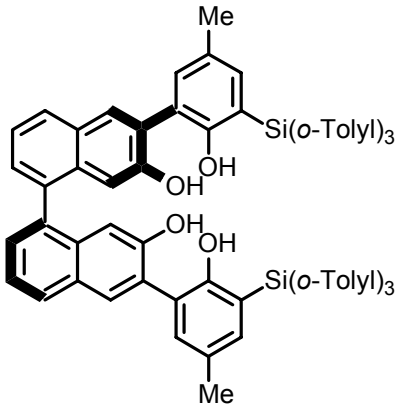
plane in a molecule. In the process they act as ligands and/or catalysts in various chemical reactions as outlined below. This section will highlight some recent examples and is not intended to be comprehensive. Focus in this section is mainly on the use of the BINOL ligand in particular, although the author is aware that ligands such as the chiral phosphine ligand 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) are also very important in this area of research. Aspect of BINAP chemistry will be highlighted in the second section of the PhD.

1.3.1. Cycloaddition reactions

1.3.1.1. Diels-Alder reactions

In recent times many examples of biaryl ligands have been utilized in assisting stereoselective Diels-Alder reactions. Some examples are highlighted below. In particular the use of BINOL ligands will be highlighted.

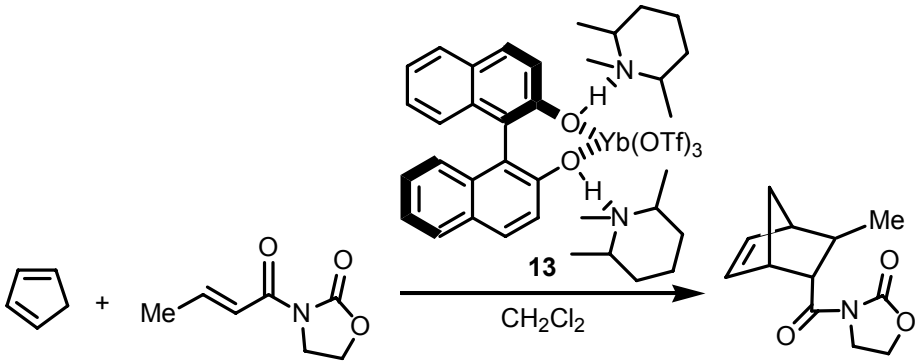
A new type of chiral helical titanium reagent has been designed based on $Ti(OPr^{i})_4$ and a chiral ligand **12** derived from enantiopure BINOL. These titanium reagents have been successfully utilized as efficient chiral templates for the conformational fixation of α,β-unsaturated aldehydes, thereby allowing excellent enantioselective recognition of the substrates to achieve uniformly high asymmetric induction in asymmetric Diels-Alder reactions of dienes at a wide variety of reaction temperatures.[41]



12

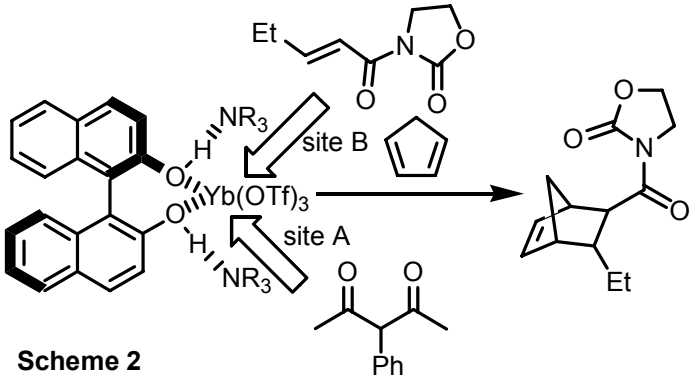
A chiral ytterbium triflate **13**, derived from $Yb(OTf)_3$, the same chiral ligand (*R*)-BINOL, and a tertiary amine, has been applied to the enantioselective Diels-Alder reaction of

cyclopentadiene with crotonoyl oxazolidinones. Among the various tertiary amines, *cis*-1,2,6-trimethylpiperidine was found to be highly effective (**Scheme 1**).[42]



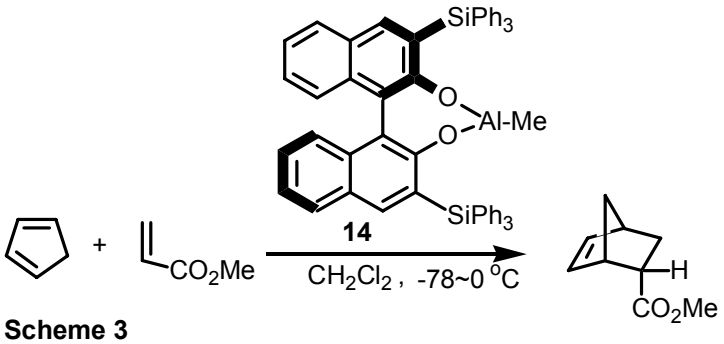
Scheme 1

The unique structure of such chiral ytterbium catalysts is characterized by hydrogen bonding between the phenolic hydrogens of (*R*)-BINOL and the nitrogen of tertiary amines. Recently Kobayashi found that both Diels-Alder adduct enantiomers were accessible with $Yb(OTf)_3$ by using a single chiral source, (*R*)-BINOL, and a choice of achiral ligands.[43] In the presence of 3-phenylacetylacetone as the achiral ligand (**Scheme 2**), one of the two active coordination sites in the chiral ytterbium catalyst is occupied, hence a dienophile coordinates to the remaining active sites, giving the one enantiomer selectively.



Scheme 2

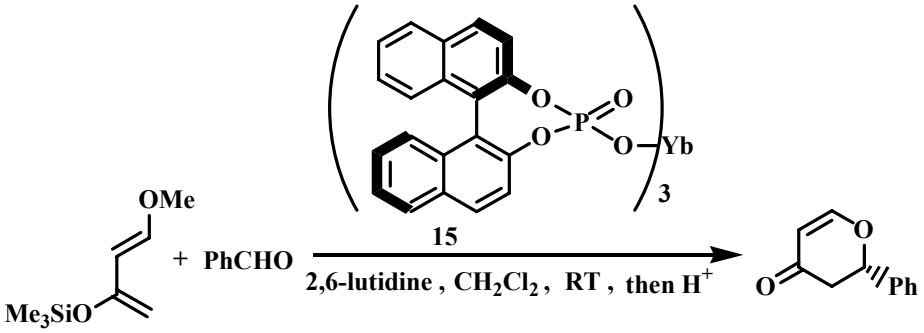
The chiral bis(silyl)BINOL-modified aluminium catalyst **14**, which was originally developed for asymmetric hetero Diels-Alder reaction,[44] has also been successfully applied to the asymmetric Diels-Alder reaction of cyclopentadiene with methyl acrylate or methyl propiolate (**Scheme 3**).[45]



Scheme 3

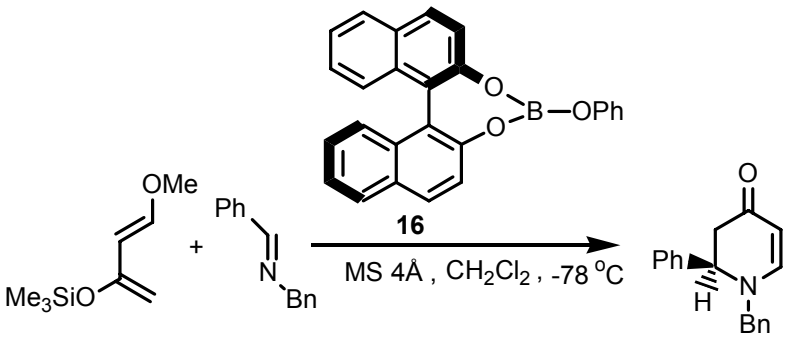
1.3.1.2. Hetero Diels-Alder reactions

A series of trivalent lanthanoid complexes, for example the tris-(*R*)-1,1'-binaphthyl-2,2'-diyl phosphonate **15** complexes of scandium, and ytterbium, have been introduced as new chiral and stable Lewis acids for the hetero Diels-Alder reaction of Danishefsky's diene and aldehydes. 2,6-Lutidine was found to be an effective additive to improve the enantioselectivity up to 89% ee (**Scheme 4**).[46]



Scheme 4

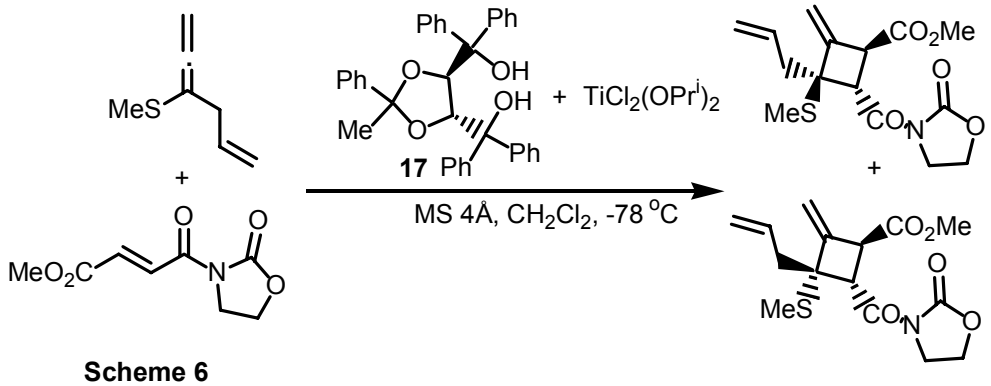
Main group elements also feature in this chemistry. For example, the chiral boron complex **16** prepared *in situ* from the same chiral BINOL and $B(OPh)_3$ was utilized for the asymmetric aza-Diels-Alder reaction of Danishefky's diene and imine(**Scheme 5**).[47] Although asymmetric reaction of prochiral imine affords products with up to 90% ee, the double asymmetric induction with chiral imine by using α-methylbenzylamine as a chiral auxiliary has achieved almost complete diastereoselectivity for both aliphatic and aromatic aldimines.



Scheme 5

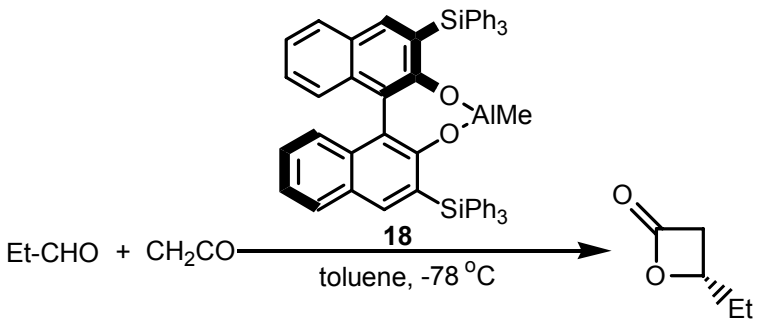
1.3.1.3. [2+2] Cycloadditions

Chiral BINOL ligands have been used to facilitate other stereoselective transformations such as [2+2] cycloadditions. Narasaka's chiral titanium catalyst, prepared from $(Pr^iO)_2TiCl_2$ and tartrate-derived (2*R*,3*R*)-1,1,4,4-tetraphenyl-2,3-*O*-(1-phenylethylidene)-1,2,3,4-butanetetrol **17**, is utilized for the [2+2] cycloaddition of *N*-acyl oxazolidinones to 1,2-propadienyl sulfides possessing α-substituents, which affords methylenecyclobutane derivatives with high enantiomeric purity (**Scheme 6**). These chiral adducts are readily transformed to seven- and eight-membered carbocycles with chiral side chains by the ring-cleavage reaction and subsequent cationic cyclization of the chiral cyclobutane derivative.[48]



Scheme 6

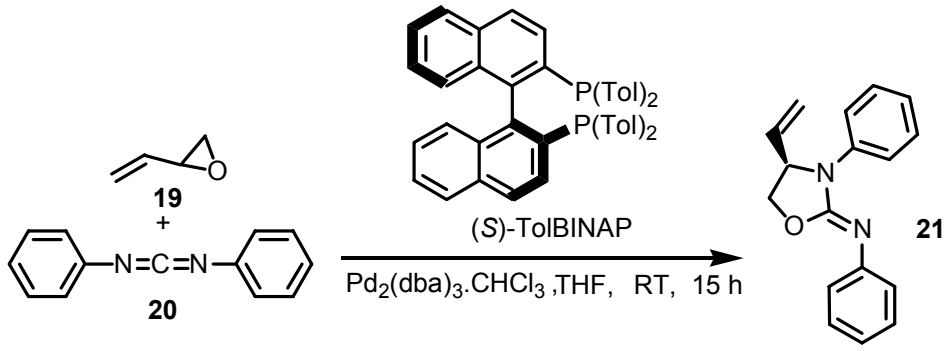
A chiral bis(silyl)BINOL-modified aluminium catalyst **18** has been successfully applied to the asymmetric [2+2] cycloaddtion of ketenes to aldehydes, giving optically active 4-substituted oxetan-2-ones with moderate enantioselectivity (**Scheme 7**).[49]



Scheme 7

1.3.1.4. Other cycloadditions

Cycloaddition of 2-vinyloxiranes (eg **19**) to carbodiimides (eg **20**) proceeds in the presence of $Pd_2(dba)_3 \cdot CHCl_3$ and the phosphorus-containing chiral ligand TolBINAP in THF at room temperature to yield 4-vinyl-1,3-oxazolidin-2-imines such as **21** with up to 95% ee (**Scheme 8**).[50]



Scheme 8

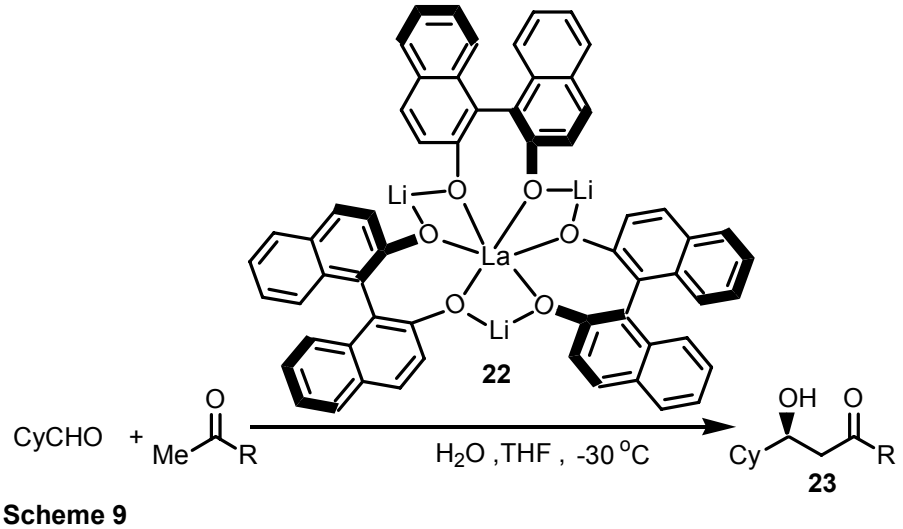
1.3.2. Aldol Reactions

The aldol reaction is one of the most important organic reactions because it is a carbon-carbon bond-forming reaction that produces highly functionalized compounds with a pair of newly generated stereogenic centres.[51] Therefore, the pursuit of high stereoselectivity in the aldol reaction has been of much interest in recent years. In 1981 Masamune *et al*.[52] and Evans *et al*.[53] independently reported highly stereoselective asymmetric aldol reactions by means of chiral boron enolates. These discoveries are milestones in the history of asymmetric synthesis. Especially Evans's boron enolates, which can easily be

prepared from optically active amino acids, have been widely applied to natural products syntheses. The next advance was made in 1982 by Iwasawa and Mukaiyama,[54] who reported highly enantioselective aldol reactions of achiral tin(II) enolates with achiral aldehydes in the presence of a stoichiometric amount of chiral diamine ligands. The following sections are intended to give the reader an impression of the kinds of biaryl ligand-metal complexes that have being used to carry out aldol condensations and related reactions. Once again, a comprehensive survey is not intended.

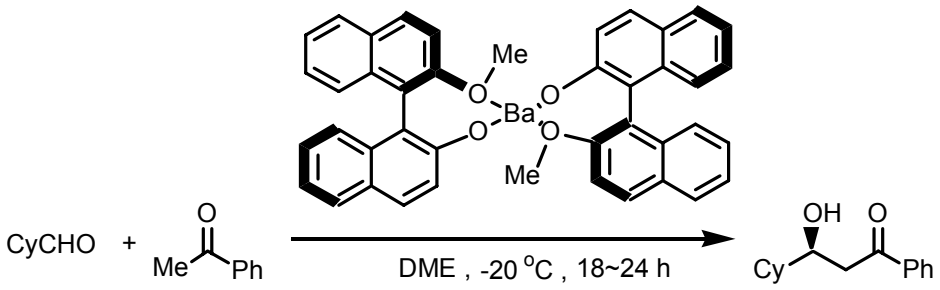
1.3.2.1. Reactions using BINOL ligands

In a series of innovative studies, Shibasaki has developed and studied a family of aldol-addition reactions that proceed by the direct deprotonation of ketone precursors (**Scheme 9**).[55,56] The addition reactions are conducted by using heterobimetallic complexes **22** that are suggested to function in a dual role of aldehyde activation and binding the enolate. In the presence of 20% **22,** excess acetophenone, acetone, or 2-butanone undergo addition to a range of aldehydes to give adducts such as **23** in good yields and up to 94% ee. One of the intriguing features of this remarkable process is that certain enolizable aldehydes such as cyclohexanecarboxaldehyde may be utilized as electrophilic partners in the reaction. In this regard, the reaction of acetophenone enolate with cyclohexane carboxaldehyde gave the aldol adduct **23** in 72% yield and 44% ee.



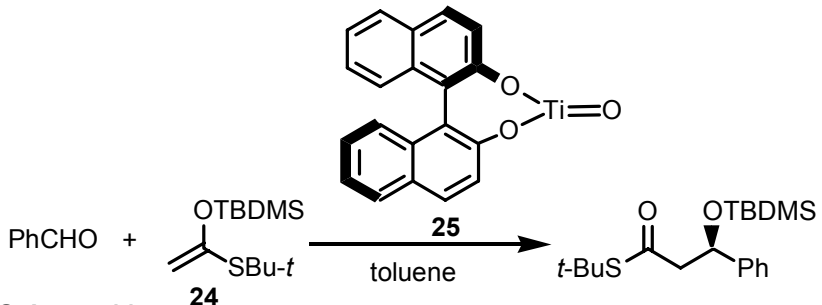
Scheme 9

Shibasaki and co-workers have also generated and studied the complex that assembles *in situ* between the mono *O*-methyl ether of BINOL and $Ba(O^iPr)_2$ in dimethoxyethane (**Scheme 10**).[57] This complex is suggested to catalyze the addition of acetophenone to aldehydes, giving adducts in 77-99% yield and up to 70% ee. An important benefit of this system over the corresponding Ln-based process is evident by the fact that fewer equivalents of ketone are utilised. Additionally, the reaction times are considerably shorter when compared with those prescribed for **22**. In contrast to the models that have been proposed for the heterobimetallic systems, in these systems the barium functions in a dual capacity of activating the aldehyde and ketone components.



Scheme 10

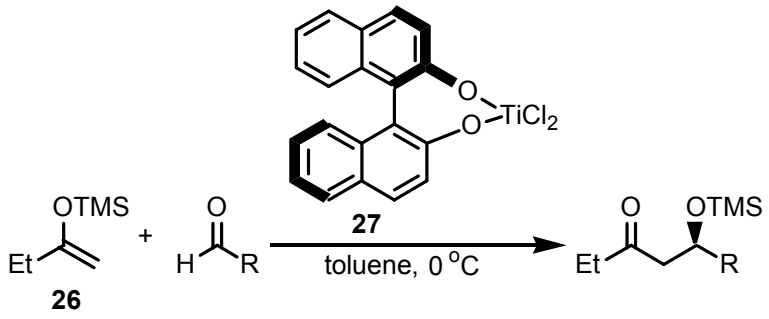
Mukaiyama *et al*.[58] have reported that the oxotitanium(IV) complex **25** is an efficient catalyst for the asymmetric aldol reaction of the silyl ether of thioester **24** with aldehydes to produce the corresponding aldol adducts with moderate-to-high ee (44 – 85% ee) (**Scheme 11**).



Scheme 11

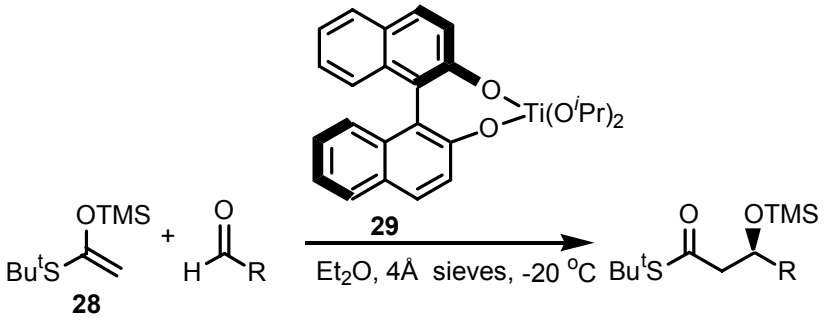
In addition to the above reactions, Mikama has also documented the aldol addition reactions of thioacetate-derived enol TMS ether such as **26** to various highly functionalized aldehydes (**Scheme 12**).[59] The active catalyst **27** is generated as before upon mixing $TiCl_2(O^iPr)_2$ and BINOL. Utilizing as little as 5 mol% of the catalyst the

addition reactions furnished adducts in excellent yields and up to 96% ee. The fact that the process tolerates aldehyde substrates containing polar substituents is noteworthy as few other transition metal-catalyzed aldol reactions exhibit such tolerance of functionality.



Scheme 12

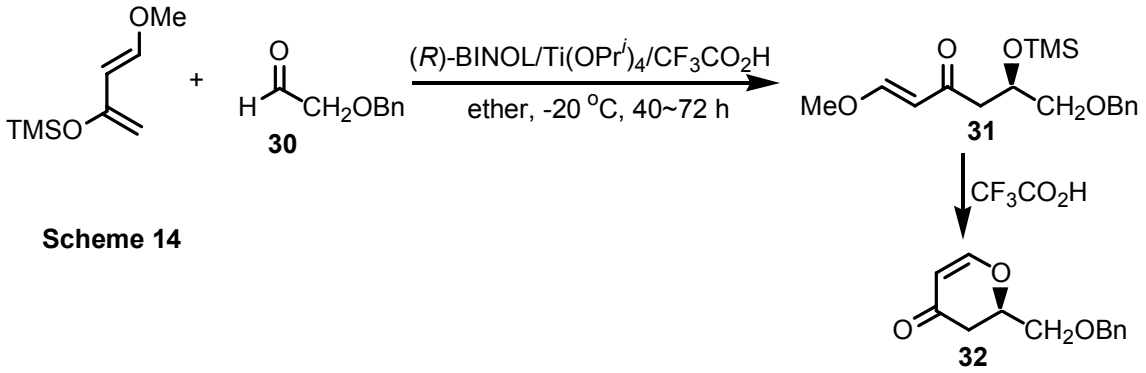
Keck has reported a catalytic enantioselective thioacetate aldol addition reaction that utilizes a Ti(IV) catalyst **29** that is readily prepared *in situ.*[60] The reaction protocol is noteworthy as a consequence of its simplicity of execution. Thus BINOL, $TiCl_2(O^iPr)_2$ and 4Å molecular sieves are mixed in Et_2O at –20 °C; after an aging period, the catalyst mix is ready for use. The addition reactions are best conducted with 10 mol% catalyst in ether at –20 °C with *tert*-butyl thioacetate-derived silyl ketene acetals such as **28**, giving adducts in 90% yield and up to 98% ee for a range of aldehyde substrates as shown in (**Scheme 13**).



Scheme 13

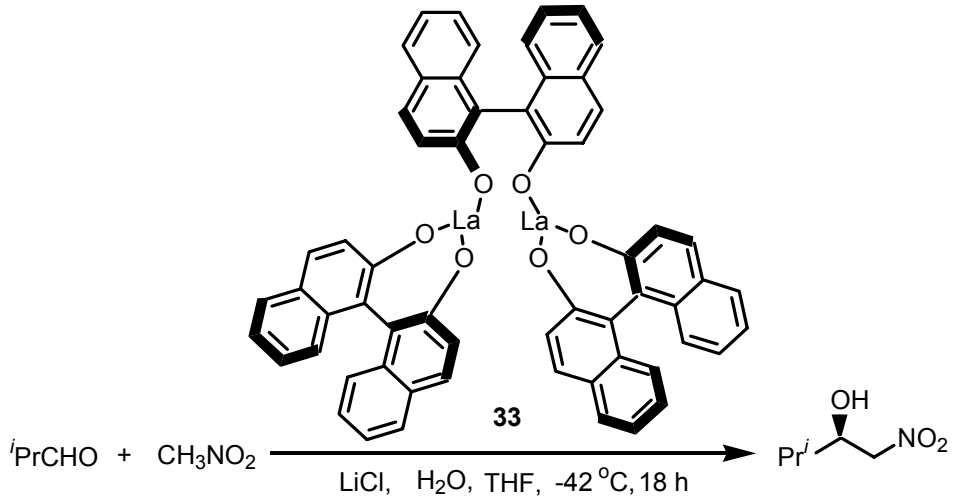
Keck[60] and Carreira[61] have independently reported catalytic asymmetric Mukaiyama aldol reactions. Keck and co-workers also reported the aldol reaction of α-benzyloxy aldehyde **30** with Danishefsky's diene. The aldol product **31** was transformed to the corresponding hetero Diels-Alder-type product **32** through acid-catalyzed cyclization. In

these reactions, the catalyst that is claimed to have BINOL-Ti(OPr^i)$_2$ structure was prepared with a 1:1 or 2:1 ratio of BINOL with Ti(OPr^i)$_4$ in the presence of oven-dried molecular sieves under reflux (**Scheme 14**).[62]



Scheme 14

Since the initial work of Masamune and Evans, many reactions related to the traditional aldol that produce asymmetric centres have been reported. This has included the nitroaldol reaction. For example Shibasaki *et al*.[63] have reported an asymmetric nitroaldol reaction catalyzed by chiral lanthanum biaryl alkoxide **33** to produce an optically active 2-hydroxy-1-nitroalkane with moderate-to-high ee (**Scheme 15**).



Scheme 15

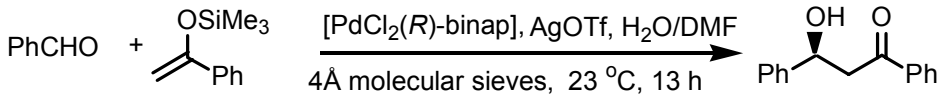
1.3.2.2. Reactions using BINAP ligands

All the reactions described so far have used BINOL as the ligand but as stated earlier BINAP is also an important biaryl compound and in this section one example of the use

of this ligand is described although many other examples exist. This aspect will be expanded on in the second part of the thesis.

Since the pioneering work of Hayashi and Ito on the Ag(I)-and Au(I)-catalyzed aldol addition reactions of isocyanoacetates to aldehyde,[64] until recently only a few reports had appeared describing the use of soft-metal complexes as catalysts for the aldol addition reaction. Most of the developments that have appeared over the past two decades have focused on the design and synthesis of Lewis acids derived from hard oxophilic metals such as titanium, boron, and tin. Among the new developments in the area of enantioselective catalytic aldol addition methods are the increasing number of processes that utilize soft metals, such as Cu(I), Cu(II), Pd(II) and Ag(I) coordination complexes.

Shibasaki has examined catalysis of a complex, prepared *in situ* from $PdCl_2$, AgOTf, (*R*)- or (*S*)-BINAP, 4Å molecular sieves and H_2O, in the aldol addition reaction of enolsilanes (**Scheme 16**).[65] Under these conditions, aryl methyl ketone-derived trimethylsilyl enolates add to benzaldehyde and hydrocinnamaldehyde, affording adducts with up to 73% ee.

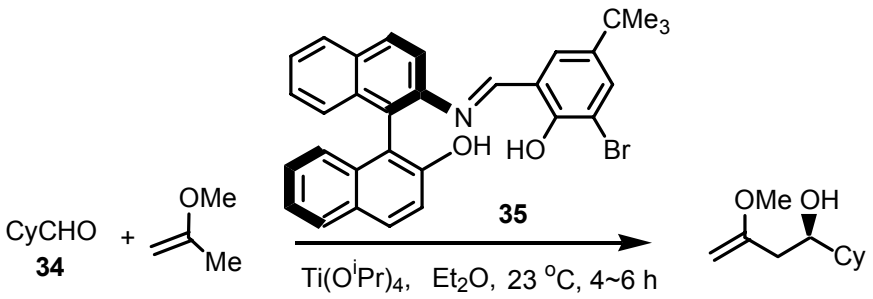


Scheme 16

1.3.2.3. Reactions using mixed N/O ligands

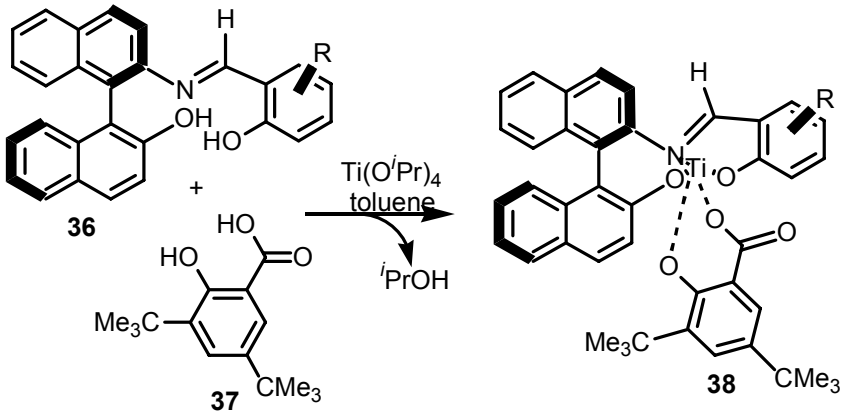
Biaryl compounds possessing "mixed" nitrogen and oxygen atoms ortho to the biaryl axis have also been used successfully in metal catalysed reactions.For example, in a series of reactions, Carreira has reported the enantioselective addition reaction of 2-methoxypropene to aldehydes such as **34** using the catalyst generated upon mixing ligand **35** and $Ti(O^iPr)_4$ with subsequent removal of the released 2-propanol(**Scheme 17**). [66] The unique features of the Ti(IV) catalyst derived from **35** result from the fact that the complex is sufficiently electrophilic to activate a bound aldehyde towards addition by 2-methoxypropene without leading to extensive polymerization of the 2-methoxypropene. An additional attractive feature of the adduct is that, in lieu of an acidic workup, selection

of various oxidative work-up procedures can provide access to the corresponding methyl acetate or the adduct of hydroxyacetone.



Scheme 17

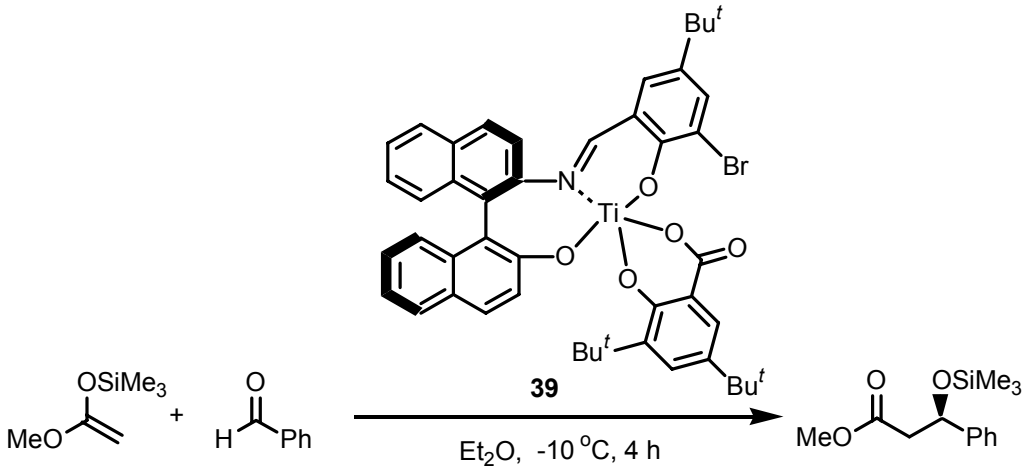
Carreira and co-workers have reported on novel Ti(IV) complexes **38** derived from Ti(O^{i}Pr)$_4$, tridentate ligands **36**, and salicylic acids such as **37**. The complexes serve as competent catalysts for the addition of the methyl acetate-derived silyl ketene acetal to a large range of aldehydes (**Scheme 18**).[67] The salient features of this system include the wide range of functionalized aliphatic and aromatic aldehydes that may be used, the ability to carry out the reaction with 0.2-5 mol% catalyst-loading, and experimental ease with which the process is executed. Thus the reaction can be carried out at –10 to 0 °C, in a variety of solvents, without recourse to slow addition of reagents. The adducts from the catalytic reaction were isolated with excellent enantiopurities up to 99% ee.



Scheme 18

Carreira *et al.*[68] have used a chiral Schiff base-titanium complex **39** as the catalyst for the aldol reactions of acetate-derived ketene silyl acetals (**Scheme 19**). The catalyst was prepared in toluene in the presence of salicylic acid, which was reported to be crucial to attain a high enantioselectivity. A similar Schiff base-titanium complex is also applicable to the carbonyl-ene type reaction with 2-methoxypropene. Although the reaction, when

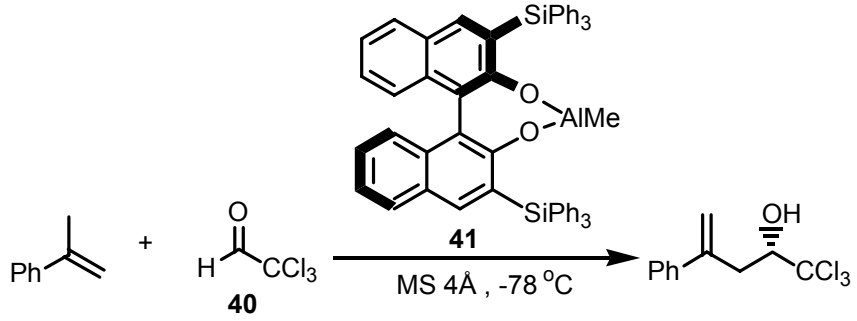
conducted in toluene or ether, did not provide any addition product, excellent chemical yield and enantioselectivity were achieved by using 2-methoxypropene as the solvent.



Scheme 19

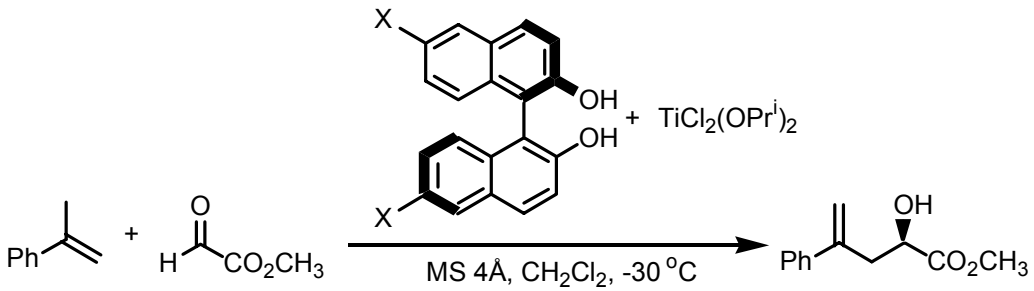
1.3.3. Ene reactions

The class of ene reactions which involves a carbonyl compound as the enophile is referred to here as the carbonyl-ene reaction.[69] This constitutes a useful synthetic method for the stereocontrolled construction of the carbon skeleton using either a stoichiometric or catalytic amount of various Lewis acids.[70,71] Ene reactions have also been successfully catalysed by BINOL derivatives. For example, Yamamoto *et al*. have reported the asymmetric catalysis of a chiral Lewis acid in a carbonyl-ene reaction, which uses chloral **40** as the enophile and an aluminium catalyst **41** with enantiopure 3,3'-bissilylated BINOL to give the corresponding homoallylic alcohol with 78% ee in 79% yield (**Scheme 20**).



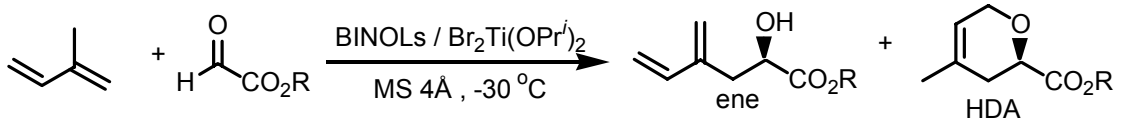
Scheme 20

Mikama and Nakai have developed a chiral titanium catalyst for the glyoxylate-ene reaction, which provides the corresponding α-hydroxy esters of biological and synthetic importance[72] in an enantioselective fashion.[73,74] Various chiral titanium catalysts were screened.[75] The best result was obtained with a titanium catalyst prepared *in situ* in the presence of MS 4Å from diisopropoxytitanium dihalide $X_2Ti(OPr^i)_2$: (X=Br[76] or Cl[77]), and enantiopure BINOL or 6-Br-BINOL (**Scheme 21**).[78] The remarkable levels of enantioselectivity and rate acceleration observed with these BINOL-Ti catalysts[79] stem from the favorable influence of the inherent C_2 symmetry and higher acidity of BINOLs compared with those of aliphatic diols. The reaction is applicable to a variety of 1,1'-disubstituted olefins to provide the ene products with extremely high enantiopurity.



Scheme 21

In the carbonyl-ene reaction with a conjugate diene having allylic hydrogen, such as isoprene, there is a problem of so-called "periselectivity", arising from the competitive formation of the ene product versus the hetero Diels-Alder product. In the reaction of glyoxylate with isoprene under the catalysis of BINOL-Ti complex, the ratio of ene/hetero Diels-Alder (HDA) products depends not only on the solvent used but also on the chiral ligand of titanium complex and further on the bulkiness of alkyl group (R) in glyoxylate (**Scheme 22**).

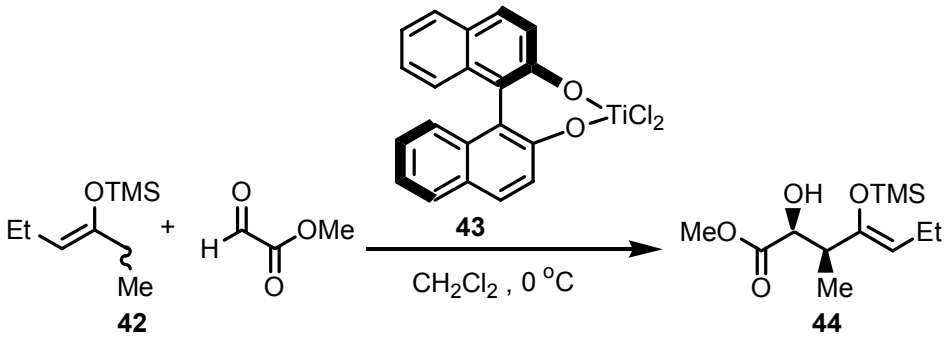


Scheme 22

Dramatic changeover is observed not only in the ene/hetero Diels-Alder product ratio, but also in the absolute stereochemistry upon changing the central metal from Ti to Al. Thus,

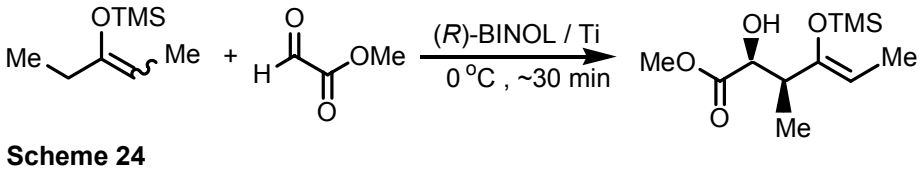
Jørgensen *et al.*[80] reported the hetero Diels-Alder-selective reaction of ethyl glyoxylate with 2,3-dimethyl-1,3-butadiene catalyzed by a BINOL-derived Al complex , where the hetero Diels-Alder product was obtained with up to 89% periselectivity and high enantiopurity. The absolute configuration was opposite to that observed when using BINOL-Ti catalyst.

Mikama has also reported a related ene-like process involving glyoxylates and ketone-derived enolsilanes such as **42** (**Scheme 23**).[81] The enol ether adducts such as **44** yield the corresponding β-hydroxy ketone upon treatment with mild acid. On the basis of an analysis of the stereo-and regiochemical outcome of the addition reaction, Mikama has invoked a monodentate complex between aldehyde and metal complex **43**, in contrast to the typical transition-state structures involving glyoxylates that are suggested to involve metal/aldehyde chelates.



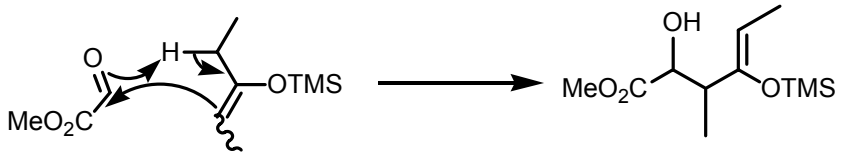
Scheme 23

An unusual ene reaction is shown in **Scheme 24** below, in which the ene component is a silyl enol ether.



Scheme 24

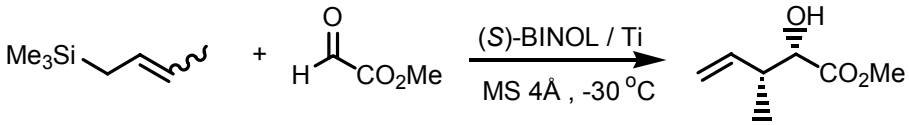
Although the product looks like an aldol product, the proposed mechanism is an ene reaction, formally represented as follows.



In general, an acyclic antiperiplanar transition-state model has been used to explain the formation of the *syn*-diastereomer from either (*E*)-or (*Z*)-silyl enol ethers.[82]

1.3.4. Allylmetal addition to carbonyl groups

BINOL-Ti complexes have been shown to serve as efficient asymmetric catalysts for the carbonyl addition reaction of allylic stannanes and silanes.[83,84] The addition reactions of (*E*)-2-butenyl-silane and –stannane to glyoxylate proceed smoothly to afford the corresponding *syn*-product with high ee (**Scheme 25**).[83] It has also been shown that Sakurai-Hosomi reaction of methallylsilanes with glyoxylates is catalyzed by the BINOL-Ti complex to give products, surprisingly, in an allylic silane (ene product) form with high enantioselectivity.[84]



Scheme 25

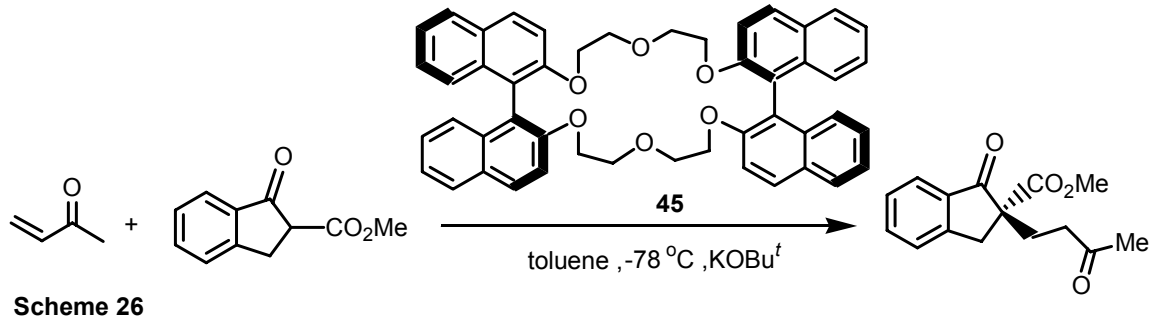
Catalysis of BINOL-Ti complexes in the reaction of aliphatic and aromatic aldehydes with an allylstannane has also been reported independently by Umani-Ronchi[85] and Keck.[86] The former group has suggested that a new complex generated by the reaction of the BINOL-Ti complex with allylstannane is the catalytic species that provides remarkably high enantioselectivity.

1.3.5. Michael additions

Michael addition of nucleophiles to α,β-unsaturated carbonyl compounds and related systems is a fundamental process in organic chemistry, because it forms a carbon-carbon, carbon-nitrogen, carbon-sulfur, or carbon-oxygen bond at the β-position of the carbonyl, and produces highly functionalized compounds with one or two stereogenic centres. The

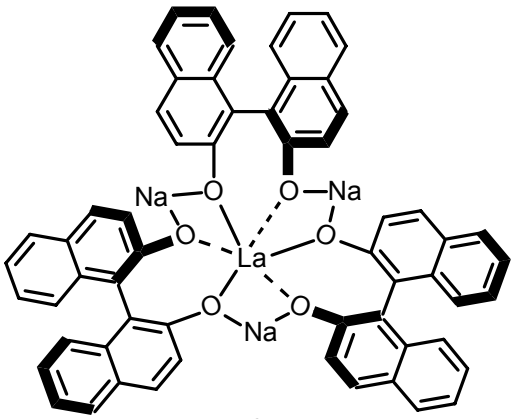
initial adduct is an enolate, and this important reactive species can perform a variety of nucleophilic reactions such as aldol condensation, Michael addition, and alkylation reaction, which again can generate new chiral centres. Chiral ligands have been used to control both the relative and the absolute stereochemistry of the products and a selection of recent examples involving such ligands is shown below.

Chiral alkoxides and naphthoxides have been used as catalysts for the Michael reaction. An early successful example was reported by Cram and co-workers, who used 4 mol% of KOBu^t-chiral crown ether **45** complex as the catalyst to afford the Michael adduct with up to 99% ee (**Scheme 26**). [87] In this case the KOBu^t complexes with chiral crown ether **45** play two roles, that is, KO^{t}Bu-**45** functions as (i) a Brønsted base to abstract a proton and (ii) a Lewis acid to activate the enone. KOBu^t may be a suitable Brønsted base for generation of an enolate, but it may not be the best Lewis acid for activating enones. If these two roles of the catalyst are separated to have both working ideally at a defined position in one catalyst, the catalyst may achieve excellent enantioselectivity as well as reactivity for a broad range of substrates.

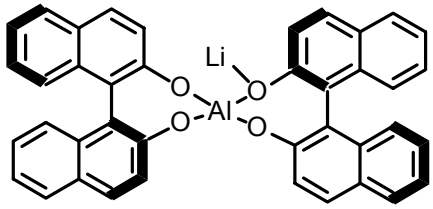


Scheme 26

This idea was realized very successfully by Shibasaki and Sasai in their heterobimetallic chiral catalysts.[88] They introduced two representative well-defined catalysts, LSB **46** (lanthanum/sodium/BINOL complex) and ALB **47** (aluminium/lithium/BINOL complex), whose structures were confirmed by X-ray crystallography. In these catalysts, the alkali metal (Na, Li, or K)-naphthoxide works as a Brønsted base and the lanthanum or aluminium ion works as a Lewis acid.



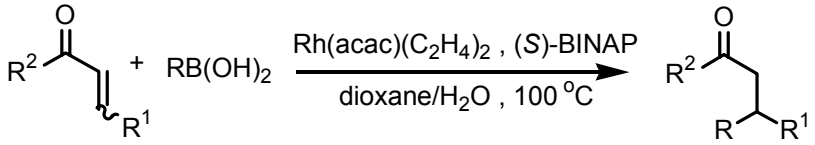
46



47

Complex LSB is readily prepared either by the reaction of $La(O^iPr)_3$ with 3 equiv. of BINOL followed by the addition of NaO^tBu (3 equiv.) or by the reaction of $LaCl_3 \cdot nH_2O$ with sodium binaphthoxide. The complex is stable to oxygen and moisture and has been proven to be effective in the catalytic Michael reaction of various enones with either malonates or β-keto esters. The Michael adducts with up to 92% ee were obtained in almost quantitative yield.[89] In general, the use of THF as solvent gave best results except for the case of the LSB-catalyzed reaction of *trans*-chalcone with dimethyl malonate, wherein the use of toluene was essential to give the adduct with good ee. The effects of the central metal (La, Pr, and Gd) on asymmetric induction were also examined in the same reaction, and LSB was found to be the best catalyst.

Hayashi and Miyaura have reported that far less nucleophilic aryl- and alkenyl-boronic acids can react with a variety of enones in the presence of a BINAP-rhodium catalyst to give adducts with high enantiopurity in general (**Scheme 27**).[90] The one pot procedure, involving the hydroboration of alkynes as the first step (R = alkenyl), was achieved in the presence of amines without affecting the enantioselectivity.[90]

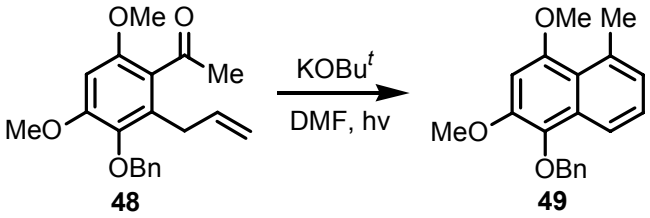


Scheme 27

From this discussion it should be clear to the reader that new methods for the synthesis of biaryl compounds can be important as these ligands are used extensively to facilitate stereoselective chemical reactions.

1.4. Origins and aims of this project

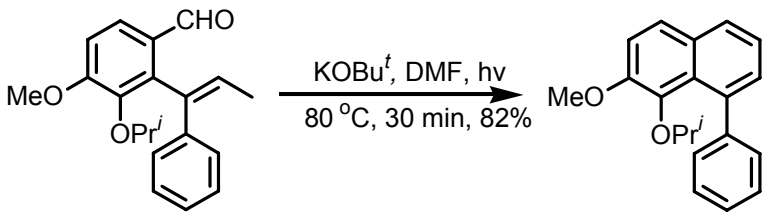
Owing to the biological activity of naphthalene based compounds and their uses as ligands for catalysis as discussed above, the synthesis of naphthalene and naphthoquinone derivatives is of extreme importance. These are not going to be described in detail in this part of thesis but they include among others Diels-Alder reactions,[91] synthesis by rearrangement of hydroxycyclobutenones,[92] from juglone dimers,[93] by transition metal-mediated cyclisations,[94] and dehydrogenation of tetralins.[95] Details of recent syntheses of naphthalenes can be found in a recent review.[96] In our laboratories we have also pursued a programme dedicated towards the synthesis of polyaromatic compounds such as naphthalenes. Novel synthetic methodology recently discovered[97] in our group resulted in the formation of substituted naphthalenes such as **49**, which was synthesized by the cyclization of 2-allyl-3-benzyloxy-4,6-dimethoxybenzene **48** using potassium *t*-butoxide in DMF in the presence of a light source (**Scheme 28**). A possible mechanism of this reaction is described in detail by both Manzini[98] and Rousseau.[38]



48 **49**

Scheme 28

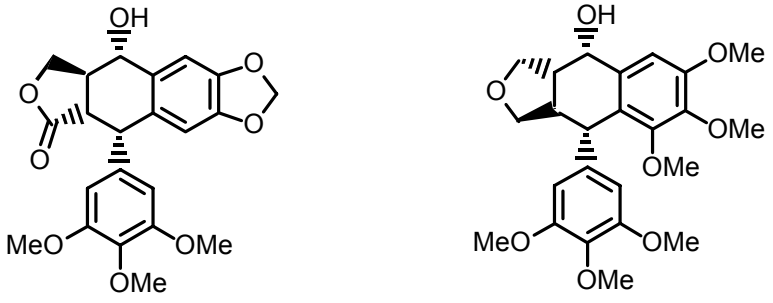
During the course of these investigations, de Koning and co-workers were able to use the same methodology to synthesize naphthalene-bearing aryl substituents **51** from substituted phenyl benzaldehyde **50** (**Scheme 29**) which stimulated our interest in the synthesis of biaryl compounds. The synthesis of biaryl compounds has also been the topic of many other research groups.[99] In general methods used to access these compounds involve the coupling of two aromatic precursors using Ullmann, Suzuki, Negishi or Stille coupling procedures. Alternatively, the synthesis of ligands such as BINOL (as described above) can be accomplished by using oxidative-coupling methods starting from 2-naphthol and its derivatives. In the procedure developed in our laborotries the traditional methods were not needed to synthesize **51** from **50**.



50 **51**

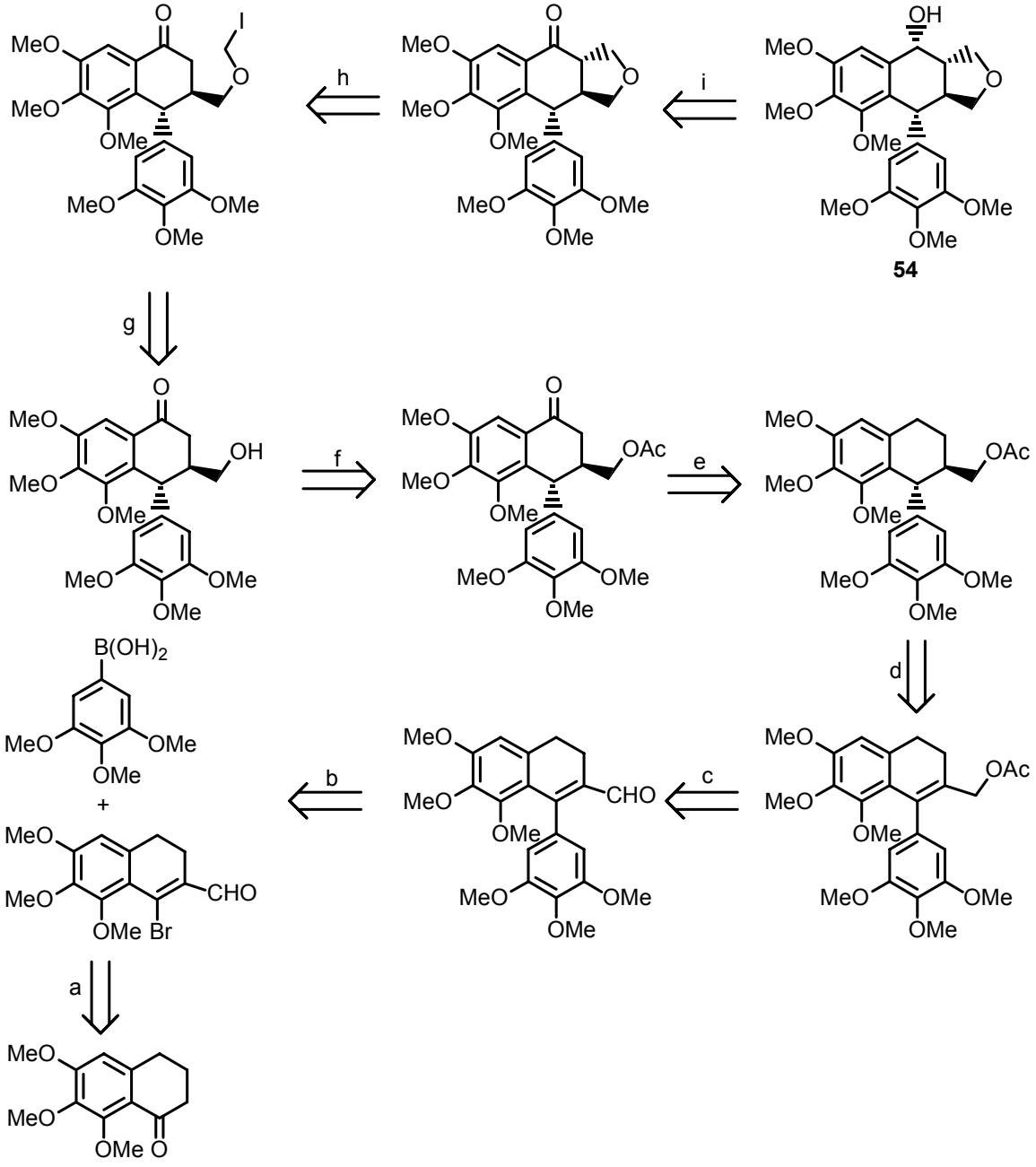
Scheme 29

The original aim of this project was quite different and we wished to examine the possibility of synthesizing aryl-substituted tetralins using our expertise gained in reactions such as the Suzuki coupling reaction to construct biaryl compounds. The plan was to look into a new synthetic route for aryltetralin lignans such as podophyllotoxin **52** and aglacins (e.g. aglacin A **53**). Isolated from *Podophyllum peltatum* and *Podophyllum emodi*, podophyllotoxin is a potent antimitotic, binding to tubulin and inhibiting microtubule formation.[99] Other congeners such as etoposide, teniposide and etopophos, have emerged as promising drug candidates.[100]

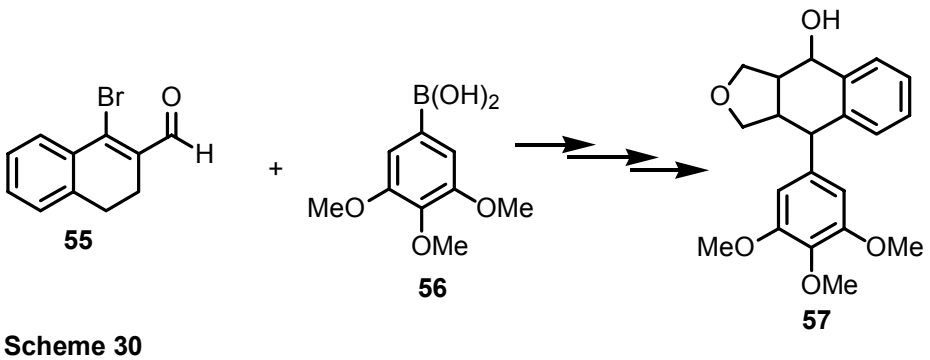


52 **53**

As can be seen from the diagrams, the structures of aglacin A **53** and podophyllotoxin **52** are very similar and thus similar strategies should be appropriate for both. For example, we planned to access aglacin A **54** via a disconnection protocol leading back to the simple and readily available tetralone (step a). Key steps in this route include a Suzuki coupling between a substituted boronic acid and brominated tetralone (step b), and a crucial benzylic oxidation (step e).

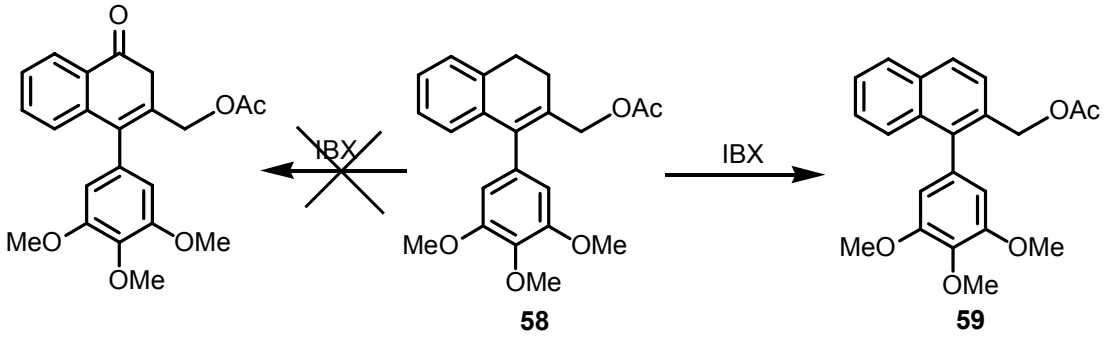


The initial phase of the project was intended to involve the achiral synthesis of the aglacin analogue **57** (**Scheme 30**) without methoxy groups on the tetralin moiety, starting with the Suzuki coupling of 1-bromo-3,4-dihydro-2-naphthaldehyde **55** and 3,4,5-trimethoxy-1-phenylboronic acid **56**.



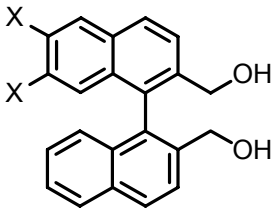
Scheme 30

However at a very early stage of the synthesis we discovered that oxidation of the substituted dihydro **58** with IBX (iodoxybenzoic acid), which was intended to bring about benzylic oxidation, in fact gave the aromatized product **59** (**Scheme 31**). We saw this as an opportunity to explore our novel method as an alternative route to assemble aryl-substituted naphthalenes. The revised primary aim of this project then became the synthesis of substituted naphthalenes containing a biaryl axis from tetralone precursors.



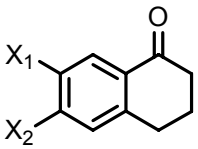
Scheme 31

As we also have already seen how arylnaphthalenes, in particular BINOL derivatives, play a key role as ligands in various chemical reactions catalyzed by transition metals, our subsidiary aim was to synthesize ligands related to the BINOL derivatives, for example, as illustrated by compounds **60**. The key difference between BINOL and the compounds we wished to prepare lay in the fact that the ligands were no longer naphthols but benzylic alcohols. These results are described in part two of the thesis. Both these aims would be pursued commencing from readily available tetralones **61**, **62** and **63** as starting materials as will be discussed in the results and discussion section of the thesis.



X = H or OMe

60



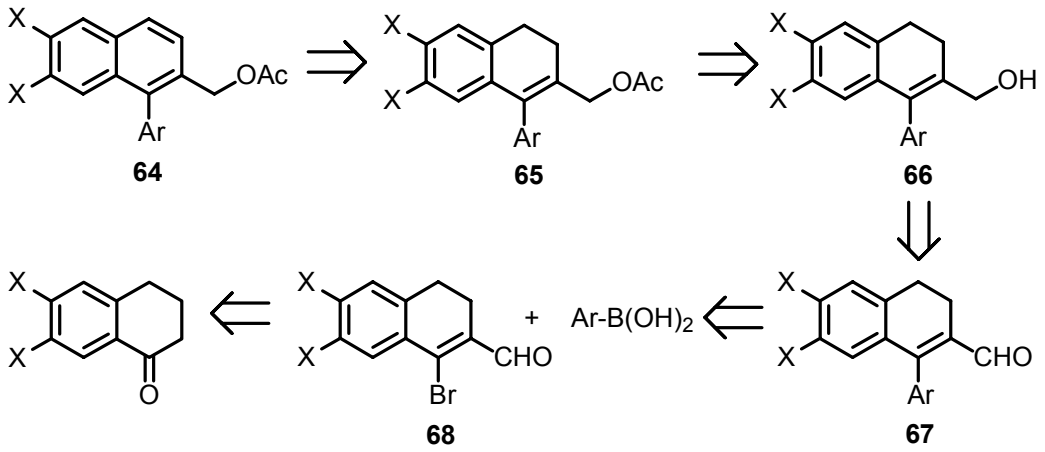
61: $X_1 = X_2 = H$

62: $X_1 = X_2 = OMe$

63: $X_1 = H$, $X_2 = OMe$

Chapter 2: Results and Discussion 1

In this chapter, results obtained in the synthesis of naphthalenes bearing aryl substituents using methodology developed in our laboratory will be discussed. A general retrosynthesis of the envisaged arylnaphthalenes is shown in **Scheme 32**.



Scheme 32

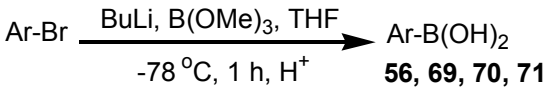
As a result of our earlier transformation of dihydro **58** into arylnaphthalene **59**, we envisaged that in general, naphthalenes **64** could be obtained by the dehydrogenation of substituted dihydro esters **65**, which in turn are achievable by the acetylation of alcohols **66**. The alcohols should, in turn, be obtainable from the reduction of dihydro naphthaldehydes **67**, which are themselves potentially available from the Suzuki coupling of the relevant arylboronic acids and bromodihydro naphthaldehydes **68**. Bromodihydronaphthaldehydes are obtainable from the appropriate α-tetralones using a known literature method.[101]

2.1 Synthesis of aryl-substituted naphthalenes from α-tetralone

Readily available α-tetralone **61** was brominated and formylated to give 1-bromo-3,4-dihydro-2-naphthaldehyde **55** using dimethylformamide and phosphorus tribromide in dichloromethane as has been described in literature.[101] The structure of product **55** was confirmed by ^{1}H nmr spectroscopy, where a singlet integrating for one proton was observed at 10.25 ppm for the aldehydic proton. Also two triplets, each integrating for

two protons and each with J = 8.3 Hz, were observed at 2.83 ppm and 2.61 ppm and are assigned to the two methylene groups.

The second precursors for the coupling reactions, boronic acids, were obtained from the requisite halogenated aryl compounds using traditional methodology i.e initial treatment with *n*-butyllithium, followed by trimethyl borate and then converting the boronic ester into the required boronic acid by treating each intermediate with hydrochloric acid. As it is known that the boronic acids derived in this way are very difficult to purify, they were used in the subsequent reaction as the crude material. The boronic acids synthesized and used in this project were 3,4,5-trimethoxyphenylboronic acid **56**, 1-naphthylboronic acid **69**, phenylboronic acid **70** and *o*-tolylboronic acid **71** (**Scheme 33**). Approximate crude yields are listed in **Table 1** below.



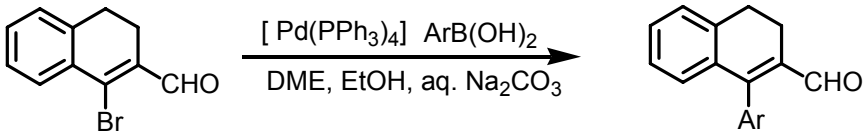
Scheme 33

Table 1: % Yields of boronic acids and aryl-substituted dihydronaphthaldehydes.

Ar	Boronic acid	% yield	Aldehyde	% yield
3,4,5-trimethoxyphenyl	**56**	100	**72**	83
1-naphthyl	**69**	63	**73**	93
phenyl	**70**	89	**74**	100
o-tolyl	**71**	85	**75**	78

The next step in our synthesis was the Suzuki coupling of 1-bromo-3,4-dihydro-2-naphthaldehyde **55** with each of the synthesized boronic acids. As shown in **Scheme 34** exposure of **55** to catalytic [$Pd(PPh_3)_4$] in the presence of aqueous Na_2CO_3 and DME/EtOH under reflux afforded the desired Suzuki coupling products **72**, **73**, **74** and **75** in good to excellent yields (**Table 1**). Our results were confirmed by the spectroscopic data. ^{1}H nmr spectroscopy of all four compounds still showed a singlet integrating for one proton at ~9 ppm (aldehyde), and two triplets integrating for two protons each at ~3 ppm and ~2 ppm (two methylene groups). The ^{13}C nmr spectra of all four compounds

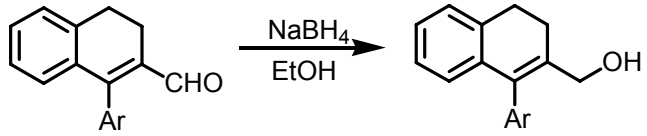
revealed signals at ~193 ppm confirming the presence of the carbonyl carbon and signals at ~20 ppm and ~27 ppm assigned to the two methylene carbons. Infrared spectra of the compounds showed a strong absorption at ~1660 cm^{-1}, a region which is characteristic for aromatic aldehydes.



55 **72 - 75**

Scheme 34

The resulting naphthaldehydes were then reduced to alcohols (**76-79**) in excellent yields (**Table 2**) using sodium borohydride in ethanol at room temperature (**Scheme 35**). It was clear from the spectroscopic data that the desired products were formed as the infrared spectra of all four compounds showed a strong broad absorption at ~3300 cm^{-1} which is diagnostic of alcohols. Also the stretching bands at about 1660 cm^{-1} (aldehyde) of the starting material were no longer present. The ^{1}H nmr spectra were characterized by the disappearance of a signal (singlet) at ~9 ppm (aldehyde) and the appearance of a new signal (singlet) at ~4 ppm (CH_2OH). The ^{13}C nmr spectra also showed the disappearance of a signal at ~193 ppm (aldehyde) and appearance of a new signal at ~64 ppm (CH_2OH).



72 - 75 **76 - 79**

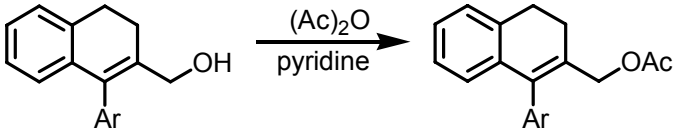
Scheme 35

Table 2: Percentage yields of aryl-substituted dihydro alcohols.

Alcohol	Ar	% yield
76	3,4,5-trimethoxyphenyl	100
77	1-naphthyl	96
78	phenyl	94
79	*o*-tolyl	94

The resultant alcohols **76-79** were then acetylated using acetic anhydride and pyridine under reflux (**Scheme 36**). Again, the infrared spectra provided evidence that the acetates

58, 80, 81, 82 had formed. All four spectra showed a disappearance of the broad signal at ~3300 cm^{-1} (OH group) and the appearance of a new signal at ~1730 cm^{-1} diagnostic of an ester functional group. The ^{1}H nmr spectra were characterized by the appearance of a new signal (singlet) at ~2 ppm integrating for three protons depicting the protons of the methyl group. The ^{13}C nmr spectra showed the appearance of two new signals, one at ~170 ppm for the carbonyl carbon of the ester group and the other one at ~28 ppm, characteristic for the methyl carbon.



76 - 79 **58, 80 - 82**

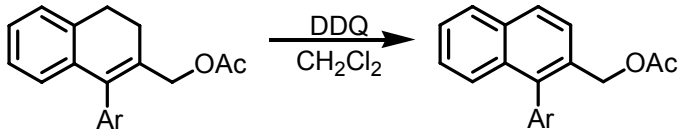
Scheme 36

Table 3: Percentage yields of aryl-substituted dihydro acetates.

Acetate	Ar	% yield
58	3,4,5-trimethoxyphenyl	98
80	1-naphthyl	94
81	phenyl	82
82	*o*-tolyl	94

At this stage all that was now required was the oxidation of 3,4-dihydro acetates to afford the desired arylnaphthalenes. The dihydro esters **58**, **80-82** were easily dehydrogenated to the desired substituted arylnaphthalenes **59**, **83-85** in good to excellent yields (**Table 4**) using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in dichloromethane (**Scheme 37**). It has to be mentioned that it was at this point that our project aims changed to the synthesis of arylnaphthalenes whilst we were using an alternative oxidant IBX, which proved to be a good dehydrogenating agent. At this stage of our new project we had run out of IBX and knowing that DDQ is also a dehydrogenating agent, we used it in the aromatization step and it proved to be successful. Also dichloromethane was found to be more successful as a solvent than acetic acid which was tried earlier but with poor yields. The ^{1}H nmr spectra of all four products showed the disappearance of two signals (triplets, J = 8 Hz) at ~3 ppm (2 x CH_2) and the appearance of new signals in the aromatic region, ~6-7 ppm. The ^{13}C nmr spectra were also characterized by the disappearance of

two signals at ~20 ppm and ~25 ppm and the appearance of two new signals in the aromatic region.



58, 80 - 82 **59, 83 - 85**

Scheme 37

Table 4: Percentage yields of aryl-substituted naphthalenes.

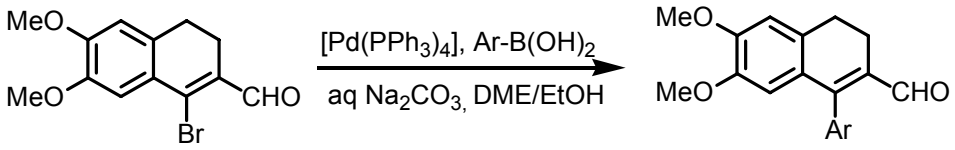
Naphthalene	Ar	% yield
59	3,4,5-trimethoxyphenyl	78
83	1-naphthyl	95
84	phenyl	93
85	*o*-tolyl	100

At this point we decided to broaden the range of aryl-naphthalenes and chose to make aryl-naphthalenes possessing oxygens on the naphthalene portion.

2.2 Synthesis of aryl-substituted naphthalenes from 6,7-dimethoxy-α-tetralone

1-Bromo-6,7-dimethoxy-3,4-dihydro-2-naphthaldehyde **86** was synthesized from 6,7-dimethoxy-α-tetralone **62** using dimethylformamide and phosphorus tribromide in dichloromethane in a similar manner to that described for tetralone except that no heating was required. Again spectroscopic data confirmed formation of the products since the ^{1}H nmr spectrum showed a singlet at 10.19 ppm for the aldehyde proton, two singlets at 7.42 ppm and 6.71 ppm showing two aromatic protons, a singlet integrating for six protons at 3.94 ppm confirming the two methoxy groups and two triplets at 2.77 ppm and 2.61 ppm. Both triplets integrate for two protons each and have a coupling constant of 8.2 Hz. Therefore they represent the two adjacent CH_2 groups.

As shown in **Scheme 38**, under aqueous Suzuki coupling reaction in the presence of catalytic [$Pd(PPh_3)_4$] the exposure of naphthaldehyde **86** to boronic acids **56, 69 70** and **71** (prepared as outlined above) gave 1-aryl-6,7-dimethoxy-3,4-dihydro-2-naphthaldehydes **87, 88, 89,** and **90** in good yields (**Table 5**). Spectroscopic data confirmed our results as the infrared spectra of the naphthaldehydes showed a signal at ~1650 cm^{-1} consistent with the carbonyl group of aldehydes. ^1H nmr spectroscopy revealed singlets at ~9.5 ppm for the aldehydic proton and two triplets at ~3 ppm and ~2 ppm confirming the two CH_2 groups. The ^{13}C nmr spectra showed signals at ~193 ppm consistent with aldehydes and two signals at ~27 ppm and ~20 ppm, confirming the presence of two methylene groups.



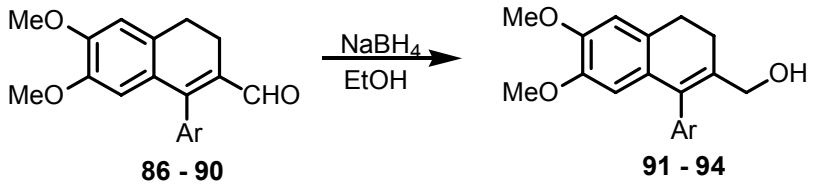
86 **87 - 90**

Scheme 38

Table 5: Percentage yields of aryl-substituted dimethoxydihydronaphthaldehydes.

Aldehyde	Ar	% yield
87	3,4,5-trimethoxyphenyl	88
88	1-naphthyl	87
89	phenyl	83
90	*o*-tolyl	98

Reduction of the naphthaldehydes using sodium borohydride in ethanol gave dimethoxydihydronaphthalene alcohols **91, 92, 93** and **94** (**Scheme 39**) in very good yields (**Table 6**). The infrared spectra of the resultant alcohols were characterized by a broad signal at ~3500 cm^{-1}. Also there was a disappearance of a signal at ~1650 cm^{-1} from the naphthaldehydes. The ^1H nmr spectra showed a disappearance of a signal (singlet) at ~9.5 ppm (aldehyde) and a new signal (singlet) appeared at ~4 ppm (CH_2OH). The ^{13}C nmr spectra revealed that the signal at ~193 ppm (aldehyde) was replaced by a signal at ~64 ppm (CH_2OH).



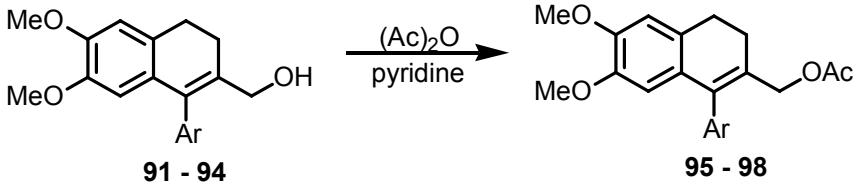
86 - 90 **91 - 94**

Scheme 39

Table 6: Percentage yields of aryl-substituted dimethoxydihydronaphthalene alcohols.

Alcohol	Ar	% yield
91	3,4,5-trimethoxyphenyl	87
92	1-naphthyl	100
93	phenyl	100
94	*o*-tolyl	87

The resultant alcohols were then esterified as described earlier to afford esters **95**, **96**, **97**, and **98** using pyridine and acetic anhydride (**Scheme 40**) in good yields (**Table 7**). The infrared spectra showed the disappearance of a broad signal at ~3500 cm^{-1} (alcohols) and emergence of a new signal at ~1730 cm^{-1} (esters). The ^{1}H nmr spectra were characterized by the appearance of a new signal (singlet) at ~2 ppm (CH_3) integrating for three protons. The ^{13}C nmr spectra showed the appearance of two new signals, one at ~170 ppm (C=O of the ester) and another one at ~28 ppm (CH_3).



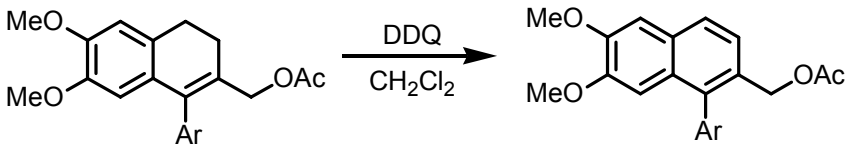
91 - 94 **95 - 98**

Scheme 40

Table 7: Percentage yields of aryl-substituted dimethoxydihydronaphthalene acetates.

Acetate	Ar	% yield
95	3,4,5-trimethoxyphenyl	80
96	1-naphthyl	89
97	phenyl	88
98	*o*-tolyl	88

The subsequent dimethoxydihydronaphthalene esters were then dehydrogenated as before to the desired substituted aryl naphthalenes **99**, **100**, **101**, and **102** using DDQ in dichloromethane (**Scheme 41**) and the products were obtained in satisfactorily yields (**Table 8**). It was clear from the spectroscopic data that the envisaged products were obtained, for example the ^{1}H nmr spectra of all four arylnaphthalenes showed the disappearance of the two triplets (J = 8.3 Hz) at ~2.4 ppm and ~2.8 ppm. New signals were observed in the aromatic region, ~6-7 ppm. Also the ^{13}C nmr spectra showed that two signals in the aliphatic region, ~21 ppm and ~26 ppm, had vanished and that new signals emerged in the aromatic region.



95 - 98 **99 - 102**

Scheme 41

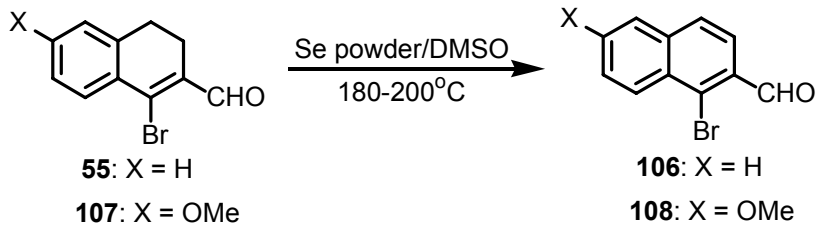
Table 8: Percentage yields of aryl-substituted dimethoxynaphthalenes.

Naphthalene	Ar	% yield
99	3,4,5-trimethoxyphenyl	74
100	1-naphthyl	78
101	phenyl	80
102	*o*-tolyl	78

2.3 Aromatization of dihydronaphthaldehydes

In an attempt to shorten the route towards the synthesis of substituted naphthalenes, we thought it would be better if the aromatization step was done earlier in the synthesis. Therefore an attempt was made to aromatize 1-bromo-3,4-dihydro naphthaldehyde **55** using DDQ in dichloromethane, as was done with the dihydro esters. In most cases only the starting material was recovered and sometimes uncharacterizable product was determined. After a thorough search in literature, it was found that selenium powder had in fact being used in aromatization reactions at very high temperatures (~300 °C). It was then decided that selenium powder be used in an attempt to aromatize compound **55**.

Although the reaction was very messy (and potentially toxic) and difficult to control since both the starting material and the product had the same R_f value by thin layer chromatography, naphthaldehyde **106** was obtained in a maximum yield of 69% using selenium powder in dimethyl sulfoxide at temperatures between 180 and 200 °C. After this success, we decided to explore the reaction further by aromatization of 1-bromo-6-methoxy-3,4-dihydro-2-naphthaldehyde **107** that was obtained by the bromination and formylation of 6-methoxy-α-tetralone **63** utilizing the same methodolody used for the bromination and formylation of α-tetralone **61**. Here too, even though the reaction was very difficult to accomplish, compound **107** was successfully aromatized to 1-bromo-6-methoxy-1-naphthaldehyde **108** using selenium powder and dimethyl sulfoxide in a satisfactory yield of 72% (**Scheme 42**).



55: X = H
107: X = OMe

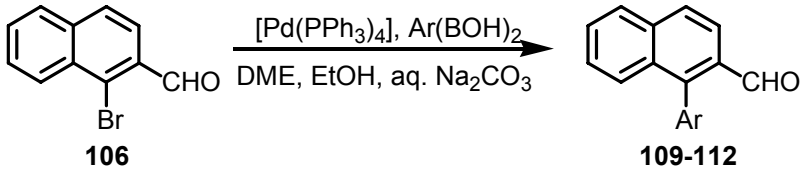
106: X = H
108: X = OMe

Scheme 42

Confirmation of the structure of the products was obtained from spectroscopy, whereby the ^{1}H nmr spectra of both compounds revealed the disappearance of two signals integrating for two protons between 2 and 3 ppm (indicative of the methylene protons). Also the number of aromatic protons had increased by two confirming the oxidation step was successful. The ^{13}C nmr spectra of the two compounds showed the disappearance of two carbons in the aliphatic region (indicative of the methylene carbons) and appearance of two extra signals in the aromatic region, indeed confirming oxidation. The next step was to use both naphthaldehydes in the Suzuki coupling reactions and the steps that follow.

2.4 Synthesis of aryl substituted naphthalenes from 1-bromo-2-naphthaldehyde

The resultant 1-bromo-2-naphthaldehyde **106** was then coupled to arylboronic acids **56**, **69**, **70** and **71** (prepared as mentioned above) using the aqueous Suzuki coupling conditions (**Scheme 43**). The envisaged aryl-substituted naphthaldehydes **109**, **110**, **111**, and **112** were obtained in good to excellent yields (**Table 9**). Confirmation was again obtained from nmr spectroscopy. ^{1}H nmr spectroscopy indicated a substantial increase in the number of aromatic protons for all four products in comparison to the six that were present in the 1H nmr spectra of the reactant **106**. Also the aldehydic protons of the products were now observed at ~9.8 ppm whilst the one for reactant **106** was observed at 10.65 ppm indicating that indeed new products were formed. The ^{13}C nmr spectra of the four products revealed an increase in the number of aromatic carbons in comparison to the six observed for the starting material **106**.



106 **109-112**

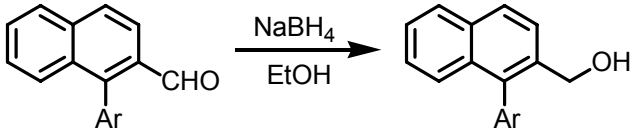
Scheme 43

Table 9: Percentage yields of aryl-substituted naphthaldehydes.

Naphthaldehyde	Ar	% yield
109	3,4,5-trimethoxyphenyl	94
110	1-naphthyl	89
111	phenyl	87
112	*o*-tolyl	94

The next step was the reduction of the obtained naphthaldehydes into the desired alcohols. This was done by treating a solution of the naphthaldehydes **109-112** in ethanol with sodium borohydride at room temperature (**Scheme 44**). The envisaged alcohols **113-116** were produced in good to excellent yields (**Table 10**), and their structures were confirmed by spectroscopy. Infrared spectra of the four compounds revealed a strong broad absorption at ~3400 cm^{-1} which confirms the presence of the hydroxyl group. Also

a strong absorption that was observed at ~1600 cm^{-1} for the starting materials had disappeared. This confirms the reduction of the carbonyl group. ^{1}H nmr spectroscopy showed the disappearance of the singlet at ~9 ppm for all the products. The new singlet integrating for two protons was observed at ~4.5 ppm (CH_2OH) in all four compounds. The ^{13}C nmr spectra of the four compounds revealed a disappearance of a signal at ~193 ppm for the aldehydic carbon and the appearance of a new signal at ~63 ppm confirming the presence of CH_2OH group.



109-112 **113-116**

Scheme 44

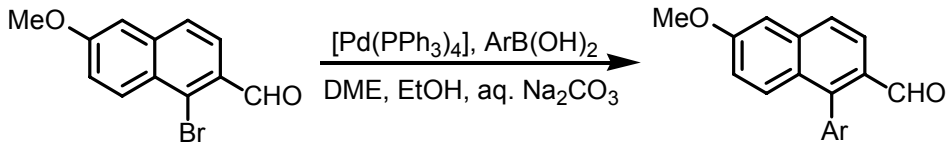
Table 10: Percentage yields of aryl-substituted naphthalene alcohols.

Alcohol	Ar	% yield
113	3,4,5-trimethoxyphenyl	82
114	1-naphthyl	93
115	phenyl	91
116	*o*-tolyl	95

2.5 Synthesis of aryl substituted naphthalenes from 1-bromo-6-methoxy-2-naphthaldehyde

The Suzuki coupling of 1-bromo-6-methoxy-2-naphthaldehyde **108** with the arylboronic acids **59**, **69**, **70** and **71** gave aryl-substituted naphthaldehydes **117**, **118**, **119** and **120** in yields ranging from acceptable to good (**Table 11**). The envisaged products were obtained by boiling a solution of bromomethoxynaphthaldehyde **108** in dimethoxyethane together with an excess solution of both aqueous sodium carbonate and individual arylboronic acids in ethanol in the presence of the catalytic amount of [$Pd(PPh_3)_4$] (**Scheme 45**). Confirmation of the structure of the naphthaldehydes was obtained from nmr spectroscopy. ^{1}H nmr spectra of the four compounds indicated an increase in the number of aromatic protons in comparison to the five aromatic protons showed by

naphthaldehyde **108**. Also an aldehydic proton from compound **108** shows an absorption at 10.58 ppm whereas the aldehydic protons of the products absorps at ~9 ppm. This indeed showed that new products were obtained and not the starting material **108**. The ^{13}C nmr spectra of naphthaldehydes **117-120** revealed an increase in the number of aromatic carbons in comparison to the five aromatic carbons revealed by naphthaldehyde **108**.



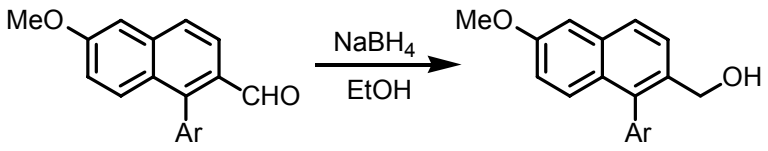
108 **117-120**

Scheme 45

Table 11: Percentage yields of aryl-substituted methoxynaphthaldehydes.

Naphthaldehyde	Ar	% yield
117	3,4,5-trimethoxyphenyl	80
118	1-naphthyl	74
119	phenyl	90
120	*o*-tolyl	71

The resultant aryl-substituted naphthaldehydes were successfully reduced to the desired alcohols using sodium borohydride in ethanol at room temperature (**Scheme 46**). The envisaged aryl-substituted naphthalene alcohols **121-124** were obtained in excellent yields (**Table 12**). Structures of the products obtained were confirmed by nmr spectroscopy and the infrared spectra of the four compounds revealed a strong broad absorption at ~3400 cm^{-1} which is diagnostic of the hydroxyl functional group. The IR spectra also showed the disappearance of the strong signal at ~1600 cm^{-1} indicative of the carbonyl functional group. The ^{1}H nmr spectra of the four compounds showed a disappearance of a singlet integrating for one proton at ~9 ppm for an aldehydic proton. A new singlet integrating for two protons had appeared at ~4.4 ppm in the spectra of all four compounds. This signal confirms the reduction of the carbonyl group had taken place. The ^{13}C nmr spectra of the compounds showed the appearance of a new signal at ~63 ppm (confirming the presence of CH_2OH) and the disappearance of the signal at ~192 ppm (confirming the disappearance of the aldehyde).



117-120 **121-124**

Scheme 46

Table 12: Percentage yields of aryl-substituted methoxynaphthalene alcohols.

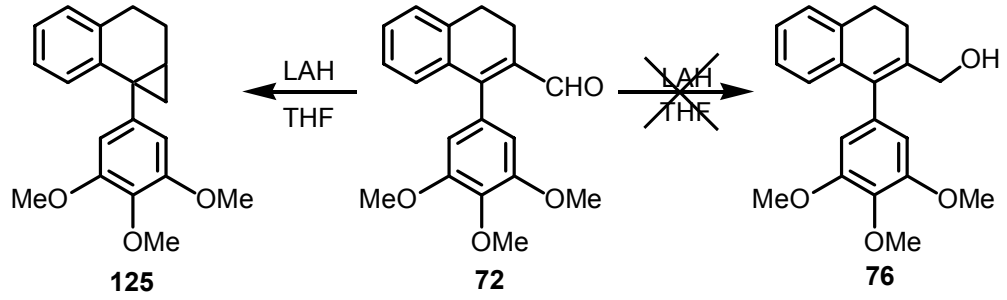
Alcohol	Ar	% yield
121	3,4,5-trimethoxyphenyl	89
122	1-naphthyl	95
123	phenyl	100
124	*o*-tolyl	93

This brought to an end the range of aryl-naphthalenes that were readily prepared from tetralones but this direction of the project was expanded on in the second part of the thesis.

2.6 The synthesis of tetrahydrocyclopropa[a]naphthalenes

In our earlier attempts to reduce 1-(3,4,5-trimethoxyphenyl)-3,4-dihydro-2-naphthaldehyde **72** to the alcohol **76** we initially used $LiAlH_4$ in tetrahydrofuran, but an unexpected result was obtained. It was clear from the ^1H nmr spectrum that more than reduction of the aldehyde had taken place. The aldehyde signal at 9.65 ppm was no longer evident, and there was also no signal at ~4 ppm integrating for two protons that would reflect the methylene protons adjacent to the alcohol substituent of **76**. This was further confirmed by the lack of a broad signal at ~3000 cm^{-1} in the infrared spectrum that would indicate the presence of an OH group. Over and above, there were more signals than expected in the aliphatic region. The observed signals in this region, all multiplets integrating for a single proton each, accounted for seven protons in total. Signals were observed at 2.71 ppm, 2.67 ppm, 2.18 ppm, 2.00 ppm, 1.74 ppm, 1.39 ppm and 1.25 ppm. A low resonance mass spectrum showed that the molecular mass of the compound appeared to be 310 instead of the expected 326. Taking this molecular mass into account and most especially, considering the signals at 1.39 ppm and

1.25 ppm, a region more characteristic of protons in a cyclopropane ring, the mysterious compound was predicted to be 7b-(3,4,5-trimethoxyphenyl)-1a,2,3,7b-tetrahydro-1*H*-cyclopropa[*a*]naphthalene **125** (**Scheme 47**). This was confirmed by an X-ray crystal structure (**Figure 1**). The HRMS calculated for $C_{20}H_{22}O_3$ is M^+ 310.1569 and the observed m/z was found to be 310.1579. Details of the X-ray crystallographic data can be found in Appendix A.



Scheme 47

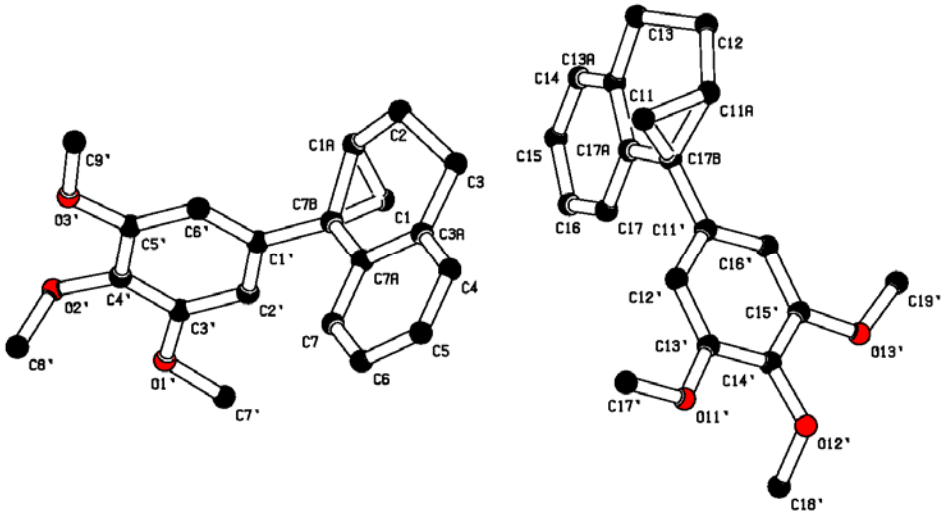
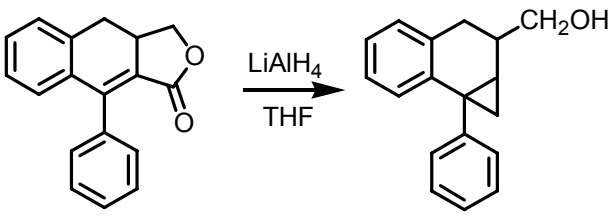


Figure 1: X-ray crystal structure of 7b-(3,4,5-trimethoxyphenyl)-1a,2,3,7b-tetrahydro-1*H*-cyclopropa[*a*]naphthalene (125) showing both molecules in the asymmetric unit. Hydrogen atoms are omitted for clarity.

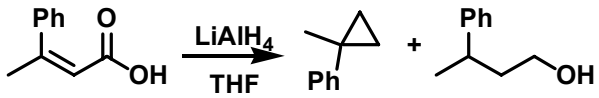
Reviewing the literature, we found that Klemm and coworkers[102] had also reduced related cyclolignan lactones, e.g. **126** to 2-hydroxymethyl-7b-phenyl-1a,2,3,7b-tetrahydro-1*H*-cyclopropa[*a*]naphthalene **127 (Scheme 48)** using excess lithium aluminium hydride.



126 **127**

Scheme 48

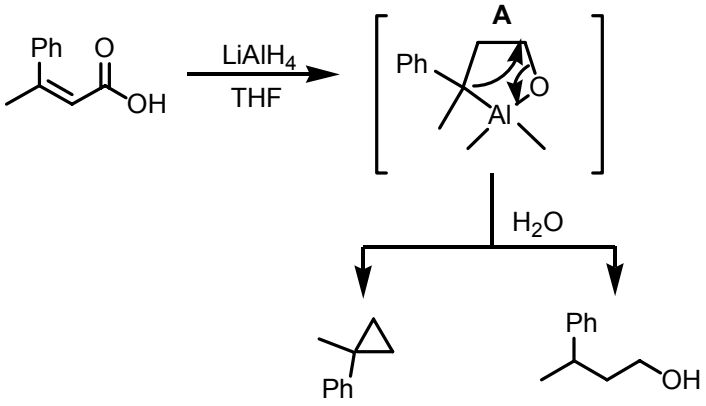
Unfortunately they did not obtain an X-ray crystal structure of this compound, but they justified their results by citing the work done by Uyeda.[103] In this work the reduction of β-methylcinnamic acid **128** with excess lithium aluminium hydride in tetrahydrofuran, gave a methylphenylcyclopropane **129** in addition to the expected alcohol (**Scheme 49**).



128 **129**

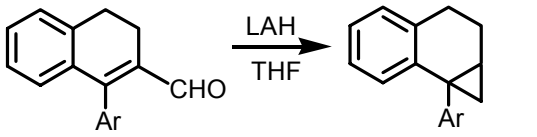
Scheme 49

The possible mechanism as outlined by Uyeda[103] is that the reaction proceeds by reduction of the carbonyl group followed by intramolecular hydroalumination of the C=C bond to give intermediate **A** (**Scheme 50**) before proceeding to either an alcohol or cyclopropane. The key aspect here is the time factor. When the reaction is run for a shorter period, e.g. 3 h, an alcohol is formed. When the reaction is run for days, the intermediate can ring-close to form a cyclopropane due to an excess of $LiAlH_4$. Uyeda's proposal seemed to be appropriate to rationalise our own results.



Scheme 50

In order to try and generalize this reaction, two more naphthaldehydes i.e. phenyl- and *o*-tolyl-3,4-dihydro-2-naphthaldehydes **74** and **75** respectively, were reduced by excess lithium aluminium hydride in tetrahydrofuran to afford the desired cyclopropanes **130** and **131** respectively in promising yields that have not been optimised (**Scheme 51**) (**Table 13).**



72, 74, 75 **125, 130, 131**

Scheme 51

Table 13: Percentage yields of aryl-substituted cyclopropanetetrahydronaphthalene.

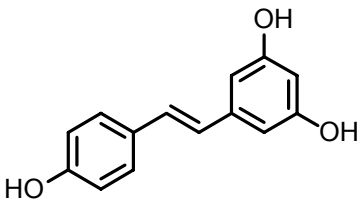
Entry	Ar	% yield
125	3,4,5-trimethoxyphenyl	44
130	phenyl	43
131	*o*-tolyl	53

Again it was clear from the ^{1}H nmr spectra that the desired products were formed since the singlets integrating for one proton at ~9 ppm (aldehydes) had disappeared in both compounds and the new extra signals (multiplets) in the aliphatic region, integrating for seven protons including the ones in the familiar cyclopropane region, were observed. Also from the ^{13}C nmr spectra it was observed that the aldehyde signals at ~190 ppm had disappeared in both compounds and three new signals had emerged in the aliphatic region.

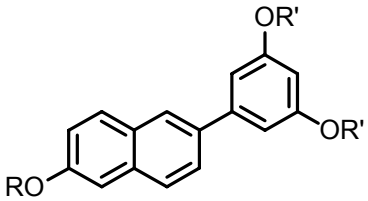
2.7 Biological activity of aryl-substituted naphthalenes.

As has been discussed in the introduction section, many naphthalene-containing compounds show biological activities. This sub-section of the thesis aims at presenting some aryl-substituted naphthalenes that have been reported to show some biological activities and further present results obtained from testing our own aryl-substituted naphthalenes against malignant cancer cells.

Resveratrol, a naturally occurring phyloalexin (3,5,4'-*trans*-trihydroxystilbene) **132** (**Figure 2**) present in medicinal plants, peanuts, and red wine,[104] has been reported to have chemopreventative activity,[105] by exerting antiproliferative and proapoptotic effects in human cancer cells.[106] It has also being shown that resveratrol can affect cancer cell growth and induce apoptosis by triggering the synthesis of endogenous ceramide,[107,108] a bioactive sphingolipid. Resveratrol leads to the accumulation of ceramide in association with apoptosis both in metastatic breast[112] and prostate[113] cancer cells. Ceramide is a promising pharmacological target when either major apoptotic pathways are disrupted or resistance to DNA damage is elevated. Moreover, drugs that trigger ceramide, while highly effective in malignant cells, are less toxic to normal cells and tissues.[109]



132



133a: R = R '= H
133b: R = Me, R '= H
133c: R = H, R '= Me
133d: R = R '= Me

Figure 2

In an attempt to synthesize analogues of resveratrol, Macchia *et al*.[110] designed and studied the effectiveness of compounds **133a-d** (**Figure 2**) at inducing ceramide-mediated apoptosis in the metastatic breast cancer cell line, MDA-MB-231In these cells resveratrol was reported to induce ceramide by activation of its *de novo* synthesis. The synthesis of phenyl-substituted naphthalenes **133a-d** was influenced by an attempt to overcome both the chemical and metabolic instability of resveratrol by substituting the stilbene double bond present in resveratrol with a naphthalene ring. This change enables preservation of the original geometrical orientation of the pharmacophoric groups of resveratrol, while adding more conformational rigidity to the whole structure. When resveratrol analogues **133a-d** were tested against ceramide-mediated proapoptotic activity, compound **133a** was found to be the most effective in triggering apoptosis coupled to the induction of endogenous ceramide in the human breast cancer cell line.

Binding of the 3,5,3'-triidothyronine **134** (**Figure 3**) to the thyroid hormone receptor controls multiple physiological endpoints (e.g. heart rate, bone and muscle metabolism, cholesterol levels, and metabolic rate) through transcriptional control of various gene targets.[111] Levels of compound **134** in excess of normal physiologic amounts produce bradycardia and weight gain. The amount of compound **134** needed to provide clinically relevant weight loss causes unwanted cardiac side effects, preventing its use for anti-obesity therapy.

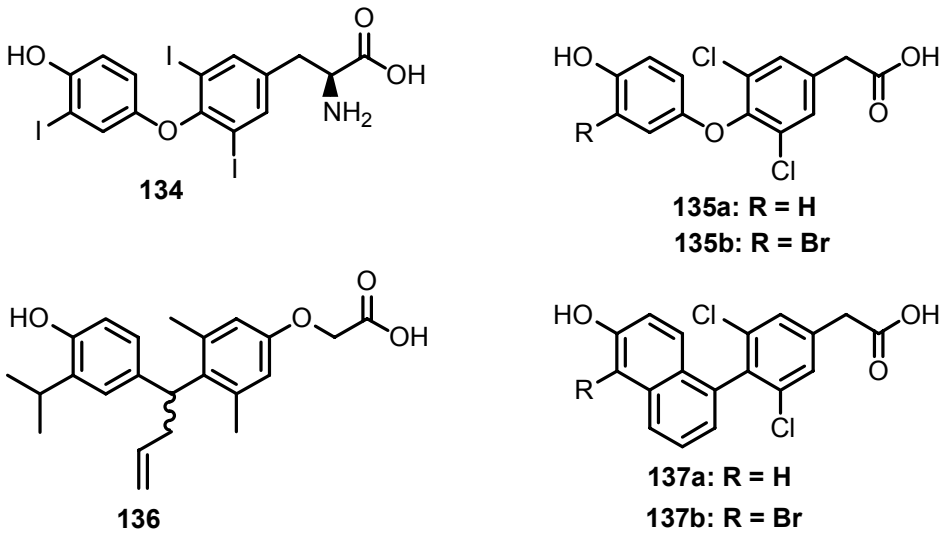


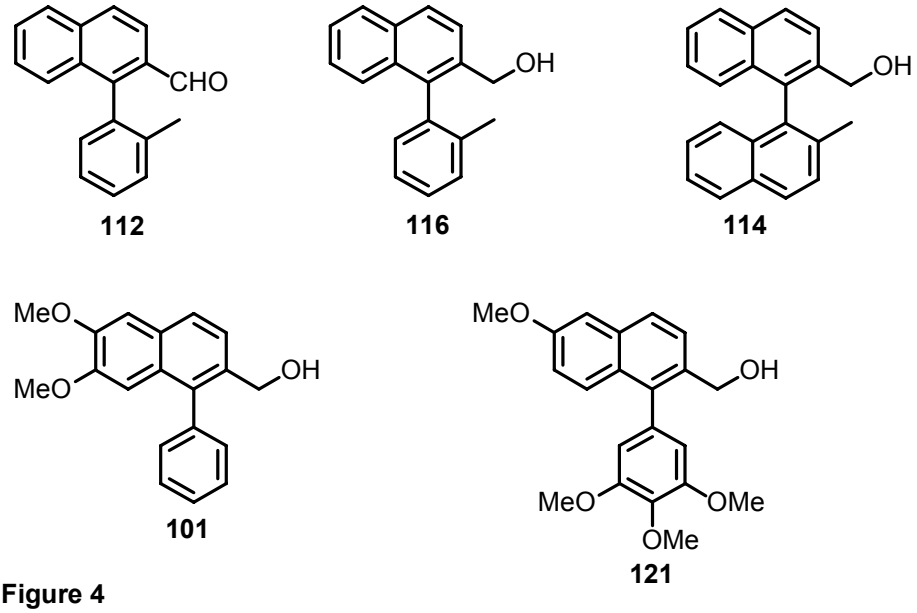
Figure 3

The vast majority of reported thyromimetics retain two features of the core structure of compound **134**: a diphenyl ether and a 3,5-disubstituted right-hand ring, the two acting in concert to orient the phenyl rings in a skewed relationship. The skewed conformation is labeled 'ideal'[112] when the right-hand phenyl ring is orthogonal to the C-O-C plane and the left-hand phenyl ring is co-planar to the C-O-C plane. Two examples of thyromimetics (**135a-b**, **Figure 3**) were synthesized by Hangeland *et al.*[113] and were reported to have shown improved affinity for both α- and β-thyroid hormone receptors. Another analogue of compound **134** is compound **136** which contains substitution on the bridging methylene carbon linking the two phenyl rings. This compound was synthesized by Scanlan and co-workers and has been reported to be a low-potency agonist.[114]

In an attempt to test if forcing the two phenyl rings to be orthogonal would lead to high affinity thyromimetics or it would contribute to the selectivity for one thyroid hormone receptor isoform over the other, Hangeland and co-workers synthesized new analogues of compound **134** with a phenyl-naphthalene core (**137a-b**, **Figure 3**).[118] This new core retained the essential relationship between the two phenyl rings, locked into position the distal conformational relationship of the 3'-substituent to the inner phenyl ring, and enforced co-planarity of outer phenyl ring with the C-O-C plane. The 2'-position of the outer phenyl ring was tied to the bridging carbon via a three carbon linker to form the second ring of the naphthalene moiety. In comparison to its ether analogue **135a**, compound **137a** was reported to have modest affinity for both α-and β-thyroid hormone receptors but was slightly selective for the β-thyroid hormone receptor. On the other hand compound **137b** was reported to have greater improvement in affinity for β-thyroid hormone receptor versus α-thyroid hormone receptor than both its bis-aryl ether analogue **135a** and compound **137a**.

In view of the biological activity shown by aryl-substituted naphthalenes as described above and the fact that in general aromatic compounds appear to be active against cancer cells, we subjected our aryl-substituted naphthalenes to biological anti-cancer testing. Our compounds were tested against HT-29-colon cancer cells, MCF-7 breast cancer cells and Grahams kidney epithelial cells. Of the twelve aryl-substituted naphthalenes tested against these cells, only five (**Figure 4**) showed some activity. In general our compounds were most active against the Grahams kidney epithelial cells and much less active against the other two cancer cells. Compound **121** was the most active against the Grahams cells with an IC_{50} value of 40.1 μM. It was followed by compound **101** with an IC_{50} value of 44.7 μM. Compounds **112** and **114** had both recorded an IC_{50} value of 47.4 μM and compound **116** had recorded an IC_{50} value of 50.4 μM when tested against the Grahams cells. All compounds with the exception of compound **112**, which had an IC_{50} value of 67.3 μM, had registered and an IC_{50} value of >100 μM when tested against the HT-29 colon cancer cells. Compounds **112** and **114** are the only two compounds that recorded an IC_{50} value of <100 μM against the MCF-7 breast cancer cells, they registered an IC_{50} value of 60.1 μM and 77.5 μM respectively. However it must be mentioned that our

compounds were only tested against malignant cells, therefore their activity remain to be probed against normal healthy cells in order to ascertain a selectivity profile. However it is promising that a number of our aryl-naphthalenes show activity against cancer cells.



112 **116** **114**

101 **121**

Figure 4

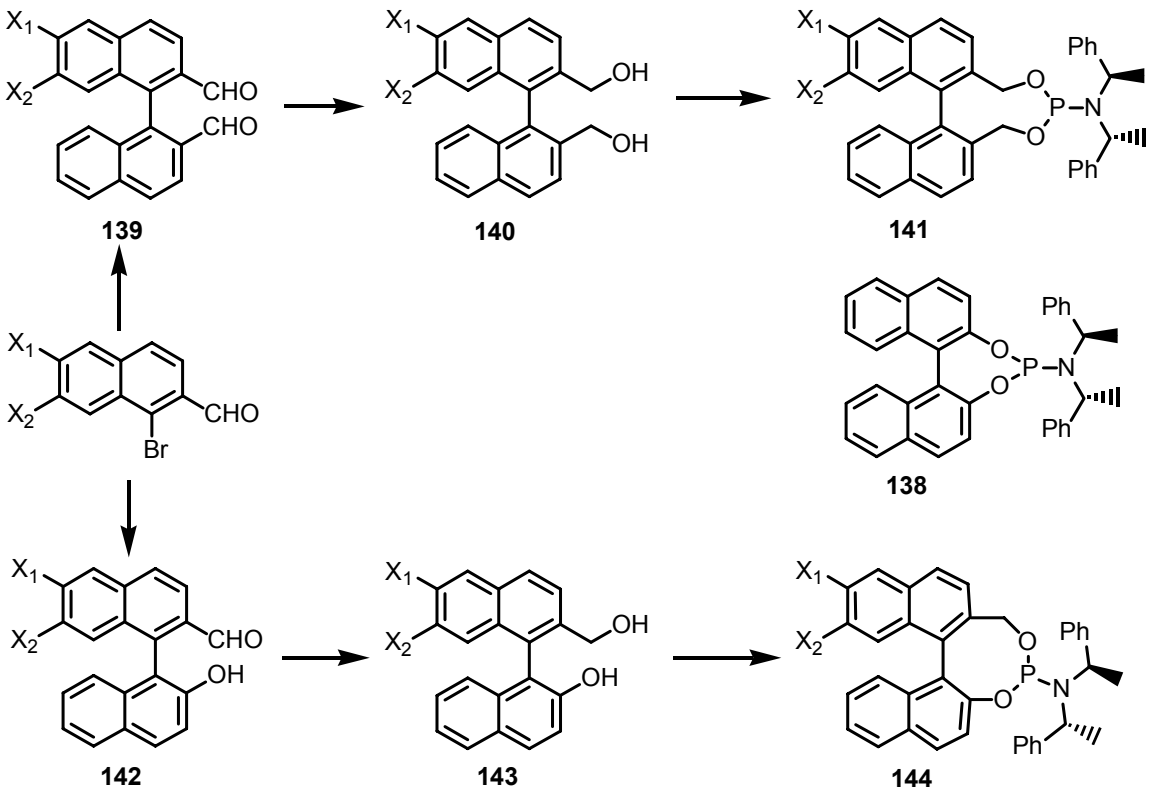
PART TWO

Synthesis of aromatic phosphorus-containing compounds

Preface To Part 2

After successfully utilizing three different α-tetralones in the synthesis of aryl-substituted naphthalenes, we thought that we could extend our methodology further by synthesizing precursors for monophosphorus ligands (similar to the Feringa ligand **138**) that could potentially be used in metal catalysed reactions. This could be done by Suzuki coupling of bromo(methoxy)naphthaldehydes **106** and **108** to 1-naphthyl boronic acids with a substituent in the 2-position. Examples of these boronic acids would include 2-formyl-1-naphthylboronic acid and 2-hydroxy-1-naphthylboronic acid. The resultant naphthaldehydes **139** and **142** as shown in **Scheme 52** can be easily reduced to their respective diols **140** and **143** by using sodium borohydride in ethanol as has been shown in the results and discussion chapter. Diols **140** and **143** can be reacted with phosphorus trichloride in the presence of a secondary amine like the Simpkins base to afford Feringa ligand-like analogues **141** (with nine-membered heteroatom containing ring) and **144** (with eight-membered heteroatom containing ring). The next step after synthesizing and designing the Feringa ligands analogues **141** and **144**, would be to test their activity in the rhodium-catalyzed asymmetric hydrogenation of dehydroamino acid derivatives as has been done with the Feringa ligand **138**, where ee's of >90% have been reported.[115]

Therefore this part of the project looks at the study of various phosphorus ligands and their use in different metal-catalyzed asymmetric hydrogenation reactions and is by no means comprehensive. It goes without saying that some excellent phosphorus ligands and their applications will be omitted in this discussion since there has been a vast amount of literature on asymmetric hydrogenation. Fortunately, many previous books and reviews in this field are available.[116]



Scheme 52

Chapter 3: Introduction 2

The demand for optically active compounds is increasing in the pharmaceutical, agrochemical, fragrance and flavours industries, among others.[117] Legislation was introduced in 1988 and implemented by the U.S. Food and Drug Administration (FDA), who require any company wishing to license a novel active ingredient as a racemic mixture to establish the activity of both enantiomers and also to show that the unwanted enantiomer does not cause any adverse effects. Two thirds of the 1200 drugs development in 1996 were chiral and 51% were being developed as single enantiomer drugs. In meeting this demand, asymmetric synthesis has played a significant role that is on par with other methods, including optical and enzymatic resolutions.[118] Acknowledgement of the importance of this field led to the awarding of the 2001 Nobel Prize to Knowles,[119] Noyori[120] and Sharpless[121] for their exceptional contributions to asymmetric syntheses.

Striking progress in this area has been made due to developments in organometallic chemistry, in particular where a chiral ligand creates an asymmetric environment around a metal by controlling the binding of reactants and their subsequent reaction paths through steric and electronic interactions. Commonly used donor atoms, which include phosphorus, nitrogen, oxygen and sulfur, help to electronically tune the metal.

Typically, once novel ligands have been prepared, their metal complexes are tested for their catalytic activity and enantiodifferentiating ability in standard transformations. These ‘test’ reactions include (among others) hydrogenation of olefins and carbonyl groups, allylic substitutions and the addition of diethylzincs to aldehydes, whilst the oxidative transformations of epoxidation, hydroboration and hydrosilylation are also important. The ligands employed in these metal-catalyzed processes possess elements of central, planar and axial chirality and/or combinations of these.[120] Researchers around the world have designed and synthesized large numbers of ligands aiming for greater levels of selectivity, among which chiral phosphorus ligands represent a large category.

3.1 Bidentate phosphorus ligands

3.1.1 Bisphosphines

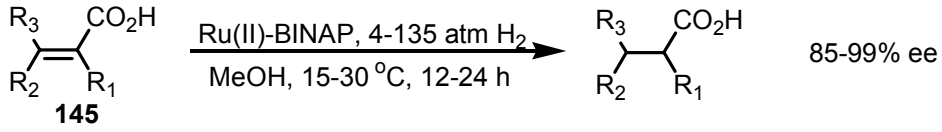
3.1.1.1 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (BINAP)

In 1960 many new discoveries were reported which had great impact on later asymmetric hydrogenations; for example, homogeneous catalytic hydrogenation with Ru(II) by Halpern[122] and [$RhCl(PPh_3)_3$] by Wilkinson[123] as well as heterogeneous asymmetric hydrogenation using fibroin-supported palladium catalysts.[124] These findings led to the first homogeneous catalytic hydrogenations using a rhodium catalyst ligated by chiral phosphines of moderate selectivity, independently developed by Knowles[125] and Horner.[126] The first major breakthrough in asymmetric homogeneous catalysis was made by Kagan using a DIOP-Rh complex, yielding a 72% ee in asymmetric hydrogenation reactions of dehydroamino acid derivatives.[127] DIOP not only attracted researchers' attention to this reaction, but also provided an important guideline for future developments; that is using bidentate phosphines with C_2 symmetry.

Hence it was not surprising that in 1980 Noyori and Takaya[128] synthesized the most well-known example of the axially chiral diphosphine ligand, BINAP. This ligand very effectively induces asymmetry by intra-complex steric interactions between the bulky triarylphosphine system and the reactants bound to the metal. Its application in asymmetric catalysis was reviewed in 1990[129] and 1992[130] and subsequently its use has been well documented in numerous textbooks.[1] Therefore only a summary of its application is detailed and emphasis will be placed on its more recent successes.

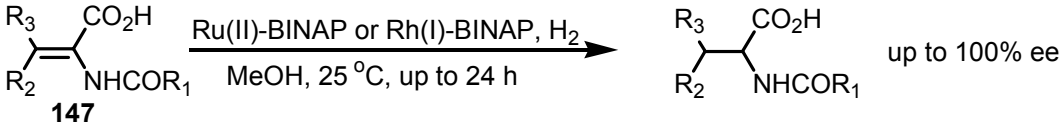
Ruthenium complexes of BINAP have proven to be successful in inducing high to excellent enantioselectivities in the hydrogenation of olefinic substrates, such as a range of α,β-unsaturated carboxylic acids **145** (**Scheme 53**).[131] *N*-acylaminoacrylic acids **147** were also successfully reduced using Ru(II)-BINAP and Rh(I)-BINAP complexes in high to excellent enantioselectivities (**Scheme 54**).[132] The scope of Rh(I)-BINAP catalysis is,

however, limited to a small range of suitably functionalized olefin substrates, whereas Ru(II)-BINAP chemistry has a broad utility.



R_1 = alkyl, aryl, hydroxycarbonylalkyl
R_2 = H, hydroxyalkyl
R_3 = H, alkyl

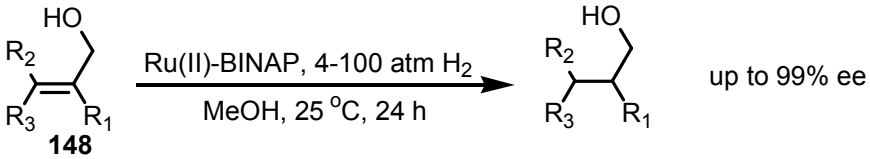
Scheme 53



R_1 = alkyl, aryl
R_2 = H
R_3 = H, alkyl, aryl

Scheme 54

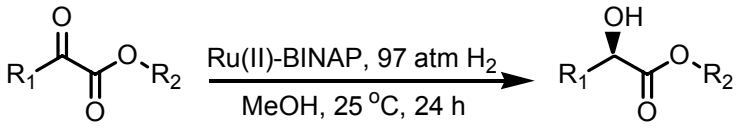
Highly enantioselective reduction of the substituted allylic alcohols **148** has also been achieved (**Scheme 55**). With the latter substrates, the sense and extent of asymmetric induction are highly dependent on the substitution pattern and the reaction conditions, and in particular the hydrogen pressure employed.[133]



R_1 = alkyl, aryl
R_2 = R_3 = H, alkyl

Scheme 55

As with olefin hydrogenations, the application of BINAP-Ru complexes to the enantioselective reduction of carbonyl groups has reached a high level of success. α-Keto acid derivatives **149** have been reduced in quantitative yields with enantioselectivities of up to 89% (**Scheme 56a**).[134]



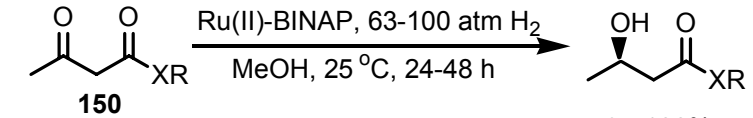
149

R_1 = alkyl, aryl

R_2 = alkyl

Scheme 56a

Similarly, excellent reactivities and enantioselectivities were obtained with β-keto esters **150** as the substrates (**Scheme 56b**).[135] The asymmetric reduction of 1,3-dicarbonyl systems with Ru-biarylphosphine catalysts was reviewed by Ager in 1997.[136]



150

R = alkyl

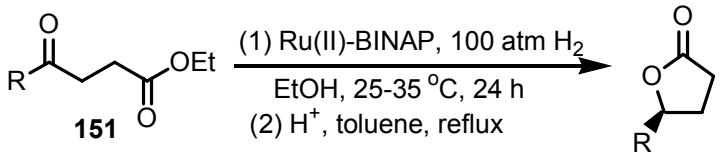
X = O, NR, SR

95-100%

93-99% ee

Scheme 56a

The hydrogenation of γ-keto esters **151** by BINAP–Ru complexes affords the corresponding γ-lactones in excellent enantioselectivities (**Scheme 57**).[137]



151

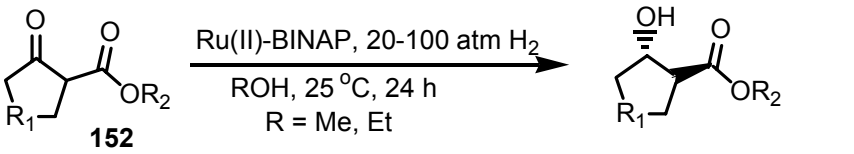
R = alkyl, aryl

up to 95%

97-99.5% ee

Scheme 57

A particularly efficient dynamic kinetic resolution of the α-substituted β-keto esters **152** using BINAP-Ru catalysts has also been developed, where >95% yield of one of the four possible diastereomeric hydroxyl esters is obtained in excellent enantiomeric and diastereomeric excess (**Scheme 58**).[138]



152

R_1 = CH_2, $(CH_2)_2$, $(CH_2)_3$

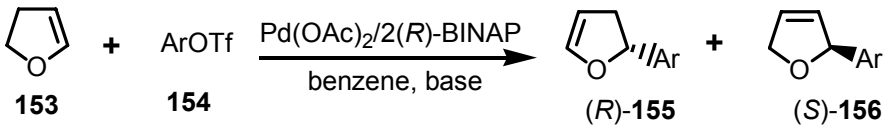
R_2 = Me, Et

anti:syn = 93:7 to 99:1

92-99% ee

Scheme 58

One of the most studied carbon-carbon bond forming reactions of palladium complexes of BINAP is the Heck reaction.[139] In the intermolecular variant, the test reaction is between 2,3-dihydrofuran **153** and the aryl triflates **154**. Hayashi reported that this reaction, which proceeded in the presence of a base and a palladium catalyst generated *in situ* from catalytic $Pd(OAc)_2$ and *R*-BINAP, gave the (*R*)-2-aryl-2,3-dihydrofuran **155** and a small amount of the (*S*)-2-aryl-2,5-dihydrofuran **156** (**Scheme 59**).[140] The base affected the enantiomeric purity of (*R*)-**155** and the sterically demanding 1,8-bis(dimethylamino)naphthalene (proton sponge) afforded the best results for a range of aryl triflates (**Table 1**).



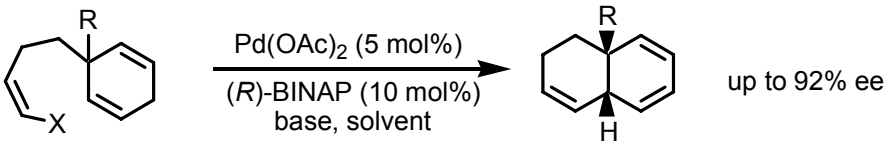
153 **154** (*R*)-**155** (*S*)-**156**

Scheme 59

Table 1: Enantioselective palladium-catalysed Heck reaction with (*R*)-BINAP

ArOTf(Ar)	ee (%), (%yield)	ee (%), (%yield)
	(*R*)-**155**	(*S*)-**156**
p-ClC_6H_4	>96 (54)	6 (21)
m-ClC_6H_4	>96 (66)	39 (22)
o-ClC_6H_4	96 (53)	53 (21)
p-AcC_6H_4	>96 (50)	7 (24)

The first successful intramolecular asymmetric Heck reactions using BINAP-Pd complexes were reported in 1989 by Shibasaki who focused on the preparation of the *cis*-decalin derivatives **158** from the prochiral alkenyl iodides or triflates **157** and obtained enantioselectivities of up to 92% in moderate chemical yields of 60% (**Scheme 60**).[141]



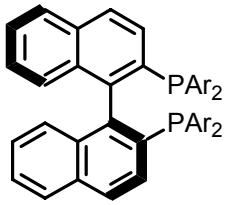
157 **158**

R = CO_2Me, CH_2OAc, CH_2OPv, $CH_2OTBDMS$

X = I, OTf

Scheme 60

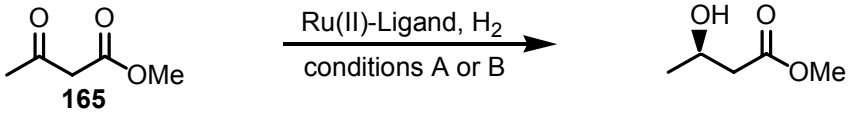
Taking the above summary of applications of metal complexes of BINAP as being representative of its success in inducing such high levels of asymmetry, it is not surprising that the synthesis and design of other atropisomeric disphosphines became an active area of research in the late 1980s and continues to the present day. The electronic properties at phosphorus were the first variation to be investigated and this led to the preparation and application of a series of BINAP analogues (**159-164**) (**Figure 5**), which retain the 1,1'-binaphthyl backbone but differ in the bis-arylphosphine group.[132c,142]



159: Ar = 3-MeC_6H_4
160: Ar = 4-MeC_6H_4
161: Ar = 4-$MeOC_6H_4$
162: Ar = 3,5-$(Me)_2C_6H_3$
163: Ar = 4-ClC_6H_4
164: Ar = 4-FC_6H_4

Figure 5

These modified BINAP analogues have been applied to ruthenium-catalyzed hydrogenation processes and there are examples where reaction rates and selectivities are improved compared to the parent BINAP catalyst system. For example in hydrogenation of the β-keto ester **165**, Ru-(**161**) complexes gave products in 99% ee after 27 h using a higher substrate/catalyst (S/C) ratio (**Scheme 61**).[143,144] Use of [RuI(p-cymene)(bisphosphine)] catalysts prepared from ligands **160**, **162**, and **164** resulted in loss of enantioselectivities in the reduction of **165** compared to BINAP (97, 93 and 97% vs 99%, respectively).[146]



165

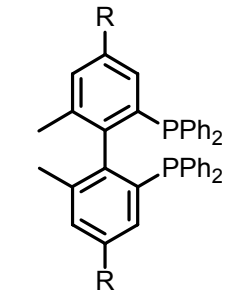
A; BINAP, MeOH, 1500 psi H_2, 50 ^oC, S/C 1000, 48 h, 98% ee

B; Ligand **161**, MeOH/CH_2Cl_2, 1500 psi H_2, 30 ^oC, S/C 4000, 27 h, 99% ee

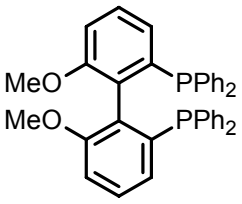
Scheme 61

The biphenyl system is easier to modify geometrically, sterically or electronically than the binaphthyl system, leading to the synthesis of a variety of atropisomeric biphenyl diphosphines (**Figure 6**) and the application of their metal complexes in asymmetric catalysis. The group of Schmid and Frejd have independently prepared 2,2'-bis(diphenylphosphino)-6,6'-dimethyl biphenyl (BIPHEMP) **166** and the related analogues **167**-**168**.[145,146] As the biphenyl group, like the binaphthyl group, is not completely rigid it can form a variety of stable chelate complexes with many transition metals. It was, however, necessary to substitute the 6,6'-position in order to prevent racemization. MeO-BIPHEMP **169,** an analogue of BIPHEMP **166**, was also reported by Schmid and is an example in which the electronic properties at phosphorus have been varied.[147] The dialkylmonoaryl-phosphine, BICHEP **170**, reported by Takaya is particularly electron rich.[148] The diphosphine **171**, prepared by Jendralla, is the first example of an electron-poor biphenyl-type ligand.[149] Similar electron-deficient biarylphosphines, FUPMOP-**172** and BIFUP-**173**, were reported by Achiwa.[150]

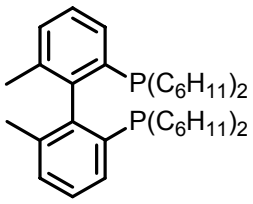
[RuI(p-cymene)(bisphosphine)] catalysts prepared from the majority of the ligands **166**-**173** were applied in the reduction of β-keto esters and gave similar reactivities and enantioselectivities compared to BINAP as long as the ligand employed contained at least one electron-donating substituent, regardless of whether the ligand also possessed electron-withdrawing substituents. The reactivity was deleteriously affected by the presence of only electron-withdrawing groups on the biphenyl backbone and the enantioselectivities were lowered slightly.[140,154]



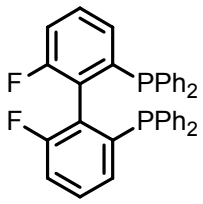
R = H **166** (BIPHEMP)
R = Me **167**
R = NMe_2 **168**



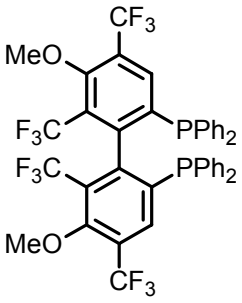
169
(MeO-BIPHEMP)



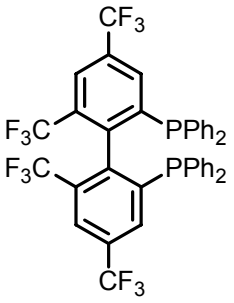
170
BICHEP



171



172
(FUPMOP)

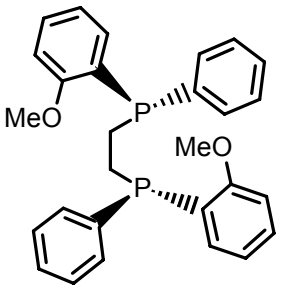


173
(BIFUP)

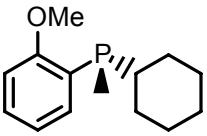
Figure 6

3.1.2 1,2'-Bis[(phenyl-*o*-methoxyphenyl)phosphino]ethane (DIPAMP)

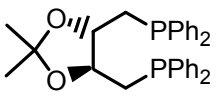
DIPAMP **174** (**Figure 7**) was first discovered by Knowles[151] in 1977. Due to its high catalytic efficiency in Rh-catalyzed asymmetric hydrogenation of dehydroamino acids, it was quickly employed in the industrial production of L-DOPA (3,4-dihydroxyphenylalanine), a drug used for treating Parkinson's disease. Knowles *et al.* devised a synthesis of DIPAMP after it was discovered that in the 1970s the rhodium-phosphine system worked much better on a highly functionated olefin such as α-acetamidocinnamic acids **177** (**Scheme 63**), than on the original models (olefins with alkyl-substituents only).



174 (*S*,*S*)-DIPAMP

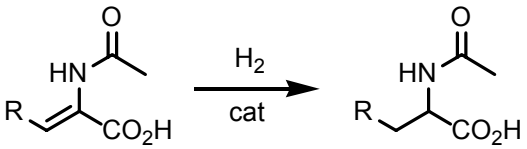


175 (*S*)-CAMP



176 (*S*,*S*)-DIOP

Figure 7



177

Scheme 63

However asymmetric hydrogenation was started with Horner's ligand, methylpropylphenylphosphine[152] and products obtained in only 28% ee and no improvement was achieved by varying the small, medium and large groups.[153] It was only by the introduction of an *o*-methoxyphenyl group on the ligand (PAMP) that there was real progress. Then, further conversion of the phenyl into a cyclohexyl group resulted in the synthesis of CAMP (cyclohexyl-*o*-anisylmethylphosphine) **175 (Figure 7)**.[157] This product at 80-88% ee became the first commercial candidate used for the manufacture of L-DOPA. Finally, dimerizing PAMP to DIPAMP **174 (Figure 7)** gave the present optimum structure. Further obvious manipulations such as the dimerization of CAMP **175** to DiCAMP led to an inferior product that is typical of the surprises encountered in synthetic work in this field.[154] At first it was thought that it would be necessary to have chirality directly on the phosphorus, but the discovery of DIOP **176 (Figure 7)** proved this reasoning to be wrong.

Other bisphosphine ligands with an ethane backbone include the efficient chiral bisphospholane ligands 1,2-bis(2,5-dialkylphospholanyl)ethanes, BPE (**178a-c**) (**Figure 8**) which were synthesized by Burk *et al.*[155] in the early 1990s. The invention of these ligands has expanded the substrate scope of Rh-catalyzed enantioselective hydrogenation.

For example, with Rh-BPE as catalysts, extremely high efficiencies have been observed in asymmetric hydrogenation of α-(acylamino)acrylic acids, enamides, enol acetates, β-keto esters, unsaturated carboxylic acids and itaconic acids.[156] Since the 1,2-phenylene backbone would be expected to be more rigid than the ethane backbone, Burk had also synthesized the 1,2-bis(2,5-diakylphospholanyl)benzene, DuPHOS (**179a-c**) (**Figure 8**). Also high efficiencies in asymmetric hydrogenation of the above mentioned substrates were observed when using Rh-DuPHOS as catalysts.



(*S*,*S*)-**178a**, R = Me
(*S*,*S*)-**178b**, R = Et
(*S*,*S*)-**178c**, R = *i*-Pr

(*S*,*S*)-**179a**, R = Me
(*S*,*S*)-**179b**, R = Et
(*S*,*S*)-**179c**, R = *i*-Pr

Figure 8

3.1.3 Bisphosphine ligands from the modification of DuPHOS and BPE

Since Burk reported excellent results of DuPHOS and BPE ligands in asymmetric hydrogenation of functionalized olefins and ketones, many bisphosphines have been developed based on the structural variations of DuPHOS and BPE ligands (**Figure 9**). Börner,[157] Zhang[158] and RajanBabu[159] have independently reported a series of modified DuPHOS and BPE ligands with ether, ketal or hydroxyl groups at the 3 and 4 positions of the phospholanes. These types of ligands maintain the high efficiency of DuPHOS or BPE in Rh-catalyzed hydrogenation. One major advantage of these ligands is their ease of preparation from D-mannitol.

The ligand with four hydroxyl groups **180** (**Figure 9**) also enabled the hydrogenation to be conducted in aqueous solution and high enantioselectivities are maintained. Another "four hydroxyl water-soluble" ligand BASPHOS **181a-c** (**Figure 9**) developed by Holtz and Börner also exhibits high efficiency for asymmetric hydrogenation in water.[160] Structural variations can also be made on the backbone of DuPHOS and BPE. Holtz and

Börner have reported a bisphosphine ligand bearing a maleic anhydride backbone, MAIPHOS **182** (**Figure 9**), which has provided good enantioselectivities in hydrogenation of β-(acylamino)acrylates.[161]

Marinetti reported a series if bisphosphetane ligands such as CnrPHOS **183a-b** (**Figure 9**) and BPE-4 **184a-b** (**Figure 9**) ligands.[162] Compared with their bisphosphine analogues DuPHOS and BPE, CnrPHOS and BPE-4 provides only moderate enantioselectivity in Rh-catalyzed hydrogenation of dehydroamino acid derivatives. However, these bisphosphetane ligands have shown excellent enantioselectivities in Ru-catalyzed hydrogenation. Helmchen has developed a bisoxaphosphinane ligand **185** (**Figure 9**) for Rh-catalyzed hydrogenation of dehydroamino and itaconic acid derivatives and up to 97% ee have been obtained.[163]

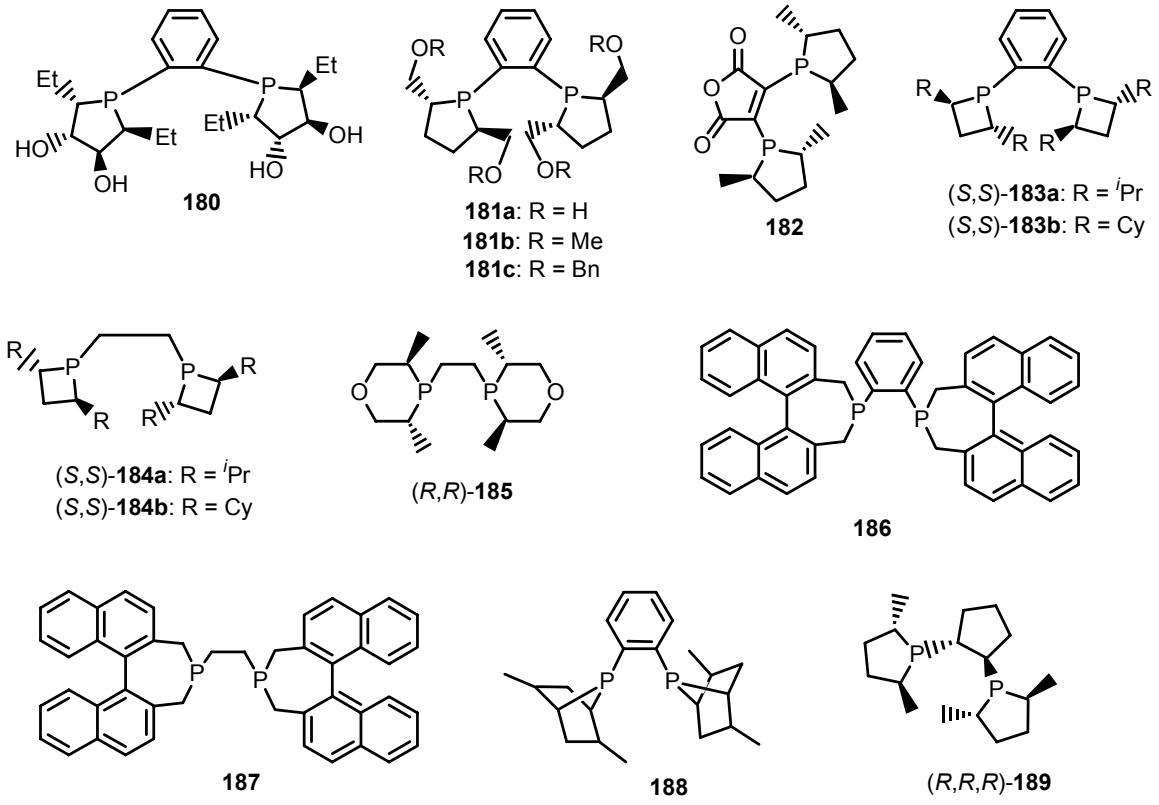


Figure 9

Zhang has reported two bisdinaphthophosphepine analogues, BINAPHANE **186** and **187**, (**Figure 9**) which have being applied in Rh-catalyzed hydrogenation of enamides.[164]

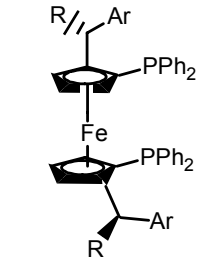
These two ligands, with axial chirality, provide excellent enantioselectivities (up to 99% ee) for hydrogenation of *E*/*Z* isomeric mixtures of β-substituted arylenamides. A sterically bulky and conformationally rigid bisphosphine PennPhos **188** (**Figure 9**), developed by Zhang has different hydrogenation properties compared to other DuPhos-type ligands.[165] With 2,6-lutidine and KBr as additives, PennPhos has shown excellent enantioselectivities for Rh-catalyzed hydrogenation of both aryl and alkyl methyl ketones. The PennPhos ligand has shown high efficiency in Rh-catalyzed hydrogenation of cyclic enamides and cyclic enol acetates, which are difficult substrates for most DuPhos-type ligands.[166] An improved BPE analogue has been developed by incorporating two additional chiral carbon centers on the backbone. The matched (*R*,*R*,*R*)-1,2-bis(phospholano)cyclopentane **189** (**Figure 9**), provides better enantioselectivity than BPE in hydrogenation of dehydroamino acids.[167]

3.1.4 Chiral ferrocene-based bisphosphines

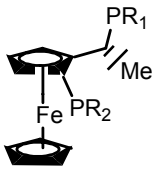
Many excellent chiral ferrocene-based bisphosphine ligands with great structural variations have been developed recently. Ito has successfully developed a series of trans-chelating bisphosphine ligands TRAPs **190a-d** (**Figure 10**), which have shown great capabilities for asymmetric hydrogenation.[168] EtTRAP **190a** and BuTRAP **190c** have shown excellent reactivity for Rh-catalyzed hydrogenation of β,β-disubstituted α-acetamidoacrylates and up to 88% ee have being obtained.[53b] The TRAP ligands have also being applied for hydrogenation of β-oxy-α-acetamidoacrylates, and PrTRAP **190b** has been proved to be the best ligand in terms of enantioselectivity.[169] In the presence of 10 mol % of Et_3N or $CsCO_3$, a PhTRAP-Rh **190d** complex is able to hydrogenate *N*-acetyl-2-substituted indoline in high ee's.[170]

Togni and Spindler have reported a class of non-C_2-symmetrical ferrocene-based bisphosphines: the Josiphos-type ligands **191a-d** (**Figure 10**).[171] Josiphos **191a** has being found to be effective for Rh-catalyzed hydrogenation of α-acetamidocinnamate, dimethyl itaconate, and β-keto esters. Some excellent industrial applications have been realized with Josiphos-type ligands. For example, PPF-^{t}Bu$_2$ **191b**, a Josiphos type ligand with di(tert-butyl)phosphino group, has being applied as a ligand in asymmetric hydrogenation

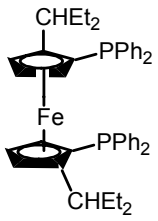
for commercial synthesis of (+)-biotin.[172] Another notable example is the application of XyliPhos **191c** in Ir-catalyzed hydrogenation of an amine for the synthesis of herbicide (*S*)-metolachlor.[173] Weissensteiner and Spindler have also reported a class of rigidified Josiphos type ligands by incorporating a mono-or heteroannular bridge in the structure.[174] However, their applications in asymmetric hydrogenation are less efficient than the original Josiphos-type ligands.



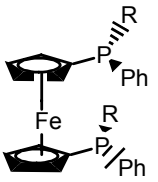
EtTRAP **190a**: R = Et
PrTRAP **190b**: R = Pr
BuTRAP **190c**: R = Bu
PhTRAP **190d**: R = Ph



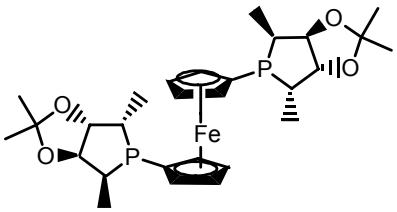
(*R*)-(*S*)-**191a**: R_1 = Cy, R_2 = Ph
(*R*)-(*S*)-**191b**: R_1 = ^{t}Bu, R_2 = ^{t}Bu
(*R*)-(*S*)-**191c**: R_1 = 3,5-Me_2Ph, R_2 = Ph
(*R*)-(*S*)-**191d**: R_1 = Cy, R_2 = Cy



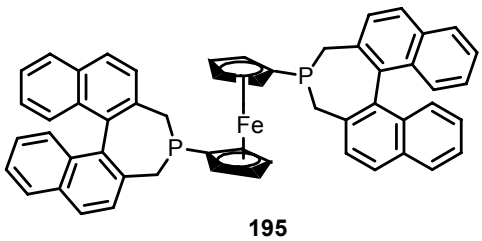
192



(*S*)-(*S*)-**193a**: R = 2-anisyl
(*S*)-(*S*)-**193b**: R = 2-Np



194



195

Figure 10

A C_2-symmetric bisphosphine FerroPhos **192** (**Figure 10**) has been developed by Kang and is found to be efficient for Rh-catalyzed hydrogenation of α-dehydroamino acid derivatives.[175] Mezzetti[176] and van Leeuwen/Widhalm[177] have independently reported P-chiral ferrocenyl bisphosphines **193a-b** (**Figure 10**). These two ligands have shown excellent enantioselectivities (up to 99% ee) for asymmetric hydrogenation of α-dehydroamino acid derivatives. Zhang has reported a 1,1'-bis(phospholanyl)ferrocene ligand **194** (**Figure 10**) with ketal susbtituents at the 3 and 4 positions.[178] The ligand has shown excellent enantioselectivities in hydrogenation of α-dehydroamino acid

derivatives. The ketal groups of the ligand are important for achieving the high enantioselectivity, since the corresponding ligand without the ketal groups only provides moderate ee's.[179] Zhang has also developed a 1,1'-bis(dinaphthophosphepinyl)ferrocene ligand, f-binaphane **195** (**Figure 10**), which has been successfully applied in Ir-catalyzed hydrogenation of acyclic arylimines.[180]

3.2 Monodentate phosphorus ligands.

Monophosphines were the first chiral ligands employed in the pioneering studies on the rhodium-catalyzed asymmetric hydrogenation of prochiral olefins.[157] Following the introduction of DIOP,[131] the field was soon taken over by chiral bidentate phosphorus ligands, and for more than thirty years, hundreds of these ligands were developed[181] on the assumption that bidentate ligands were essential for achieving high enantioselectivities in the hydrogenation reaction.[120(a)] However, this widespread notion has recently been challenged since monodentate phosphines,[182] phosphonites,[183] phosphites,[184] and phosphoramidites[185] have been successfully used in a number of asymmetric hydrogenation reactions with enantioselectivities of up to 99%.[186]

In the last few years, this small but rapidly expanding class of monodentate ligands has shown enantioselectivities comparable to or better than those reached with bidentate ligands reported so far.[187] The synthesis of these monodentate ligands is easily achievable since the creation of a P–X bond is easier synthetically than that of a P−C bond. By far the most studied ligands are those bearing three heteroatoms around the phosphorus atom: phosphites and phosphoramidites. In all cases the phosphorus atom is incorporated in a ring, formed from a diol or an amino alcohol. The chirality is introduced through the diol unit, or by an exocyclic alcohol or amine, or by both. In the last case, a matched or mismatched relationship may exist, with different catalytic behavior for each of the two diastereomeric ligands. Most favoured for the cyclic moiety are C_2-symmetrical diols as variously substituted binaphthols or biphenols, or TADDOL-type diols or tartrate derivatives (**Figure 11**). This subsection of the thesis presents monophosphite and

monophosphoramidite ligands and their applications in various metal-catalyzed asymmetric reactions.

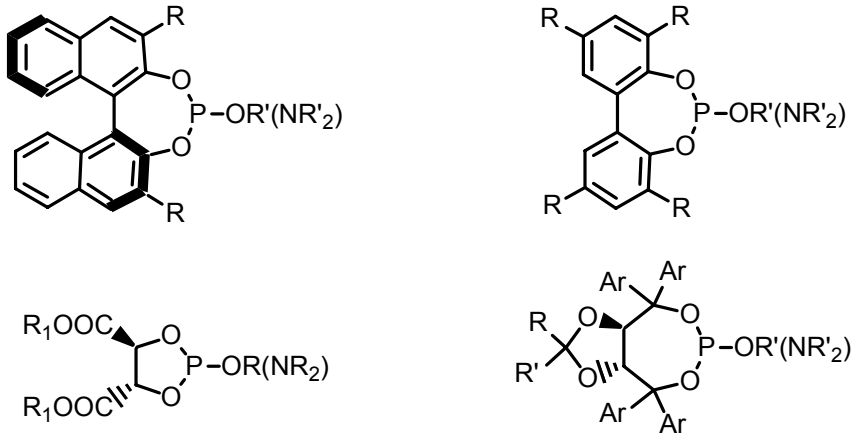


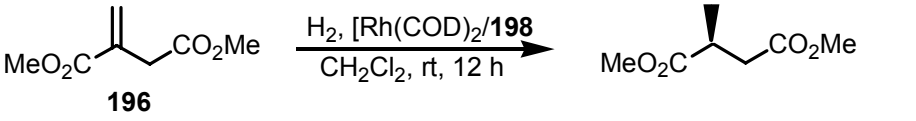
Figure 11

3.2.1 Binaphthol-based monodentate phosphorus ligands

Binaphthol-based ligands are the most intensely studied of the monodentate phosphorus ligands. The chirality of the binaphthol backbone alone is efficient enough to induce high levels of asymmetric induction, as seen in the examples given below. By far the most efficient ligands of this class, however, are those bearing a chiral exocyclic moiety, an alcohol for phosphites or an amine for phosphoramidites.

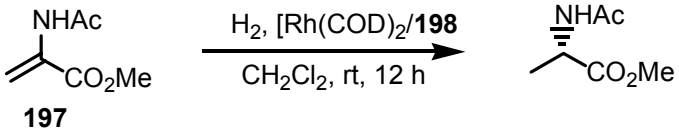
3.2.1.1 Binaphthol-based monophosphites.

Several dozen of this type of ligands have being tested in many asymmetric hydrogenation reactions. Xiao[188] has reported that phosphite **198** with menthol as the exocyclic moiety (**Figure 12**) is a good ligand in the rhodium-catalyzed asymmetric hydrogenation of prochiral olefins such as itaconic acid dimethyl ester **196** (**Scheme 64**) and methyl-2-acetamido acrylate **197** (**Scheme 65**) with ee's of >95% and 85% respectively. Both reactions yielded a 100% conversion in dichloromethane as a solvent using 10 bar H_2.



196

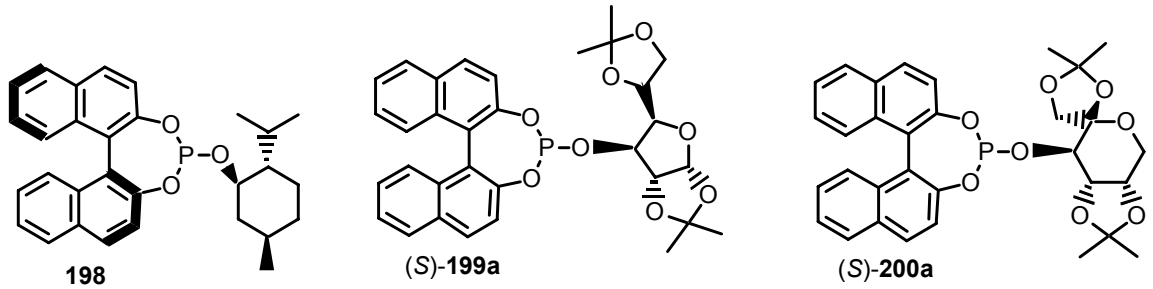
Scheme 64



197

Scheme 65

Reetz[189] and Zheng[190] independently synthesized chiral monophosphites ligands **199** and **200** (**Figure 12**) based on carbohydrates. Zheng *et al.* had tested their ligands on the rhodium-catalyzed asymmetric hydrogenation of dimethyl itaconate and several enamides with ee's of up to 99.6% and 98.5% being obtained respectively. Reetz *et al.* applied their ligands on the rhodium-catalyzed asymmetric hydrogenation of alkyl-substituted vinylcarboxylates, which are famous for showing poor enantioselectivities when traditional chiral diphosphines are used. High conversion yields (~100%) and ee's of up to 94% were obtained.



198 (*S*)-**199a** (*R*)-**199b** (*S*)-**200a** (*R*)-**200b**

Scheme 76

3.2.1.2 Binaphthol-based monophosphoramidites.

Monodentate phosphoramidite ligands with a binaphthol backbone (**Figure 13**) have also been used in several hydrogenation reactions.

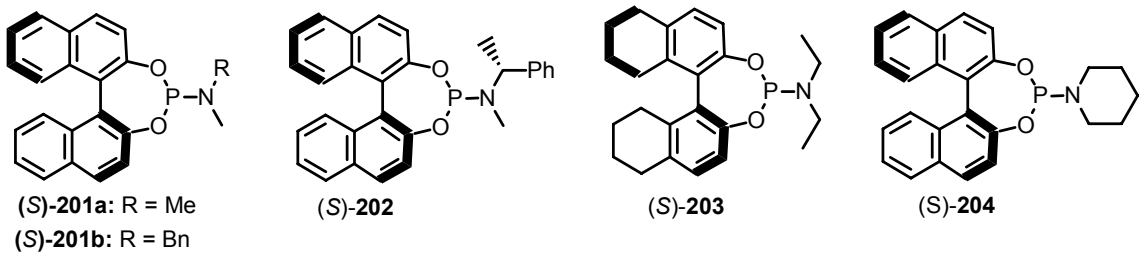
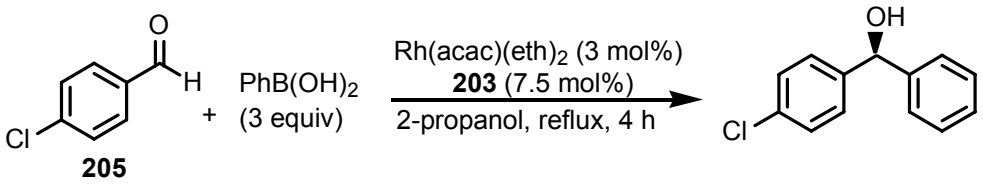


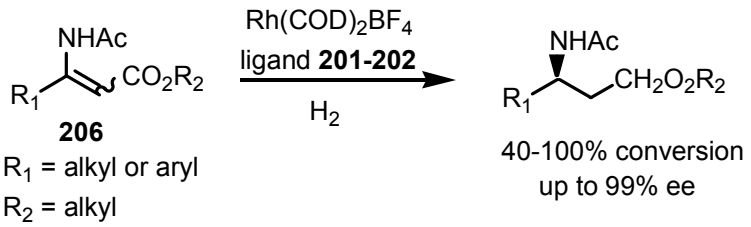
Figure 13

Minnaard *et al.*[191] have reported that a monodentate phosphoramidite **204** (**Figure 13**), called PinPhos, is an excellent ligand for the rhodium-catalyzed asymmetric hydrogenation of aromatic enol acetates, enol carbamates and 2-dienol carbamates, with ee's of up to 98% obtained. de Vries *et al*.[192] applied a monophosphoramidite **203**, based on the H_8-BINOL backbone, for the rhodium-catalyzed asymmetric arylation of aldehyde **205** with phenylboronic acid (**Scheme 66**). Conversion of 99% in 2-propanol as a solvent and ee of up to 75% was obtained.



Scheme 66

Feringa[193] and coworkers have reported a monodentate phosphoramidite **201a** called MonoPhos, which was synthesized from (*S*)-BINOL and hexamethylphosphorous triamide (HMPA). This ligand, together with ligands **201b** and **202** has been used in the rhodium-catalyzed hydrogenation of (*E/Z*)-β-dehydroamino acid derivatives **206** (**Scheme 67**), leading to excellent enantioselectivity (up to 99% ee). Chiral phosphoramidite **202** showed the highest enantioselectivity amongst the ligands used in this particular reaction.



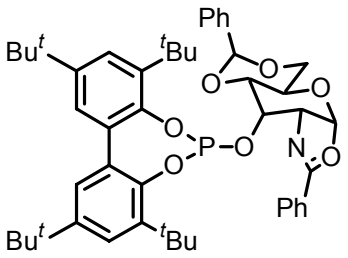
Scheme 67

In an attempt to improve enantioselectivity even further in the hydrogenation of the above-mentioned reaction, Feringa[194] and co-workers introduced a new combinatorial approach of mixing chiral ligands. Since ligand **202** (**Figure 13**) had shown the highest enantioselectivity, it was used in combination with the other two ligands **201a** and **201b**. Experiments carried out in dichloromethane as solvent showed that all the ee's obtained using only one particular ligand were lower than those obtained from the combination of ligands.

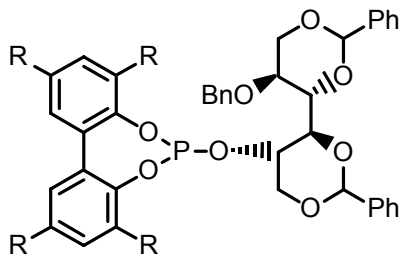
3.2.2 Biphenol-based monodentate phosphorus ligands

Biphenol-type ligands are similar to the binaphthol-based ones, but with the advantage of being much less expensive.[195] Unlike the binaphthol moiety, the biphenol unit is not atropisomerically stable. However, the chirality of the exocyclic part induces favourable atropisomerism, which in turn controls the enantioselectivity. Thus the matched/mismatched problem is avoided.

3.2.2.1 Biphenol-based monophosphites.



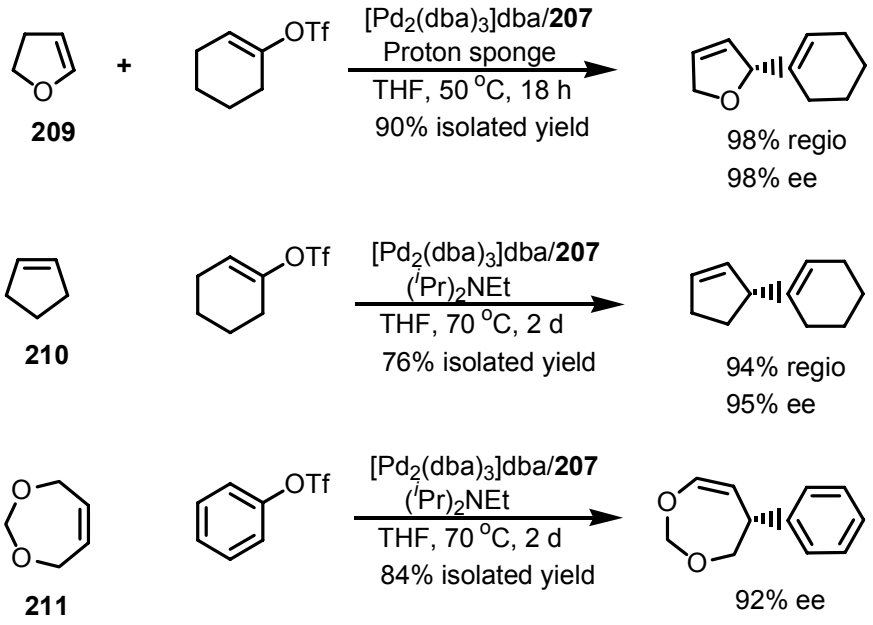
207



208a: R = H
208b: R = ^{t}Bu

Figure 14

Diéguez *et al*.[196] had synthesized a biphenol-based monophosphite-oxazoline ligands **207** (**Figure 14**), derived from readily available D-glucosamine. This ligand was used for the first time in the palladium-catalyzed Heck reaction of substrates **209-211** (**Scheme 68**) with high regio-and enantioselectivities (ee's up to 99%) being obtained.



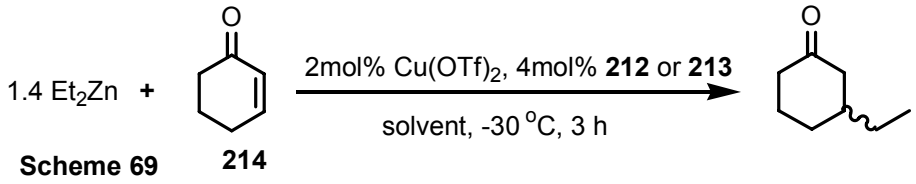
Scheme 68

Zheng *et al.*[197] had synthesized other different types of monophosphite ligands **208a-b** (**Figure 14**) which have a double six-membered ring. They have applied their ligands to rhodium-catalyzed hydrogenation of enamides, α-dehydroamino acid esters, dimethyl itaconate, and β-(acylamino)acrylates. Ee's of up to 98% were obtained for the asymmetric hydrogenation of α-dehydroamino acid esters, and ee values of over 99% were obtained for the other three types of substrates.

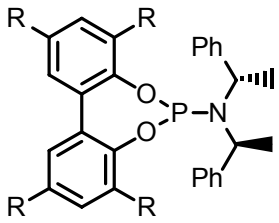
3.2.2.2 Biphenol-based monophosphoramidites.

Alexakis and co-workers have reported the synthesis of biphenol-based monophosphoramidites **212a-b** and **213** (**Figure 15**). They tested their ligands on the copper-catalyzed conjugate addition of ethylzinc onto cyclohexenone **214** using the above-mentioned ligands in different organic solvents (**Scheme 69**).[198] Their solvents of

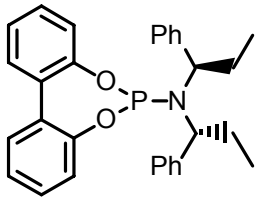
choice were toluene, diethyl ether, dichloromethane, tetrahydrofuran and ethyl acetate. Their results had shown that this reaction affords higher ee values (up to 90%) in ethereal solvents (diethyl ether, tetrahydrofuran and ethyl acetate) and this is in contrast to the usual belief that a noncoordinating solvent such as toluene (ee's up to 82%) is the most appropriate for the copper-catalyzed conjugate addition of dialkyl zincs.[199]



Scheme 69 **214**



212a: R = H
212b: R = CH_3

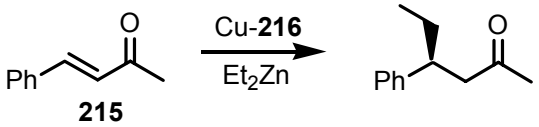


213

Figure 15

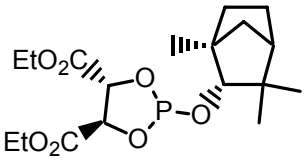
3.2.3 Tartrate-based monodentate phosphorus ligands

Generally with this type of ligand the phosphorus is incorporated into a five-membered ring. Despite the variety of structures tested, only low to moderate ee values have been attained in the conjugate addition reactions.[200] The best result was obtained with benzalacetone **215** (**Scheme 70**) and the most hindered ligand **216** (65% ee), bearing a fenchol as the chiral exocyclic component. These ligands do not show any matched or mismatched effects, both diastereomeric ligands being equal. In contrast to most ligands, it seems that the ester functionality of the tartrate part of the ligand also participates in the coordination of the organometallic species, especially in the copper-catalyzed conjugate addition reactions.[201]



215

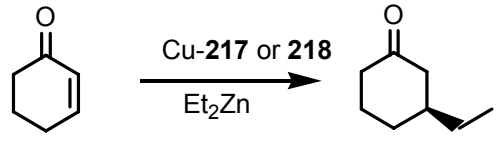
Scheme 70



216

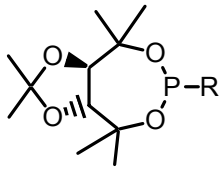
3.2.4 TADDOL-based monodentate phosphorus ligands

In contrast to tartrate-based ligands, TADDOL-based ligands incorporate the phosphorus atom in a seven-membered ring. Many ligands of this type have been prepared and tested mostly in the conjugate addition reactions.[202] This family includes both ligands that possess an additional exocyclic chiral group and those that do not. In the absence of exocyclic chirality, the TADDOL part of the ligand induces low to moderate enantioselectivities on enones (up to 71% ee on cyclohexenone) **214** (**Scheme 71**).[201b] When an exocyclic chiral alcohol is attached, however, high enantioselectivity has been attainable. With 2-phenylcyclohexanol, for example, a 96% ee was obtained with cyclohexenone. Ligands with two chiral moieties (the TADDOL part and the exocyclic part) show strong matched/mismatched character. For example, ligand **217** affords a 96% ee with cyclohexenone, whereas its diastereomer **218** affords a racemic mixture.



214

Scheme 71



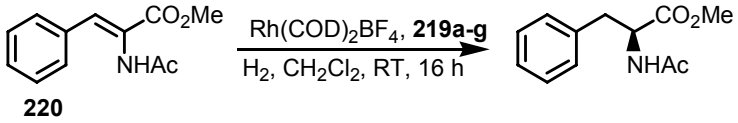
217 R = (1*R*,2*S*)-Ph-cyclohexanol

218 R = (1*S*,2*R*)-Ph-cyclohexanol

3.2.5 Catechol-based monodentate phosphorus ligands

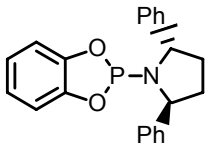
The Feringa and Minnaard groups have reported a new class of monophosphoramidite ligands **219** (**a-g**) for the rhodium-catalyzed asymmetric hydrogenation of enamides, based on an achiral catechol backbone.[203] Just like the tartrate-based ones, these ligands have their phosphorus atom incorporated into a five-membered ring. The ligands were

tested in the rhodium-catalyzed asymmetric hydrogenation of *N*-acyldehydrophenylalanine methyl ester **220** (**Scheme 72**). The ee's were found to be disappointing when using ligands **219a-f** (~3%). A sharp increase in both yield and enantioselectivity of >92% was reached when ligand **219g** was tested. Although ligands **219a** and **219g** have a similar kind of structure, a remarkable difference in activity was observed by introduction of a ring structure into the ligand.

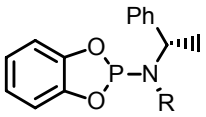


220

Scheme 72



(S,S)-**219g**



(*S*,*S*)-**219a**: R = methylbenyl amine
(*S*)-**219b**: R = benzyl
(*R*)-**219c**: R = *i*-propyl
(*S*)-**219d**: R = ethyl
(*S*)-**219e**: R = methyl
(*S*)-**219f**: R = H

3.3 Aims of this project.

When one looks at all the phosphorus-containing biaryl ligands (phosphoramidites and phosphites) discussed above, we realize that many of them contain an embedded seven membered hetero-atom ring. As a result of our previous work in the synthesis of aryl-substituted naphthalenes from simple tetralones,[204] we believe that we could design an entirely new class of phosphorus-containing ligands that contain either an embedded eight-or a nine-membered hetero-atom ring (**Figure 16**).

This new class of envisaged ligands will need to have their chirality induced by exocyclic groups as they will be synthesized from racemic biaryl diols. The chosen exocyclic moiety for the envisaged phosphites will be the cheap and readily available L-menthol e.g. compounds **221** and **223** (**Figure 16**) whereas in the case of phosphoramidites, chirality will be induced through (R,R)-(+)-bis(α-methylbenzyl)amine e.g. compounds **222** and **224** (**Figure 16**). We believe that these new phosphorus ligands could be used in asymmetric hydrogenation reactions, analogous to their seven member hetero-atom counterparts.

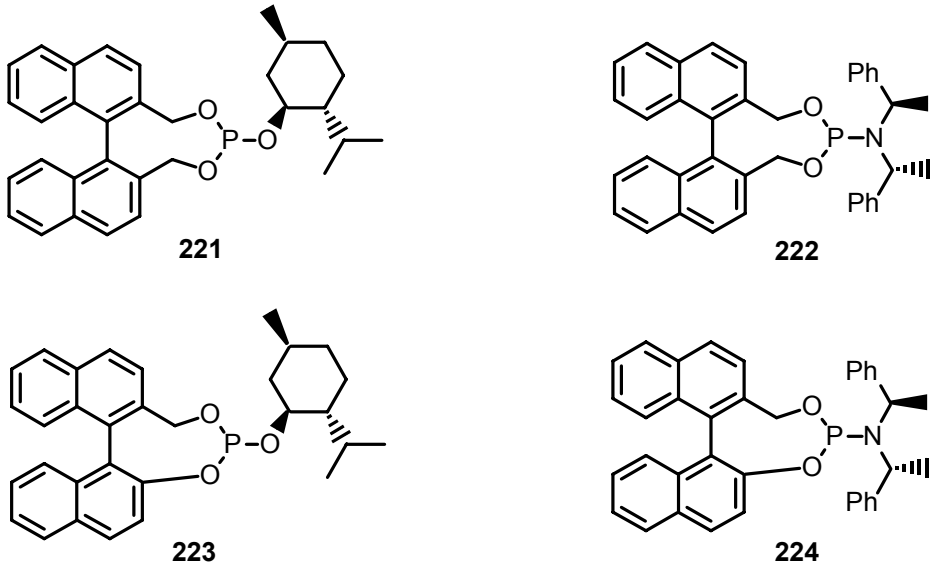
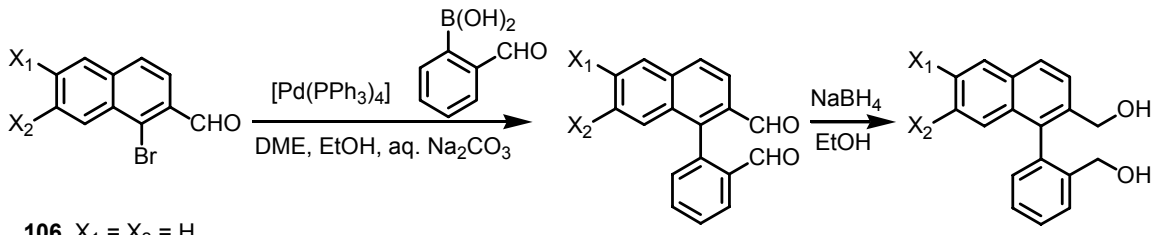


Figure 16

We also believed that by functionalizing our aryl rings (arylboronic acids) with different substituents, we can synthesize a library of different biaryl diols that can be reacted with the chiral amines or alcohols described in the last page in the presence of phosphorus trichloride or phosphorus oxychloride to design a library of phosphates, phosphites, phosphoramidates and phosphoramidites. Our synthesis we believed would be similar to the one we followed for the synthesis of aryl-substituted naphthalenes by starting from the bromo(methoxy)naphthalenaldehyde made in part 1. The next step, the Suzuki coupling step, will be done using different kinds of arylboronic acids to the ones used before in order to yield the required diols. Three different arylboronic acids will be extensively used in this part of project, one was 2-formylphenylboronic acid which is commercially available. Examples of the Suzuki coupling of this boronic acid with 1-bromo-2-naphthaldehyde **106**, 1-bromo-6-methoxy-2-naphthaldehyde **107** and 1-bromo-6,7-dimethoxy-2-naphthaldehyde **108** (all from part 1) towards the synthesis of dials **225**, **226** and **227** respectively is shown in **Scheme 73** below. The reduction of the resultant dials **225-227** with sodium borohydride in ethanol should give biaryl diols **228**, **229** and **230** respectively. The other two arylboronic acids used in this project are 2-isopropoxyphenylboronic acid and 2-isopropoxy-1-naphthylboronic acid, which will be synthesized using a known literature method.[205] Other biaryl diols will be synthesized using the Ullmann coupling reaction as will be explained below.



106, $X_1 = X_2 = H$
107, $X_1 = OMe$, $X_2 = H$
108, $X_1 = X_2 = OMe$

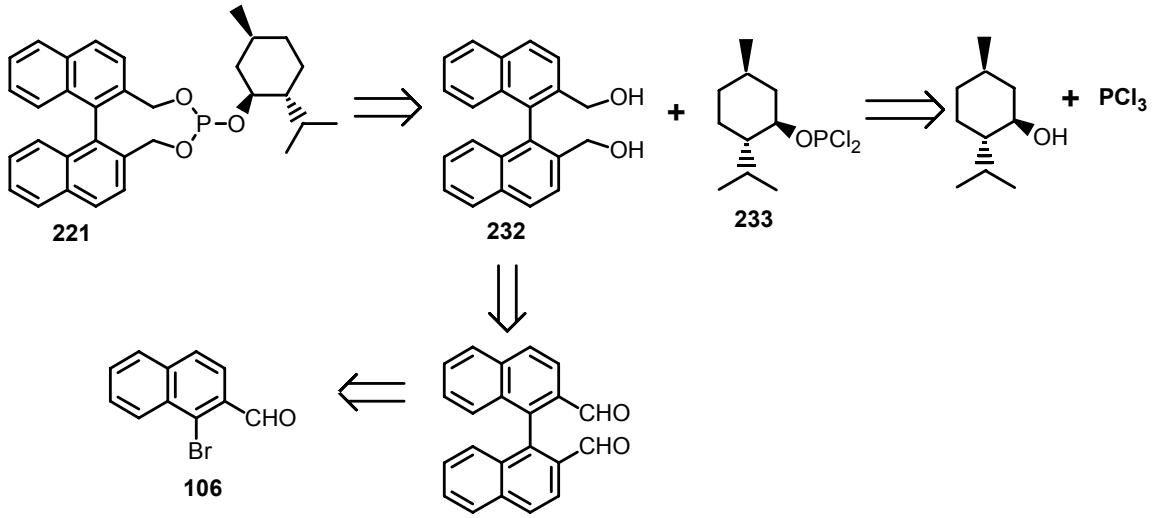
225, $X_1 = X_2 = H$
226, $X_1 = OMe$, $X_2 = H$
227, $X_1 = X_2 = OMe$

228, $X_1 = X_2 = H$
229, $X_1 = OMe$, $X_2 = H$
230, $X_1 = X_2 = OMe$

Scheme 73

Chapter 4: Results and Discussion 2

This chapter presents the results obtained in this part of the project, i.e. the syntheses of biaryl diols and their utilization in the attempted design of monodentate phosphorus ligands. Two key reaction steps are used in the synthesis of desired aromatic diols, one being the homo-Ullmann coupling of bromo(methoxy)naphthaldehydes and the second being the aqueous Suzuki coupling of bromo(methoxy)naphthaldehydes and boronic acids. A general retrosynthetic procedure towards the synthesis of one of the phosphite ligands, using Ullmann coupling reaction as the key step, is presented below (**Scheme 74**). Other monophosphorus ligands synthesized, followed the same retrosynthetic procedure.



221 **232** **233** **106** **231**

Scheme 74

Since we found that 1-bromo-3,4-dihydro-(methoxy)-2-naphthaldehydes **55**, **86** and **107** could be aromatized to bromo(methoxy)naphthaldehydes **106**, **107** and **108** respectively as described in part 1, we though it would be straight-forward to synthesize aromatic monodentate phosphate, phosphite, phosphoramidite and phosphoramidate ligands starting from simple α-tetralones. The synthesis (using an example from the above-mentioned retrosynthesis) would start with the copper-induced Ullmann coupling of bromonaphthaldehyde **106** (from part 1) to give binaphthaldehyde **231** which would in turn be reduced to diol **232** using sodium borohydride in ethanol**.**

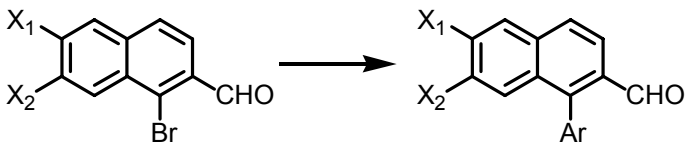
The next step would be the synthesis of the envisaged monodentate phosphorus ligand **221**. It has been reported that chirality in both phosphites[187] and phosphoramidites[188] can be introduced either through the diol or through an exocyclic chiral alcohol (in the case of phosphites) or chiral amine (in the case of phosphoramidites). We thus decided, since all our diols are racemic, to introduce chirality in our envisaged monodentate phosphorus ligands by using a cheap and readily available chiral L-menthol to synthesize phosphites and chiral (*R*,*R*)-(+)-*bis*(α-methylbenzyl)amine to design phosphoramidites. Therefore to synthesize our exocyclic chiral moiety for monophosphite ligand **221**, menthyl phosphodichloridite **233** would be synthesized by reacting L-menthol with phosphorus trichloride using a literature procedure.[206] The resultant product **233** would then be reacted with diol **232** to form the envisaged phosphorus ligand **221**. The remaining phosphites and phosphoramidites would also be synthesized from various diols utilizing the same kind of reaction procedures. Other biaryl diols used in this part of the project were synthesized using the experimental procedures that are discussed below.

4.1 Suzuki coupling reactions

As has already being mentioned, the Suzuki coupling reaction was used in this project as a key step in synthesizing some of our biaryl diols. Most of the arylboronic acids used in this step were synthesized from their respective halogenated precursors using known literature procedures[207] as described in part one. One exception was the *o*-formylphenylboronic acid which is available commercially. Another two arylboronic acids, *o*-isopropoxyphenylboronic acid and 2-isopropopoxy-1-naphthylboronic acid, were synthesized first by the protection of the hydroxyl group of the commercially available *o*-bromophenol and 1-bromo-2-naphthol as their isopropyl ethers. The second step was the lithiation of the resultant bromo-ethers using butyllithium and then the *in situ* formation of boronic esters using trimethyl borates which were eventually hydrolyzed to their respective boronic acids using hydrochloric acid solution.

The fourth boronic acid used in the project was *o*-benzyloxyphenylboronic acid which was synthesized using the same procedure mentioned above, but with the hydroxyl group protected as a benzyl ether rather than isopropyl ether. As mentioned in the literature, boronic acids prepared in this manner are not easy to purify, hence they were used as crude products throughout the project.

After the syntheses of the above-mentioned aryl boronic acids, the next step was the Suzuki coupling of each of the resultant boronic acids with 1-bromo-2-naphthaldehyde **106**, 1-bromo-6,7-dimethoxy-2-naphthaldehyde **108** and 1-bromo-6-methoxy-2-naphthaldehyde **107** (all prepared as explained in part one). As shown in **Scheme 75**, exposure of the above-mentioned naphthaldehydes to a catalytic amount of $[Pd(PPh_3)_4]$ in the presence of aryl boronic acids (mentioned above), together with aqueous sodium carbonate and DME/EtOH under reflux, afforded the desired Suzuki coupling products **225-227** and **234-241** in good to excellent yields (**Table 2**).



106-108 **225-227, 234-241**

Scheme 75

Table 2: Percentage yields of aryl-substituted naphthaldehydes.

Ar	Naphthaldehyde	% Yield
o-formylphenyl: $X_1=X_2=H$	**225**	76
X_1=OMe, X_2=H	**226**	70
$X_1=X_2$=OMe	**227**	80
2-isopropoxynaphthyl: $X_1=X_2=H$	**234**	79
X_1=OMe, X_2=H	**235**	87
$X_1=X_2$=OMe	**236**	60
o-isopropoxyphenyl: $X_1=X_2=H$	**237**	97
X_1=OMe, X_2=H	**238**	74
$X_1=X_2$=OMe	**239**	80
o-benzyloxyphenyl: $X_1=X_2=H$	**240**	94
$X_1=X_2$=OMe	**241**	97

The structures of all products were deduced by both nmr and infrared spectroscopy. The ^{1}H nmr spectroscopic data of dials **225**, **226** and **227** were characterized by two singlets integrating for one proton at ~9.7 ppm and ~9.5 ppm indicative of the two aldehydic protons present in these compounds. Also very clear in compounds **226** and **227** were distinct singlets integrating for three protons observed at ~4 ppm, confirming the methoxy substituents present in the desired products (one singlet at 3.95 ppm for compound **226** and two singlets at 3.95 ppm and 4.05 ppm for compound **227**). The ^{13}C nmr spectroscopic data of the three compounds mentioned above showed two signals at ~190 ppm and ~191 ppm verifying the presence of the two carbonyl carbons. Further confirmation for compounds **226** and **227** was from signals observed at ~55 ppm, identifying the presence of methoxy groups (one signal at 55.5 ppm for **226** and two signals at 56.1 ppm and 55.6 ppm for compound **227**). The infrared spectra of all three compounds showed a strong to very strong absorption at ~1700 wavenumbers which clearly suggests the presence of a carbonyl group (aromatic aldehyde) in all three compounds.

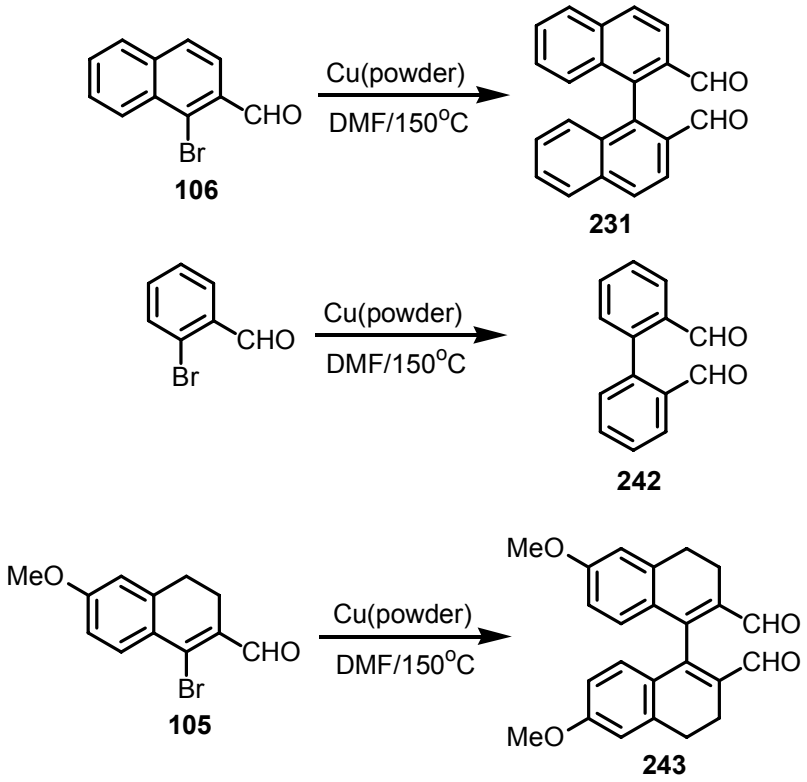
Spectroscopic data for compounds **234-239** were also very conclusive. The ^{1}H nmr spectroscopic data of compounds **234-236** showed a singlet integrating for one proton at ~9.6 ppm whilst data for compounds **237-239** showed the same singlet at ~9.8 ppm, confirming the presence of aldehydic protons. Also present in the spectra of the six compounds was a septet at ~4 ppm integrating for a single proton, indicative of the methine proton of the isopropyl moiety and the two doublets, each integrating for three protons, observed at ~1.1 ppm and ~0.9 ppm. These two doublets confirmed the presence of the two methyl groups from the isopropyl moiety.

Further confirmation for the identity of compounds **235**, **236**, **238** and **239** was provided by the singlets integrating for three protons observed at ~4 ppm, diagnostic of the methoxy groups (one singlet each for compounds **235** and **238** and two singlets each for compounds **236** and **239**). The ^{13}C nmr spectroscopic data of the six compounds revealed signals at ~193 ppm which confirmed the presence of a carbonyl carbon. Also present in the data were one signal at ~70 ppm (confirming the methine carbon of the isopropyl moiety) and two more signals at ~22 ppm (confirming two methyl groups of the isopropyl moiety). Further confirmation for compounds **235**, **236**, **238** and **239** was revealed in the form of extra signals at ~56 ppm that verify the presence of methoxy groups in the compounds. The infrared spectra of the six compounds showed a strong to a very strong absorption at ~1700 cm^{-1} which suggests the presence of a carbonyl functional group.

4.2 Ullmann coupling reactions

The second key reaction step in synthesizing another small library of aryl diols that were not achievable by using the Suzuki coupling reaction was accomplished using the Ullmann coupling reaction. This type of coupling procedure was first reported in 1901 by Ullmann[208] as a reaction that generates a carbon-carbon bond between two aromatic nuclei. It involves heating the mixture of the aryl halides with copper powder or copper bronze at 100-360 °C either with or without any solvent. Products of this reaction are the desired biaryl(s) and the corresponding copper(I) halide. In this project 1-bromo-2-

naphthaldehyde **106** (from part one) was converted into binaphthaldehyde **231** using excess copper powder in DMF at 150 °C (**Scheme 76).** The structure obtained was confirmed by nmr and infrared spectroscopies. ^{1}H nmr spectroscopy of dinaphthaldehyde **231** revealed a singlet integrating for one proton at 9.63 ppm, diagnostic of the aldehydic proton. The chemical shift of the aldehydic proton of product **231** looked much like the ones of the aryl substituted naphthaldehydes mentioned above (δ~9 ppm) and was very different to the one of the starting material **106** that was observed at 10.67 ppm. Further evidence for the identity of the new product **231** was provided by high resolution mass spectrometry. ^{13}C nmr spectroscopy revealed a signal at 191.0 ppm, suggesting the presence of an aldehydic carbon. Finally the infrared spectrum of binaphthaldehyde **231** showed a very strong absorption at 1691 cm^{-1}, indicating that the carbonyl functional group of an aldehyde was present.



Scheme 76

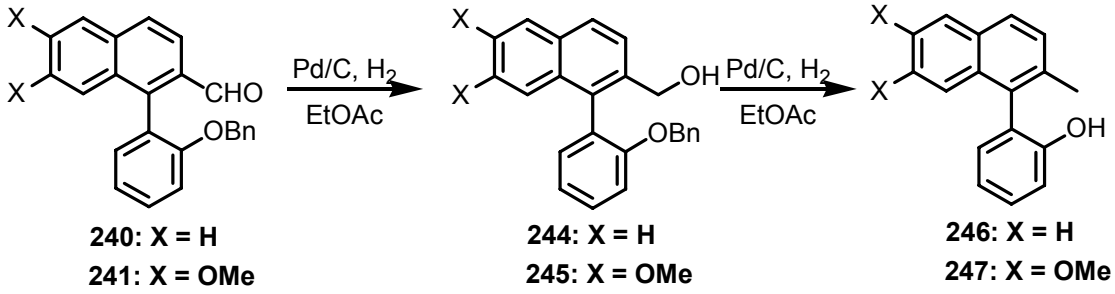
Also *o*-bromobenzaldehyde, which is commercially available, was converted into dial **242** using the Ullmann coupling reaction as reported in literature.[209] The third and the last binaphthaldehyde to be synthesized using Ullmann coupling reaction was dial **243**, which was synthesized from 1-bromo-6-methoxy-3,4-dihydro-2-naphthaldehyde **105**

(synthesized from part one) in 59% yield (**Scheme 76**). ^{1}H nmr spectroscopy revealed a singlet integrating for two protons at 9.69 ppm which confirmed the presence of the aldehydic protons. Further confirmation from the ^{1}H nmr spectroscopy was the presence of another singlet integrating for six protons at 3.81 ppm, diagnostic of a methoxy substituent present in the desired product.

Also two multiplets, each integrating for two protons, were observed between 2.99 and 2.66 ppm. These multiplets confirm the presence of the two pairs of equivalent methylene protons of dinaphthaldehyde **243**. ^{13}C nmr spectroscopic data revealed a signal at 191.5 ppm which confirms the presence of carbonyl carbon. Also present in this spectrum was a signal at 55.3 ppm confirming the presence of methoxy moieties of compound **243**. The infrared spectrum of the compound revealed a strong absorption at 1618 cm^{-1}, diagnostic of a carbonyl functional group of the aldehyde.

4.3 Hydrogenolysis of benzyl groups to afford phenols

In an attempt to deprotect benzyl ethers **240** and **241** to the corresponding phenols using a catalytic amount of Pd/C in the presence of a hydrogen gas (as reported in the literature[210]), slightly unexpected results were obtained (**Scheme 77**). The two resultant products were obtained as light yellow viscous oils. ^{1}H nmr spectroscopy of both products showed that the benzyl group was still intact but the aldehyde moieties of compounds **240** and **241** were reduced to alcohols. This was revealed by the fact that in both spectra there was no longer a singlet integrating for one proton at ~9 ppm, but new signals (two doublets each integrating for one proton with a coupling constant of 12.3 Hz) had emerged at ~5.2 ppm. These signals which indicate geminal coupling, are diagnostic of the CH_2OH group of the two compounds and confirms the reduction of an aldehyde to afford alcohols **244** and **245** (**Scheme 77**).



240: X = H
241: X = OMe

244: X = H
245: X = OMe

246: X = H
247: X = OMe

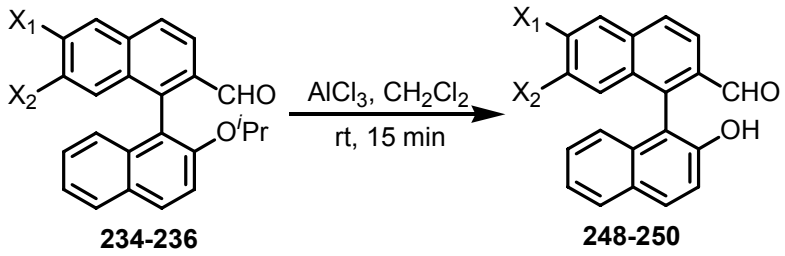
Scheme 77

Since the aldehyde moiety was going to be reduced to the alcohol in any case, we thought that this was not the end of the road as we could add extra Pd/C and hydrogen gas to remove the benzyl group. However when this was perfomed and the reaction mixture was filtered and purified by column chromatography, we found that over-reduction had taken place i.e alcohols **244** and **245** were now converted to methylphenylnaphthalenes **246** and **247** respectively (**Scheme 77**). ^{1}H nmr spectroscopy of both compounds revealed that indeed the benzyl group was no longer present as additional aromatic signals and the singlet integrating for two protons at ~5 ppm had disappeared. However a new singlet integrating for three protons had emerged at ~2.2 ppm and this confirmed that even the naphthyl alcohol was now reduced to a methyl group. It was thus decided that the hydroxyl group must now be protected as an isopropyl ether rather than a benzyl ether.

4.4 Removal of isopropyl groups to afford naphthols

The next step towards the synthesis of diols from compounds **234-236** was the removal of the isopropyl group to afford naphthols **248-250** (**Scheme 78**) using stoichiometric amounts of aluminum trichloride in dichloromethane as reported in the literature.[211] The resultant naphthols **248-250** were obtained in good to excellent yields (**Table 3**). Confirmation of the identity of the envisaged naphthols was obtained from both nmr and infrared spectroscopy. ^{1}H nmr spectroscopy of the three naphthols revealed the disappearance of a septet integrating for one proton at ~4.5 ppm (methine proton) and two doublets each integrating for three protons at ~1 ppm (methyl protons). ^{13}C nmr spectroscopy showed the disappearance of three signals, one signal at ~70 ppm (methine

carbon) and two signals at ~22 ppm (two diastereotopic methyl carbons). The disappearance of these three signals confirmed that the isopropyl group in all three compounds was no longer present.



234-236 **248-250**

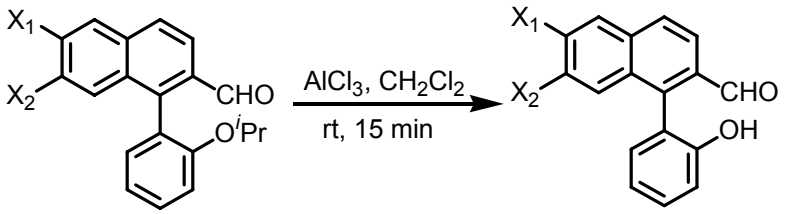
Scheme 78

Table 3: Percentage yields of biaryl naphthols

X	Naphthol	% Yield
X_1=X_2=H	**248**	98
X_1=OMe, X_2=H	**249**	60
X_1=X_2=OMe	**250**	86

4.5 Removal of isopropyl groups to afford phenols

After an isopropyl group was successfully removed from compounds **234-236** to afford naphthols **248-250** respectively, as explained above, it was thought that it would be easy to remove the same isopropyl group from compounds **237-239** to afford phenols (**Scheme 79**). This proved not to be the case as the resultant products obtained after column chromatography were always contaminated, as detected by nmr spectroscopy. Since the expected signals were observed at the expected chemical shifts in the spectra, it was decided that the products obtained should be treated as intermediates and be treated with sodium borohydride in order to reduce the aldehydes to alcohols, which could be purer.

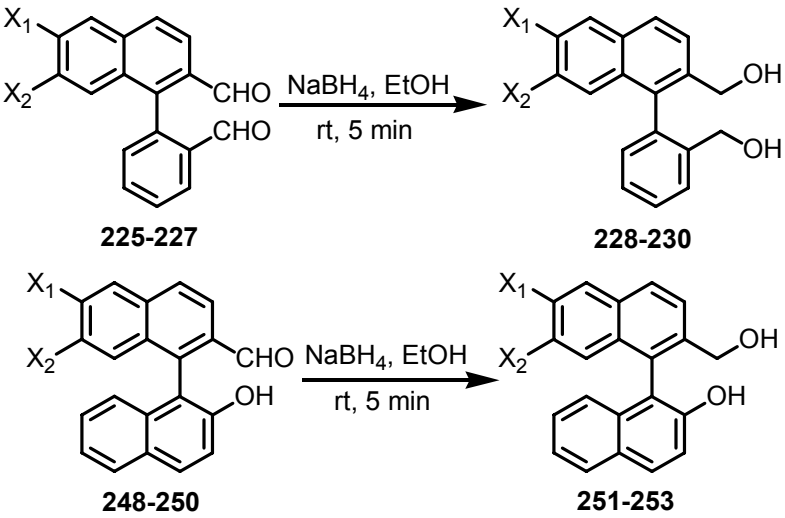


237-239

Scheme 79

4.6 Reduction of naphthaldehydes to naphthyl alcohols

Biary naphthaldehydes **225, 226, 227, 248, 249,** and **250** were successfully reduced to their respective biaryl diols **228, 229, 230, 251**, **252,** and **253** (**Schemes 80**) in excellent yields (**Table 4**) using sodium borohydride in ethanol at room temperature. In the reduction of naphthaldehydes **237-239**, the compounds were first treated with aluminium chloride in dichloromethane at room temperature and the resultant intermediates treated with sodium borohydride in ethanol at room temperature to afford diols **254-256** (**Scheme 81**) in acceptable yields (**Table 4**).



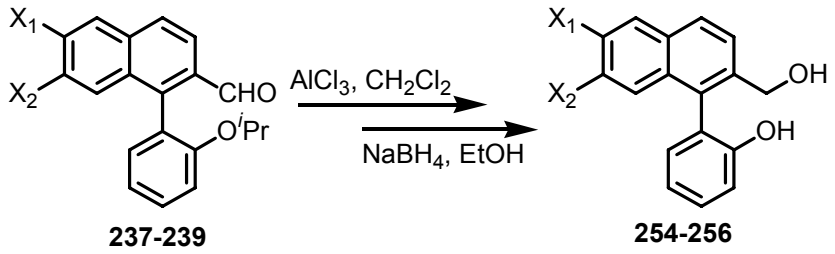
225-227 **228-230**

248-250 **251-253**

Scheme 80

Table 4: Percentage yields of biaryl diols.

Naphthaldehyde	Diol	% Yield
225	**228**	98
226	**229**	77
227	**230**	94
248	**251**	99
249	**252**	92
250	**253**	98
237	**254**	45
238	**255**	41
239	**256**	52



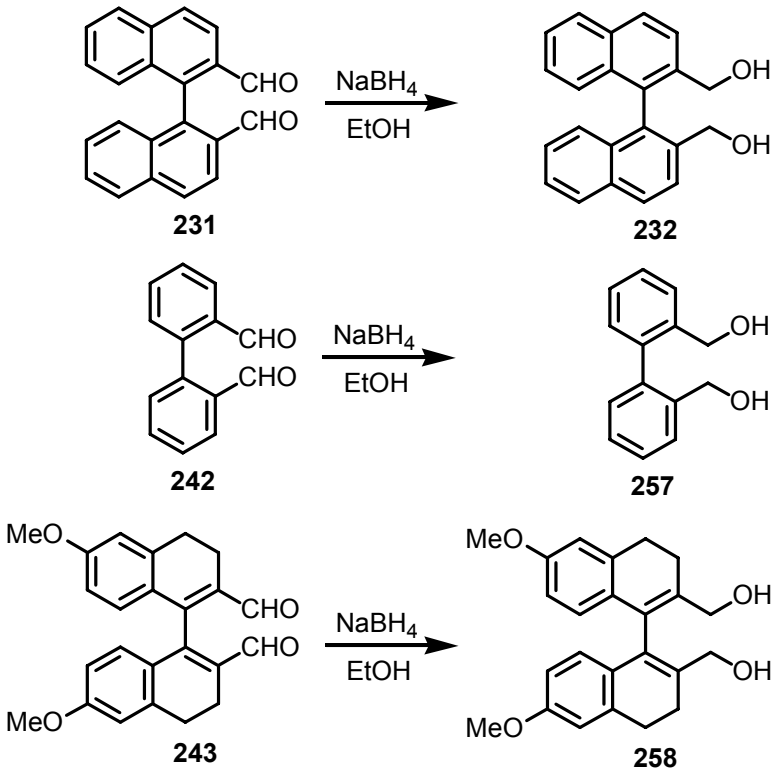
237-239 **254-256**

Scheme 81

Confirmation of the products was deduced from both nmr and infrared spectroscopy. Infrared spectra of all nine compounds revealed the disappearance of the signals at ~1700 cm^{-1} which was indicative of the carbonyl functional group and the appearance of a broad signal at ~3400 cm^{-1} that confirmed the presence of the hydroxyl group in the products. ^{1}H nmr spectroscopic data of the all nine products revealed the disappearance of the aldehyde signals at ~9.5 ppm. Spectra of compounds **228-230** were characterized by the appearance of four doublets, each with a coupling constant of ~12 Hz, and each integrating for one proton at ~4 ppm confirming the presence of a CH_2OH group. Spectra of compounds **251-256** were characterized by the appearance of a singlet integrating for two protons at ~4 ppm confirming the presence of the CH_2OH group.

The ^{13}C nmr spectroscopic data of all diols showed the disappearance of the characteristic aldehyde carbonyl signals at ~191 ppm and the appearance of new signals at ~63 ppm (indicative of the presence of CH_2OH) in the spectra of all nine compounds. The infrared spectroscopy of the small library of nine compounds showed a strong and broad absorption at ~3400 cm^{-1} which clearly indicates the presence of the hydroxyl functional group in the compounds. Also the strong absorption previously detected in the spectra of the naphthaldehydes at ~1700 cm^{-1} was longer present.

Three more naphthaldehydes were reduced to biaryl diols using sodium borohydride in ethanol. Bis(naphthaldehyde) **231** was reduced to biaryl diol **232** in 96% yield whereas dibenzylaldehyde **242** was reduced to diol **257** in 82% yield and dial **243** reduced to diol **258** in 94% yield (**Scheme 82**). Here too the infrared spectra of all three compounds showed a broad strong absorption at ~3400 cm^{-1}, indicative of hydroxyl functional group. The ^{1}H nmr spectroscopic data of the three compounds revealed the disappearance of the singlet integrating for one proton at ~9 ppm (aldehydic proton) and the appearance of the familiar two doublets each integrating for one proton at ~4 ppm. These doublets, which have a coupling constant of ~12 Hz, confirmed the presence of the CH_2OH group.



Scheme 82

4.7 Syntheses of monodentate phosphorus ligands

4.7.1 Phosphite and phosphoramidite ligands

After the library of twelve different aryl diols (**Figure 17**) was synthesized by different methods as described previously, the next step was to design monodentate phosphites and phosphoramidites from these diols utilizing experimental procedures as outlined in the literature.[187,212]

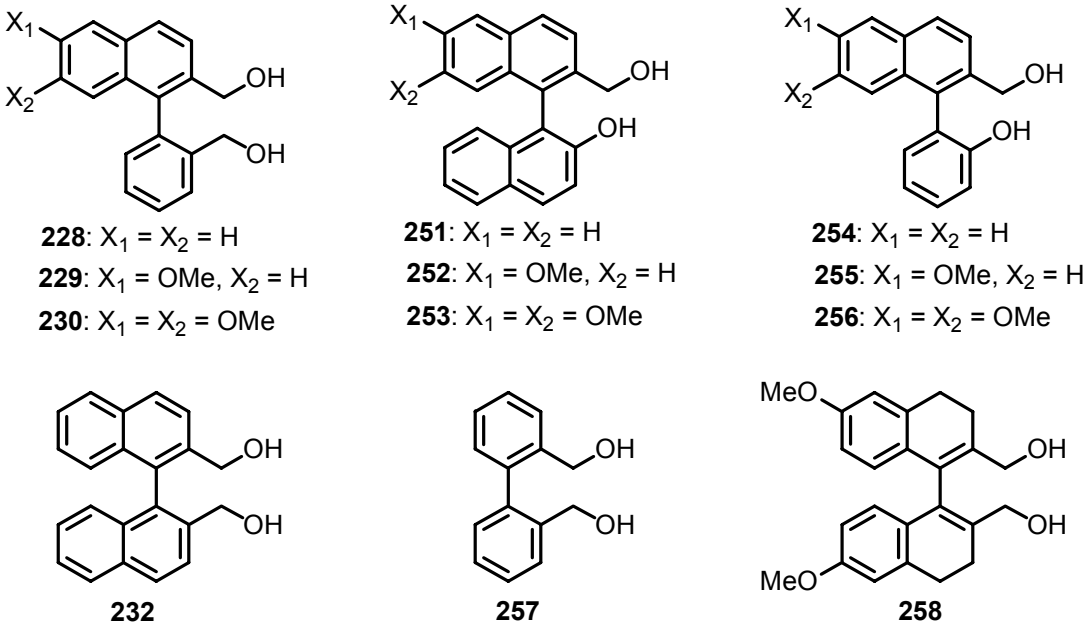
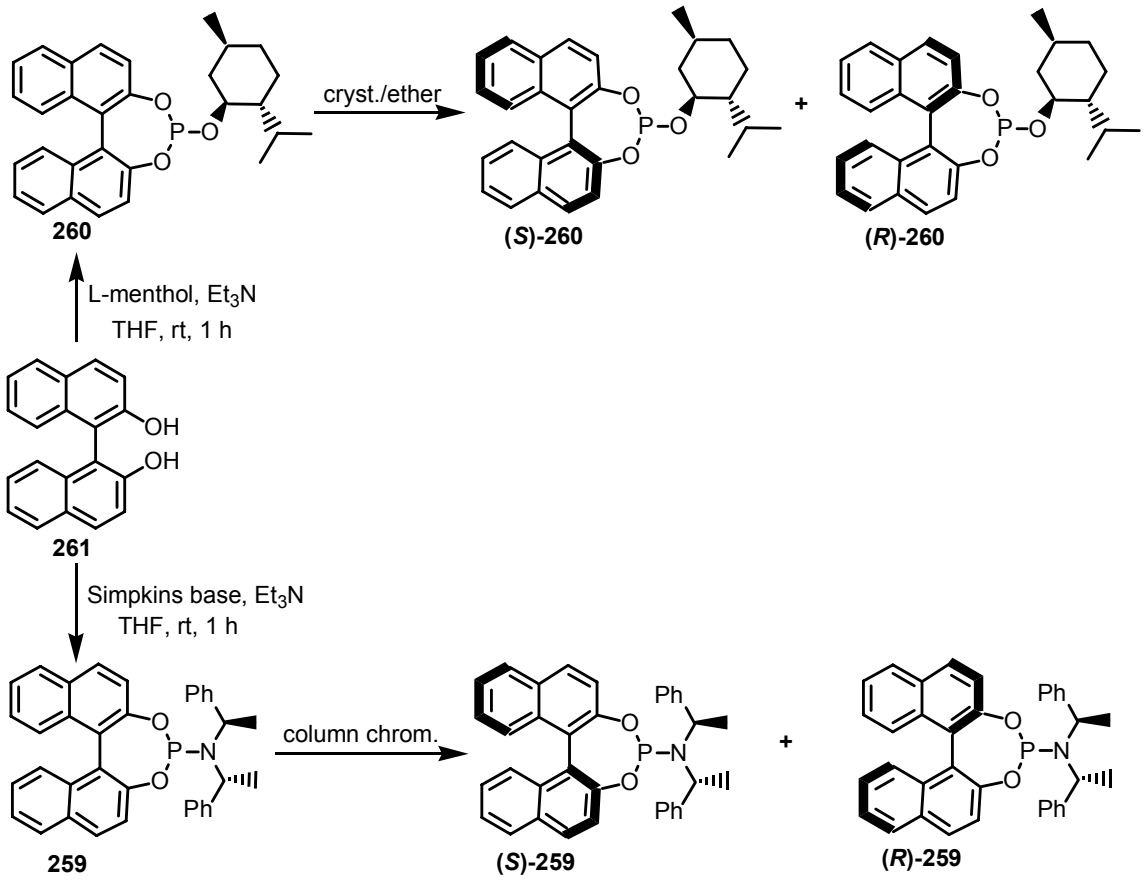


Figure 17

To familiarize ourselves with the methodology for the design of monodentate phosphorus ligands, it was thought best to synthesize *O,O'*-1,1'-binaphthyl-2,2'-diyl-*N,N*-(*S,S*)-*bis*(1-phenylethyl)phosphoramidite **259** and L-menthyl-1,1'binaphthalene-2,2'-diyl phosphite **260** as known phosphorus containing ligands reported in the literature.[7,8] Phosphite **260** was synthesized by introducing a mixture of racemic 1,1'-binaphthalene-2,2'-diol **261** and triethylamine in THF into a mixture of phosphorus trichloride and (1*R*,2*S*,5*R*)-(−)-menthol drop-wise as reported by Xiao *et al.*[126] (**Scheme 83**). The resultant diastereomers were separated by fractional recrystallization from diethyl ether. ^{31}P nmr spectra of the two diastereomers showed a singlet each at δ 152.4 ppm and 155.6 ppm. Xiao had reported their signals at δ 147.9 ppm and 151.0 ppm. Phosphoramidite **259** was synthesized in the same manner as mentioned above but L-menthol was replaced with (*R*,*R*)-(+)-*bis*(α-methylbenzyl)amine (**Scheme 83**). Even though Sewald *et al.*[127] had used toluene instead of THF as a solvent, the results obtained were comparable. The resultant diastereomers were separated by silica gel column chromatography and the ^{31}P nmr spectra of the diastereomers showed one singlet each at δ 145.9 ppm and 151.1 ppm whilst Sewald reported their signals at 146.5 ppm and 151.6 ppm.



Scheme 83

Although several researchers have synthesized seven-membered heterocyclic monodentate phosphite[213] and phosphoramidite[214] ligands, no one, to the best of our knowledge had synthesized nine- or eight-membered heterocyclic monodentate phosphite, phosphate, phosphoramidite or phosphoramidate ligands. Hence our major aim after synthesizing a library of different aryl diols, was to design hetero nine and eight membered ring phosphorus ligands utilizing an experimental procedure as outlined by Xiao (for phosphites) and Sewald (for phosphoramidites). Therefore the following subsection outlines the twenty-two different phosphite, phosphate, phosphoramidite and phosphoramidate ligands designed, and some of the problems encountered in the separation of the resultant diastereomers.

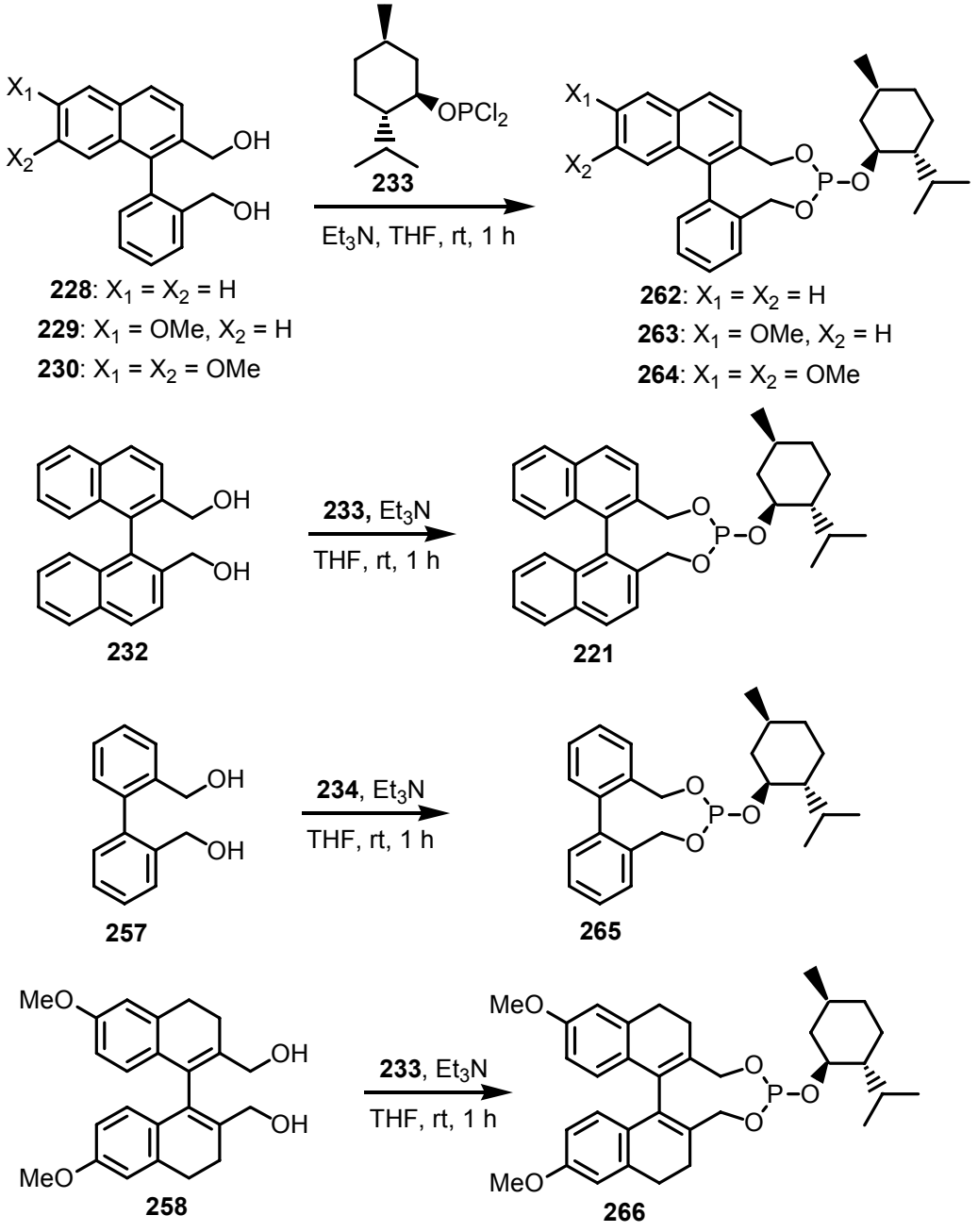
4.7.1.1 Phosphites containing a nine-membered heterocycle

Six nine-membered ring phosphites **262**, **263**, **264**, **221**, **265** and **266** were synthesized from aryl diols **228**, **229**, **230**, **232**, **257** and **258** respectively by reacting diols with a mixture of L-menthyl phosphodichloridite **233** (prepared by reacting L-menthol with phosphorus trichloride in tetrahydrofuran at room temperature and purified by distillation at low pressures) and triethylamine in THF at room temperature (**Scheme 84**). The phosphites were obtained in good to excellent yields (**Table 7**). Confirmation of the identity of the products was mainly derived from ^{31}P nmr spectroscopy. Since racemic aryl diols were used together with L-menthyl phosphodichloridite, the resultant diastereomers were expected to show two singlets in the regions of ~150 ppm in ^{31}P nmr spectra of the phosphites. The two singlets would indicate the presence of both the *M*-(L-menthyl) phosphite and the *P*-(L-menthyl) phosphate aromatic derivatives.

Table 7: Percentage yields of nine-membered ring phosphites.

Aryl Diol	Phosphite	% Yield
228	**262**	84
229	**263**	88
230	**264**	89
232	**221**	92
257	**265**	82
258	**266**	73

Indeed it was found that the ^{31}P nmr spectra of phosphites **221** (δ 151.9 ppm and 149.8 ppm), **264** (δ 152.0 ppm and 151.3 ppm), **265** (δ 149.2 ppm and 147.2 ppm) and **266** (δ 153.2 ppm and 154.6 ppm) did show the expected signals in the expected range. Even though ^{31}P nmr spectra of phosphites **262** (152.4 ppm, 150.4 ppm, 149.6 ppm and 147.5 ppm) and **263** (149.6 ppm, 149.5 ppm, 149.2 ppm and 148.5 ppm) showed signals in the expected range, four singlets were observed instead of two. Further confirmation for phosphite **265** was obtained from high resolution mass spectrometry using electron impact ionization method. For compounds **263**, **264** and **221**, further confirmation was obtained from low resolution mass spectrometry using the fast atom bombardment ionization method.



Scheme 84

In an attempt to separate the diastereomers, two well trusted methods were utilized, crystallization and chromatography. Attempted crystallization of phosphites **262**, **263**, **235** and **266** (all white to yellowish flakes) using organic solvents (ether, dichloromethane, benzene, toluene and acetonitrile) and a mixture of organic solvents (dichloromethane + hexane, benzene + hexane and toluene + hexane) proved unfruitful as the products always oiled out after the slow evaporation of the solvents. Both column and

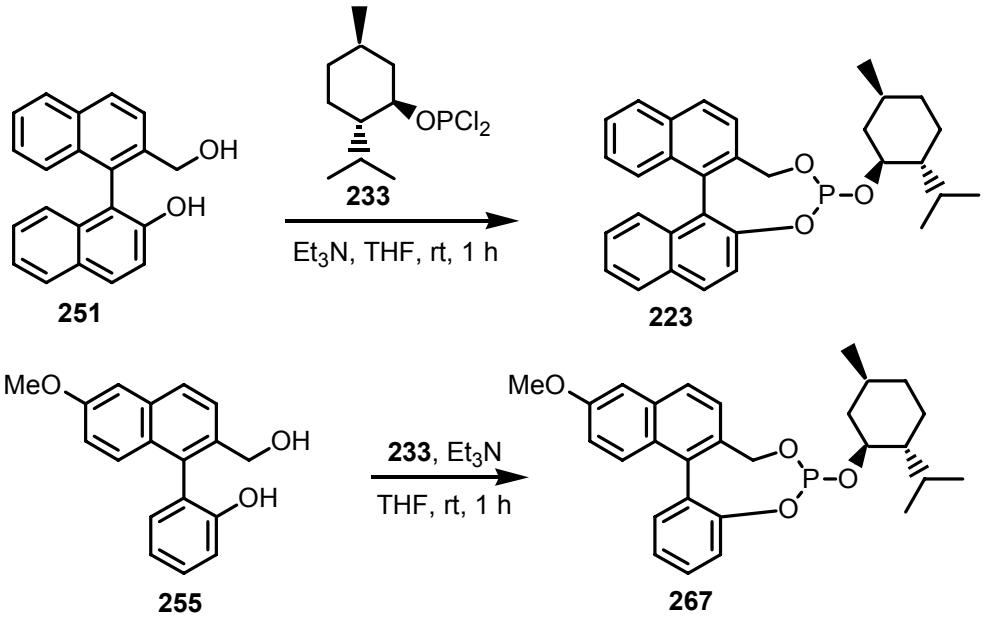
flash chromatography of the four above-mentioned phosphites (flakes) and phosphites **264** and **265** (thick oils) also proved unfruitful as the resultant ^{31}P nmr spectra of the compounds showed a cluster of signals at ~6 ppm. This region of the ^{31}P nmr spectrum is characteristic of phosphates[215] and phosphonic acids[216], therefore it is safe to assume that chromatography only results in the oxidation of the afore-mentioned phosphites to their respective phosphates or phosphonic acids.

4.7.1.2 Phosphites containing an eight-membered heterocycle.

Two eight-membered ring phosphites **223** and **267** were obtained by mixing solutions of aryl diols **251** and **255** in tetrahydrofuran respectively, with menthyl phosphodichloridite **233** in the presence of triethylamine at room temperature (**Scheme 85**). The resultant phosphites were obtained in excellent yields (**Table 8**). Confirmation of the identity of our ligands was obtained from ^{31}P nmr spectroscopy which showed two singlets at 105.7 ppm and 104.2 ppm for phosphite **267** and four singlets at 144.0 ppm, 142.9 ppm, 142.5 ppm and 140.4 ppm for phosphite **223**. Again attempted separation of the diastereomers using both crystallization and chromatography was unsuccessful.

Table 8: Percentage yields of eight-membered ring phosphites.

Biaryl Diol	Phosphite	% Yield
251	**223**	91
255	**267**	85



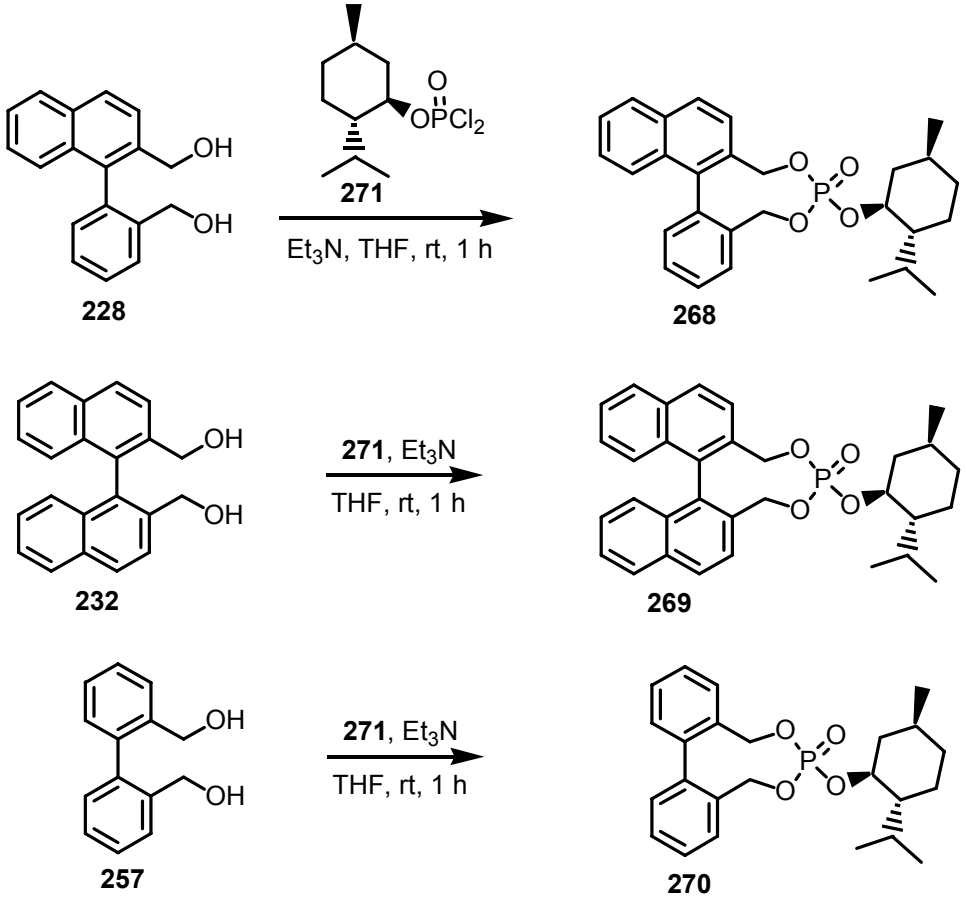
Scheme 85

4.7.1.3 Phosphates containing a nine-membered heterocycle.

Phosphorus containing ligands **268**, **269** and **270** (all thick oils) were synthesized by reacting aryl diols **228**, **232** and **257** respectively with a mixture of L-menthyl phosphodichloridate **271** (prepared by reacting L-menthol with phosphorus oxychloride in tetrahydrofuran at room temperature and purified by distillation at low pressures) and triethylamine in THF at room temperature (**Scheme 86**). The envisaged ligands were obtained in good to excellent yields (**Table 9**). Confirmation of the products was again obtained using ^{31}P nmr spectroscopy. Two singlets were observed for compounds **269** (0.286 ppm and 0.107 ppm) and **270** (1.207 ppm and 0.967 ppm), characteristic signals for phosphates and confirming that two diastereomers for each phosphate were obtained. Strangely, one signal was observed for compound **268** (δ 4.072 ppm). Further confirmation for compounds **269** and **270** was obtained from low resolution mass spectrometry using the fast atom bombardment ionization method.

Table 9: Percentage yields of nine-membered ring phosphates.

Biaryl Diol	Phosphate	% Yield
228	**268**	88
232	**269**	79
257	**270**	90

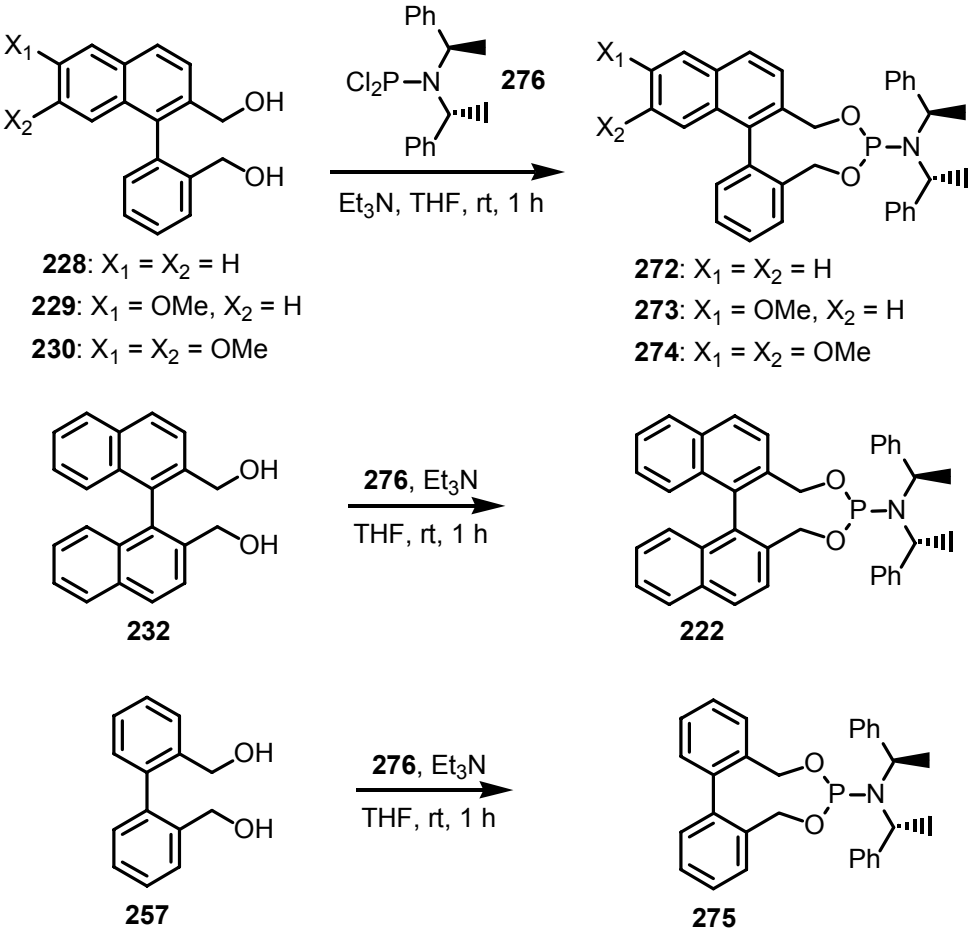


Scheme 86

4.7.1.4 Phosphoramidites containing a nine-membered heterocycle

In total five phosphoramidites **272, 273, 274, 222 and 275** were designed respectively from the reaction of biaryl diols **228**, **229**, **230**, **232** and **257** with a mixture of *N*-phosphodichloridite *bis*-(α-methylbenzyl)amine **276** (prepared by reacting (*R*,*R*)-(+)-*bis*-(α-methylbenzyl)amine with phosphorus trichloride in tetrahydrofuran at room temperature and purified by distillation at low pressure) and triethylamine in THF at

room temperature (**Scheme 87**). The products were synthesized in good to excellent yields (**Table 10**). For the characterization of these products by ^{31}P nmr spectroscopy, we expected to see a singlet at~150 ppm if a non-racemic diol is used. In our case, since we are using only racemic aryl diols, we expected to see two singlets at~150 ppm from the ^{31}P nmr spectra of our envisaged ligands. This proved to be the case as the ^{13}P nmr spectrum of phosphoramidite **222** showed two singlets at 149.8 ppm and 149.6 ppm. Also two singlets were observed from ^{31}P nmr spectra of compounds **275** (δ 149.4 ppm and 147.8 ppm), **272** (δ 149.7 ppm and 148.7 ppm), **273** (δ 152.6 ppm and 150.4 ppm) and **274** (δ 152.0 ppm and 151.3 ppm). Further confirmation of these compounds was obtained from mass spectrometry by the FAB ionization method. Again attempted separation of the resultant diastereomeric phosphoramidites by both crystallization and chromatography was unsuccessful.



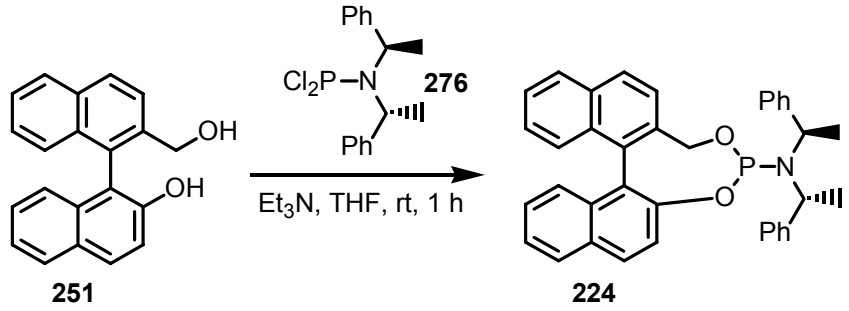
Scheme 87

Table 10: Percentage yields of nine-membered ring phosphoramidites.

Biaryl Diol	Phosphoramidite	% Yield
228	**272**	87
229	**273**	70
230	**274**	85
232	**222**	94
257	**275**	82

4.7.1.5 Phosphoramidites containing an eight-membered heterocycle

Only one eight-membered ring phosphoramidite ligand **224** was successfully synthesized from aryl diol **251** in 83% yield using the same procedure as for the nine-membered ring phosphoramidites (**Scheme 88**). Two singlets (δ 109.9 ppm and 108.2 ppm) were observed from the ^{31}P nmr spectrum of phosphoramidite **224** confirming the identity of the product and that it was afforded as a mixture of diastereomers. Further confirmation was obtained from mass spectrometry.



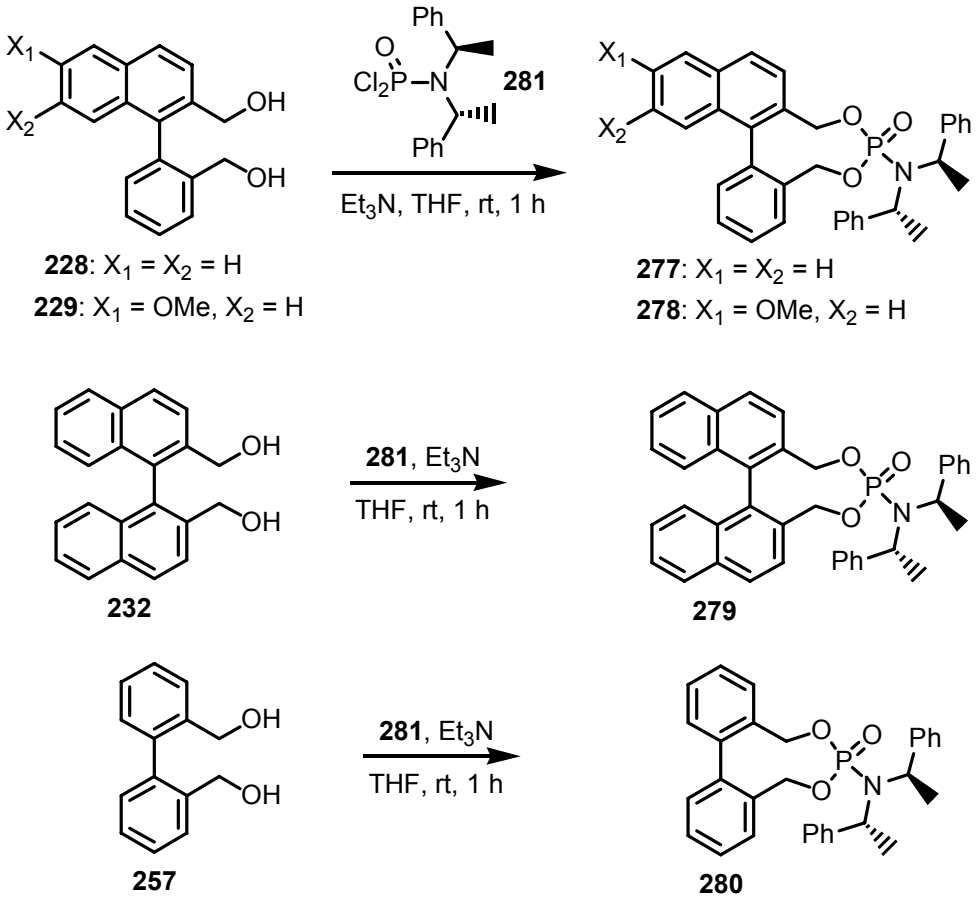
251 **224**

Scheme 88

4.7.1.6 Phosphoramidates containing a nine-membered heterocycle

Four phosphorus-containing ligands **277**, **278**, **279** and **280** were successfully designed from aryl diols **228**, **229**, **232** and **257** respectively in excellent yields (**Table 11**). These phosphoramidates were synthesized from a reaction of diols **228**, **229**, **232** and **257** with a mixture of *N*-phosphodichloridate *bis*-(α-methylbenzyl)amine **281** (prepared by reacting (*R*,*R*)-(+)-*bis*-(α-methylbenzyl)amine with phosphorus oxychloride in tetrehydrofuran at room temperature and purified by distillation at low pressure) and triethylamine in THF

at room temperature (**Scheme 89**). Confirmation of the products was obtained from ^{31}P nmr spectroscopy. The spectra of compounds **278** (δ = 0.432 ppm and −0.858 ppm) and **279** (δ = −4.358 ppm and −6.213 ppm) each showed two signals whereas spectra of compounds **277** (δ = −5.115 ppm) and **280** (δ = −4.511ppm) showed only one signal each. Further confirmation for compounds **277** and **280** was obtained from low resolution mass spectrometry using fast atom bombardment ionization method.



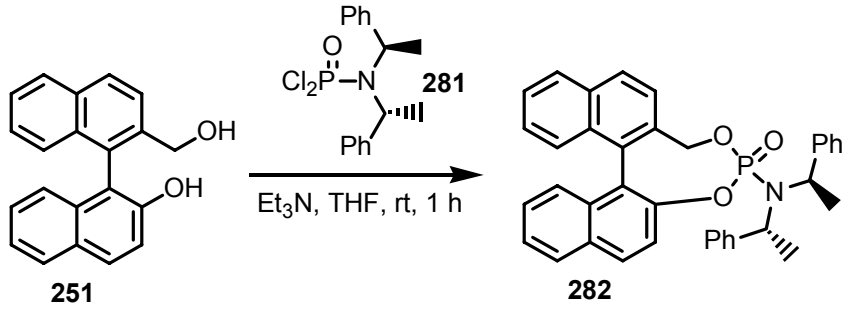
Scheme 89

Table 11: Percentage yields of nine-membered ring phosphoramidates.

Biaryl Diol	Phosphoramidate	% Yield
228	**277**	93
229	**278**	94
232	**279**	92
257	**280**	93

4.7.1.7 Phosphoramidates containing an eight-membered heterocycle

Eight-membered ring phosphoramidate **282** was successfully prepared by reaction of biaryl diol **251** with a mixture of *N*-phosphodichloridate *bis*-(α-methylbenzyl)amine **281** and triethylamine in THF at room temperature in 86% yield over an hour (**Scheme 90**). Confirmation of the compound was obtained from a ^{31}P nmr spectrum that showed a singlet at −16.27 ppm.



Scheme 90

In summary we had synthesized biaryl aromatic compounds containing a phosphorus atom in either an oxidation state of three or five. In addition each of these compounds had a chiral moiety embedded. However time constraints did not allow for the testing of these ligands in metal catalysed reactions.

Chapter 5: Conclusion and Future Work

Novel methodology for the synthesis of aryl-substituted naphthalenes was developed and explored in this project. Substituted arylnaphthalene acetates **59**, **83**, **84**, **85** were synthesized in 78%, 95%, 93% and 100% respectively in five steps starting from 1-bromo-3,4-dihydro-2-naphthaldehyde **55**. Other types of aryl-substituted naphthalenes with a biaryl axis and containing additional methoxy substituents i.e. 6,7-dimethoxynaphthalenes acetates **99**, **100**, **101** and **102** were synthesized in 74%, 78%, 80% and 78% respectively in five steps starting from 1-bromo-6,7-dimethoxy-3,4-dihydro-2-naphthaldehyde **86**.

In an attempt to reduce steps towards the synthesis of aryl-substituted naphthalenes, we were able to oxidize 1-bromo-3,4-dihydro-2-naphthaldehyde **55** and 1-bromo-6-methoxy-3,4-dihydro-2-naphthaldehyde **105** to their respective naphthaldehydes **106** and **108**. This

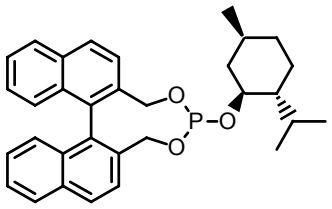
helped us to synthesize aryl-substituted naphthalene alcohols **113**, **114**, **115** and **116** in two steps starting from 1-bromo-3,4-dihydro-2-naphthaldehyde **55** in yields of 82%, 93%, 91% and 95% respectively. Also aryl-substituted methoxynaphthalene alcohols **121**, **122**, **123** and **124** were synthesized in two steps starting from 1-bromo-6-methoxy-2-naphthaldehyde **105** in 89%, 95%, 100% and 93% yields respectively.

Some of our aryl-substituted naphthalenes were subjected to anti-cancer testing against malignant cancer cells. Compounds **101**, **112**, **114**, **116** and **121** showed promising results when tested against cancer cells. Future work in this area will include testing our compounds against normal healthy cells.

Also we were able to explore unexpected methodology for the synthesis of three aryl-substituted cyclopropanetetrahydronaphthalenes **125**, **130** and **131** by treating aryl-substituted dihydronaphthaldehydes **72**, **74** and **75** with an excess of lithium aluminum hydride (in tetrahydrofuran) in unoptimized yields of 44%, 43% and 53% respectively. Future work in this part will involve optimization of the percentage yields and the further exploration of this reaction by treating other aryl-substituted dihydronaphthaldehydes with excess lithium aluminum hydride in tetrahydrofuran. Other work will include developing methods for opening the three membered ring to afford larger ring structures.

The methodology developed in part one was further explored in part two of the project through the design and synthesis of twelve biaryl diols **228-232**, **251-258.** These diols were successfully synthesized from three different naphthaldehydes 1**06**, 1**07** and 1**08** which were in turn synthesized from simple α-tetralones **61-63** over two steps. Biaryl diols **228**, **232**, **251** and **252** were synthesized from 1-bromo-2-naphthaldehyde 1**06** over two to three steps in very good yields utilizing the Suzuki and Ullmann coupling reactions as key steps. In turn biaryl diols **229**, **252** and **255** were synthesized from 1-bromo-6-methoxy-2-naphthaldehyde 1**07** in almost quantitative yields over three steps. 1-Bromo-6,7-dimethoxy-2-naphthaldehyde 1**08** was utilized in the successful synthesis of aryl diols **230**, **253** and **256** in excellent yields. The other two aryl diols, **257** and **258** were synthesized from *ortho*-bromobenzaldehyde (commercially available) and 1-bromo-6-methoxy-3,4-dihydro-2-naphthaldehyde (from part 1) respectively over two steps in very good yields after utilizing the Ullmann coupling reaction as the key step.

After successfully synthesizing the twelve different biaryl diols, we convincingly designed the novel phosphite, phosphate, phosphoramidite and phosphoramidate ligands with either a nine-or an eight-membered heterocyclic ring starting from the aryl diols, albeit in about 75-80% purity. Six phosphites **262**, **263**, **264**, **221**, **265** and **266** with a nine-membered heterocyclic ring were designed from aryl diols **228**, **229**, **230**, **232**, **257** and **258** respectively in acceptable to good yields. Five phosphoramidites **272, 273, 274, 222** and **275** with a nine-membered ring were synthesized from diols **228**, **229**, **230**, **232** and **257** respectively in satisfactorily to excellent yields. Aryl diols **251** and **255** were used in the successful synthesis of phosphites **223** and **267** with an eight-membered ring respectively. Three phosphates **268**, **269** and **270**, with a nine-membered heteroatom ring, were designed from diols **228**, **232** and **257** respectively in very good yields. Aryl diols **228**, **229**, **230**, **232** and **257** were successfully converted into phosphoramidates **277-280** respectively in excellent yields. Only one phosphoramidite **224** and phosphoramidate **282** each were successfully designed from aryl diol **251** in 83% and 86% respectively.



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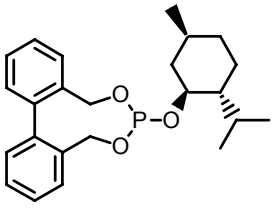

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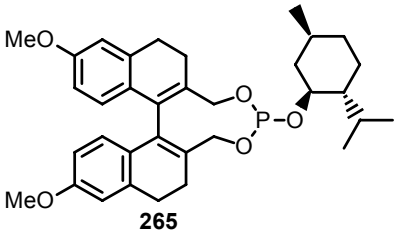
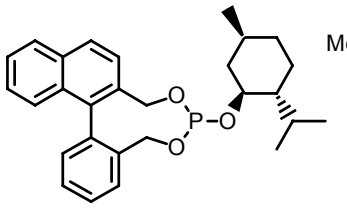
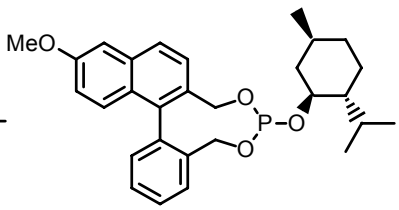


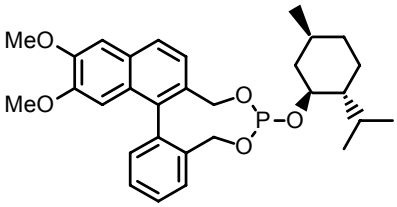
265



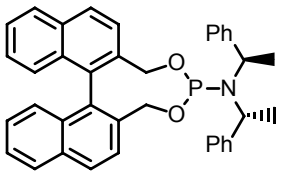
262



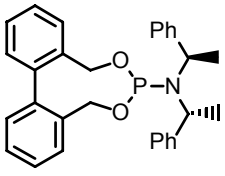
263



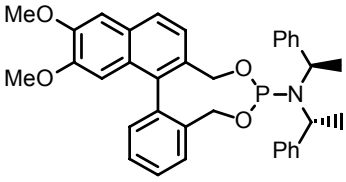
264



222



275



274

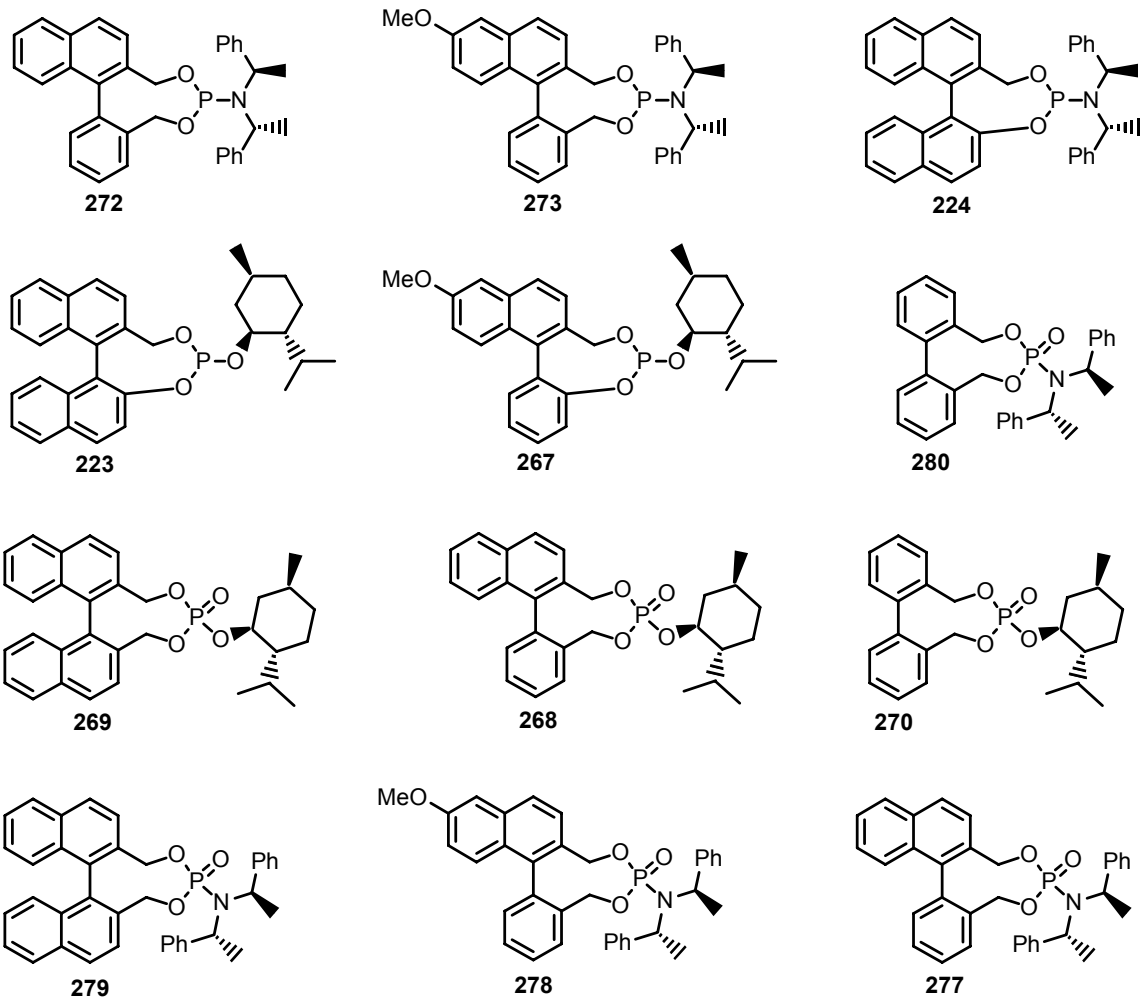


Figure 17

Future work in this section includes an attempt to purify the prepared ligands to their maximum purity by finding a way of separating the diastereomers. One way of achieving the maximum separation of diastereomers would be to use enantiomerically pure biaryl diols. After this has been attained, activity of these novel monophosphorus ligands should be investigated in the metal-catalyzed asymmetric hydrogenation reactions. Substrates of choice could include enamides, dehydroamino acid derivatives etc.

Chapter 6: Experimental Procedures To Part One

6.0 General procedures

All reagents used were Analytical Grade Reagents from Fluka and Aldrich. *n*-BuLi was obtained from Aldrich and used as supplied.

THF was dried by distillation from sodium wire/benzophenone, DMF by distillation from CaH_2. All other solvents were BDH/HP high purity grade and distilled before use.

Thin Layer Chromatography was carried out on Macherey-Nagel Alugram Sil G/UV_{254} Plates, pre-coated with 0.25mm silica gel 60. Detection was done under ultra violet light at 254 nm. For column chromatography, Macherey-Nagel silica gel (32-63 microns) was used, with gel mass 30 times that of sample, eluting with the stated solvent mixtures.

Melting points were determined on a Reichert hot-stage microscope.

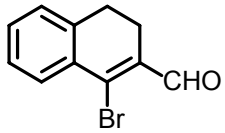
Infrared spectra were run on the Bruker Vector 22 Fourier Transform spectrometer. Absorption maxima are reported in wavenumbers (cm^{-1}), with s = strong, m = medium and w = weak.

NMR spectroscopic analysis was done on an Ultrashield 300 MHz/54 Bohr magnet. The frequency at which ^{1}H nmr spectra were reported was 300.131 MHz (rounded to 300 MHz) using tetramethylsilane at 0.000 ppm as a standard. These spectra are reported as parts per million (ppm), with s = singlet, d = doublet, dd = doublet of a doublet, t = triplet, dt = doublet of a triplet, m = multiplet. The ^{13}C nmr spectra were reported at a frequency of 75.475 MHz (rounded to 75 MHz) using $CDCl_3$ at 77.000 ppm as a standard. The ^{31}P nmr spectra were reported at a frequency of 100 MHz using phosphoric acid as an external standard.

6.1 Synthesis of precursors for Suzuki coupling reactions

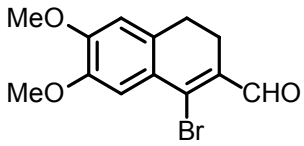
6.1.1 Bromination and formylation of tetralones

6.1.1.1 1-Bromo-3,4-dihydro-2-naphthaldehyde (55):



Dry DMF (8.02 ml, 103 mmol) in dry dichloromethane (50 ml) was cooled to 0 °C and phosphorus tribromide (8.00 ml, 89.5 mmol) was added drop-wise. The mixture was stirred at 0 °C for 1 h and a pale yellow suspension was formed. A solution of α-tetralone (4.58 ml, 5.03 g, 34.4 mmol) in dry dichloromethane (90 ml) was added and the mixture was heated under reflux for 1 h. After cooling to 0 °C, aqueous sodium hydrogen carbonate was added slowly until the effervescence had subsided. Extraction of the organic material into dichloromethane (3 × 100 ml) was followed by drying the organic layer ($MgSO_4$). The solution was filtered through a celite plug and evaporation of the excess solvent resulted into brown oil. Column chromatography eluting with 30% ethyl acetate/hexane gave the product **55** as a brown solid (5.71 g, 70%) with identical spectroscopic data to that described in the literature.[105]

6.1.1.2 1-Bromo-6,7-dimethoxy-3,4-dihydro-2-naphthaldehyde (86):

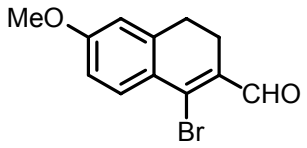


Dry DMF (0.56 ml, 7.27 mmol) in dry dichloromethane (20 ml) was cooled to 0 °C and phosphorus tribromide (0.60 ml, 6.30 mmol) was added drop-wise. The mixture was stirred at 0 °C for 2 h and a pale yellow suspension was formed. A solution of 6,7-dimethoxy-α-tetralone (0.50 g, 2.42 mmol) in dry dichloromethane (30 ml) was added and the mixture was stirred at room temperature for 12 h. After cooling to 0 °C, aqueous sodium hydrogen carbonate was added slowly until the effervescence had subsided.

Extraction of the organic material into dichloromethane (3 × 100 ml) was followed by drying of the organic layer ($MgSO_4$), filtration through a celite plug and evaporation of the excess solvent which resulted into a yellow oil. Column chromatography eluting with 30% ethyl acetate/hexane gave **86** as a yellow crystalline solid (0.45 g, 63% yield).

mp = 119–123 °C; IR ν_{max} (cm^{-1}) 2938 (w, C-H stretch), 1659 (s, C=O stretch), 1601, 1549 (s, C=C stretch), 1033 (s, C–O stretch); ^{1}H nmr δ/ppm 10.19 (1H, s, CHO), 7.42 (1H, s, Ar-H), 6.71 (1H, s, Ar-H), 3.94 (6H, s, 2 × OMe), 2.80-2.75 (2H, m, CH_2), 2.64-2.58 (2H, m, CH_2); ^{13}C nmr δ/ppm 23.0 (CH_2), 27.0 (CH_2), 56.1 (OCH_3), 56.2 (OCH_3), 110.5 (CH), 112.1 (CH), 125.6 (C) 132.4 (C), 133.0 (C), 139.2 (C), 147.7 (C), 151.5 (C), 192.9 (CHO); MS (EI) *m/z* (%) 298 (M^+ ^{81}Br, 94), 296 (M^+ ^{79}Br, 100), 286 (17), 286 (50), 189 (53), 174 (19), 145 (35), 102 (22), 63 (18); HRMS calculated for $C_{13}H_{13}O_3{}^{79}Br$ M^+ 296.0048, found 296.0019.

6.1.1.3 6-Methoxy-1-bromo-3,4-dihydro-2-naphthaldehyde (107):



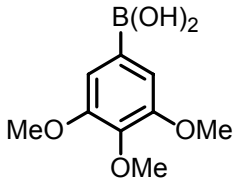
Dry DMF (8.0 ml, 102 mmol) in dry dichloromethane (60.0 ml) was cooled to 0 °C and phosphorus tribromide (8.4 ml, 88.5 mmol) was added drop-wise. The mixture was stirred at 0 °C for 1 h and a cream-white suspension was formed. A solution of 6,7-dimethoxy-α-tetralone (6.00 g, 34.0 mmol) in dry dichloromethane (50 ml) was added and the mixture was heated under reflux for 16 h. After cooling to 0 °C, aqueous sodium hydrogen carbonate was added slowly until the effervescence had subsided. Extraction of the organic material into dichloromethane (3 × 100 ml) was followed by drying the organic layer ($MgSO_4$). The solution was filtered through a celite plug and evaporation of the excess solvent resulted into brown oil. Column chromatography eluting with 30% ethyl acetate/hexane gave the product **107** as a yellow solid (7.79 g, 86%).

mp = 61-62 °C; IR ν_{max} (cm^{-1}) 2944 (w, C-H stretch), 1659 (s, C=O stretch), 1606, 1586 (s, C=C stretch), 1038 (s, C–O stretch); ^{1}H nmr δ/ppm 10.20 (1H, s, CHO), 7.83 (1H, d, *J* = 8.7 Hz, Ar-H), 6.82 (1H, dd, *J* = 2.6 Hz; 8.7 Hz, Ar-H), 6.72 (1H, d, *J* = 2.5 Hz, Ar-H),

3.86 (3H, s, OMe), 2.83-2.76 (2H, m, CH_2), 2.63-2.61 (2H, m, CH_2); ^{13}C nmr δ/ppm 22.7 (CH_2), 27.7 (CH_2), 55.4 (OCH_3), 112 (CH), 113.3 (CH), 125.9 (C), 130.7 (CH), 132.1 (C), 139.0 (C), 141.2 (C), 162.0 (C), 192.9 (CHO); MS (EI) *m/z* (%) 267 (M^+ ^{81}Br, 80), 265 (M^+ ^{79}Br, 83), 236 (28), 187 (46), 159 (97), 158 (100), 144 (59), 128 (41), 115 (81); HRMS calculated for $C_{12}H_{11}O_2{}^{79}Br$ M^+ 265.9942, found 265.9936.

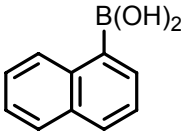
6.1.2 Syntheses of arylboronic acids

6.1.1.1 3,4,5-Trimethoxyphenylboronic acid (56):



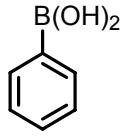
To a stirred solution of 1-bromo-3,4,5-trimethoxybenzene (0.50 g, 2.02 mmol) in THF (30 ml) at –78 °C under nitrogen was added n-BuLi (1.56 ml, 2.22 mmol) drop-wise. The reaction mixture was stirred at –78 °C for 30 min before trimethylborate (0.68 ml, 6.07 mmol) was added and the mixture stirred for another 30 min at –78 °C. The subsequent mixture was then allowed to warm to room temperature before being acidified with aqueous 10% HCl. Extraction of the organic layer into dichloromethane (3 × 100 ml) was followed by drying the organic layer ($MgSO_4$) before being concentrated under reduced pressure to give a cream white semi-solid (0.43 g, 100%) that was not purified further.

6.1.1.2 1-Naphthylboronic acid (69):



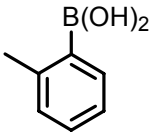
In a similar manner to that described above 1-bromonaphthalene (0.50 g, 2.41 mmol) in THF (40 ml) was converted into boronic acid **69** (0.26 g, 63%) using *n*-BuLi (1.90 ml, 12.6 mmol) and $B(OMe)_3$ (0.81 ml, 7.24 mmol).

6.1.1.3 Phenylboronic acid (70):



Boronic acid **70,** a cream white semi-solid (1.47 g, 89%) was synthesized from bromobenzene (1.43 ml, 13.5 mmol), *n*-BuLi (1.87 ml, 14.9 mmol) and $B(OMe)_3$ (1.96 ml, 4.07 mmol) in a similar way as described above.

6.1.1.4 *o*-Tolylboronic acid (71):

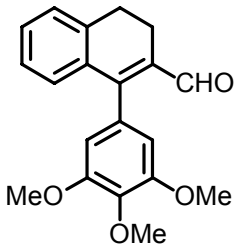


Using the same procedure as described above 2-bromotoluene (1.40 ml, 11.6 mmol) was converted into boronic acid **71,** a white solid (1.34 g, 85%).

6.2 Suzuki coupling reactions

6.2.1 Suzuki coupling reactions using 1-bromo-3,4-dihydro-2-naphthaldehyde (**55**)

6.2.1.1 1-(3,4,5-Trimethoxyphenyl)-3,4-dihydro-2-naphthaldehyde (72):

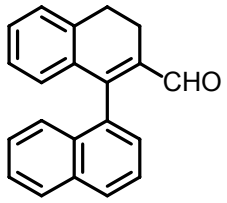


To $[Pd(PPh_3)_4]$ (0.22 g, 0.194 mmol) was added a deoxygenated solution of **55** (0.46 g, 1.94 mmol) in DME (10 ml). This was followed by a deoxygenated solution of boronic acid **56** (0.62 g, 2.91 mmol) in ethanol (5 ml), and then a deoxygenated solution of aqueous sodium carbonate (1.77 g, 16.5 mmol in 8.2 ml water). The resultant mixture

was refluxed under nitrogen for 46 h over which time it turned deep red. After allowing to cool to room temperature, the mixture was quenched with water (50 ml) and the organic material extracted with dichloromethane (3 × 100 ml). The resultant organic extracts were combined, dried ($MgSO_4$), filtered through a celite plug and the excess solvent removed using a rotary evaporator. The subsequent oil was purified by column chromatography using 30% ethyl acetate/hexane as eluent and afforded a desired product **72** as a brown solid (4.80g, 83%). R_f = 0.58 (30% EtOAc/hexane).

mp = 112–114 °C; IR ν_{max} (cm^{-1}) 1659 (s, C=O stretch), 1575 (s, C=C stretch), 1129 (s, C–O stretch); ^{1}H nmr δ/ppm 9.65 (1H, s, CHO), 7.31–7.26 (2H, m, 2 × ArH), 7.19–7.16 (1H, m, ArH), 6.99–6.96 (1H, m, ArH), 6.51 (2H, s, 2 × ArH), 3.93 (3H, s, OCH_3), 3.84 (6H, s, 2 × OCH_3), 2.94-2.89 (2H, m, CH_2), 2.71-2.65 (2H, m, CH_2); ^{13}C nmr δ/ppm 20.2 (CH_2), 27.5 (CH_2), 56.2 (2 × OCH_3), 60.9 (OCH_3), 107.7 (2 × CH), 126.7 (CH), 127.8 (CH), 128.3 (CH), 130.2 (CH), 130.7 (C), 134.2 (C), 134.8 (C), 138.0 (C), 138.5 (C), 153.1 (2 × C), 154.2 (C), 193.4 (CHO); MS (EI) *m/z* (%) 325 (M+1, 22), 324 (M^+, 100), 309 (5), 296 (9), 293 (22), 281 (52), 265 (18), 249 (6), 234 (6), 168 (31), 153 (25), 51 (11); HRMS calculated for $C_{20}H_{20}O_4$ M^+ 324.1362, found 324.1362.

6.2.1.2 1-(1-Naphthyl)-3,4-dihydro-2-naphthaldehyde (73):

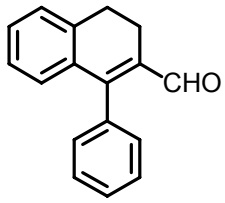


Using the same procedure as outlined above naphthaldehyde **73**, a brown oil (0.55 g, 92%) was synthesized from a mixture of [$Pd(PPh_3)_4$] (0.25 g, 0.211 mmol), dihydro **55** (0.50 g, 2.11 mmol), boronic acid **69** (0.54 g, 3.16 mmol) and aqueous sodium carbonate (1.90 g, 17.9 mmol in 8.9 ml of water). R_f = 0.44 (30% EtOAc/Hexane).

IR ν_{max} (cm^{-1}) 3015 (m, C–H stretch), 1660 (s, C=O stretch), 1607, 1561 (m, C=C stretch); ^{1}H nmr δ/ppm 9.40 (1H, s, CHO), 7.92 (2H, t, *J* = 8.8 Hz, 2 × ArH), 7.59–7.34 (5H, m, 5 × ArH), 7.31–7.24 (2H, m, 2 × ArH), 6.97 (1H, t, *J* = 7.7 Hz, ArH), 6.64 (1H, d, *J* = 7.7 Hz, ArH), 3.08–3.02 (2H, m, CH_2), 2.94–2.84 (1H, m, CH), 2.77–2.66 (1H, m, CH); ^{13}C nmr

δ/ppm 20.1 (CH_2), 27.7 (CH_2), 125.1 (CH), 125.9 (CH), 126.3 (CH), 126.76 (CH), 126.79 (CH), 127.9 (CH), 128.1 (CH), 128.39 (CH), 128.4 (CH), 128.9 (CH), 130.2 (CH), 132.6 (C), 132.9 (C), 133.5 (C), 135.0 (C), 135.8 (C), 138.1 (C), 153.0 (C), 193.0 (CHO); MS (EI) *m/z* (%) 285 (M+1, 62), 284 (M^+, 100), 283 (89), 268 (27), 265 (39), 256 (62), 255 (89), 254 (33), 253 (68), 252 (73), 250 (27), 241 (27), 240 (43), 239 (67), 228 (33), 226 (22), 165 (21), 129 (22), 128 (73), 127 (39), 126 (42), 119 (22), 113 (20); HRMS calculated for $C_{21}H_{16}O$ M^+284.1201, found 284.1202.

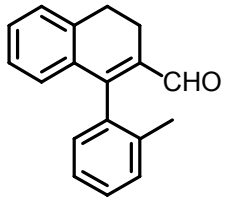
6.2.1.3 1-Phenyl-3,4-dihydro-2-naphthaldehyde (74):



In a similar manner as described above a mixture of [$Pd(PPh_3)_4$] (0.25 g, 0.211 mmol), dihydro **55** (0.50 g, 2.11 mmol), boronic acid **70** (0.39 g, 3.16 mmol) and aqueous sodium carbonate (1.90 g, 17.9 mmol in 8.9 ml of water) was used to synthesize **74** as brown crystalline solid (0.49 g, 100%). R_f = 0.73 (30% EtOAc/Hexane).

mp = 68-71 °C; IR ν_{max} (cm^{-1}) 3019 (m, C–H stretch), 1658 (s, C=O stretch), 1596 (m, C=C stretch); ^{1}H nmr δ/ppm 9.63 (1H, s, CHO), 7.50–7.47 (3H, m, 2 × ArH), 7.35−7.30 (4H, m, 4 × ArH), 7.18–7.12 (1H, dt, *J* = 1.9 Hz, 7.8 Hz, ArH), 6.90 (1H, d, *J* = 7.7 Hz, ArH), 2.97-2.92 (2H, m, CH_2), 2.76-2.71 (2H, m, CH_2); ^{13}C nmr δ/ppm 20.3 (CH_2), 27.6 (CH_2) 126.6 (CH), 127.8 (CH), 128.1 (2 × CH), 128.2 (2 × CH), 130.2 (CH), 130.4 (2 × CH), 134.3 (C), 135.1 (C), 135.2 (C), 138.6 (C), 154.4 (C), 193.3 (CHO); MS (EI) *m/z* (%) 234 (M^+, 100), 233 (52), 205 (73), 202 (66), 189 (26), 178 (35), 165 (26), 128 (49), 127 (27), 78 (25), 29 (31); HRMS calculated for $C_{17}H_{14}O$ M^+ 234.1045, found 234.1045.

6.2.1.4 1-(*o*-Tolyl)-3,4-dihydro-2-naphthaldehyde (75):



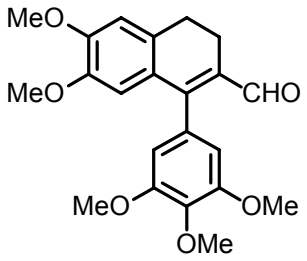
Similarly [$Pd(PPh_3)_4$] (0.24 g, 0.211 mmol), solution of dihydro **55** (0.50 g, 2.11 mmol) in DME (10 ml), solution of boronic acid **71** (0.43 g, 3.16 mmol) in ethanol (5 ml), and a solution of aqueous sodium carbonate (1.90g, 17.9 mmol in 8.9 ml of water) was used to synthesize naphthaldehyde **75** as a yellow crystalline solid (0.41g, 78%).

R_f = 0.59 (30% EtOAc/Hexane).

mp = 59–61 °C; IR ν_{max} (cm^{-1}) 3014 (s, C–H stretch), 1660 (s, C=O stretch), 1606 (m, C=C stretch); ^{1}H nmr δ/ppm 9.48 (1H, s, CHO), 7.35–7.25 (5H, m, 5 × ArH), 7.16 (1H, d, *J* = 6.9 Hz, ArH), 7.10 (1H, dt, *J* = 2.4 Hz, 7.8 Hz, ArH), 6.73 (1H, d, *J* = 7.8 Hz, ArH), 2.94 (2H, t, *J* = 8.0 Hz, CH_2), 2.83–2.73 (1H, m, CH), 2.66–2.55 (1H, m, CH), 2.08 (3H, s, CH_3); ^{13}C nmr δ/ppm 19.6 (CH_2), 19.8 (CH_2), 27.5 (CH_3), 125.7 (CH), 126.7 (CH), 127.5 (CH), 127.9 (CH), 128.5 (CH), 130.19 (CH), 130.22 (CH), 130.5 (CH), 134.3 (C), 134.4 (C), 134.8 (C), 136.7 (C), 138.4 (C), 154.2 (C), 193.1 (CHO); MS (EI) *m/z* (%) 248 (M^+, 35), 233 (100), 229 (12), 215 (15), 203 (18), 202 (19); HRMS calculated for $C_{18}H_{16}O$ M^+ 248.1198, found 248.1201.

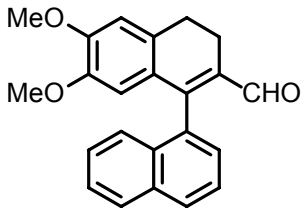
6.2.2 Suzuki coupling reactions using 1-bromo-6,7-dimethoxy-3,4-dihydro-2-naphthaldehyde (**86**)

6.2.2.1 6,7-Dimethoxy-1-(3,4,5-trimethoxyphenyl)-3,4-dihydro-2-naphthaldehyde (**87**):



To $[Pd(PPh_3)_4]$ (0.19 g, 0.162 mmol) was added a deoxygenated solution of dihydro **86** (0.48 g, 1.62 mmol) in DME (10 ml). This was followed by a deoxygenated solution of boronic acid **56** (0.51 g, 2.42 mmol) in ethanol (5 ml), then a deoxygenated solution of aqueous sodium carbonate (1.45 g, 13.7 mmol in 6.9 ml water). The resultant mixture was refluxed under nitrogen for 64 h over which time it turned deep red. After allowing to cool down to room temperature, the mixture was quenched with water (50 ml) and the organic material extracted with dichloromethane (3 × 100 ml). The resultant organic extracts were combined, dried ($MgSO_4$), and then filtered through a celite plug and the excess solvent removed using a rotary evaporator. The subsequent oil was purified by column chromatography using 30% ethyl acetate/hexane as eluent to afford naphthaldehyde **87** as yellow crystalline solid (0.55 g, 88%). R_f = 0.17 (30% EtOAc/Hexane); mp = 139–141 °C; IR ν_{max} (cm^{-1}) 3016 (s, C–H stretch), 1652 (s, C=O stretch), 1556 (m, C=C stretch), 1129 (s, C–O stretch); ^{1}H nmr δ/ppm 9.59 (1H, s, CHO), 6.79 (1H, s, ArH), 6.52 (2H, s, 2 x ArH), 6.49 (1H, s, ArH), 3.94 (3H, s, CH_3), 3.93 (3H, s, OCH_3), 3.85 (6H, s, 2 × OCH_3), 3.65 (3H, s, OCH_3), 2.88–2.82 (2H, m, CH_2), 2.70–2.64 (2H, m, CH_2); ^{13}C nmr δ/ppm 20.9 (CH_2), 27.8 (CH_2), 56.3 (OCH_3), 56.4 (OCH_3), 56.6 (2 × OCH_3), 61.3 (OCH_3), 108.1 (2 × CH), 111.4 (CH), 112.4 (CH), 127.6 (C), 131.3 (C), 132.8 (C), 133.1 (C), 138.4 (C), 147.8 (C), 151.2 (C), 153.4 (2 × C), 154.9 (C), 193.5 (CHO); MS (EI) *m/z* (%) 385 (M+1, 27), 384 (M^+, 100), 372 (52), 371 (31), 370 (45), 369 (31), 368 (93), 366 (24), 353 (30), 343 (39), 337 (32), 195 (20), 181 (20), 28 (70); HRMS calculated for $C_{22}H_{24}O_6$ M^+ 384.1573, found 384.1573.

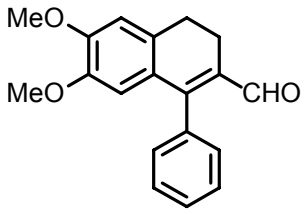
6.2.2.2 6,7-Dimethoxy-1-(1-naphthyl)-3,4-dihydro-2-naphthaldehyde (88):



Using the same procedure as outlined above, a mixture of [$Pd(PPh_3)_4$] (0.12 g, 0.101 mmol), dihydro **86** (0.30 g, 1.01 mmol), boronic acid **69** (0.26 g, 1.51 mmol) and aqueous sodium carbonate (0.91 g, 8.58 mmol in 4.5 ml of water) was used to synthesize naphthaldehyde **88** as a brown oil (0.28 g, 87%). R_f = 0.41 (30% EtOAc/Hexane).

IR ν_{max} (cm^{-1}) 3018 (m, C–H stretch), 1652 (s, C=O stretch), 1604, 1557 (s, C=C stretch), 1120 (s, C–O stretch); ^{1}H nmr δ/ppm 9.62 (1H, s, CHO), 7.84 (2H, t, *J* = 9.0 Hz, 2 × ArH), 7.51–7.27 (5H, m, 5 × ArH), 6.74 (1H, s, ArH), 6.07 (1H, s, ArH), 3.84 (3H, s, OCH_3), 3.26 (3H, s, OCH_3), 2.94–2.76 (3H, m, CH_2+CH), 2.67–2.56 (1H, m, CH); ^{13}C nmr δ/ppm 20.7 (CH_2), 27.5 (CH_2), 55.8 (OCH_3), 55.9 (OCH_3), 110.9 (CH), 111.6 (CH), 124.9 (CH), 125.9 (CH), 126.3 (CH), 126.7 (CH), 127.6 (C), 128.28 (CH), 128.32 (CH), 128.8 (CH), 132.2 (C), 132.5 (C), 133.0 (C), 133.4 (C), 133.9 (C), 147.4 (C), 150.7 (C), 153.2 (C), 192.7 (CHO); MS (EI) *m/z* (%) 345 (M+1, 63), 344 (M^+, 100), 315 (49), 313 (22), 262 (50), 239 (27), 232 (24), 226 (21), 205 (31), 189 (23), 128 (79), 119 (29), 115 (24), 85 (35), 83 (52); HRMS calculated for $C_{23}H_{20}O_3$ M^+ 344.1412, found 344.1412.

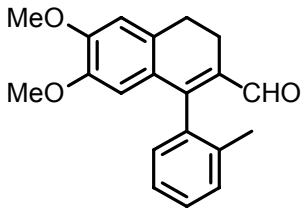
6.2.2.3 6,7-Dimethoxy-1-phenyl-3,4-dihydro-2-naphthaldehyde (89):



In a similar manner as described above [$Pd(PPh_3)_4$] (0.12 g, 0.101 mmol), dihydro **86** (0.30 g, 1.01 mmol), boronic acid **70** (0.18 g, 1.51 mmol) and aqueous sodium carbonate (0.91 g, 8.58 mmol in 4.3 ml of water) afforded **89** as a yellow solid (0.22 g, 83%). R_f = 0.44 (30% EtOAc/Hexane).

mp = 114–117 °C; IR ν_{max} (cm^{-1}) 3020 (s, C–H stretch), 1650 (s, C=O stretch), 1557 (s, C=C stretch), 1109 (m, C–O stretch); ^{1}H nmr δ/ppm 9.53 (1H, s, CHO), 7.48–7.45 (3H, m, 3 × ArH), 7.32–7.29 (2H, m, 2 × ArH), 6.81 (1H, s, ArH), 6.39 (1H, s, ArH), 3.95 (3H, s, OCH_3), 3.61 (3H, s, OCH_3), 2.90–2.85 (2H, m, CH_2), 2.72–2.68 (2H, m, CH_2); ^{13}C nmr δ/ppm 20.4 (CH_2), 27.4 (CH_2), 55.9 (2 × OCH_3), 110.9 (CH), 111.9 (CH), 127.5 (C), 128.4 (2 × CH), 128.6 (CH), 130.4 (2 × CH), 132.4 (C), 132.6 (C), 135.4 (C), 147.2 (C), 150.6 (C), 154.6 (C), 192.9 (CHO); MS (EI) *m/z* (%) 295 (M+1, 26), 294 (M^+, 100), 293 (21), 189 (15), 178 (19); HRMS calculated for $C_{19}H_{18}O_3$ M^+ 294.1256, found 294.1256.

6.2.2.4 6,7-Dimethoxy-1-(*o*-tolyl)-3,4-dihydro-2-naphthaldehyde (90):

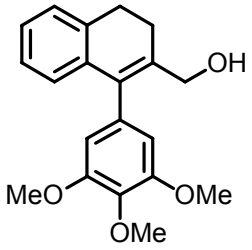


Similarly [$Pd(PPh_3)_4$] (0.20 g, 0.168 mmol), dihydro **86** (0.50 g, 1.68 mmol) in DME (10 ml), boronic acid **71** (0.36 g, 2.52 mmol) in ethanol (6 ml) and aqueous sodium carbonate (1.56 g, 14.3 mmol in 7.4 ml of water) afforded naphthaldehyde **90** as brown oil (0.51 g, 98%). R_f = 0.52 (30% EtOAc/Hexane).

IR ν_{max} (cm^{-1}) 1656 (s, C=O stretch), 1606 (m, C=C stretch), 1102 (m, C–O stretch); ^{1}H nmr δ/ppm 9.41 (1H, s, CHO), 7.35–7.25 (3H, m, 3 × ArH), 7.16 (1H, d, *J* = 7.4 Hz, ArH), 6.79 (1H, s, ArH), 6.24 (1H, s, ArH), 3.93 (3H, s, OCH_3), 3.57 (3H, s, OCH_3), 2.90–2.83 (2H, m CH_2), 2.78–2.76 (1H, m, CH), 2.64–2.55 (1H, m, CH), 2.08 (3H, s, CH_3); ^{13}C nmr δ/ppm 19.6 (CH_2), 19.9 (CH_2), 27.4 (CH_3), 55.9 (2 × OCH_3), 110.9 (CH), 111.0 (CH), 125.7 (CH), 126.9 (C), 128.5 (CH), 130.2 (CH), 130.4 (CH), 132.4 (C), 134.5 (C), 134.9 (C), 136.6 (C), 147.6 (C), 150.7 (C), 154.5 (C), 192.8 (CHO); MS (EI) *m/z* (%) 308 (M^+, 100), 249 (16), 108 (31), 58 (20); HRMS calculated for $C_{20}H_{20}O_3$ M^+ 308.1412, found 308.1396.

6.3 Reduction of aldehydes.

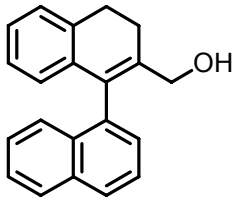
6.3.1 [1-(3,4,5-Trimethoxyphenyl)-3,4-dihydronaphthalen-2-yl]methanol (**76**):



To a solution of naphthaldehyde **72** (0.51 g, 1.57 mmol) in ethanol (30 ml) was added $NaBH_4$ (0.07 g, 1.96 mmol). The reaction mixture was stirred at room temperature for 5 min after which time it turned cream white. The mixture was then extracted with CH_2Cl_2 (3 × 100 ml). The organic extracts were combined, dried ($MgSO_4$), and then filtered through a celite plug and concentrated *in vacuo*. The subsequent colourless oil was purified by column chromatography using 30% ethyl acetate/hexane as eluent to afford **76** as a white crystalline solid (0.51 g, 100%). R_f = 0.16 (30% EtOAc/hexane).

mp = 115–116 °C; IR ν_{max} (cm^{-1}) 3421 (m, broad, OH stretch), 3015 (s, C–H stretch), 1583, 1507(s, C=C stretch), 1128 (s, C–O stretch); ^{1}H nmr δ/ppm 7.17–7.02 (3H, m, 3 × ArH), 6.72 (1H, dd, *J* = 7.3 Hz, 1.0 Hz, ArH), 6.39 (2H, s, 2 × ArH), 4.12 (2H, s, C*H*$_2$OH), 3.89 (3H, s, OCH_3), 3.80 (6H, s, 2 × OCH_3), 2.90 (2H, dd, *J* = 8.4 Hz, *J* = 7.6 Hz, CH_2), 2.54 (2H, t, *J* = 8.4 Hz, *J* = 7.5 Hz CH_2), 1.85 (1H, s, CH_2OH); ^{13}C nmr δ/ppm. 20.5 (CH_2), 28.1 (CH_2), 55.9 (2 × OCH_3), 60.8 (OCH_3), 63.5 (CH_2OH), 106.9 (2 × CH), 126.1 (CH), 126.2 (CH), 126.8 (CH), 127.1 (CH), 133.9 (C), 135.4 (C), 135.8 (C), 135.9 (C), 136.8 (C), 153.0 (2 × C); MS (EI) *m/z* (%) 327 (M+1, 22), 326 (M^+, 100), 297 (25), 295 (27) 181 (10), 168 (24), 165 (14), 129 (21); HRMS calculated for $C_{20}H_{22}O_4$ M^+ 326.1518, found 326.1519.

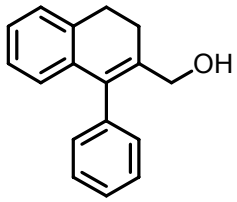
6.3.2 [1-(1-Naphthyl)-3,4-dihydronaphthalen-2-yl]methanol (**77**):



Similarly using $NaBH_4$ (0.05 g, 1.32 mmol) in EtOH (10 ml), naphthaldehyde **73** (0.30 g, 1.06 mmol) was reduced to alcohol **77,** a cream-white semi-solid (0.29 g, 94%). R_f = 0.44 (30% EtOAc/Hexane).

IR ν_{max} (cm^{-1}) 3384 (s, broad, OH stretch), 3010 (m, C–H stretch), 1588, 1516 (m, C=C stretch), 1084 (s, C–O stretch); ^{1}H nmr δ/ppm 7.87 (2H, t, *J* = 7.3 Hz, 2 × ArH), 7.68 (1H, d, *J* = 8.5 Hz, ArH), 7.54–7.43 (2H, m, 2 × ArH), 7.38–7.29 (2H, m, 2 × ArH), 7.24–7.20 (1H, m, ArH), 7.12–7.07 (1H, m, ArH), 6.90 (1H, t, *J* = 7.5 Hz, ArH), 6.41 (1H, d, *J* = 7.7 Hz, ArH), 3.92 (2H, s, C*H*$_2$OH), 3.08–3.02 (2H, m, CH_2), 2.73–2.65 (2H, m, CH_2); ^{13}C nmr δ/ppm 25.2 (CH_2), 28.4 (CH_2), 63.8 (CH_2OH), 125.5 (CH), 125.7 (CH), 125.9 (CH), 126.1 (CH), 126.3 (CH), 126.4 (CH), 126.9 (CH), 127.2 (CH), 127.5 (CH), 127.7 (CH), 128.3 (CH), 132.6 (C), 133.7 (C), 133.9 (C), 135.3 (C), 135.9 (C), 137.7 (C), (one quartenary carbon missing); MS (EI) *m/z* (%) 286 (M^+, 21), 268 (32), 267 (45), 255 (41), 253 (62), 251 (77), 249 (19), 239 (24), 238 (64), 229 (19), 228 (24), 225 (31), 215 (29), 165 (28), 152 (21), 141 (36), 129 (50), 128 (100), 127 (52), 115 (55), 77 (21), 31 (42); HRMS calculated for $C_{21}H_{18}O$ M^+ 286.1358, found 286.1356.

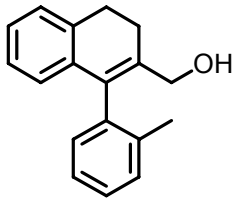
6.3.3 (1-Phenyl-3,4-dihydronaphthalen-2-yl)methanol (**78**):



Using the same procedure as outlined above, $NaBH_4$ (0.03 g, 0.899 mmol) in EtOH (10 ml), naphthaldehyde **74** (0.17 g, 0.719 mmol) afforded alcohol **78** as a yellow oil (0.16 g, 94%). R_f = 0.44 (30% EtOAc/Hexane).

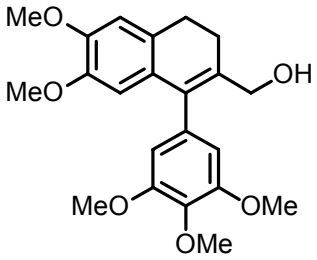
IR ν_{max} (cm^{-1}) 3386 (s, broad, OH stretch), 3015 (m, C–H stretch), 1598 (m, C=C stretch), 1044 (s, C–O stretch); ^{1}H nmr δ/ppm 7.37–7.29 (3H, m, 3 × ArH), 7.13–7.11 (3H, 3 × ArH), 7.08–7.06 (1H, dd, *J* = 7.3 Hz, 1.1 Hz, ArH), 6.99 (1H, t, *J* = 7.2 Hz, ArH), 6.60 (1H, d, *J* = 7.6 Hz, ArH), 4.02 (2H, s, C*H*$_2$OH), 2.86 (2H, dd, *J* = 8.4 Hz, *J* = 7.6 Hz CH_2), 2.51 (2H, t, *J* = 8.4 Hz, *J* = 7.5 Hz CH_2); ^{13}C nmr δ/ppm.) 25.0 (CH_2), 28.1 (CH_2), 63.3 (CH_2OH), 126.0 (CH), 126.1 (CH), 126.7 (CH), 126.9 (CH), 127.0 (CH), 128.2 (2 × CH), 129.8 (2 x CH), 135.5 (C), 135.8 (C), 135.9 (C), 136.1 (C), 138.3 (C); MS (EI) *m/z* (%) 237 (M+1, 20), 236 (M^+, 100), 235 (20), 234 (62), 233 (33), 224 (24), 218 (38), 217 (36), 215 (24), 208 (36), 205 (77), 204 (25), 203 (46), 202 (25), 189 (21), 179 (26), 178 (36), 165 (23), 159 (21), 130 (23), 129 (34), 128 (22), 115 (35), 105 (23), 101 (23), 91 (76), 77 (26); HRMS calculated for $C_{17}H_{16}O$ M^+ 236.1201, found 236.1201.

6.3.4 [1-(*o*-Tolyl)-3,4-dihydronaphthalen-2-yl]methanol (**79**):



Similarly using $NaBH_4$ (0.06 g, 1.59 mmol) in EtOH (10 ml), naphthaldehyde **75** (0.32 g, 1.28 mmol) was reduced to alcohol **79,** a white semi-solid (0.30 g, 94%). R_f = 0.59 (30% EtOAc/Hexane); IR ν_{max} (cm^{-1}) 3416 (s, broad, OH stretch), 3011 (s, C–H stretch), 1629 (m, C=C); ^{1}H nmr δ/ppm 7.26–6.99 (7H, m, 7 × ArH), 6.50 (1H, d, *J* = 7.6 Hz, ArH), 3.98 (2H, s, C*H*$_2$OH), 2.93 (2H, dd, *J* = 8.3 Hz, *J* = 7.7 Hz CH_2), 2.56 (2H, dd, *J* = 8.5 Hz, *J* = 7.5 Hz CH_2), 2.06 (3H, s, CH_3); ^{13}C nmr δ/ppm 19.4 (CH_2), 24.9 (CH_2), 28.3 (CH_3), 63.6 (CH_2OH), 125.5 (CH), 125.8 (CH), 126.4 (CH), 126.8 (CH), 127.2 (CH), 127.4 (CH), 129.9 (CH), 130.1 (CH), 135.1 (C), 135.4 (C), 135.5 (C), 135.7 (C), 136.8 (C), 137.7 (C); MS (EI) *m/z* (%) 251 (M+1, 40), 250 (M^+, 100), 235 (66), 232 (26), 219 (59), 218 (27), 217 (74), 216 (20), 215 (44), 204 (38), 203 (47), 202 (53), 179 (23), 178 (27), 159 (30), 129 (36), 128 (25), 119 (34), 115 (29), 105 (52), 101 (20), 91 (43), 43 (39); HRMS calculated for $C_{18}H_{18}O$ M^+ 250.1358, found 250.1358.

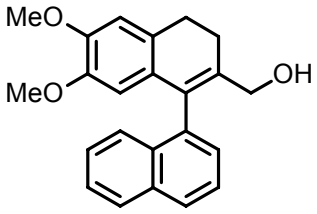
6.3.5 [6,7-Dimethoxy-1-(3,4,5-trimethoxyphenyl)-3,4-dihydronaphthalen-2-yl]methanol (**91**):



In a similar manner as described above, $NaBH_4$ (0.06 g, 1.72 mmol) in EtOH (10 ml) was used to reduce naphthaldehyde **87** (0.53 g, 1.34 mmol) to alcohol **91**, a white semi-solid (0.46 g, 87%). R_f = 0.05 (30% EtOAc/Hexane).

IR ν_{max} (cm^{-1}) 3517 (s, broad, OH stretch), 2937 (s, C–H stretch), 1651 (m, C=C stretch), 1015 (s, C–O stretch); ^{1}H nmr δ/ppm 6.66 (1H, s, ArH), 6.33 (2H, s, 2 × ArH), 6.24 (1H, s, ArH), 4.04 (2H, s, C*H*$_2$OH), 3.83 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.75 (6H, s, 2 × OCH_3), 3.54 (3H, s, OCH_3), 2.78 (2H, dd, *J* = 8.4 Hz, *J* = 7.6 Hz CH_2), 2.46 (2H, t, *J* = 8.5 Hz, *J* = 7.6 Hz CH_2); ^{13}C nmr δ/ppm 25.5 (CH_2), 27.9 (CH_2), 55.9 (OCH_3), 56.1 (3 × OCH_3), 60.9 (OCH_3), 63.8 (CH_2OH), 106.9 (2 × CH), 110.7 (CH), 110.9 (CH), 128.5 (C), 128.6 (C), 133.6 (C), 133.9 (C), 135.8 (C), 136.9 (C), 146.9 (C), 147.9 (C), 153.4 (2 × C); MS (EI) *m/z* (%) 387 (M+1, 63), 386 (M^+, 100), 357 (22), 355 (44), 189 (21), 164 (18), 152 (16), 31 (12); HRMS calculated for $C_{22}H_{24}O_6$ M^+ 386.1729, found 386.1729.

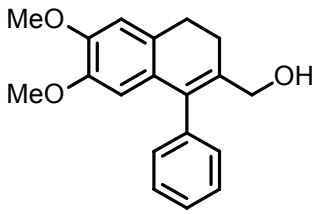
6.3.6 [6,7-Dimethoxy-1-(1-naphthyl)-3,4-dihydronaphthalen-2-yl]methanol (**92**):



Similarly $NaBH_4$ (0.03 g, 0.903 mmol) in EtOH (10 ml) was used to reduce naphthaldehyde **88** (0.25 g, 0.722 mmol) to alcohol **92,** a brown oil (0.25 g, 100%). R_f = 0.16 (30% EtOAc/Hexane); IR ν_{max} (cm^{-1}) 3481 (m, broad, OH stretch), 3014 (m, C–H stretch), 1604 (m, C=C stretch), 1116 (s, C–O stretch); ^{1}H nmr δ/ppm 7.76 (2H, t, *J* = 7.3

Hz, 2 × ArH), 7.58 (1H, d, *J* = 8.4 Hz, ArH), 7.42–7.31 (2H, m, 2 × ArH), 7.27–7.19 (2H, m, 2 × ArH), 6.67 (1H, s, ArH), 5.89 (1H, s, ArH), 3.78 (2H, s, C*H*$_2$OH), 3.77 (3H, s, OCH_3), 3.23 (3H, s, OCH_3), 2.91–2.84 (2H, m, CH_2), 2.59–2.54 (2H, m, CH_2); ^{13}C nmr δ/ppm 25.3 (CH_2), 28.1 (CH_2), 55.8 (OCH_3), 55.9 (OCH_3), 63.7 (CH_2OH), 110.5 (CH), 110.9 (CH), 125.4 (CH), 125.7 (CH), 125.8 (CH), 126.1 (CH), 127.3 (CH), 127.6 (CH), 128.2 (CH), 128.8 (C), 132.5 (C), 133.4 (C), 133.6 (C), 135.5 (2 × C), 135.9 (C), 146.9 (C), 147.9 (C); MS (EI) *m/z* (%) 347 (M+1, 43), 346 (M^+, 100), 345 (21), 244 (53), 330 (25), 315 (34), 239 (24), 226 (18), 215 (19); HRMS calculated for $C_{23}H_{22}O_3$ M^+ 346.1569, found 346.1569.

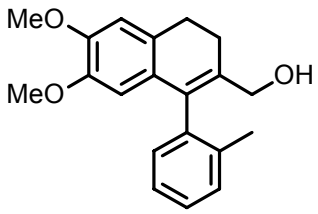
6.3.7 (6,7-Dimethoxy-1-phenyl-3,4-dihydronaphthalen-2-yl)methanol (**93**):



Using the same procedure as described above, $NaBH_4$ (0.03 g, 0.814 mmol) in EtOH (10 ml), reduced aldehyde **89** (0.17 g, 0.658 mmol) to alcohol **93** as a light yellow oil (0.20 g, 100%). R_f = 0.21 (30% EtOAc/Hexane).

IR ν_{max} (cm^{-1}) 3449 (m, broad, OH stretch), 3019 (s, C–H stretch), 1573 (m, C=C stretch), 1216 (s, C–O stretch); ^{1}H nmr δ/ppm 7.41–7.33 (3H, m, 3 × ArH), 7.18–7.15 (2H, m, 2 × ArH), 6.72 (1H, s, ArH), 6.19 (1H, s, ArH), 4.06 (2H, s, C*H*$_2$OH), 3.88 (3H, s, OCH_3) 3.56 (3H, s, OCH_3), 2.85 (2H, t, *J* = 8.1 Hz, CH_2), 2.54 (2H, t, *J* = 8.1 Hz, CH_2); ^{13}C nmr δ/ppm 25.5 (CH_2), 28.0 (CH_2), 55.8 (OCH_3), 55.9 (OCH_3), 63.7 (CH_2OH), 110.8 (CH), 110.9 (CH), 127.1 (CH), 128.2 (2 × CH), 128.5 (C), 128.8 (C), 129.9 (2 × CH), 133.8 (C), 135.8 (C), 138.4 (C), 146.9 (C), 147.9 (C); MS (EI) *m/z* (%) 296 (M^+, 12), 263 (14), 219 (69), 154 (43), 57 (100), 43 (23); HRMS calculated for $C_{19}H_{20}O_3$ M^+ 296.1412, found 296.1403.

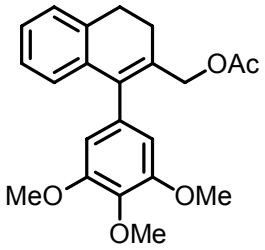
6.3.8 [6,7-Dimethoxy-1-(*o*-tolyl)-3,4-dihydronaphthalen-2-yl)methanol (**94**):



Similarly $NaBH_4$ (0.05 g, 1.29 mmol) in EtOH (10 ml), was used to reduce aldehyde **90** (0.32 g, 1.04 mmol) to alcohol **94** as a yellow semi-solid (0.28 g, 87%). R_f = 0.26 (30% EtOAc/Hexane); IR ν_{max} (cm^{-1}) 3508 (m, broad, OH stretch), 2934 (s, C–H stretch), 1605 (m, C=C stretch), 1104 (m, C–O stretch); ^{1}H nmr δ/ppm 7.27–7.19 (3H, m, 3 × ArH), 7.06 (1H, d, *J* = 6.7 Hz, ArH), 6.74 (1H, s, ArH), 6.06 (1H, s, ArH), 3.97 (2H, s, C*H*$_2$OH), 3.87 (3H, s, OCH_3), 3.54 (3H, s, OCH_3), 2.89–2.84 (2H, m, CH_2), 2.57–2.52 (2H, m, CH_2), 2.06 (3H, s, CH_3); ^{13}C nmr δ/ppm 19.9 (CH_2), 25.2 (CH_2), 28.1 (CH_3), 55.9 (OCH_3), 56.0 (OCH_3), 63.8 (CH_2OH), 110.0 (CH), 111.1 (CH), 125.8 (CH), 127.5 (CH), 128.2 (C), 128.4 (C), 130.0 (2 × CH), 133.5 (C), 135.0 (C), 136.7 (C), 137.8 (C), 147.2 (C), 147.9 (C); MS (EI) *m/z* (%) 311 (M+1, 19), 310 (M^+, 80), 309 (23), 308 (75), 294 (33), 293 (35), 279 (56), 191 (26), 189 (26), 166 (40), 148 (100), 83 (30), 57 (38), 43 (27), 41 (22); HRMS calculated for $C_{23}H_{18}O_2$ M^+ 326.1307, found 326.1307.

6.4 Protection of alcohols as acetates

6.4.1 [1-(3,4,5-Trimethoxyphenyl)-3,4-dihydronaphthalen-2-yl]methyl acetate (**58**):

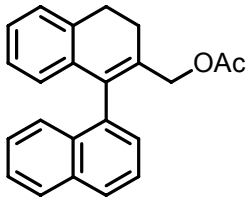


A mixture of alcohol **76** (0.38 g, 1.16 mmol), pyridine (5 ml) and acetic anhydride (5 ml) was refluxed under nitrogen for 16 h over which time it turned black. After cooling to room temperature, excess solvent was removed under reduced pressure and the resultant

oil purified by column chromatography using 30% ethyl acetate/hexane as eluent to afford arylsubstituted dihydronaphthyl acetate **58** as yellow crystalline solid (0.42 g, 98%). R_f = 0.16 (30% EtOAc/hexane).

mp = 81–83 °C; IR ν_{max} (cm^{-1}) 3017 (s, C–H stretch), 1734 (s, C=O stretch), 1584 (s, C=C stretch), 1123 (s, C–O stretch); ^{1}H nmr δ/ppm 7.16–7.07 (3H, m, 3 × ArH), 6.74 (1H, d, *J* = 7.3 Hz, ArH), 6.41 (2H, s, 2 × ArH), 4.61 (2H, s, C*H*$_2$OAc), 3.90 (3H, s, OCH_3), 3.82 (6H, s, 2 × OCH_3), 2.92 (2H, dd, *J* = 8.4 Hz, *J* = 7.7 Hz CH_2), 2.46 (2H, t, *J* = 8.4 Hz, *J* = 7.7 Hz CH_2), 2.07 (3H, s, CH_3); ^{13}C nmr δ/ppm 20.9 (CH_2), 25.4 (CH_2), 27.9 (CH_3), 56.0 (2 × OCH_3), 60.8 (OCH_3), 65.6 (*C*H_2OAc), 106.8 (2 × CH), 126.28 (CH), 126.31 (CH), 127.1 (CH), 127.2 (CH), 131.0 (C), 133.4 (C), 135.4 (C), 135.6 (C), 137.0 (C), 138.3 (C), 153.1 (2 × C), 170.9 (O*C*OCH_3); MS (EI) *m/z* (%) 369 (M+1, 11), 368 (M^+, 51), 309 (12), 308 (18), 293 (22), 278 (33), 277 (100), 246 (17); HRMS calculated for $C_{22}H_{24}O_5$ M^+ 368.1624, found 368.1620.

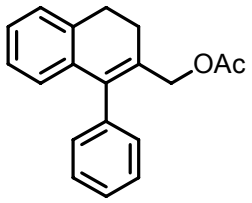
6.4.2 [1-(1-Naphthyl)-3,4-dihydronaphthalen-2-yl]methyl acetate (**80**):



In a similar manner described above alcohol **77** (0.25 g, 0.872 mmol gave naphthyldihydronaphthyl acetate **80** as a yellow oil (0.27 g, 94%). R_f = 0.68 (30% EtOAc/Hexane); IR ν_{max} (cm^{-1}) 3021 (s, C–H stretch), 1734 (s, C=O stretch), 1593 (m, C=C stretch), 1029(s, C–O stretch); ^{1}H nmr δ/ppm 7.86–7.82 (2H, m, 2 × ArH), 7.65 (1H, d, *J* = 8.5 Hz, ArH), 7.52–7.42 (2H, m, 2 × ArH), 7.39–7.29 (2H, m, 2 × ArH), 7.18 (1H, d, *J* = 7.3 Hz, ArH), 7.08 (1H, t, *J* = 7.4 Hz, ArH), 6.87 (1H, t, *J* = 7.5 Hz, ArH), 6.41 (1H, d, *J* = 7.7 Hz, ArH), 4.42 (2H, s, C*H*$_2$OAc), 3.02 (2H, m, CH_2), 2.60–2.54 (2H, m, CH_2), 1.92 (3H, s, CH_3); ^{13}C nmr δ/ppm 20.8 (CH_2), 25.5 (CH_2), 28.2 (CH_3), 65.6 (*C*H_2OAc), 125.6 (CH), 125.9 (CH), 126.0 (CH), 126.1 (CH), 126.2 (CH), 126.3 (CH), 127.3 (2 × CH), 127.6 (CH), 128.0 (CH), 128.4 (CH), 132.5 (C), 133.0 (C), 133.8 (C),

135.3 (C), 135.6 (C), 135.8 (C), 136.3 (C), 171.0 (O*C*OCH$_3$); MS (EI) *m/z* (%) 329 (M+1, 25), 328 (M$^+$, 77), 270 (29), 269 (100), 268 (53), 267 (53), 266 (58), 265 (74), 263 (21), 255 (41), 254 (52), 253 (99), 252 (97), 249 (22), 241 (25), 240 (31), 239 (67), 228 (25), 226 (23), 165 (23), 141 (60), 133 (20), 129 (32), 128 (29), 127 (25), 126 (51), 117 (26), 115 (28), 91 (30), 43 (63); HRMS calculated for $C_{23}H_{20}O_2$ M$^+$ 328.1463, found 328.1463.

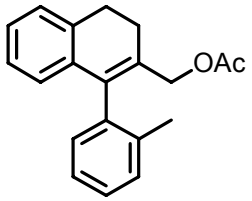
6.4.3 (1-Phenyl-3,4-dihydronaphthalen-2-yl)methyl acetate (**81**):



Similarly alcohol **78** (0.25 g, 1.06 mmol) afford aryl-substituted dihydronaphthyl acetate **81** as yellow oil (0.24 g, 82%). R_f = 0.70 (30% EtOAc/Hexane).

IR ν_{max} (cm^{-1}) 2938 (m, C–H stretch), 1735 (s, C=O stretch), 1025 (s, C–O stretch); ^{1}H nmr δ/ppm 7.39–7.33 (3H, m, 3 × ArH), 7.18–7.09 (5H, m, 5 × ArH), 7.02 (1H, t, *J* = 7.3 Hz, ArH), 6.63 (1H, d, *J* = 7.6 Hz, ArH), 4.56 (2H, s, C*H*$_2$OAc), 2.92 (2H, dd, *J* = 8.3 Hz, *J* = 7.7 Hz CH$_2$), 2.46 (2H, t, *J* = 8.3 Hz, *J* = 7.7 Hz CH$_2$), 2.04 (3H, s, CH$_3$); ^{13}C nmr δ/ppm.) 20.9 (CH$_2$), 25.7 (CH$_2$), 27.6 (CH$_3$), 65.5 (*C*H$_2$OAc), 126.2 (CH), 126.4 (CH), 127.2 (CH), 127.3 (CH), 127.6 (CH), 128.3 (2 × CH), 129.9 (2 x CH), 131.1 (C), 135.6 (C), 135.8 (C), 137.9 (C), 138.3 (C), 170.9 (O*C*OCH$_3$); MS (EI) *m/z* (%) 278 (M$^+$, 55), 266 (20), 234 (22), 220 (29), 219 (100), 218 (62), 217 (62), 216 (75), 215 (76), 205 (42), 204 (55), 203 (95), 202 (92), 191 (40), 189 (41), 179 (23), 178 (51), 165 (33), 141 (26), 129 (37), 128 (31), 127 (21), 115 (44), 101 (23), 91 (89), 77 (22), 43 (73); HRMS calculated for $C_{19}H_{18}O_2$ M$^+$ 278.1307, found 278.1307.

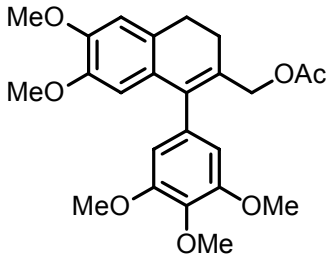
6.4.4 [1-(*o*-Tolyl)-3,4-dihydronaphthalen-2-yl]methyl acetate (**82**):



Similarly alcohol **79** (0.20 g, 0.807 mmol) gave acetate **82** as a brown oil (0.22 g, 94%). R_f = 0.79 (30% EtOAc/Hexane).

IR ν_{max} (cm^{-1}) 3019 (s, C–H stretch), 1725 (s, C=O stretch), 1605 (m, C=C stretch), 1045 (s, C–O stretch); ^{1}H nmr δ/ppm 7.27–7.01 (7H, m, 7 × ArH), 6.52 (1H, d, *J* = 7.6 Hz, ArH), 4.50 (1H, d, *J* = 14.4 Hz C*H*$_a$H$_b$OAc), 4.43 (1H, d, *J* = 14.4 Hz CH$_a$*H*$_b$OAc), 2.93 (2H, dd, *J* = 8.4 Hz, *J* = 7.7 Hz CH_2), 2.47 (2H, dd, *J* = 8.4 Hz, *J* = 7.5 Hz CH_2), 2.06 (3H, s, $ArCH_3$), 2.03 (3H, s, OCOC*H*$_3$); ^{13}C nmr δ/ppm 19.4 (CH_2), 20.9 (CH_2), 25.1 ($ArCH_3$), 28.1 (OCO*C*H$_3$), 65.4 (*C*H$_2$OAc), 125.6 (CH), 125.8 (CH), 126.4 (CH), 127.1 (CH), 127.2 (CH), 127.7 (CH), 130.0 (2 x CH), 131.0 (C), 135.0 (C), 135.4 (C), 136.7 (C), 137.2 (C), 137.4 (C), 170.9 (O*C*OC*H*$_3$); MS (EI) *m/z* (%) 292 (M^+, 10), 232 (24), 217 (100), 105 (6), 91 (5), 43 (9); HRMS calculated for $C_{20}H_{20}O_2$ M^+ 292.1463, found 292.1425.

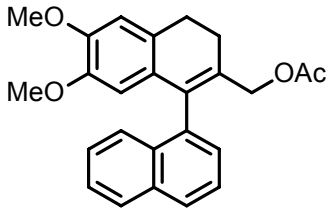
6.4.5 [6,7-Dimethoxy-1-(3,4,5-trimethoxyphenyl)-3,4-dihydronaphthalen-2-yl]methyl acetate (**95**):



Using the same procedure as outlined above alcohol **91** (0.37 g, 0.964 mmol), afforded dihydronaphthyl acetate **95** as light yellow oil (0.33 g, 80%). R_f = 0.05 (30% EtOAc/Hexane); IR ν_{max} (cm^{-1}) 3019 (s, C–H stretch), 1731 (s, C=O stretch), 1583 (s, C=C stretch), 1129 (s, C–O stretch); ^{1}H nmr δ/ppm 6.73 (1H, s, ArH), 6.42 (2H, s, 2 × ArH),

6.32 (1H, s, ArH), 4.60 (2H, s, C*H*$_2$OAc), 3.90 (3H, s, OCH$_3$), 3.89 (3H, s, OCH$_3$), 3.82 (6H, s, 2 × OCH$_3$), 3.62 (3H, s, OCH$_3$), 2.85 (2H, dd, *J* = 8.4 Hz, *J* = 7.6 Hz CH$_2$), 2.44 (2H, dd, *J* = 8.4 Hz, *J* = 7.8 Hz CH$_2$), 2.07 (3H, s, CH$_3$); ^{13}C nmr δ/ppm 20.9 (CH$_2$), 25.8 (CH$_2$), 27.7 (CH$_3$), 55.8 (OCH$_3$), 55.9 (OCH$_3$), 56.1 (2 × OCH$_3$), 60.9 (OCH$_3$), 65.8 (*C*H$_2$OAc), 106.9 (2 × CH), 110.8 (CH), 110.9 (CH), 128.2 (C), 128.5 (C), 128.7 (C), 133.5 (C), 137.0 (C), 138.1 (C), 147.0 (C), 148.2 (C), 153.1 (2 × C), 171.0 (O*C*OCH$_3$); MS (EI) *m/z* (%) 427 (M+1, 19), 426 (M$^+$, 70), 81 (18), 69 (41), 57 (29), 55 (23), 43 (27), 41 (21), 31 (23), 28 (100); HRMS calculated for $C_{24}H_{26}O_7$ M$^+$ 426.1679, found 426.1678.

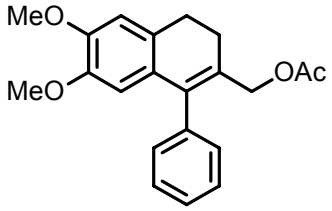
6.4.6 [6,7-Dimethoxy-1-(1-naphthyl)-3,4-dihydronaphthalen-2-yl]methyl acetate (**96**):



Similarly alcohol **92** (0.17 g, 0.493 mmol) afforded acetate **96** as yellow semi-solid (0.17 g, 89%). R_f = 0.45 (30% EtOAc/Hexane).

IR ν_{max} (cm^{-1}) 3015 (s, C–H stretch), 1730 (s, C=O stretch), 1605 (m, C=C stretch), 1119, 1023 (s, C–O stretch); ^{1}H nmr δ/ppm 7.88–7.84 (2H, m, 2 × ArH), 7.65 (1H, d, *J* = 8.4 Hz, ArH), 7.54–7.42 (2H, m, 2 × ArH), 7.37–7.31 (2H, m, 2 × ArH), 6.77 (1H, s, ArH), 5.99 (1H, s, ArH), 4.43 (1H, d, *J* = 12.2 Hz, C*H*$_a$H$_b$OAc), 4.38 (1H, d, *J* = 12.2 Hz, CH$_a$*H*$_b$OAc), 3.87 (3H, s, OCH$_3$), 3.33 (3H, s, OCH$_3$), 2.97–2.89 (2H, m, CH$_2$), 2.57–2.53 (2H, m, CH$_2$), 1.95 (3H, s, CH$_3$); ^{13}C nmr δ/ppm.20.8 (CH$_2$), 25.7 (CH$_2$), 27.9 (CH$_3$), 55.8 (OCH$_3$), 55.9 (OCH$_3$), 65.6 (*C*H$_2$OAc), 110.6 (CH), 110.9 (CH), 125.4 (CH), 125.8 (2 × CH), 126.0 (CH), 127.4 (CH), 127.9 (CH), 128.2 (CH), 128.5 (C), 130.5 (2 × C), 132.3 (C), 133.6 (C), 135.5 (C), 135.9 (C), 147.0 (C), 148.1 (C), 170.9 (O*C*OCH$_3$); MS (EI) *m/z* (%) 389 (M+1,29), 388 (M$^+$, 100), 329 (32), 328 (71), 327 (23), 298 (25), 297 (54), 239 (24), 141 (19); HRMS calculated for $C_{25}H_{24}O_4$ M$^+$ 388.1886, found 388.1886.

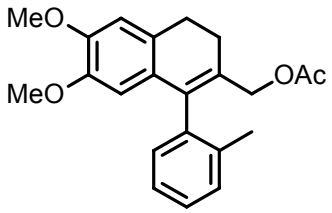
6.4.7 (6,7-Dimethoxy-1-phenyl-3,4-dihydronaphthalen-2-yl)methyl acetate (**97**):



Similarly alcohol **93** (0.15 g, 0.589 mmol) gave substituted dihydronaphthyl acetate **97** as a yellow solid (0.17 g, 88%). R_f = 0.55 (30% EtOAc/Hexane).

mp = 106 °C; IR ν_{max} (cm^{-1}) 3022 (m, C–H stretch), 1732 (s, C=O stretch), 1605, 1573 (m, C=C stretch), 1110, 1026 (s, C–O stretch); ^{1}H nmr δ/ppm 7.43–7.34 (3H, m, 3 × ArH), 7.19–7.16 (2H, m, 2 × ArH), 6.72 (1H, s, ArH), 6.20 (1H, s, ArH), 4.54 (2H, s, C*H*$_2$OAc), 3.89 (3H, s, OCH_3) 3.56 (3H, s, OCH_3), 2.85 (2H, dd, *J* = 8.5 Hz, *J* = 7.6 Hz CH_2), 2.44 (2H, dd, *J* = 8.4 Hz, *J* = 7.7 Hz CH_2), 2.04 (3H, s, CH_3); ^{13}C nmr δ/ppm 20.9 (CH_2), 25.7 (CH_2), 27.7 (CH_3), (55.8 (OCH_3), 55.9 (OCH_3), 65.6 (*C*H_2OAc), 110.8 (CH), 110.9 (CH), 127.3 (CH), 128.2 (2 × CH), 128.5 (C), 128.8 (C), 129.8 (2 × CH), 137.9 (C), 138.1 (C), 146.9 (C), 148.0 (2 × C), 171.1 (O*C*OCH_3); MS (EI) *m/z* (%) 339 (M+1, 31), 338 (M^+, 100), 336 (36), 279 (71), 278 (95), 277 (53), 248 (41), 247 (64), 245 (32), 203 (27), 189 (24), 165 (21), 91 (21), 43 (66); HRMS calculated for $C_{21}H_{22}O_4$ M^+ 338.1518, found 338.1519.

6.4.8 [6,7-Dimethoxy-1-(*o*-tolyl)-3,4-dihydronaphthalen-2-yl]methyl acetate (**98**):



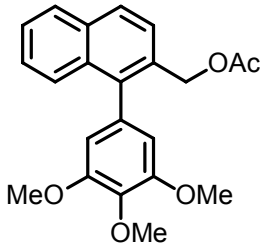
In a similar manner as described above alcohol **94** (0.28 g, 0.907 mmol) afforded acetate **98** as cream-white semi-solid (0.28 g, 88%). R_f = 0.26 (30% EtOAc/Hexane).

IR ν_{max} (cm^{-1}) 3020 (s, C–H stretch), 1731 (s, C=O stretch), 1510 (s, C=C stretch), 1025 (m, C–O stretch); ^{1}H nmr δ/ppm 7.26–7.21 (3H, m, 3 × ArH), 7.07 (1H, d, *J* = 6.6 Hz,

ArH), 6.73 (1H, s, ArH), 6.08 (1H, s, ArH), 4.49 (1H, d, J = 12.1 Hz, CH_aH$_b$OAc), 4.42 (1H, d, J = 12.1 Hz, CH$_a$$H_b$OAc), 3.88 (3H, s, OCH_3), 3.54 (3H, s, OCH_3), 2.90–2.84 (2H, m, CH_2), 2.45 (2H, dd, J = 8.7 Hz, J = 7.4 Hz CH_2), 2.06 (3H, s, OCOCH_3), 2.03 (3H, s, ArCH_3); ^{13}C nmr δ/ppm 19.3 (CH_2), 20.9 (CH_2), 25.4 (ArCH_3), 27.8 (OCOCH$_3$), 55.9 (2 × OCH_3), 65.5 (CH$_2$OAc), 109.9 (CH), 110.9 (CH), 125.8 (CH), 127.6 (CH), 127.9 (C), 128.4 (C), 128.7 (C), 129.93 (CH), 129.98 (CH), 136.6 (C), 137.1 (C), 137.3 (C), 147.2 (C), 148.1 (C), 171.1 (OCOCH$_3$); MS (EI) *m/z* (%) 352 (M^+, 54), 188 (28), 87 (14), 57 (77), 43 (100); HRMS calculated for $C_{22}H_{24}O_4$ M^+ 352.1675, found 352.1743.

6.5 Aromatization reactions.

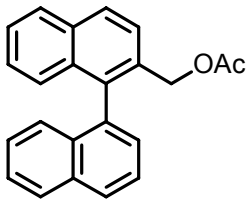
6.5.1 [1-(3,4,5-Trimethoxyphenyl)naphthalen-2-yl]methyl acetate (**59**):



To a solution of acetate **58** (0.50 g, 1.46 mmol) in dry CH_2Cl_2 (30 ml) was added DDQ (0.85 g, 1.98 mmol) and the mixture immediately turned green. The reaction mixture was then refluxed under nitrogen for 16 h over which time it turned pale green. After allowing to cool to room temperature, the mixture was poured into an aqueous solution of 5% $NaHCO_3$ (50 ml) and extracted with CH_2Cl_2 (3 × 100 ml). The organic extracts were combined, washed with brine (20 ml), dried ($MgSO_4$), filtered through celite plug and the excess solvent removed *in vacou*. The resultant oil was purified by column chromatography using 30% ethyl acetate as eluent to obtain substituted naphthalene **59** as an orange solid (0.39 g, 78%). R_f = 0.55 (30% EtOAc/Hexane); mp = 85–87 °C; IR ν_{max} (cm^{-1}) 3015 (s, C–C stretch), 1734 (s, C=O stretch), 1582 (s, C=C stretch), 1128 (s, C–O stretch); ^{1}H nmr δ/ppm 7.89–7.85 (2H, m, 2 × ArH), 7.60–7.57 (2H, m, 2 × ArH), 7.51–7.38 (2H, m, 2 × ArH), 6.55 (2H, s, 2 × ArH), 5.07 (2H, s, CH_2OAc), 3.96 (3H, s, OCH_3), 3.82 (6H, s, 2 × OCH_3), 2.07 (3H, s, CH_3); ^{13}C nmr δ/ppm 20.9 (CH_3), 56.0 (2 × OCH_3),

60.9 (OCH_3), 64.7 (CH_2OAc), 107.3 (2 × CH), 126.0 (2 × CH), 126.2 (CH), 126.7 (CH), 127.7 (CH), 127.9 (CH), 130.8 (C), 132.6 (C), 133.0 (C), 133.2 (C), 137.3 (C), 139.3 (C), 153.0 (2 × C), 170.6 ($OCOCH_3$); MS (EI) *m/z* (%) 367 M+1, 66), 366 (M^+, 100), 320 (39), 305 (48), 291 (33), 277 (29), 276 (28), 275 (24), 189 (23), 43 (29); HRMS calculated for $C_{22}H_{22}O_5$ M^+ 366.1467, found 366.1468.

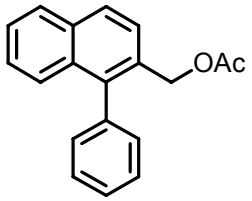
6.5.2 [1-(1-Naphthyl)naphthalen-2-yl]methyl acetate (**83**):



In a similar manner as described above DDQ (0.21 g, 0.915 mmol) was used to convert acetate **80** (0.20 g, 0.618 mmol) a binaphthyl **83**, a light yellow oil (0.19 g, 95%). R_f = 0.62 (30% EtOAc/ hexane).

IR ν_{max} (cm^{-1}) 3059 (m, C–H stretch), 1738 (s, C=O stretch), 1593, 1587 (m, C=C stretch), 1027 (s, C–O stretch); ^{1}H nmr δ/ppm 7.98–7.89 (4H, m, 4 × ArH), 7.67–7.58 (2H, m, 2 × ArH), 7.47–7.39 (3H, m, 3 × ArH), 7.24–7.16 (4H, m, 4 × ArH), 4.94 (1H, d, *J* = 12.5 Hz, CH_aH_bOAc), 4.84 (1H, d, *J* = 12.5 Hz, CH_aH_bOAc), 1.84 (3H, s, CH_3); ^{13}C nmr δ/ppm 20.6 (CH_3), 64.7 (CH_2OAc), 125.4 (CH), 125.9 (CH), 126.1 (2 × CH), 126.2 (CH), 126.3 (CH), 126.4 (CH), 126.8 (CH), 127.8 (CH), 127.9 (CH), 128.1 (CH), 128.2 (CH), 128.4 (CH), 132.0 (C), 132.8 (C), 133.1 (C), 133.2 (C), 133.6 (C), 135.4 (C), 137.4 (C), 171.0 ($OCOCH_3$); MS (EI) *m/z* (%) 327 (M+1, 51), 326 (M^+, 97), 284 (21), 268 (20), 267 (60), 266 (85), 265 (100), 263 (27), 262 (43), 253 (40), 251 (64), 249 (21), 238 (23), 43 (19); HRMS calculated for $C_{23}H_{18}O_2$ M^+ 326.1307, found 326.1307.

6.5.3 (1-Phenylnaphthalen-2-yl)methyl acetate (**84**):

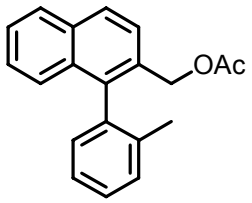


Similarly acetate **81** (0.14 g, 0.507 mmol) afforded an arylsubstituted naphthyl **84** as light yellow oil (0.13 g, 93%) using DDQ (0.17 g, 0.758 mmol) in CH_2Cl_2 (15 ml).

R_f = 0.74 (30% EtOAc/Hexane).

IR ν_{max} (cm^{-1}) 2959 (m, C–H stretch), 1738 (s, C=O stretch), 1597 (m, C=C stretch), 1029 (s, C–O stretch); ^{1}H nmr δ/ppm 7.88–7.83 (2H, m, 2 × ArH), 7.57 (1H, d, *J* = 8.5 Hz, ArH), 7.47–7.43 (5H, m, 5 × ArH), 7.30–7.15 (3H, m, 3 × ArH), 5.00 (2H, s, C*H*$_2$OAc), 2.02 (3H, s, CH_3); ^{13}C nmr δ/ppm.) 20.9 (CH_3), 64.7 (*C*H_2OAc), 125.9 (CH), 126.1 (CH), 126.2 (CH), 126.7 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 128.2 (2 × CH), 130.2 (2 × CH), 130.8 (C), 132.7 (C), 133.1 (C), 137.8 (C), 139.5 (C), 170.6 (O*C*OCH_3); MS (EI) *m/z* (%) 276 (M^+, 100), 234 (13), 215 (71), 107 (7), 43 (8); HRMS calculated for $C_{19}H_{16}O_2$ M^+ 276.1150, found 276.1113.

6.5.4 [1-(*o*-Tolyl)naphthalen-2-yl]methyl acetate (**85**):



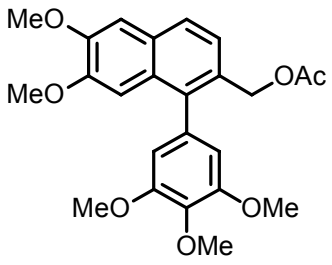
Similarly using DDQ (0.46 g, 1.53 mmol) in CH_2Cl_2 (30 ml) acetate **82** (0.20 g, 0.514 mmol) afforded a substituted naphthalene **85** as a brown crystalline solid (0.20 g, 100%).

R_f = 0.79 (30% EtOAc/Hexane).

mp = 86–90 °C; IR ν_{max} (cm^{-1}) 3020 (s, C–H stretch), 1736 (s, C=O stretch), 1658, 1600 (m, C=C stretch), 1029 (s, C–O stretch); ^{1}H nmr δ/ppm 7.88–7.83 (2H, m, 2 × ArH), 7.58 (1H, d, *J* = 8.5 Hz, ArH), 7.46–7.41 (1H, m, ArH), 7.35–7.24 (5H, m, 5 × ArH), 7.13 (1H, d, *J* = 7.5 Hz, ArH), 4.97 (1H, d, *J* = 12.4 Hz CH_aH$_b$OAc), 4.95 (1H, d, *J* = 12.4 Hz

CH_aH_bOAc), 2.00 (3H, s, $ArCH_3$), 1.91 (3H, s, $OCOCH_3$); ^{13}C nmr δ/ppm 19.9 ($ArCH_3$), 20.7 ($OCOCH_3$), 64.7 (CH_2OAc), 125.8 (CH), 126.0 (CH), 126.12 (CH), 126.14 (CH), 126.3 (CH), 127.7 (CH), 127.8 (CH), 127.9 (CH), 129.9 (CH), 130.0 (CH), 130.7 (C), 132.2 (C), 133.1 (C), 136.9 (C), 137.1 (C), 138.7 (C), 170.9 ($OCOCH_3$); MS (EI) *m/z* (%) 291 (M+1,30), 290 (M^+, 85), 231 (80), 229 (89), 216 (75), 215 (100), 202 (50), 189 (22), 149 (31), 43 (71); HRMS calculated for $C_{20}H_{18}O_2$ M^+ 290.1307, found 290.1307.

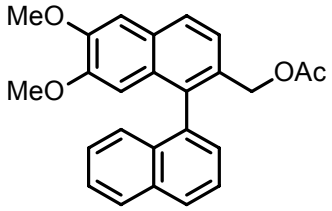
6.5.5 [6,7-Dimethoxy-1-(3,4,5-trimethoxyphenyl)naphthalen-2-yl]methyl acetate (**99**):



Using DDQ (0.48 g, 2.10 mmol) in CH_2Cl_2 (30 ml) in the same procedure as outlined above acetate **95** (0.30 g, 0.702 mmol) gave arylsubstituted naphthalene **99** as yellow crystalline solid (0.22 g, 74%). R_f = 0.22 (30% EtOAc/Hexane).

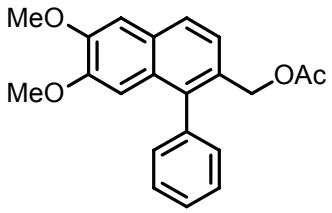
mp = 150–152 °C; IR ν_{max} (cm^{-1}) 3019 (s, C–H stretch), 1736 (s, C=O stretch), 1583 (s, C=C stretch), 1021 (s, C–O stretch); ^1H nmr δ/ppm 7.64 (1H, d, *J* = 8.4 Hz, ArH), 7.36 (1H, d, *J* = 8.4 Hz, ArH), 7.08 (1H, s, ArH), 6.76 (1H, s, ArH), 6.48 (2H, s, 2 × ArH), 4.94 (2H, s, CH_2OAc), 3.93 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.76 (6H, s, 2 × OCH_3), 3.67 (3H, s, OCH_3), 1.98 (3H, s, CH_3); ^{13}C nmr δ/ppm 20.9 (CH_3), 55.7 (OCH_3), 55.8 (OCH_3, 56.1 (2 × OCH_3), 60.9 (OCH_3), 64.9 (CH_2OAc), 105.4 (CH), 106.2 (CH), 107.2 (2 × CH), 124.8 (CH), 126.2 (CH), 128.2 (C), 129.1 (C), 129.2 (C), 133.6 (C), 137.2 (C), 138.1 (C), 149.5 (C), 149.6 (2 × C), 153.1 (C), 170.6 ($OCOCH_3$); MS (EI) *m/z* (%) 427 (M+1, 19), 426 (M^+, 70), 81 (18), 69 (41), 57 (29), 55 (23), 43 (27), 41 (21), 31 (23), 28 (100); HRMS calculated for $C_{24}H_{26}O_7$ M^+ 426.1678, found 426.1678.

6.5.6 [6,7-Dimethoxy-1-(1-naphthyl)naphthalen-2-yl]methyl acetate (**100**):



Similarly acetate **96** (0.22 g, 0.575 mmol) gave a substituted binaphthyl **100,** a yellow solid (0.17 g, 78%) using DDQ (0.13 g, 0.574 mmol) in CH_2Cl_2 (15 ml). R_f = 0.45 (30% EtOAc/Hexane); mp = 110–114 °C; IR ν_{max} (cm^{-1}) 3022 (m, C–H stretch), 1738 (s, C=O stretch), 1624 (m, C=C stretch), 1162 (s, C–O stretch); ^{1}H nmr δ/ppm; 7.85 (2H, t, *J* = 7.8 Hz, 2 × ArH), 7.72 (1H, d, *J* = 8.4 Hz, ArH), 7.53–7.32 (4H, m, 4 × ArH), 7.18–7.12 (2H, m, 2 × ArH), 7.11 (1H, s, ArH), 6.35 (1H, s, ArH), 4.82 (1H, d, *J* = 12.3 Hz, CH_aH$_b$OAc), 4.69 (1H, d, *J* = 12.3 Hz, CH$_a$$H_b$OAc), 3.91 (3H, s, OCH_3), 3.36 (3H, s, OCH_3), 1.72 (3H, s, CH_3); ^{13}C nmr δ/ppm 20.6 (CH_3), 55.4 (OCH_3), 55.8 (OCH_3), 64.9 (*C*H_2OAc), 105.5 (CH), 106.2 (CH), 124.9 (CH), 125.4 (CH), 125.9 (CH), 126.0 (2 × CH), 126.4 (CH), 127.8 (CH), 128.16 (CH), 128.18 (CH), 128.8 (C), 129.2 (C), 130.3 (C), 132.6 (C), 133.6 (C), 135.7 (C), 136.1 (C), 149.6 (C), 149.7 (C), 170.5 (O*C*OCH_3); MS (EI) *m/z* (%) 387 (M+1, 25), 386 (M^+, 100), 385 (26), 384 (90), 372 (32), 371 (22), 370 (27), 368 (19), 344 (20), 343 (27), 149 (25); HRMS calculated for $C_{25}H_{22}O_4$ M^+ 386.1518, found 386.1519.

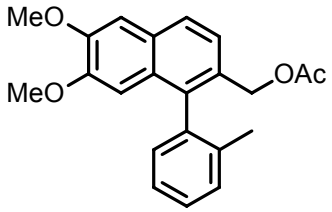
6.5.7 (6,7-Dimethoxy-1-phenylnaphthalen-2-yl)methyl acetate (**101**):



Similarly dihydronaphthalene **97** (0.17 g, 0.567 mmol) gave substituted naphthalene **101** as a yellow crystalline solid (0.17 g, 100%) using DDQ (0.38 g, 1.66 mmol) in CH_2Cl_2 (20 ml). R_f = 0.40 (30% EtOAc/Hexane); mp = 75–78 °C; IR ν_{max} (cm^{-1}) 3022 (m, C–H stretch), 1736 (s, C=O stretch), 1624 (m, C=C stretch), 1024 (s, C–O stretch); ^{1}H nmr

δ/ppm 7.62 (1H, d, *J* = 8.4 Hz, ArH), 7.41–7.33 (4H, m, 4 × ArH), 7.23–7.19 (2H, m, 2 × ArH), 7.06 (1H, s, ArH), 6.63 (1H, s, ArH), 4.87 (2H, s, C*H*$_2$OAc), 3.90 (3H, s, OCH_3) 3.59 (3H, s, OCH_3), 1.93 (3H, s, CH_3); ^{13}C nmr δ/ppm 20.9 (CH_3), 55.4 (OCH_3), 55.8 (OCH_3), 64.9 (*C*H_2OAc), 105.4 (CH), 106.1 (CH), 124.9 (CH), 126.1 (CH), 127.5 (CH), 128.3 (2 × CH), 129.09 (C), 129.12 (C), 129.9 (2 × CH), 137.9 (C), 138.1 (C), 138.3 (C), 146.4 (C), 149.5 (C), 170.6 (O*C*OCH_3); MS (EI) *m/z* (%) 337 (M+1,59), 336 (M^+, 100), 265 (19), 246 (37), 245 (56), 215 (24), 203 (26), 202 (33), 191 (22), 189 (40), 43 (42); HRMS calculated for $C_{21}H_{20}O_4$ M^+ 336.1362, found 336.1362.

6.5.8 [6,7-Dimethoxy-1-(*o*-tolyl)naphthalen-2-yl]methyl acetate (**102**):

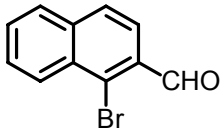


In a similar manner as described above dihydronaphthalene **98** (0.31 g, 0.881 mmol) was converted into naphthalene **102** as yellow solid (0.24 g, 78%) using DDQ (0.20 g, 0.881 mmol) in CH_2Cl_2 (20 ml). R_f = 0.48 (30% EtOAc/Hexane).

mp = 91–93 °C; IR ν_{max} (cm^{-1}) 3022 (m, C–H stretch), 1736 (s, C=O stretch), 1624 (m, C=C stretch), 1129 (m, C–O stretch); ^{1}H nmr δ/ppm 7.73 (1H, d, *J* = 8.4 Hz, ArH), 7.45 (1H, d, *J* = 8.4 Hz, ArH), 7.36–7.25 (3H, m, 3 × ArH), 7.16 (1H, s, ArH), 7.14 (1H, s, ArH), 6.53 (1H, s, ArH), 4.93 (1H, d, *J* = 12.2 Hz, C*H*$_a$H$_b$OAc), 4.87 (1H, d, *J* = 12.2 Hz, CH$_a$*H*$_b$OAc), 4.00 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 2.00 (3H, s, ArCH_3), 1.94 (3H, s, OCOC*H*$_3$); ^{13}C nmr δ/ppm 19.5 (ArCH_3), 20.8 (OCO*C*H_3), 55.5 (OCH_3), 55.8 (OCH_3), 64.9 (*C*H_2OAc), 104.8 (CH), 106.3 (CH), 124.9 (CH), 125.9 (CH), 126.0 (CH), 127.9 (CH), 129.0 (C), 129.1 (C), 129.9 (2 × CH), 136.8 (C), 137.5 (C), 137.6 (C), 149.6 (C), 149.7 (C), 170.7 (O*C*OCH_3); MS (EI) *m/z* (%) 351 (M+1, 44), 350 (M^+, 100), 291 (26), 290 (28), 276 (15), 275 (19), 260 (17), 259 (46), 202 (17), 189 (16), 43 (18); HRMS calculated for $C_{22}H_{22}O_4$ M^+ 350.1518, found 350.1517.

6.6 Aromatization of bromo(methoxy)naphthaldehydes.

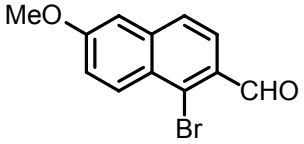
6.6.1 1-Bromo-2-naphthaldehyde (**106**):



1-Bromo-3,4-dihydro-2-naphthaldehyde **55** (0.45 g, 1.89 mmol), selenium powder (0.30 g, 5.69 mmol) and dimethyl sulfoxide (0.5 ml) were slowly heated to 180 °C. The reaction mixture was heated at the same temperature for 5 min where sputtering was taking place. After sputtering had ceased, the mixture was allowed to cool to room temperature before being filtered and washed with excess dichloromethane. Excess solvent was removed on a rotary evaporator to obtain a black oil that was purified by column chromatography using 5% ethyl acetate/hexane as eluant to give the desired product **106** as a bright yellow solid (0.31 g, 69% yield).

mp = 106-108 °C; IR ν_{max} (cm^{-1}) 3019 (w, C-H stretch), 1687 (s, C=O stretch), 1619, 1597 (s, C=C stretch); ^{1}H nmr δ/ppm 10.67 (1H, s, CHO), 8.53-8.50 (1H, m, Ar-H), 7.95-7.84 (3H, m, 3 × Ar-H), 7.72-7.67 (2H, m, 2 × Ar-H); ^{13}C nmr δ/ppm 124.1 (CH), 128.1 (CH), 128.21 (CH), 128.27 (CH), 128.4 (CH), 128.5 (C), 129.7 (CH), 131.1 (C), 132.1 (C), 137.2 (C), 192.8 (CHO); MS (EI) *m/z* (%) 235 (M^{+} ^{81}Br, 99), 233 (M^{+} ^{79}Br, 100), 206 (28), 127 (35), 126 (89), 63 (15); HRMS calculated for $C_{11}H_7O^{79}Br$ M^{+} 233.9680, found 233.9708.

6.6.2 1-Bromo-6-methoxy-2-naphthaldehyde (**108**).



Using the same procedure as described above, 6-methoxy-1-bromo-3,4-dihydro-2-naphthaldehyde **107** (3.98 g, 14.9 mmol) was converted to 6-methoxy-1-bromo-2-naphthaldehyde **108** in the presence of selenium powder (2.30 g, 29.8 mmol) and

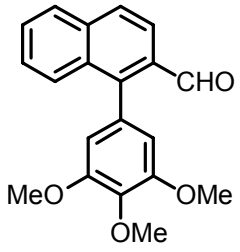
dimethyl sulfoxide (2 ml). The product was obtained as a light-brown solid (2.85 g, 72% yield).

mp = 123-126 °C; IR ν_{max} (cm^{-1}) 3020 (s, C-H stretch), 1682 (s, C=O stretch), 1560 (s, C=C stretch), 1215 (s, C–O stretch); ^{1}H nmr δ/ppm 10.58 (1H, s, CHO), 8.36 (1H, d, *J* = 9.4 Hz, ArH), 7.87 (1H, d, *J* = 8.6 Hz, ArH), 7.68 (1H, d, *J* = 8.8 Hz, ArH), 7.28 (1H, dd, *J* = 2.5 Hz, 9.4 Hz, ArH), 7.11 (1H, d, *J* = 2.5 Hz, ArH), 3.96 (3H, s, OMe); ^{13}C nmr δ/ppm 55.6 (OCH_3), 106.4 (CH), 120.7 (CH), 124.7 (CH), 126.9 (CH) 127.2 (C), 129.4 (C), 129.8 (CH), 130.4 (C), 1739.0 (C), 160.6 (C), 192.5 (CHO); MS (EI) *m/z* (%) 265 (M^{+} ^{81}Br, 47), 263 (M^{+} ^{79}Br, 46), 261 (100), 202 (17), 156 (16), 113 (22), 73 (17), HRMS calculated for $C_{12}H_9O_2{}^{79}Br$ M^{+} 263.9785, found 265.9750.

6.7 Coupling reactions using aromatized naphthaldehydes.

6.7.1 Suzuki coupling reactions using 1-bromo-2-naphthaldehyde (**106**).

6.7.1.1 1-(3,4,5-Trimethoxyphenyl)-2-naphthaldehyde (109):

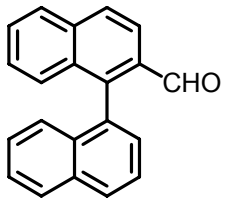


To $[Pd(PPh_3)_4]$ (0.14 g, 0.127 mmol) was added deoxygenated solutions of **106** (0.30 g, 1.27 mmol) in DME (10 ml) and 3,4,5-trimethoxy-1-phenylboronic acid (0.38 g, 1.91 mmol) in ethanol (5 ml). This was followed by a deoxygenated solution of aqueous sodium carbonate (1.06 g, 10.8 mmol in 5.0 ml water). The resultant mixture was refluxed under nitrogen for 46 h over which time it turned deep red. After allowing to cool to room temperature, the mixture was quenched with water (10 ml) and the organic material extracted with dichloromethane (3 × 25 ml). The resultant organic extracts were combined, dried ($MgSO_4$), filtered through a celite plug and the excess solvent removed using a rotary evaporator. The subsequent oil was purified by column chromatography

using 30% ethyl acetate/hexane as eluent and afforded a desired product **109** as a yellow solid (0.40g, 94%).

mp = 89-92 °C; IR ν_{max} (cm^{-1}) 2939 (s, C-H stretch), 1694 (s, C=O stretch), 1626,1597 (s, C=C stretch), 1115 (s, C–O stretch); ^{1}H nmr δ/ppm 9.96 (1H, s, CHO), 8.05 (1H, d, *J* = 8.6 Hz, ArH), 7.93 (2H, d, *J* = 8.4 Hz, 2 × ArH), 7.76 (1H, d, *J* = 8.2 Hz, ArH), 7.63 (1H, t, *J* = 6.9 Hz, ArH), 7.50 (1H, t, *J* = 7.0 Hz, ArH), 6.63 (2H, s, 2 × ArH), 3.85 (9H, s, 3 × OCH_3); ^{13}C nmr δ/ppm 56.0 (OCH_3), 56.1 (2 × OCH_3), 108.2 (2 × CH), 121.9 (CH), 123.5 (C), 126.9 (CH), 127.6 (CH), 128.1 (CH), 128.3 (CH), 128.7 (CH), 130.6 (C), 131.1 (C), 132.4 (C), 136.0 (C), 146.3 (C), 152.9 (2 × C), 192.7 (CHO); MS (EI) *m/z* (%) 323 (M+1, 22), 322 (M^+, 100), 279 (63), 219 (15), 165 (24); HRMS calculated for $C_{20}H_{18}O_4$ M^+ 322.1205, found 322.1186.

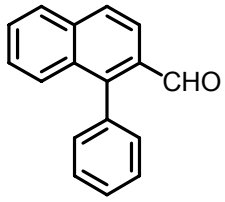
6.7.1.2 1-(1-Naphthyl)-2-naphthaldehyde (110):



Using the same procedure as described above, naphthaldehyde **106** (0.30 g, 1.27 mmol) was coupled with 1-naphthylboronic acid (0.31 g, 1.91 mmol) to give aryl-substituted naphthaldehyde **110** as a yellow crystalline solid (0.32 g, 89% yield).

mp = 112-114 °C; IR ν_{max} (cm^{-1}) 3019 (m, C–H stretch), 1676 (s, C=O stretch), 1619 (m, C=C stretch), 1244 (s, C–O stretch); ^{1}H nmr δ/ppm 9.68 (1H, s, CHO), 8.15 (1H, d, *J* = 8.6 Hz, ArH), 8.02-7.92 (4H, m, 4 × ArH), 7.62-7.54 (2H, m, 2 × ArH), 7.49-7.44 (2H, m, 2 × ArH), 7.36 (1H, d, *J* = 8.1 Hz, ArH), 7.31-7.25 (2H, m, 2 × ArH), 7.20 (1H, d, *J* = 8.4 Hz, ArH); ^{13}C nmr δ/ppm 122.1 (CH), 125.0 (CH), 126.2 (CH), 126.3 (CH), 126.8 (CH), 126.9 (CH), 127.7 (CH), 128.2 (CH), 128.3 (CH), 128.6 (CH), 128.8 (CH), 128.9 (CH), 129.1 (CH), 132.1 (C), 132.9 (C), 133.0 (C), 133.3 (C), 133.5 (C), 136.1 (C), 144.8 (C), 192.4 (CHO); MS (EI) *m/z* (%) 283 (M+1, 23), 282 (M^+, 100), 281 (M-1, 81), 265 (26), 253 (86), 252 (97), 126 (35), 113 (15); HRMS calculated for $C_{21}H_{14}O$ M^+ 282.1044, found 282.1035.

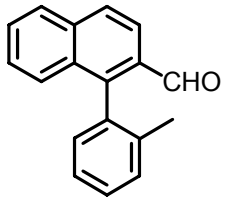
6.7.1.3 1-Phenyl-2-naphthaldehyde (111):



Substituted naphthaldehyde **111** was obtained as a light-yellow oil (0.26 g, 87% yield) from the coupling of bromonaphthaldehyde **106** (0.30g, 1.27 mmol) and 1-phenylboronic acid (0.22 g, 1.91 mmol) using the same procedure as outlined above.

^{1}H nmr δ/ppm 9.89 (1H, s, CHO), 8.06 (1H, d, *J* =8.6Hz, ArH), 7.92 (2H, d, *J* =9.7Hz, 2 × ArH) 7.58–7.67 (2H, m, 2 × ArH), 7.51–7.52 (3H, m, 3 × ArH), 7.47 (1H, d, *J* = 8.2 Hz, ArH), 7.39–7.41 (2H, m, 2 × ArH); ^{13}C nmr δ/ppm 122.1 (CH), 126.8 (CH), 127.7 (CH), 128.18 (CH), 128.21 (2 × CH), 128.3 (2 × CH) 128.7 (CH), 130.9 (2 × CH), 131.2 (C), 132.4 (C), 135.2 (C), 136.1 (C), 146.5 (C), 192.6 (CHO); MS (EI) *m/z* (%) 233 (M+1, 18), 232 (M^+, 100), 202 (64), 101 (18); HRMS calculated for $C_{17}H_{12}O$ M^+ 232.0888, found 232.0865.

6.7.1.4 1-(*o*-Tolyl)-2-naphthaldehyde (112):



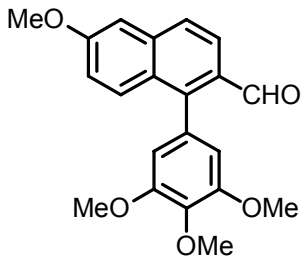
Using the same procedure as outlined above, tolyl naphthaldehyde **112** was synthesized as a yellow crystalline solid (0.29 g, 94% yield) from the coupling of naphthaldehyde **106** (0.30 g, 1.27 mmol) and *ortho*-tolylboronic acid.

mp = 60-61 °C; IR ν_{max} (cm^{-1}) 3020 (s, C-H stretch), 1687 (s, C=O stretch), 1618, 1596 (s, C=C stretch); ^{1}H nmr δ/ppm 9.82 (1H, s, CHO), 8.07 (1H, d, *J* =8.6Hz, ArH), 7.93 (1H, d, *J* =9.1Hz, ArH), 7.67 (1H, td, *J* =7.2Hz; 2.0Hz, ArH), 7.31–7.48 (5H, m, 5 × ArH), 7.24 (1H, d, *J* = 6.6 Hz, ArH), 1.96 (3H, s, $ArCH_3$); ^{13}C nmr δ/ppm 20.0 ($ArCH_3$), 122.0 (CH), 125.7 (CH), 126.9 (CH), 127.2 (CH), 128.3 (CH), 128.6 (CH), 128.8 (CH) 130.1 (CH), 130.9 (CH), 131.0 (C), 132.1 (C), 134.8 (C), 136.2 (C), 137.2 (C), 146.3 (C),

192.6 (CHO); MS (EI) *m/z* (%) 246 (M^+, 100), 231 (38),218 (88), 202 (43), 130 (39), 99 (10); HRMS calculated for $C_{18}H_{14}O$ M^+ 246.1045, found 246.1049.

6.7.2 Suzuki coupling reactions using 1-bromo-6-methoxy-2-naphthaldehyde (**108**).

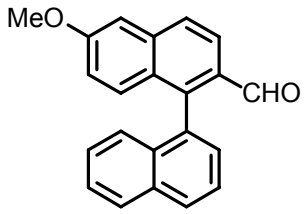
6.7.2.1 6-Methoxy-1-(3,4,5-trimethoxyphenyl)-2-naphthaldehyde (117):



In the same way as outlined above, 6-methoxy-1-bromo-2-naphthaldehyde **108** (0.30 g, 1.13 mmol) and 3,4,5-trimethoxy-1-phenylboronic acid **56** (0.36 g, 1.69 mmol) were coupled to give the desired product **117,** a light-yellow crystalline solid (0.32 g, 80% yield).

mp = 132-134°C; IR ν_{max} (cm^{-1}) 2964 (s, C-H stretch), 1690 (s, C=O stretch), 1623 (s, C=C stretch), 1113 (s, C–O stretch); ^{1}H nmr δ/ppm 9.89 (1H, s, CHO), 8.02 (1H, d, *J* = 8.6Hz, ArH), 7.80 (1H, d, *J* = 8.7Hz, ArH), 7.65 (1H, d, *J* = 9.2Hz, ArH), 7.21 (1H, d, *J* = 2.5Hz, ArH), 7.15-7.10 (1H, dd, *J* = 9.2Hz, 2.6Hz, ArH), 6.61 (2H, s, 2 × ArH), 3.96 (6H, s, 2 × OCH_3), 3.84 (6H, s, 2 × OCH_3); ^{13}C nmr δ/ppm 55.4 (OCH_3), 56.2 (2 × OCH_3), 61.0 (OCH_3), 106.3 (CH), 108.2 (2 × CH), 119.2 (CH), 122.7 (CH), 127.0 (CH), 127.4 (C), 129.3 (CH), 129.5 (C), 130.8 (C), 137.7 (C), 137.9 (C), 146.4 (C), 152.9 (2 × C), 159.9 (C), 192.4 (CHO); MS (EI) *m/z* (%) 352 (M^+, 57), 309 (23), 304 (25), 246 (100), 231 (36), 215 (37), 202 (35), 185 (30), 115 (19); HRMS calculated for $C_{21}H_{20}O_5$ M^+ 352.1310, found 352.1340.

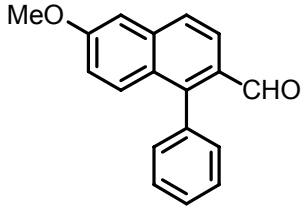
6.7.2.2 6-Methoxy-1-(1-naphthyl)-2-naphthaldehyde (118):



Using the same procedure as described above, bromonaphthaldehyde **108** (0.30 g, 1.13 mmol) and 1-naphthylboronic acid (0.29 g, 1.69 mmol) were coupled to give biaryl **118**, a yellow solid (0.26 g, 74% yield).

mp = 181-184 °C; IR ν_{max} (cm^{-1}) 3019 (m, C–H stretch), 1676 (s, C=O stretch), 1619 (m, C=C stretch), 1244 (s, C–O stretch); ^{1}H nmr δ/ppm 9.61 (IH, s, CHO), 8.12 (1H, d, *J* = 8.6 Hz, ArH), 8.01 (1H, d, *J* = 8.3 Hz, ArH), 7.96 (1H, d, *J* = 8.3 Hz, ArH), 7.89 (1H, d, *J* = 8.7 Hz, ArH), 7.63-7.58 (1H, m, ArH), 7.50-7.46 (2H, m, 2 × ArH), 7.32–7.19 (4H, m, 4 × ArH), 6.96 (1H, dd, *J* = 2.6 Hz, 9.2 Hz, ArH), 3.93 (3H, s, OCH_3); ^{13}C nmr δ/ppm. 55.4 (OCH_3), 106.3 (CH), 119.5 (CH), 122.8 (CH), 124.9 (CH), 126.1 (CH), 126.2 (CH), 126.7 (CH), 127.3 (CH), 128.1 (C), 128.2 (CH), 128.8 (CH), 129.0 (CH), 129.4 (CH), 130.4 (C), 133.0 (C), 133.2 (C), 133.4 (C), 138.0 (C), 144.9 (C), 159.9 (C), 192.2 CHO); MS (EI) *m/z* (%) 313 (M+1, 23), 312 (M^+, 100), 239 (33), 218 (43), 144 (13), 130 (19), 68 (33); HRMS calculated for $C_{22}H_{16}O_2$ M^+ 312.1150, found 312.1173.

6.7.2.3 6-Methoxy-1-phenyl-2-naphthaldehyde (119):

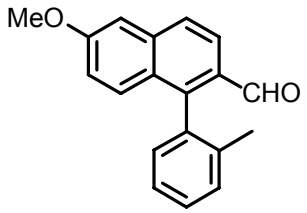


In the same manner as detailed above, methoxyphenylnaphthaldehyde **119**, a thick yellow oil (0.27 g, 90% yield) was synthesized from the Suzuki coupling of bromonaphthaldehyde **108** (0.30 g, 1.13 mmol) and phenylboronic (0.20 g, 1.69 mmol).

IR ν_{max} (cm^{-1}) 3019 (s, C-H stretch), 1681 (s, C=O stretch), 1616, 1573 (s, C=C stretch), 1244 (s, C–O stretch); ^{1}H nmr δ/ppm 9.81 (1H, s, CHO), 8.04 (1H, d, *J* =8.7 Hz, ArH), 7.79 (1H, d, *J* =8.7Hz, ArH) 7.51–7.49 (4H, m, 4 × ArH), 7.38–7.35 (2H, m, 2 × ArH),

7.21–7.19 (1H, m, ArH), 7.08 (1H, dd, *J* = 2.6 Hz, 9.3 Hz, ArH), 6.85 (1H, d, *J* =8.7 Hz, ArH), 3.93 (3H, s, OCH_3); ^{13}C nmr δ/ppm 55.4 (OCH_3), 106.3 (CH), 119.3 (CH), 120.3 (C), 122.8 (CH), 127.0 (CH), 127.4 (CH), 128.1 (2 × CH) 129.3 (CH), 129.5 (CH), 130.8 (2 × CH), 135.2 (C), 137.9 (C), 146.7 (C), 159.9 (C), 192.5 (CHO) MS (EI) *m/z* (%) 263 (M+1, 33), 262 (M^+, 40), 218 (100), 130 (61), 99 (11), 68 (82); HRMS calculated for $C_{18}H_{14}O_2$ M^+ 262.0993, found 262.0991.

6.7.2.4 6-Methoxy-1-(*o*-tolyl)-2-naphthaldehyde (120):

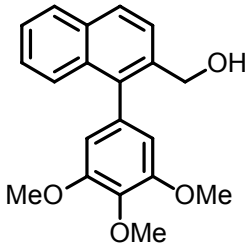


1-Bromo-6-methoxy-2-naphthaldehyde **108** (0.30 g, 1.13 mmol) and *ortho*-tolylboronic **71** (0.22 g, 1.69 mmol) were coupled in the same manner as described above to give the desired product **120**, light-yellow oil (0.22 g, 71% yield).

IR ν_{max} (cm^{-1}) 3018 (s, C-H stretch), 1674 (s, C=O stretch), 1618 (s, C=C stretch), 1245 (s, C–O stretch); ^1H nmr δ/ppm 9.74 (1H, s, CHO), 8.04 (1H, d, *J* =8.6 Hz, ArH), 7.80 (1H, d, *J* =8.7 Hz, ArH), 7.44–7.29 (4H, m, 4 × ArH), 7.25-7.21 (2H, m, 2 × ArH), 7.07 (1H, dd, *J* = 2.5 Hz, 9.2 Hz, ArH), 3.94 (3H, s, OCH_3), 1.96 (3H, s, $ArCH_3$); ^{13}C nmr δ/ppm 19.9 (Ar*C*H_3), 55.4 (OCH_3), 106.4 (CH), 119.4 (CH), 122.8 (CH), 125.6 (CH), 126.9 (CH), 128.5 (CH), 128.9 (CH) 129.3 (C), 130.0 (CH), 130.7 (CH), 130.9 (C), 134.9 (C), 137.2 (C), 138.0 (C), 146.3 (C), 160.0 (C), 192.3 (CHO); MS (EI) *m/z* (%) 277 (M+1, 21), 276 (M^+, 100), 261 (32), 245 (16), 215 (22), 202 (24); HRMS calculated for $C_{19}H_{16}O_2$ M^+ 276.1150, found 276.1156.

6.8 The synthesis of arylnaphthalene alcohols.

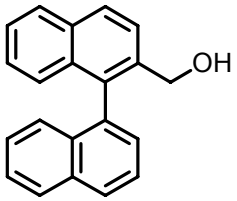
6.8.1 [1-(3,4,5-Trimethoxyphenyl)naphthalen-2-yl]methanol (**113**):



To a solution of naphthaldehyde **109** (0.17 g, 0.527 mmol) in ethanol (5 ml) was added $NaBH_4$ (0.03 g, 0.659 mmol). The reaction mixture was stirred at room temperature for 5 min after which time it turned cream white. The mixture was quenched with water (5 ml) before being extracted with CH_2Cl_2 (3 × 15 ml). The organic extracts were combined, dried ($MgSO_4$), and then filtered through a celite plug and concentrated *in vacuo*. The subsequent colourless oil was purified by column chromatography using 30% ethyl acetate/hexane as eluent to afford **113** as light-yellow crystalline solid (0.14 g, 82%). R_f = 0.16 (30% EtOAc/hexane).

mp = 89–91 °C; IR ν_{max} (cm^{-1}) 3488 (s, broad, OH stretch), 2939 (s, C–H stretch), 1582 (s, C=C stretch), 1000 (s, C–O stretch); ^{1}H nmr δ/ppm 7.90-7.85 (2H, m, 2 × ArH), 7.68 (1H, d, *J* = 8.5 Hz, ArH), 7.53 (1H, d, *J* = 8.3 Hz, ArH), 7.48-7.36 (2H, m, 2 × ArH), 6.53 (2H, s, 2 × ArH), 4.61 (2H, s, CH_2OH), 3.95 (3H, s, OCH_3), 3.81 (6H, s, 2 × OCH_3); ^{13}C nmr δ/ppm 56.0 (2 × OCH_3), 60.9 (OCH_3), 63.3 (CH_2OH), 107.2 (2 × CH), 125.7 (2 × CH), 126.0 (CH), 126.5 (CH), 127.7 (CH), 127.9 (CH), 132.5 (C), 132.8 (C), 133.6 (C), 135.5 (C), 137.1 (C), 137.8 (C), 153.1 (2 × C); MS (EI) *m/z* (%) 325 (M+1, 10), 324 (M^+, 47), 87 (19), 57 (100), 46 (69), 42 (34), 41 (35); HRMS calculated for $C_{20}H_{20}O_4$ M^+ 324.1361, found 324.1351.

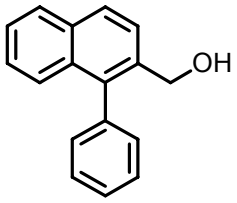
6.8.2 [1-(1-Naphthyl)naphthalen-2-yl]methanol (**114**):



In the same manner as outlined above, naphthylnaphthaldehyde **110** (0.30 g, 1.06 mmol) was converted into a biaryl alcohol **114**, a brown solid (0.28 g, 93%) using sodium borohydride (0.05 g, 1.32 mmol). R_f = 0.62 (30% EtOAc/ hexane).

mp = 116-118 °C; IR ν_{max} (cm^{-1}) 3386 (s, broad, OH stretch), 3011 (m, C–H stretch), 1592, 1568 (m, C=C stretch), 1258 (s, C–O stretch); ^{1}H nmr δ/ppm 7.89–8.01 (4H, m, 4 × ArH), 7.79 (1H, d, *J* = 8.5Hz, ArH), 7.59 (1H, t, *J* = 8.1Hz, ArH), 7.38–7.48 (3H, m, 3 × ArH), 7.15–7.28 (4H, m, 4 × ArH), 4.41 (2H, s, C*H*$_2$OH); ^{13}C nmr δ/ppm 63.3 (CH_2OH), 125.4 (CH), 125.7 (2 × CH), 125.8 (CH), 126.0 (CH), 126.1 (CH), 126.4 (CH), 126.9 (CH), 127.8 (CH), 127.9 (CH), 128.1 (CH), 128.3 (2 × CH), 132.7 (C), 132.8 (C), 133.0 (C), 133.6 (C), 135.5 (C), 135.7 (C), 136.7 (C); MS (EI) *m/z* (%):284 (M^+, 30), 252 (23), 128 (100), 82 (99), 75 (20), 46 (20); HRMS calculated for $C_{21}H_{16}O$ M^+ 284.1201, found 284.1201.

6.8.3 (1-Phenylnaphthalen-2-yl)methanol (**115**):

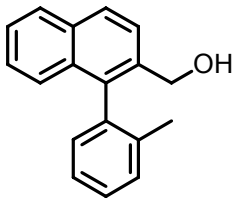


Using sodium borohydride (0.05 g, 1.23 mmol) in the manner as outlined above, phenylnaphthyldehyde **111** (0.23 g, 0.990 mmol) was converted into an alcohol **115**, a yellow sticky oil (0.21 g, 91% yield). R_f = 0.74 (30% EtOAc/Hexane).

IR ν_{max} (cm^{-1}) 3420 (m, broad, OH stretch), 3018 (s, C–H stretch), 1215 (s, C–O stretch); ^{1}H nmr δ/ppm 7.84 (2H, t, *J* = 8.4 Hz, 2 × ArH), 7.64 (1H, d, *J* = 8.5 Hz, ArH), 7.40–7.45 (5H, m, 5 × ArH), 7.32–7.35 (3H, m, 3 × ArH), 4.51 (2H, s, C*H*$_2$OH); ^{13}C nmr δ/ppm) 63.3 (CH_2OH), 125.6 (CH), 125.7 (CH), 125.9 (CH), 126.5 (CH), 127.4 (CH), 127.7

(CH), 127.9 (CH), 128.3 (2 × CH), 130.0 (2 × CH), 132.6 (C), 132.8 (C), 135.5 (C), 137.8 (C), 138.1 (C); MS (EI) *m/z* (%) 234 (M^+, 96), 218 (100), 215 (34), 202 (30), 30 (33), 68 (74); HRMS calculated for $C_{17}H_{14}O$ M^+ 234.1045, found 234.1046.

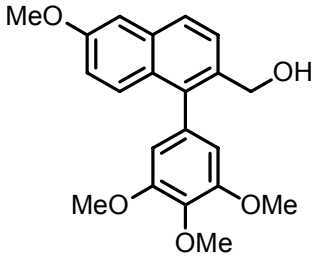
6.8.4 [1-(*o*-Tolyl)naphthalen-2-yl]methanol (**116**):



Desired product **116**, thick yellow oil (0.19 g, 95% yield) was synthesized from naphthaldehyde **112** (0.20 g, 0.812 mmol) using sodium borohydride (0.04 g, 1.01 mmol) in the way as described above.

IR ν_{max} (cm^{-1}) 3408 (s, broad, OH stretch), 3016 (s, C–H stretch), 1596 (s, C=C stretch), 1209 (s, C–O stretch); ^{1}H nmr δ/ppm 7.88 (2H, t, *J* = 7.8 Hz, 2 × ArH), 7.70 (1H, d, *J* = 8.5 Hz, ArH), 7.45 (1H, d, *J* = 7.4 Hz, ArH), 7.24–7.35 (5H, m, 5 × ArH), 7.14 (1H, d, *J* = 7.3 Hz, ArH), 4.48 (2H, s, C*H*$_2$OH), 1.91 (3H, s, ArCH_3); ^{13}C nmr δ/ppm 19.7 (Ar*C*H_3), 63.4 (CH_2OH), 125.7 (2 × CH), 125.9 (CH), 126.0 (CH), 126.1 (CH), 127.88 (2 × CH), 127.94 (CH), 130.0 (CH), 130.1 (CH), 132.2 (C), 132.9 (C), 135.4 (C), 136.9 (C), 137.1 (C), 137.6 (C); MS (EI) *m/z* (%) 248 (M^+, 60), 230 (100), 218 (20), 215 (69), 202 (34), 82 (19); HRMS calculated for $C_{18}H_{16}O$ M^+ 248.1201, found 248.1248.

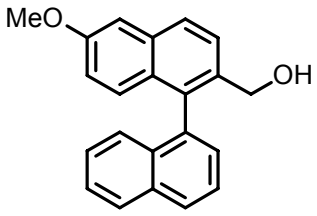
6.8.5 [6-Methoxy-1-(3,4,5-trimethoxyphenyl)naphthalen-2-yl]methanol (**121**):



Using the same procedure as described above, naphthaldehyde **117** (0.18 g, 0.511 mmol) in ethanol (5 ml) was converted into alcohol **121,** white flakes (0.16 g, 89% yield) using sodium borohydride (0.02 g, 0.638 mmol).

mp = 163-164 °C; IR ν_{max} (cm^{-1}) 2964 (s, C-H stretch), 1690 (s, C=O stretch), 1623 (s, C=C stretch), 1113 (s, C–O stretch); ^{1}H nmr δ/ppm 7.79 (1H, d, *J* = 8.5Hz, ArH), 7.63 (1H, d, *J* = 8.5Hz, ArH), 7.44 (1H, d, *J* = 9.2Hz, ArH), 7.17 (1H, d, *J* = 2.5Hz, ArH), 7.08-7.04 (1H, dd, *J* = 9.2Hz, 2.6Hz, ArH), 6.52 (2H, s, 2 × ArH), 4.58 (2H, s, Ar*C*H_2OH), 3.95 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 3.82 (6H, s, 2 × OCH_3); ^{13}C nmr δ/ppm 55.3 (OCH_3), 56.1 (2 × OCH_3), 60.9 (OCH_3), 63.4 (Ar*C*H_2OH), 105.7 (CH), 107.1 (2 × CH), 118.7 (CH), 126.5 (CH), 126.8 (CH), 128.0 (C), 128.2 (CH), 133.3 (C), 133.7 (C), 134.1 (C), 137.1 (C), 138.0 (C), 153.1 (2 × C), 157.5 (C); MS (EI) *m/z* (%) 354 (M^+, 42), 304 (100), 264 (23), 213 (35), 175 (21), 152 (11); HRMS calculated for $C_{21}H_{22}O5$ M^+ 354.1467, found 354.1448.

6.8.6 [6-Methoxy-1-(1-naphthyl)naphthalen-2-yl]methanol (**122**):

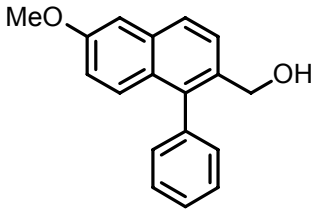


Sodium borohydride (0.03 g, 0.880 mmol) was used as explained above to convert methoxynaphthaldehyde **118** (0.22 g, 0.704 mmol) in ethanol (8 ml) into alcohol **122**, a light-brown solid (0.21 g, 95% yield).

mp = 142-143 °C; IR ν_{max} (cm^{-1}) 3366 (s, broad, OH stretch), 3015 (m, C–H stretch), 1579 (m, C=C stretch), 1129 (s, C–O stretch); ^{1}H nmr δ/ppm 7.94 (2H, t, *J* = 6.6 Hz, 2 ×

ArH), 7.87 (1H, d, *J* = 8.5 Hz, ArH), 7.73 (1H, d, *J* = 8.5 Hz, ArH), 7.58 (1H, t, *J* = 7.6 Hz, ArH), 7.46 (1H, t, *J* = 6.8 Hz, ArH), 7.39 (1H, d, *J* = 7.0 Hz, ArH), 7.18–7.28 (3H, m, 3 × ArH), 7.07 (1H, d, *J* = 9.2 Hz, ArH), 6.88–6.92 (1H, dd, *J* = 2.5 Hz, 9.2 Hz, ArH), 4.37 (2H, s, C*H*$_2$OH), 3.91 (3H, s, OCH_3); ^{13}C nmr δ/ppm 55.3 (OCH_3), 63.4 (CH_2OH), 105.8 (CH), 118.7 (CH), 125.4 (CH) 125.8 (CH), 126.0 (CH), 126.4 (CH), 126.6 (CH), 127.1 (CH), 127.8 (CH), 128.0 (CH), 128.2 (CH), 128.3 (CH), 128.5 (C), 132.8 (C), 133.6 (C), 134.2 (C), 134.6 (C), 135.8 (C), 135.9 (C), 157.5 (C); MS (EI) *m/z* (%) 315 (M+1, 24), 314 (M^+, 100), 252 (16), 239 (17), 218 (39), 130 (14), 68 (28); HRMS calculated for $C_{22}H_{18}O_2$ M^+ 314.1306, found 314.1352.

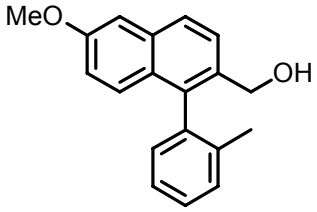
6.8.7 (6-Methoxy-1-phenylnaphthalen-2-yl)methanol (**123**):



Methoxyphenylnaphthaldehyde **119** (0.18 g, 0.686 mmol) in ethanol (5 ml) was converted into alcohol **123**, a thick yellow oil (0.18 g, 100% yield) using sodium borohydride (0.03 g, 0.858 mmol) in the same manner as outlined above.

IR ν_{max} (cm^{-1}) 3385 (s, broad, OH stretch), 3013 (s, C–H stretch), 1575 (s, C=C stretch), 1115 (s, C–O stretch); ^{1}H nmr δ/ppm 7.70 (1H, d, *J* = 8.4 Hz, ArH), 7.55 (1H, d, *J* = 8.5 Hz, ArH), 7.36–7.46 (4H, m, 4 × ArH), 7.09–7.24 (3H, m, 3 × ArH), 6.94 (1H, d, *J* = 9.2 Hz, ArH),4.44 (2H, s, C*H*$_2$OH), 3.84 (3H, s, OCH_3); ^{13}C nmr δ/ppm 55.3 (OCH_3), 63.4 (CH_2OH), 105.8 (CH), 118.6 (CH), 126.6 (CH), 126.8 (CH), 127.4 (CH), 128.2 (CH), 128.3 (2 × CH), 130.1 (2 × CH), 130.9 (C), 133.4 (C), 134.2 (C), 138.1 (C), 138.2 (C), 157.5 (C); MS (EI) *m/z* (%) 264 (M^+, 100), 235 (26), 202 (24), 159 (12), 94 (32), 82 (85); HRMS calculated for $C_{18}H_{16}O_2$ M^+ 264.1150, found 264.1146.

6.8.8 [6-Methoxy-1-(*o*-tolyl)naphthalen-2-yl]methanol **(124):**

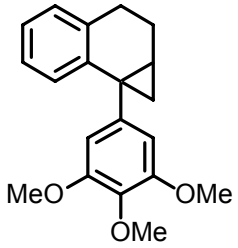


In the same way as described above, sodium borohydride (0.02 g, 0.678 mmol) was used to convert naphthaldehyde **120** (0.15 g, 0.543 mmol) in ethanol (5 ml) into alcohol **124**, a light-yellow oil (0.14 g, 93% yield).

IR ν_{max} (cm^{-1}) 3405 (s, broad, OH stretch), 3014 (s, C–H stretch), 1601 (s, C=C stretch), 1034 (s, C–O stretch); ^{1}H nmr δ/ppm 7.78 (1H, d, *J* = 8.4 Hz, ArH), 7.64 (1H, d, *J* = 8.5 Hz, ArH), 7.24–7.36 (3H, m, 3 × ArH), 7.12–7.18 (3H, m, 3 × ArH), 6.98-7.02 (1H, dd, *J* = 2.6 Hz, 9.2 Hz, ArH), 4.45 (2H, s, C*H*$_2$OH), 3.91 (3H, s, OCH_3), 1.91 (3H, s, $ArCH_3$); ^{13}C nmr δ/ppm 19.7 ($ArCH_3$), 55.3 (OCH_3), 63.3 (CH_2OH), 105.9 (CH), 118.7 (CH), 125.8 (CH), 126.5 (CH), 126.7 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 129.9 (CH), 130.0 (CH), 133.2 (C), 134.2 (C), 136.9 (C), 137.2 (C), 137.7 (C), 157.5 (C); MS (EI) *m/z* (%) 278 (M^+, 19), 260 (14), 129 (15), 108 (43), 84 (63), 82 (100), 46 (20); HRMS calculated for $C_{19}H_{18}O_2$ M^+ 278.1306, found 278.1297.

6.9 The synthesis of tetrahydrocyclopropa[a]naphthalene.

6.9.1 7b-(3,4,5-Trimethoxyphenyl)-1a,2,3,7b-tetrahydro-1*H*-cyclopropa-[*a*]naphthalene (**125**):

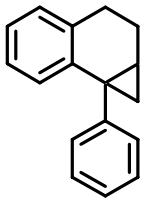


To a solution of dihydronaphthaldehyde **72** (2.49 g, 7.68 mmol) in THF (50 ml) at 0 °C was added $LiAlH_4$ (0.87 g, 23.1 mmol) portion-wise. The resultant mixture was allowed

to warm to room temperature and stirred for 52 h. Thereafter it was cooled to 0 °C and water (0.8 ml) was poured into the mixture before 10% NaOH (3 × 0.87 ml) was introduced. The mixture was allowed to settle before being filtered using celite/silica gel plug and washed with dichloromethane. Excess solvent was removed under reduced pressure and the resultant oil was purified using column chromatography with 30% ethyl acetate/hexane as eluent to give substituted tetrahydronaphthalene **125** as white crystalline solid (1.06 g, 44%). R_f = 0.68 (30% EtOAc/hexane).

mp = 114-115 °C; IR ($CHCl_3$ solution) ν_{max} (cm^{-1}) 3100 (m, C-H stretch), 1588 (m, C=C stretch), 1129 (s, C-O stretch); ^{1}H nmr δ/ppm 7.01-7.06 (3H, m, 3 x ArH), 6.80-6.83 (1H, dd, *J* = 6.2 Hz, 2.4 Hz, ArH), 6.59 (2H, s, 2 x ArH), 3.87 (3H, s, OCH_3), 3.83 (6H, s, 2 x OCH_3), 2.54-2.78 (2H, m, CH_2), 2.15-2.22 (1H, m, CH), 1.94-2.05 (1H, m, CH), 1.72-1.77 (1H, m, CH), 1.36-1.40 (1H, m, CH), 1.25 (1H, t, *J* = 5.4 Hz, CH); ^{13}C nmr δ/ppm 15.2 (CH_2), 19.4 (CH), 24.0 (C), 26.3 (CH_2), 28.8 (CH_2), 55.9 (2 x OCH_3), 60.7 (OCH_3), 107.4 (2 x CH), 124.7 (CH), 125.8 (CH), 128.2 (CH), 128.4 (CH), 133.8 (C), 136.5 (C), 140.8 (C), 141.4 (C), 152.9 (2 x C); MS (IE) *m/z* (%) 310(M^+, 50), 279 (100), 264 (5), 248 (17), 203 (4), 181 (6), 151 (14), 142 (7), 128 (3), 115 (3), 91 (3). HRMS calculated for $C_{20}H_{22}O_3$ M^+ 310.1569, found 310.1579.

6.9.2 7b-Phenyl-1a,2,3,7b-tetrahydro-1*H*-cyclopropa[*a*]naphthalene (**130**):

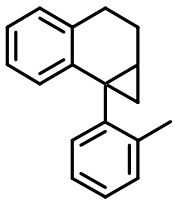


In a similar manner as described above, naphthaldehyde **74** (0.37 g, 1.58 mmol) was converted into cyclopropane **130** a colourless oil (0.15 g, 43%) using $LiAlH_4$ (0.18 g, 4.74 mmol) in THF (20 ml).

^{1}H nmr δ/ppm 7.22-7.38 (5H, m, 5 x ArH), 6.95-7.06 (3H, m, 3 x ArH), 6.73 (1H, d, *J* = 7.2 Hz, ArH), 2.61-2.73 (2H, m, CH_2), 2.14-2.20 (1H, m, CH), 1.99-2.06 (1H, m, CH), 1.68-1.73 (1H, m, CH), 1.40-1.45 (1H, m, CH), 1.23-1.27 (1H, m, CH); ^{13}C nmr δ/ppm

15.0 (CH_2), 19.7 (CH), 23.9 (CH), 28.4 (CH_2), 29.7 (C), 124.7 (CH), 125.8 (CH), 126.4 (CH), 128.3 (2 x CH), 128.4 (2 x CH), 130.6 (2 x CH), 134.1 (C), 141.6 (C), 145.4 (C).

6.9.3 7b-(*o*-Tolyl)-1a,2,3,7b-tetrahydro-1*H*-cyclopropa[*a*]naphthalene (**131**):



Similarly cyclopropane **131**, light yellow oil (0.20 g, 53%) was synthesized from 1-*o*-tolyl-3,4-dihydro-2-naphthaldehyde **75** (0.40 g, 1.61 mmol) and $LiAlH_4$ (0.19 g, 4.83 mmol) in THF (20 ml).

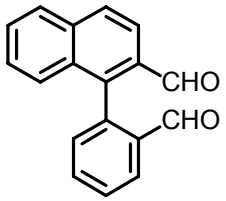
mp=41-42°C; ^{1}H nmr δ/ppm 7.40 (1H, d, *J* = 6.3 Hz, ArH), 7.21-7.17 (3H, m, 3 x ArH), 7.01-7.03 (2H, m, ArH), 6.91-6.99 (1H, m, ArH), 6.61 (1H, d, *J* = 8 Hz, ArH), 2.64-2.72 (2H, m, CH_2), 2.20-2.27 (1H, m, CH), 2.05 (3H, s, CH_3), 1.58 (1H, s, CH), 1.43-1.49 (1H, m, CH), 1.32 (1H, t, *J* = 5.4 Hz, CH); ^{13}C nmr δ/ppm 15.4 (CH_3), 18.9 (CH_2), 20.0 (CH), 23.8 (CH_2), 26.3 (CH_2), 27.7 (C), 124.7 (CH), 125.7 (CH), 125.9 (CH), 126.7 (CH), 127.2 (CH), 128.6 (CH), 130.4 (CH), 131.3 (CH), 133.4 (C), 139.0 (C), 140.8 (C), 142.9 (C).

Chapter 7: Experimental Procedures To Part Two

7.1 Syntheses of arylnaphthaldehydes using Suzuki coupling reaction

7.1.1 Suzuki coupling reactions using 1-bromo-2-naphthaldehyde (**106**)

7.1.1.1 1-(2-Formylphenyl)-2-naphthaldehyde (225):

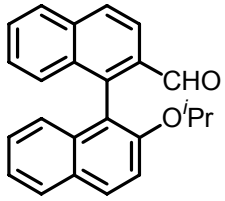


To $[Pd(PPh_3)_4]$ (0.52 g, 0.440 mmol) was added deoxygenated solutions of 1-bromo-2-naphthaldehyde **106** (1.00 g, 4.42 mmol) in DME (15 ml) and 2-formylphenylboronic acid (1.00 g, 6.64 mmol) in ethanol (10 ml). This was followed by a deoxygenated solution of aqueous sodium carbonate (4.06 g, 37.6 mmol in 19 ml water). The resultant mixture was refluxed under nitrogen for 46 h over which time it turned deep red. After allowing to cool to room temperature, the mixture was quenched with water (50 ml) and the organic material extracted with dichloromethane (3 × 100 ml). The resultant organic extracts were combined, dried ($MgSO_4$), filtered through a celite plug and the excess solvent removed using a rotary evaporator. The subsequent oil was purified by column chromatography using 30% ethyl acetate/hexane as eluent to afford dial **225** as a thick brown oil (0.87 g, 76%).

IR ν_{max} (cm^{-1}) 3019 (s, C–H stretch), 1694 (vs, C=O), 1595 (s, C=C stretch); ^{1}H nmr δ/ppm 9.84 (1H, s, CHO), 9.56 (1H, s, CHO), 8.17 (1H, dd, *J* = 1.5 Hz, *J* = 7.6 Hz, ArH), 8.10 (1H, d, *J* = 8.6 Hz, ArH), 8.00 (1H, d, *J* = 8.7 Hz, ArH), 7.95 (1H, d, *J* = 8.1 Hz, ArH), 7.78–7.60 (3H, m, 3 × ArH), 7.48–7.41 (2H, m, 2 × ArH), 7.38 (1H, d, *J* = 8.3 Hz, ArH); ^{13}C nmr δ/ppm) 191.2 (CHO), 190.5 (CHO), 141.9 (C), 138.6 (C), 135.7 (C), 135.6 (C), 133.7 (CH), 132.8 (C), 132.2 (CH), 131.9 (C), 129.2 (CH), 129.1 (CH), 129.1 (CH), 128.4 (CH), 128.3 (CH), 127.5 (CH), 127.1 (CH), 122.2 (CH); MS (EI) *m/z* (%)

260 (M^+, 25), 232 (28), 231 (100), 200 (11), 101 (9), 43 (3); HRMS calculated for $C_{18}H_{12}O_2$ M^+ 260.0837, found 260.0844.

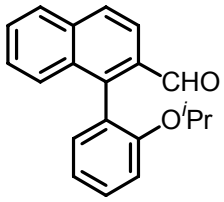
7.1.1.2 1-(2-Isopropoxynaphthyl)-2-naphthaldehyde (234):



Similarly 1-bromo-2-naphthaldehyde **106** (1.00 g, 4.25 mmol) in DME (15 ml) was stirred together with 2-isopropoxynaphthylboronic acid (1.28 g, 6.38 mmol) in ethanol (7 ml) using [$Pd(PPh_3)_4$] (0.48 g, 0.425 mmol) and sodium carbonate (3.71 g, 36.2 mmol in 16 ml of water) to give naphthaldehyde **234** as a thick brown oil (1.52 g, 79%).

IR ν_{max} (cm^{-1}) 2962 (s, C–H stretch), 1687 (s, C=O), 1594 (s, C=C stretch), 1111 (s, C–O stretch); ^{1}H nmr δ/ppm 9.69 (1H, s, CHO), 8.15 (1H, d, *J* = 8.6 Hz, ArH), 8.01–7.86 (4H, m, 4 × ArH), 7.56 (1H, t, *J* = 7.1 Hz, ArH), 7.42 (1H, d, *J* = 9.0 Hz, ArH), 7.35–7.23 (4H, m, 4 × ArH), 6.96 (1H, d, *J* = 8.3 Hz, ArH), 4.56 [1H, septet, *J* = 5.9 Hz, OC*H*$(CH_3)_2$], 1.06 [3H, d, *J* = 5.9 Hz, OCH(C*H*$_3)_2$], 0.94 [3H, d, *J* = 5.9 Hz, OCH(C*H*$_3)_2$]; ^{13}C nmr δ/ppm) 192.8 (CHO), 153.7 (C), 142.0 (C), 136.2 (C), 134.6 (C), 132.7 (C), 132.1 (C), 130.3 (CH), 128.6 (C), 128.5 (CH), 128.2 (CH), 128.1 (CH), 127.9 (CH), 127.2 (CH), 126.9 (CH), 126.5 (CH), 125.0 (CH), 123.8 (CH), 121.9 (CH), 118.6 (C), 115.6 (CH), 71.0 [O*C*H$(CH_3)_2$], 22.1 [OCH(*C*H$_3)_2$], 21.9 [OCH(*C*H$_3)_2$]; MS (EI) *m/z* (%) 342 (M+2, 16), 341 (M+1, 16), 340 (M^+, 62), 298 (88), 281 (28), 269 (32), 252 (34), 239 (69), 155 (13), 144 (100), 127 (17), 63 (5); HRMS calculated for $C_{24}H_{20}O_2$ M^+ 340.1463, found 340.1463.

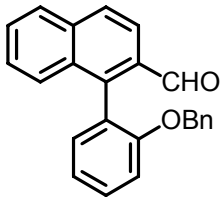
7.1.1.3 1-(2-Isopropoxyphenyl)-2-naphthaldehyde (237):



Bromonaphthaldehyde **106** (1.00 g, 4.25 mmol) in DME (10 ml) was stirred together with 2-isopropoxyphenyl boronic acid (1.15 g, 6.38 mmol) in ethanol (8 ml) using $[Pd(PPh_3)_4]$ (0.49 g, 0.425 mmol) in a similar way as described above to give product **237** as a thick brown oil (1.21 g, 97 % yield).

IR ν_{max} (cm^{-1}) 3019 (vs, C–H stretch), 1676 (s, C=O), 1618 (s, C=C stretch), 1032 (s, C–O stretch); ^{1}H nmr δ/ppm 9.88 (1H, s, CHO), 8.06 (1H, d, *J* = 8.6 Hz, ArH), 7.90 (2H, d, *J* = 8.9 Hz, 2 × ArH), 7.64–7.56 (2H, m, 2 × ArH), 7.49–7.35 (2H, m, 2 × ArH), 7.26–7.23 (2H, m, 2 × ArH), 7.11–7.05 (1H, m, ArH), 4.23 [1H, septet, *J* = 6.0 Hz, OC*H*$(CH_3)_2$], 1.06 [3H, d, *J* = 6.0 Hz, OCH(C*H*$_3)_2$], 0.97 [3H, d, *J* = 6.0 Hz, OCH(C*H*$_3)_2$]; ^{13}C nmr δ/ppm.) 193.2 (CHO), 156.0 (C), 143.6 (C), 136.2 (C), 132.8 (CH), 132.5 (C), 132.0 (C), 131.2 (C), 129.9 (CH), 128.4 (CH), 128.1 (CH), 127.9 (CH), 127.5 (CH), 126.4 (CH), 124.9 (CH), 120.2 (CH), 113.7 (CH), 70.4 [O*C*H$(CH_3)_2$], 21.8 [OCH(*C*H$_3)_2$], 21.7 [OCH(*C*H$_3)_2$]; MS (EI) *m/z* (%) 292 (M+2, 18), 291 (M+1, 15), 290 (M^+, 63), 249 (40), 248 (72), 247 (50), 231 (100), 219 (31), 202 (28), 189 (28), HRMS calculated for $C_{20}H_{18}O_2$ M^+ 290.1307, found 290.1295.

7.1.1.4 1-(2-Benzyloxyphenyl)-2-naphthaldehyde (240):

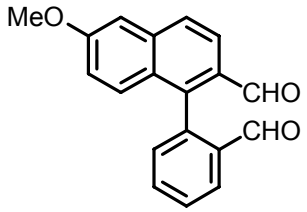


Using the same experimental procedure as described above bromonaphthaldehyde **106** (1.50 g, 6.81 mmol) in DME (15 ml) was stirred together to 2-benzyloxyphenyl boronic acid (2.17 g, 9.57 mmol) in ethanol (10 ml) using $[Pd(PPh_3)_4]$ (0.74 g, 0.681 mmol) to attain the desired naphthaldehyde **240** as a thick brown oil (2.04 g, 94% yield).

IR ν_{max} (cm^{-1}) 3019 (vs, C–H stretch), 1675 (s, C=O), 1618 (s, C=C stretch), 1023 (s, C–O stretch); ^{1}H nmr δ/ppm 9.90 (1H, s, CHO), 8.07 (1H, d, *J* = 8.6 Hz, ArH), 7.93–7.89 (2H, m, 2 × ArH), 7.63–7.56 (2H, m, 2 × ArH), 7.47–7.39 (3H, m, 3 × ArH), 7.28–7.25 (2H, m, 2 × ArH), 7.15–7.08 (5H, m, 5 × ArH), 6.93–6.93 (2H, m, 2 × ArH), 4.96 (2H, s, OCH_2); ^{13}C nmr δ/ppm 192.3 (CHO), 156.5 (C), 144.3 (C), 136.6 (C), 136.2 (C), 132.6 (CH), 132.5 (C), 131.3 (C), 130.0 (CH), 128.5 (CH), 128.2 (2 × CH), 128.1 (CH), 127.6 (CH), 127.4 (CH), 126.6 (2 × CH), 124.5 (C), 121.9 (CH), 120.8 (CH), 112.8 (CH), 70.0 (OCH_2); MS (EI) *m/z* (%) 338 (M^+, 5), 276 (3), 231 (8), 200 (4), 184 (4), 91 (100), 65 (12), HRMS calculated for $C_{24}H_{18}O_2$ M^+ 338.1307, found 338.1298.

7.1.2 Suzuki coupling reactions using 1-bromo-6-methoxy-2-naphthaldehyde (**107**)

7.1.2.1 1-(2-Formylphenyl)-6-methoxy-2-naphthaldehyde (226):

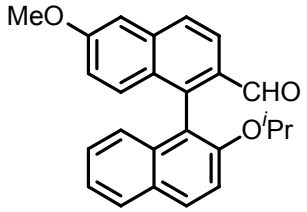


In a similar way as described above 1-bromo-6-methoxy-2-naphthaldehyde **107** (2.06 g, 7.77 mmol) in DME (20 ml) was stirred together with 2-formylphenylboronic (1.75 g, 11.6 mmol) ethanol (10 ml) using $[Pd(PPh_3)_4]$ (0.90 g, 0.777 mmol) to give naphthaldehyde **226** as brown oil (1.58 g, 70%).

IR ν_{max} (cm^{-1}) 1959 (s, C–H stretch), 1677 (s, C=O stretch), 1601 (s, C=C stretch), 1169 (s, C–O stretch); ^{1}H nmr δ/ppm 9.76 (1H, s, CHO), 9.56 (1H, s, CHO), 8.15 (1H, d, *J* = 7.5 Hz, ArH), 8.07 (1H, d, *J* = 8.7 Hz, ArH), 7.88 (1H, d, *J* = 8.6 Hz, ArH), 7.75–7.68 (2H, m, 2 × ArH), 7.42 (1H, d, *J* = 6.9 Hz, ArH), 7.26–7.24 (2H, m, 2 × ArH), 7.09 (1H, dd, *J* = 2.6 Hz, *J* = 9.2 Hz, ArH), 3.95 (3H, s, OCH_3); ^{13}C nmr δ/ppm 190.9 (CHO), 190.5 (CHO), 160.1 (C), 141.8 (C), 138.9 (C), 137.7 (C), 135.6 (C), 133.6 (CH), 132.1 (CH), 130.4 (C), 129.2 (CH), 128.7 (CH), 128.1 (CH), 127.9 (C), 127.9 (CH), 123.0 (CH), 120.2 (CH), 106.6 (CH), 55.5 (OCH_3); MS (EI) *m/z* (%) 290 (M^+, 45), 262 (22), 261

(100), 218 (19), 189 (25), 85 (15), 71 (20), 57 (43), 43 (38), HRMS calculated for $C_{19}H_{14}O_3$ M^+ 290.0943, found 290.0940.

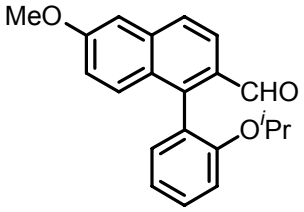
7.1.2.2 1-(2-Isopropoxynaphthyl)-6-methoxy-2-naphthaldehyde (235):



Suzuki coupling of bromomethoxynaphthaldehyde **107** (1.00 g, 3.77 mmol) in DME (10 ml) with 2-isopropoxynaphthylboronic acid (1.30 g, 5.66 mmol) in ethanol (7 ml) using $[Pd(PPh_3)_4]$ (0.59 g, 0.377 mmol) gave naphthaldehyde **235** (1.22 g, 87% yield) as a thick brown oil using the same methodological procedure as outlined above.

IR ν_{max} (cm^{-1}) 3019 (s, C–H stretch), 1694 (vs, C=O), 1595 (s, C=C stretch); ^{1}H nmr δ/ppm 9.62 (1H, s, CHO), 8.12 (1H, d, *J* = 8.6 Hz, ArH), 7.99 (1H, d, *J* = 9.0 Hz, ArH), 7.87 (2H, d, *J* = 9.0 Hz, 2 × ArH), 7.40 (1H, d, *J* = 9.0 Hz, ArH), 7.35–7.30 (1H, m, ArH), 7.25–7.21 (3H, m, 3 × ArH), 6.98–6.92 (2H, m, 2 × ArH), 4.55 [1H, septet, *J* = 6.0 Hz, OC*H*$(CH_3)_2$], 3.93 (3H, s, OCH_3), 1.06 [3H, d, *J* = 6.0 Hz, OCH(C*H*$_3)_2$], 0.96 [3H, d, *J* = 6.0 Hz, OCH(C*H*$_3)_2$]; ^{13}C nmr δ/ppm 192.8 (CHO), 159.8 (C), 153.8 (C), 142.2 (C), 138.1 (C), 134.7 (C), 130.5 (C), 130.3 (CH), 129.1 (CH), 128.7 (C), 127.9 (C), 127.9 (CH), 127.0 (CH), 126.9 (CH), 125.2 (CH), 123.9 (CH), 122.9 (CH), 119.2 (CH), 118.9 (C), 115.8 (CH), 106.3 (CH), 71.3 [O*C*H$(CH_3)_2$], 55.4 (OCH_3), 22.1 [OCH(*C*H$_3)_2$], 21.9 [OCH(*C*H$_3)_2$]; MS (EI) *m/z* (%) 371 (M+1, 17), 370 (M^+, 64), 328 (100), 311 (32), 268 (17), 255 (29), 239 (39), 226 (48), 185 (10), HRMS calculated for $C_{25}H_{22}O_3$ M^+ 370.1569, found 370.1574.

7.1.2.3 1-(2-Isopropoxyphenyl)-6-methoxy-2-naphthaldehyde (238):

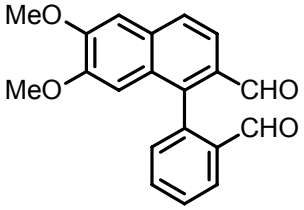


Bromomethoxynaphthaldehyde **106** (1.35 g, 5.09 mmol) in DME (10 ml) was mixed with 2-isopropoxyphenylboronic acid (1.74 g, 7.64 mmol) in ethanol (7 ml) using $[Pd(PPh_3)_4]$ (0.59 g, 0.509 mmol) to give product **238** as brown oil (1.42 g, 74% yield).

IR ν_{max} (cm^{-1}) 2978 (s, C–H stretch), 1688 (vs, C=O), 1596 (s, C=C stretch), 1046 (s, C–O stretch); ^{1}H nmr δ/ppm 9.81 (1H, s, CHO), 8.03 (1H, d, *J* = 8.6 Hz, ArH), 7.78 (1H, d, *J* = 8.6 Hz, ArH), 7.52 (1H, d, *J* = 9.2 Hz, ArH), 7.44 (1H, t, *J* = 7.8 Hz, ArH), 7.24–7.18 (2H, m, 2 × ArH), 7.09–7.04 (3H, m, 3 × ArH), 4.41 [1H, septet, *J* = 6.0 Hz, OC*H*$(CH_3)_2$], 3.97 (3H, s, OCH_3), 1.06 (3H, d, *J* = 6.0 Hz, [OCH(C*H*$_3)_2$], 0.99 (3H, d, *J* = 6.0 Hz, [OCH(C*H*$_3)_2$]; ^{13}C nmr δ/ppm 193.4 (CHO), 160.1 (C), 156.4 (C), 144.1 (C), 138.5 (C), 133.2 (CH), 129.8 (CH), 129.5 (C), 129.3 (CH), 127.6 (C), 126.7 (CH), 125.0 (C), 122.7 (CH), 120.2 (CH), 118.9 (CH), 114.2 (CH), 106.7 (CH), 70.8 [O*C*H$(CH_3)_2$], 55.8 (OCH_3), 22.2 [OCH(*C*H$_3)_2$], 22.1 [OCH(*C*H$_3)_2$]; MS (EI) *m/z* (%) 320 (M^+, 1), 263 (21), 218 (100), 130 (31), 99 (9), 68 (61), HRMS calculated for $C_{21}H_{20}O_3$ M^+ 320.1412, found 320.1399.

7.1.3 Suzuki coupling reactions using 1-bromo-6,7-dimethoxy-2-naphthaldehyde **(108)**

7.1.3.1 6,7-Dimethoxy-1-(2-formylphenyl)-2-naphthaldehyde (227):

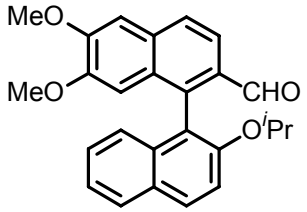


1-Bromo-6,7-dimethoxy-2-naphthaldehyde **108** (1.00 g, 3.39 mmol) in DME (10 ml) was mixed with 2-formylphenylboronic acid (0.76 g, 5.08 mmol) in ethanol (5 ml) using

$[Pd(PPh_3)_4]$ (0.39 g, 0.339 mmol) to give dial **227** as a thick brown oil (0.86 g, 80% yield) using a similar method as described above.

IR ν_{max} (cm^{-1}) 3020 (s, C–H stretch), 1682 (vs, C=O), 1619, 1595 (s, C=C stretch), 1163 (vs, C–H stretch); ^{1}H nmr δ/ppm 9.77 (1H, s, CHO), 9.57 (1H, s, CHO), 8.18 (1H, d, *J* = 7.6 Hz, ArH), 7.99 (1H, d, *J* = 8.5 Hz, ArH), 7.86 (1H, d, *J* = 8.6 Hz, ArH), 7.81–7.68 (2H, m, 2 × ArH), 7.45 (1H, d, *J* = 7.4 Hz, ArH), 7.24 (H, s, ArH), 6.56 (1H, s, ArH), 4.05 (3H, s, OCH_3), 3.95 (3H, s, OCH_3); ^{13}C nmr δ/ppm 191.2 (CHO), 190.8 (CHO), 151.9 (C), 150.6 (C), 139.8 (C), 139.4 (C), 135.5 (C), 133.8 (CH), 132.5 (C), 132.1 (CH), 130.9 (C), 129.2 (CH), 128.4 (C), 127.9 (CH), 127.4 (CH), 121.3 (CH), 106.7 (CH), 105.3 (CH), 56.1 (OCH_3), 55.6 (OCH_3); MS (EI) *m/z* (%) 320 (M^+, 33), 291 (54), 216 (53), 206 (30), 178 (10), 150 (19), 86 (10), 84 (65), 82 (100), HRMS calculated for $C_{20}H_{16}O_4$ M^+ 320.1049, found 320.1043.

7.1.3.2 6,7-Dimethoxy-1-(2-isopropoxynaphthyl)-2-naphthaldehyde (236):

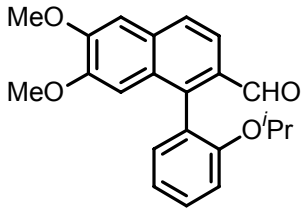


Suzuki coupling of bromodimethoxynaphthaldehyde **108** (1.00 g, 3.65 mmol) in DME (10 ml) with 2-isopropoxyphenyl boronic acid (1.07 g, 5.05 mmol) in (7 ml) using $[Pd(PPh_3)_4]$ (0.36 g, 0.365 mmol) gave naphthaldehyde **236** as yellow flakes (0.81 g, 60% yield).

mp = 64-67 °C; IR ν_{max} (cm^{-1}) 3020 (s, C–H stretch), 1679 (vs, C=O), 1621, 1594 (s, C=C stretch), 1033 (s, C–H stretch); ^{1}H nmr δ/ppm 9.61 (1H, s, CHO), 8.04 (1H, d, *J* = 8.5 Hz, ArH), 7.99 (1H, d, *J* = 9.1 Hz, ArH), 7.85 (2H, d, *J* = 7.9 Hz, 2 × ArH), 7.42 (1H, d, *J* = 9.1 Hz, ArH), 7.35–7.30 (1H, m, ArH), 7.33 (1H, t, *J* = 7.4 Hz, ArH), 7.24–7.20 (2H, m, 2 × ArH), 7.00 (1H, d, *J* = 8.4 Hz, ArH), 6.58 (1H, s, ArH), 4.53 [1H, septet, *J* = 6.0 Hz, OC*H*$(CH_3)_2$], 4.04 (3H, s, OCH_3), 3.47 (3H, s, OCH_3), 1.07 (3H, d, *J* = 6.0 Hz, [OCH(C*H*$_3)_2$], 0.99 (3H, d, *J* = 6.0 Hz, [OCH(C*H*$_3)_2$]; ^{13}C nmr δ/ppm 192.3 (CHO), 153.7 (C), 151.5 (C), 149.7 (C), 140.0 (C), 134.5 (CH), 132.8 (CH), 130.9 (CH), 130.3

(C), 130.2 (C), 128.7 (CH), 128.3 (CH), 127.9 (C), 127.8 (C), 126.9 (CH), 125.2 (CH), 123.9 (C), 121.0 (CH), 119.2 (CH), 115.8 (C), 106.6 (CH), 105.9 (CH), 55.9 [O*C*H$(CH_3)_2$], 55.5 (OCH_3), 55.4 (OCH_3), 22.3 [OCH(CH$_3)_2$], 22.2 [OCH(CH$_3)_2$]; MS (EI) *m/z* (%) 401 (M+1, 17), 400 (M^+, 62), 359 (25), 358 (100), 298 (14), 293 (22), 271 (13), 239 (16), 226 (21), 213 (20), HRMS calculated for $C_{26}H_{24}O_4$ M^+ 400.1675, found 400.1681.

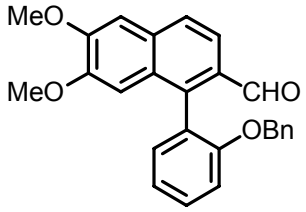
7.1.3.3 6,7-Dimethoxy-1-(2-isopropoxyphenyl)-2-naphthaldehyde (239):



Similarly bromodimethoxynaphthaldehyde **108** (0.50 g, 1.69 mmol) in DME (10 ml) was reacted with 2-isopropoxynaphthylboronic acid (0.46 g, 2.54 mmol) in ethanol (7 ml) using [$Pd(PPh_3)_4$] (0.20 g, 0.169 mmol) to give product **239** as a thick brown oil (0.47 g, 80% yield).

IR ν_{max} (cm^{-1}) 3020 (s, C–H stretch), 1678 (vs, C=O), 1598 (s, C=C stretch), 1109 (s, C–O stretch); ^{1}H nmr δ/ppm 9.81 (1H, s, CHO), 7.94 (1H, d, J = 8.5 Hz, ArH), 7.75 (1H, d, J = 8.5 Hz, ArH), 7.45 (1H, td, J = 7.8 Hz, J = 1.5 Hz, ArH), 7.26–7.24 (1H, m, ArH), 7.18 (1H, s, ArH), 7.08 (2H, t, J = 7.8 Hz, 2 × ArH), 6.87 (1H, s, ArH), 4.42 [1H, septet, J = 6.0 Hz, O*C*H$(CH_3)_2$], 4.04 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 1.07 [3H, d, J = 6.0 Hz, OCH(C$H_3)_2$], 1.01 [3H, d, J = 6.0 Hz, OCH(C$H_3)_2$]; ^{13}C nmr δ/ppm 193.2 (CHO), 155.9 (C), 151.4 (C), 149.6 (C), 142.0 (C), 136.8 (C), 132.8 (C), 132.6 (CH), 130.0 (C), 129.8 (CH), 128.0 (C), 126.2 (CH), 125.3 (C), 120.8 (CH), 120.3 (CH), 113.8 (CH), 106.5 (CH), 106.0 (CH), 69.9 [O*C*H$(CH_3)_2$], 55.9 (OCH_3), 55.6 (OCH_3), 21.8 [OCH(CH$_3)_2$], 21.7 [OCH(CH$_3)_2$]; MS (EI) *m/z* (%) 351 (M+1, 25), 350 (M^+, 100), 307 (90), 306 (41), 290 (95), 279 (29), 205 (12), 120 (18), 83 (10), HRMS calculated for $C_{22}H_{22}O_4$ M^+ 350.1518, found 350.1506.

7.1.3.4 6,7-Dimethoxy-1-(2-benzyloxyphenyl)-2-naphthaldehyde (241):

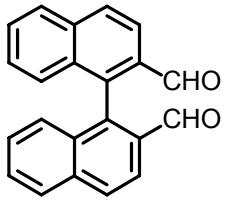


In a similar manner as described above bromodimethoxynaphthaldehyde **108** (1.00 g, 3.37 mmol) in DME (15 ml) was stirred with to 2-benzyloxyphenylboronic acid (1.16 g, 5.05 mmol) in ethanol (7 ml) using [$Pd(PPh_3)_4$] (0.39 g, 0.337 mmol) to afford naphthaldehyde **241** as a thick light yellow oil (1.30 g, 97% yield).

IR ν_{max} (cm^{-1}) 3015 (vs, C–H stretch), 1677 (s, C=O), 1509 (s, C=C stretch), 1215 (s, C–O stretch); ^{1}H nmr δ/ppm 9.84 (1H, s, CHO), 7.97 (1H, d, *J* = 8.5 Hz, ArH), 7.77 (1H, d, *J* = 8.5 Hz, ArH), 7.43 (1H, dt, *J* = 1.5 Hz, *J* = 7.9 Hz, ArH), 7.28 (1H, dd, *J* = 1.6 Hz, *J* = 7.3 Hz, ArH), 7.19 (1H, s, ArH), 7.18–7.09 (5H, m, 5 × ArH), 6.99–6.97 (2H, m, 2 × ArH), 6.81 (1H, s, ArH), 4.99 (2H, s, OCH_2), 4.04 (3H, s, OCH_3), 3.68 (2H, s, OCH_3); ^{13}C nmr δ/ppm 192.9 (CHO), 156.4 (C), 151.5 (C), 149.7 (C), 141.6 (C), 136.7 (C), 132.8 (C), 132.4 (CH), 130.2 (C), 129.9 (CH), 128.3 (2 × CH), 128.0 (C), 127.6 (CH), 126.6 (2 × CH), 126.5 (CH), 124.9 (C), 120.9 (CH), 112.9 (CH), 106.6 (CH), 105.9 (CH), 69.9 (OCH_2), 56.0 (OCH_3), 55.6 (OCH_3); MS (EI) *m/z* (%) 338 (M^+, 5), 276 (3), 231 (8), 200 (4), 184 (4), 91 (100), 65 (12), HRMS calculated for $C_{24}H_{18}O_2$ M^+ 338.1307, found 338.1298.

7.2 Syntheses of arylnaphthaldehydes using Ullmann coupling reaction

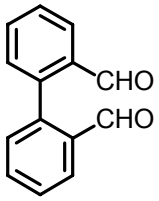
7.2.1 1-(2-Formylnaphthyl)-2-naphthaldehyde **(231):**



To a solution of 1-bromo-2-naphthaldehyde **106** (1.00 g, 4.25 mmol) in DMF (10 ml) was added copper powder (1.10 g, 17.0 mmol) in one portion. The resultant mixture was heated at 180 °C for 12 h. The mixture was then filtered on a celite and a silica gel plug while hot and washed with hot toluene (100 ml). The eluants were washed with 10% HCl (3 × 50 ml) and brine (50 ml) before being dried with magnesium sulphate and filtered on a celite plug. Excess toluene was removed on a rotary evaporatory and the resultant oil was purified with column chromatography using 10% ethyl acetate/hexane as an eluent to obtain dial **231** as brown oil (0.83 g, 63% yield). Edstrom[217] had synthesized the same dinaphthaldehyde using a different experimental procedure.

IR ν_{max} (cm^{-1}) 3019 (s, C–H stretch), 1691 (vs, C=O), 1616, 1595 (s, C=C stretch); ^{1}H nmr δ/ppm 9.63 (1H, s, CHO), 8.21 (1H, d, *J* = 8.6 Hz, ArH), 8.13 (1H, d, *J* = 8.7 Hz, ArH) 8.02 (1H, d, *J* = 8.2 Hz, ArH), 7.63 (1H, t, *J* = 7.5 Hz, ArH), 7.37 (1H, t, *J* = 7.6 Hz, ArH), 7.24 (1H, d, *J* = 8.7 Hz, ArH); ^{13}C nmr δ/ppm 191.0 (CHO), 139.6 (C), 135.9 (C), 133.4 (C), 133.2 (C), 129.7 (CH), 129.4 (CH), 128.5 (CH), 127.9 (CH), 127.2 (CH), 122.3 (CH); MS (EI) *m/z* (%) 310 (M^+, 0.3), 285 (100), 252 (3), 239 (3), 228 (2), 215 (2), 48 (19), HRMS calculated for $C_{22}H_{14}O_2$ M^+ 310.0994, found 310.0995.

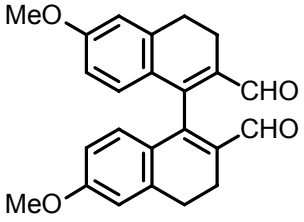
7.2.2 2-(2-Formylphenyl)benzaldehyde **(242):**



Using the same procedure as described above 2-bromobenzaldehyde (2.00 g, 10.8 mmol) in DMF (10 ml) was converted into the brown oil dial **242** (1.45 g, 64% yield), using copper powder (2.81 g, 43.2 mmol) as the reagent. Agranat *et al.*[207] had synthesized the same dinaphthaldehyde using a different experimental procedure.

IR ν_{max} (cm^{-1}) 3020 (s, C–H stretch), 1694 (vs, C=O), 1595 (s, C=C stretch); ^{1}H nmr δ/ppm 9.84 (1H, s, CHO), 8.07 (1H, d, *J* = 7.6 Hz, ArH), 7.70–7.58 (2H, m, 2 × ArH), 7.36 (1H, t, *J* = 7.4 Hz, ArH); ^{13}C nmr δ/ppm 190.9 (CHO), 141.2 (C), 134.5 (C), 133.4 (CH), 131.6 (CH), 128.8 (CH), 128.5 (CH); MS (EI) *m/z* (%) 210 (M^+, 4), 181 (100), 165 (4), 152 (32), 76 (8), 51 (4), HRMS calculated for $C_{14}H_{10}O_2$ M^+ 210.0681, found 210.0664.

7.2.3 1-(2-Formyl-6-methoxy-3,4-dihydronaphthyl)-6-methoxy-3,4-dihydro-2-naphthaldehyde (**243):**



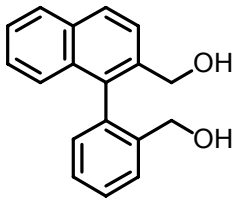
1-Bromo-6-methoxy-3,4-dihydro-2-naphthaldehyde (1.00 g, 3.74 mmol) in DMF (10 ml) was converted into product **243,** a light brown oil (0.83 g, 59% yield) using copper powder (0.97 g, 14.9 mmol) as a reagent.

IR ν_{max} (cm^{-1}) 3017 (s, C–H stretch), 1675 (s, C=O), 1618 (vs, C=C stretch), 1101 (s, C–O stretch); ^{1}H nmr δ/ppm 9.69 (1H, s, CHO), 7.07 (1H, d, *J* = 8.6 Hz, ArH), 6.82 (1H, d, *J* = 2.2 Hz, ArH) 6.61 (1H, dd, *J* = 2.5 Hz, *J* = 8.6 Hz, ArH), 3.81 (3H, s, OCH_3), 2.99–2.93 (2H, m, CH_2), 2.85–2.66 (2H, m, CH_2); ^{13}C nmr δ/ppm 191.5 (CHO), 161.8 (C), 148.5 (C), 140.2 (C), 134.5 (C), 129.1 (CH), 126.8 (C), 114.1 (CH), 112.4 (CH), 55.3

(OCH_3), 27.8 (CH_2), 19.6 (CH_2); MS (EI) *m/z* (%) 374 (M^+, 2), 346 (27), 345 (100), 202 (10), 148 (12), 115 (11), 85 (15), 83 (24), 57 (12), 43 (11), HRMS calculated for $C_{24}H_{22}O_4$ M^+ 374.1518, found 374.1519.

7.3 Reduction of aryl-substituted naphthaldehydes

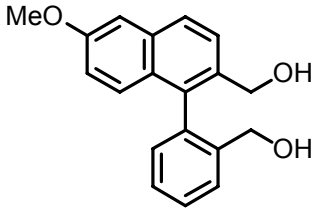
7.3.1 [1-(2-Hydroxymethyl-phenyl)-2-naphthyl]-methanol (**228**):



To a solution of dial **225** (0.83 g, 3.19 mmol) in ethanol (5 ml) was added sodium borohydride (0.30 g, 7.97 mmol) portion-wise. The reaction mixture warmed up and stirring continued at room temperature for 5 min before being poured into a separating funnel containing water (50 ml). The mixture was extracted with dichloromethane (3 × 100 ml) and the organic extracts combined and dried ($MgSO_4$) before being filtered on a celite plug. Excess dichloromethane was removed on a rotary evaporator and the resultant oil purified by column chromatography using 30-50% ethyl acetate/hexane as an eluent to obtain diol **228** as a thick yellowish oil (0.82 g, 98%).

IR ν_{max} (cm^{-1}) 3406 (s, broad, O–H stretch), 3018 (s, C–H stretch), 1605, 1567 (s, C=C stretch), 1042 (s, C–O stretch); ^{1}H nmr δ/ppm 7.91–7.86 (2H, m, 2 × ArH), 7.63 (1H, d, *J* = 8.5 Hz, ArH), 7.56 (1H, dd, *J* = 1.5 Hz, *J* = 7.2 Hz, ArH), 7.50–7.39 (3H, m, 3 × ArH), 7.33 (1H, t, *J* = 7.6 Hz, ArH) 7.18 (2H, d, *J* = 8.4 Hz, 2 × ArH), 4.46 (1H, d, *J* = 11.7 Hz, ArCH_aH_bOH), 4.42 (1H, d, *J* = 11.7 Hz, ArCH_aH_bOH), 4.26 (1H, d, *J* = 11.6 Hz, PhCH_cH_dOH), 4.04 (1H, d, *J* = 11.6 Hz, PhCH_cH_dOH); ^{13}C nmr δ/ppm 139.5 (C), 137.6 (C), 136.6 (C), 136.2 (C), 132.9 (C), 132.6 (C), 130.6 (CH), 129.9 (CH), 128.39 (CH), 128.36 (CH), 128.2 (CH), 127.9 (CH), 127.3 (CH), 126.3 (CH), 126.2 (CH), 125.9 (CH), 63.1 (CH_2OH), 63.0 (CH_2OH); MS (EI) *m/z* (%) 264 (M^+, 26), 246 (96), 215 (98), 202 (44), 68 (54), 57 (100), 43 (91), 29 (31), HRMS calculated for $C_{18}H_{16}O_2$ M^+ 264.1150, found 264.1132.

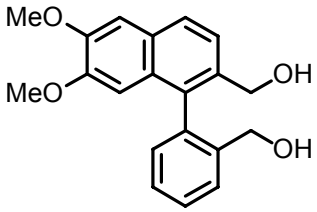
7.3.2 [1-(2-Hydroxymethyl-phenyl)-6-methoxynaphthalen-2-yl]-methanol **(229):**



Using the same methodology as outlined above dial **226** (1.35 g, 4.65 mmol) in ethanol (10 ml) was converted into diol **229** using sodium borohydride (0.44 g, 11.6 mmol).The product was obtained as sticky white flakes which were further crystallized from dichloromethane and hexane to give a white crystalline solid (1.06 g, 77 % yield)

mp = 147-148 °C; IR ν_{max} (cm^{-1}) 3385 (s, broad, O–H stretch), 3017 (s, C–H stretch), 1625, 1605 (s, C=C stretch), 1216 (s, C–O stretch); ^{1}H nmr δ/ppm 7.76 (1H, d, *J* = 8.4 Hz, ArH), 7.56–7.51 (2H, m, 2 × ArH), 7.47–7.39 (2H, m, 2 × ArH), 7.16–7.12 (2H, m, 2 × ArH), 7.07 (1H, d, *J* = 9.2 Hz, ArH), 6.98 (1H, dd, *J* = 2.5 Hz, *J* = 9.2 Hz, ArH), 4.39 (1H, d, *J* = 11.5 Hz, ArCH_aH$_b$OH), 4.35 (1H, d, *J* = 11.6 Hz, ArCH$_a$$H_b$OH), 4.22 (1H, d, *J* = 11.6 Hz, PhCH_cH$_d$OH), 4.02 (1H, d, *J* = 11.6 Hz, PhCH$_c$$H_d$OH), 3.91 (3H, s, OCH_3); ^{13}C nmr δ/ppm 157.6 (C), 139.5 (C), 137.7 (C), 136.7 (C), 134.2 (C), 133.9 (C), 130.5 (CH), 129.9 (CH), 129.3 (C), 128.3 (CH), 128.0 (2 × CH), 127.9 (CH), 118.9 (CH), 118.8 (CH), 105.9 (CH), 62.9 (CH_2OH), 62.8 (CH_2OH), 55.3 (OCH_3); MS (EI) *m/z* (%) 294 (M^+, 28), 276 (27), 264 (23), 188 (100), 171 (28), 159 (27), 144 (19), 128 (15), 91 (14), HRMS calculated for $C_{19}H_{18}O_2$ M^+ 294.1256, found 294.1256.

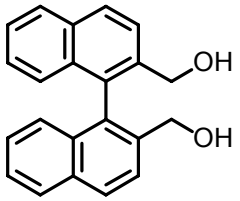
7.3.3 [1-(2-Hydroxymethyl-phenyl)-6,7-dimethoxynaphthalen-2-yl]-methanol **(230):**



Binaphthaldehyde **227** (0.80 g, 2.49 mmol) in ethanol (6 ml) was similarly converted to diol **230**, obatained as a thick yellow oil (0.75 g, 94% yield) using sodium borohydride (0.24 g, 6.24 mmol).

IR ν_{max} (cm^{-1}) 3337 (s, broad, O–H stretch), 2931 (s, C–H stretch), 1508 (s, C=C stretch), 1100 (s, C–O stretch); ^{1}H nmr δ/ppm 7.72 (1H, d, *J* = 8.3 Hz, ArH), 7.57–7.54 (1H, m, ArH), 7.48–7.39 (3H, m, 3 × ArH), 7.17 (1H, d, *J* = 8.7 Hz, ArH), 7.15 (1H, s, ArH), 6.40 (1H, s, ArH), 4.41 (1H, d, *J* = 11.5 Hz, ArCH_aH$_b$OH), 4.36 (1H, d, *J* = 11.4 Hz, ArCH$_a$$H_b$OH), 4.25 (1H, d, *J* = 11.6 Hz, PhCH_cH$_d$OH), 4.06 (1H, d, *J* = 11.6 Hz, PhCH$_c$$H_d$OH), 4.00 (3H, s, OCH_3), 3.63 (3H, s, OCH_3); ^{13}C nmr δ/ppm 149.6 (C), 149.5 (C), 139.5 (C), 137.8 (C), 135.4 (C), 134.5 (C), 130.4 (CH), 129.9 (CH), 128.8 (C), 128.3 (CH), 128.2 (C), 128.1 (CH), 126.6 (CH), 125.7 (CH), 106.4 (CH), 105.0 (CH), 63.6 (CH_2OH), 62.2 (CH_2OH), 55.8 (OCH_3), 55.5 (OCH_3); MS (EI) *m/z* (%) 325 (M+1, 16), 324 (M^+, 81), 306 (100), 291 (20), 275 (23), 215 (15), 189 (17), HRMS calculated for $C_{20}H_{20}O_4$ M^+ 324.1362, found 324.1364.

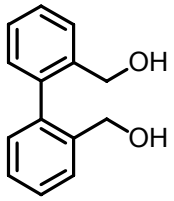
7.3.4 (2'-Hydroxymethyl-[1,1']binaphthyl-2-yl)-methanol **(232):**



Binaphthaldehyde **231** (0.85 g, 2.74 mmol) in ethanol (5 ml) was converted to diol **232** (0.83 g, 96% yield), obtained as a white crystalline solid (crystallized from dichloromethane) using sodium borohydride (0.26 g, 6.85 mmol) in a similar manner as described above.

mp = 169-170 °C. (Literature[218], ether:CH_2Cl_2 167-168 °C); IR ν_{max} (cm^{-1}) 3432 (s, broad, O–H stretch), 2936 (s, C–H stretch), 1568 (s, C=C stretch), 1030 (s, C–O stretch); ^{1}H nmr δ/ppm 7.91 (2H, d, *J* = 8.5 Hz, 2 × ArH), 7.65 (1H, d, *J* = 8.4 Hz, ArH), 7.46–7.41 (1H, m, ArH), 7.21 (1H, t, *J* = 7.8 Hz, ArH), 7.00 (1H, d, *J* = 8.4 Hz, ArH), 4.33 (1H, d, *J* = 11.5 Hz, ArCH_aH$_b$OH), 4.07 (1H, d, *J* = 11.4 Hz, ArCH$_a$$H_b$OH); ^{13}C nmr δ/ppm 137.1 (C), 134.4 (C), 133.1 (C), 133.0 (C), 128.7 (CH), 128.0 (CH), 127.5 (CH), 126.5 (CH), 126.3 (CH), 126.1 (CH), 63.1 (CH_2OH); MS (EI) *m/z* (%) 315 (M+1, 7), 314 (M^+, 30), 299 (26), 298 (100), 296 (73), 281 (40), 277 (86), 265 (64), 239 (28), 141 (21), 127 (23), 71 (19), 57 (30), HRMS calculated for $C_{22}H_{18}O_2$ M^+ 314.1307, found 314.1308.

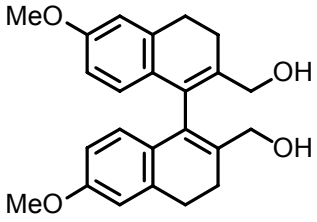
7.3.5 (2'-Hydroxymethyl-biphenyl-2-yl)-methanol **(257):**



In a similar manner as described above dial **242** (1.40 g, 6.66 mmol) in ethanol (10 ml) was reduced to the white crystalline diol **257** (crystallized from dichloromethane) (1.17 g, 82% yield), using sodium borohydride (0.64 g, 16.6 mmol).

mp = 112-113 °C. (Literature[219], benzene 109-111 °C); IR ν_{max} (cm^{-1}) 3360 (s, broad, O–H stretch), 3019 (s, C–H stretch), 1511 (s, C=C stretch), 1037 (s, C–O stretch); ^{1}H nmr δ/ppm 7.46 (1H, d, *J* = 7.4 Hz, ArH), 7.40–7.33 (2H, m, 2 × ArH), 7.13 (1H, d, *J* = 7.2 Hz, ArH), 4.33 (1H, d, *J* = 11.8 Hz, ArCH_aH$_b$OH), 4.28 (1H, d, *J* = 11.9 Hz, ArCH$_a$$H_b$OH); ^{13}C nmr δ/ppm 139.9 (C), 138.6 (C), 129.6 (CH), 129.5 (CH), 128.0 (CH), 127.6 (CH), 62.7 (CH_2OH); MS (EI) *m/z* (%) 212 (M^+, 1), 196 (100), 195 (58), 181 (31), 179 (30), 165 (53), 152 (24), 77 (9), 51 (4), HRMS calculated for $C_{14}H_{12}O_2$ M^+ 212.0837, found 212.0843.

7.3.6 (2'-Hydroxymethyl-6,6',3,4,3',4'-tetrahydro-[1,1']binaphthy-2-yl]-methanol **(258):**



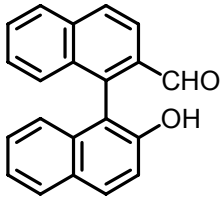
Similarly dinaphthaldehyde **243** (0.80 g, 2.14 mmol) in ethanol (5 ml) was reduced using sodium borohydride (0.20 g, 5.34 mmol) to diol **258** (0.76 g, 94% yield), afforded as a brown solid.

mp = 112-117 °C; IR ν_{max} (cm^{-1}) 3392 (s, broad, O–H stretch), 3019 (vs, C–H stretch), 1606, 1569 (m, C=C stretch), 1040 (vs, C–O stretch); ^{1}H nmr δ/ppm 6.80 (1H, d, *J* = 8.5 Hz, ArH), 6.73 (1H, d, *J* = 2.4 Hz, ArH), 6.54 (1H, dd, *J* = 2.4 Hz, *J* = 8.5 Hz, ArH), 4.15 (1H, d, *J* = 11.1 Hz, ArCH_aH$_b$OH), 3.88 (1H, d, *J* = 11.1 Hz, ArCH$_a$$H_b$OH), 3.76 (3H, s,

OCH_3), 2.95–2.86 (2H, m, 2 × CH_2), 2.74–2.63 (1H, m, CH_aH$_b$), 2.46–2.36 (1H, m, CH$_a$$H_b$); ^{13}C nmr δ/ppm 158.8 (C), 137.3 (CH), 134.3 (CH), 132.4 (CH), 127.8 (C), 126.6 (C), 113.6 (C), 111.2 (C), 63.8 (CH_2OH), 55.1 (OCH_3), 28.8 (CH_2), 26.1 (CH_2); MS (EI) *m/z* (%) 378 (M^+, 3), 360 (100), 345 (20), 331 (38), 304 (19), 219 (10), 171 (9), HRMS calculated for $C_{24}H_{26}O_4$ M^+ 378.1831, found 378.1851.

7.4 Deprotection of isopropyl ethers to afford naphthols

7.4.1 1-(2'-Hydroxynaphthalen-2-yl)-2-naphthaldehyde **(248):**

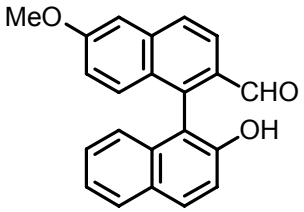


To a solution of naphthaldehyde **234** (0.96 g, 2.69 mmol) in dichloromethane (10 ml) was added aluminum trichloride (0.75 g, 5.39 mmol) in one portion. The reaction mixture turned deep red immediately whilst warming up in the process. The mixture was stirred at room temperature for 15 min after which time water was added dropwise until the effervescence had stopped. The mixture was then extracted with dichloromethane (3 × 100 ml) and the organic extracts combined before being dried ($MgSO_4$), filtered on a celite plug and excess solvent removed on a rotary evaporator. The resultant brown oil was purified using column chromatography with 10% ethyl acetate/hexane as an eluent to obtain naphthaldehyde **248** as white flakes (0.78 g, 98% yield).

mp = 97-98 °C; IR ν_{max} (cm^{-1}) 3367 (s, br, O–H stretch), 3017 (s, C–H stretch), 1684 (s, C=O), 1597 (s, C=C stretch); ^{1}H nmr δ/ppm 9.67 (1H, s, CHO), 8.16 (1H, d, J = 8.6 Hz, ArH), 8.04 (1H, d, J = 8.6 Hz, ArH), 7.96 (2H, d, J = 8.7 Hz, 2 × ArH), 7.89–7.87 (1H, m, ArH), 7.62 (1H, t, J = 7.4 Hz, ArH), 7.45 (1H, d, J = 8.2 Hz, ArH), 7.39–7.22 (4H, m, 4 × ArH), 6.93 (1H, d, J = 8.4 Hz, ArH); ^{13}C nmr δ/ppm 192.7 (CHO), 151.9 (C), 139.6 (C), 136.6 (C), 134.5 (C), 132.9 (C), 132.6 (C), 130.8 (CH), 129.4 (CH), 129.3 (CH), 128.7 (C), 128.4 (CH), 128.1 (CH), 127.5 (CH), 127.2 (CH), 126.9 (CH), 124.6 (CH), 123.7 (CH), 122.5 (CH), 117.6 (CH), 113.6 (C); MS (EI) *m/z* (%) 299 (M+1, 16), 298

(M^+, 100), 281 (21), 252 (18), 239 (21), 126 (15), 69 (29), HRMS calculated for $C_{21}H_{14}O_2$ M^+ 298.0994, found 298.0992.

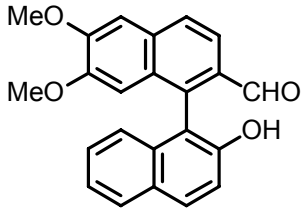
7.4.2 1-(2'-Hydroxynaphthalen-2-yl)-6-methoxy-2-naphthaldehyde **(249):**



In a similar manner as described above methoxynaphthaldehyde **235** (1.10 g, 2.97 mmol) in dichloromethane (15 ml) was converted to naphthaldehyde **249** (0.59 g, 60% yield), as a brown solid, using aluminum trichloride (0.79 g, 5.94 mmol).

mp = 187-190 °C; IR ν_{max} (cm^{-1}) 3372 (s, br, O–H stretch), 3019 (s, C–H stretch), 1683 (s, C=O), 1618 (s, C=C stretch), 1034 (s, C–O stretch); ^{1}H nmr δ/ppm 9.63 (1H, s, CHO), 8.17 (1H, d, *J* = 8.7 Hz, ArH), 7.96 (2H, d, *J* = 8.8 Hz, 2 × ArH), 7.88 (1H, d, *J* = 7.7 Hz, ArH), 7.37–7.23 (5H, m, 5 × ArH), 7.03 (1H, dd, *J* = 2.5 Hz, *J* = 9.2 Hz, ArH), 6.96 (1H, d, *J* = 8.4 Hz, ArH), 3.96 (3H, s, OCH_3); ^{13}C nmr δ/ppm 191.9 (CHO), 160.5 (C), 151.6 (C), 138.7 (C), 134.4 (C), 131.5 (C), 130.9 (CH), 128.8 (C), 128.6 (CH), 128.4 (CH), 128.2 (CH), 127.8 (C), 127.4 (CH), 124.6 (CH), 123.9 (CH), 123.5 (CH), 120.3 (CH), 117.4 (CH), 106.7 (CH), 55.5 (OCH_3); MS (EI) *m/z* (%) 329 (M+1, 25), 328 (M^+, 100), 311 (26), 219 (29), 186 (51), 68 (36), HRMS calculated for $C_{22}H_{16}O_3$ M^+ 328.1099, found 328.1110.

7.4.3 1-(2'-Hydroxynaphthalen-2-yl)-6,7-dimethoxy-2-naphthaldehyde **(250):**

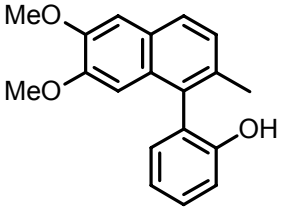


Naphthaldehyde **236** (0.70 g, 1.75 mmol) in dichloromethane (10 ml) was converted to the desired product **250** (0.54 g, 86% yield), as white flakes, using aluminum trichloride (0.47 g, 3.49 mmol) in the same manner as described above.

mp = 195-197 °C; IR ν_{max} (cm^{-1}) 3376 (s, br, O–H stretch), 3020 (s, C–H stretch), 1681 (s, C=O), 1601 (s, C=C stretch), 1038 (s, C–O stretch); ^{1}H nmr δ/ppm 9.60 (1H, s, CHO), 8.08 (1H, d, *J* = 8.5 Hz, ArH), 7.99–7.88 (3H, m, 3 × ArH), 7.38–7.26 (4H, m, 4 × ArH), 6.99 (1H, d, *J* = 8.4 Hz, ArH), 6.66 (1H, s, ArH), 4.05 (3H, s, OCH_3), 3.96 (3H, s, OCH_3); ^{13}C nmr δ/ppm 192.1 (CHO), 160.3 (C), 151.6 (C), 138.9 (C), 134.7 (C), 132.1 (C), 130.9 (CH), 128.8 (C), 128.3 (C), 128.2 (CH), 127.9 (CH), 127.3 (CH), 124.6 (CH), 123.8 (CH), 121.6 (CH), 117.4 (CH), 106.9 (CH), 106.4 (C), 104.9 (CH), 55.5 (OCH_3); MS (EI) *m/z* (%)359 (M+1, 27), 358 (M^+, 100), 341 (17), 215 (10), 83 (3), HRMS calculated for $C_{23}H_{18}O_4$ M^+ 358.1205, found 358.1202.

7.5 Deprotection of aromatic benzyl ethers

7.5.1 2-(6,7-Dimethoxy-2-methyl-naphthalen-1yl)-phenol **(247):**

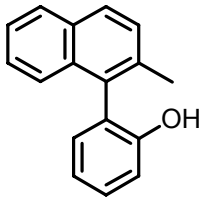


To a solution of naphthaldehyde **245** (1.50 g, 3.76 mmol) in ethyl acetate (20 ml) was added 10% Pd/C (0.04 g, 0.376 mmol) in one portion. Hydrogen gas was allowed to diffuse slowly from a ballon into the stirred reaction mixture over a period of 8 h. An aliquot of the reaction was taken and characterized by nmr and the results showed that the *o*-benzyl group was still intact but the aromatic aldehyde was reduced to an alcohol.

Therefore extra Pd/C was added to the reaction and more hydrogen gas diffused over a period of another 8 h. The mixture was filtered and ethyl acetate removed on a rotary evaporator to give a white solid that was crystallized from dichloromethane and hexane. The resultant crystalline solid proved to be product **247** (0.81 g, 73% yield).

mp = 61-62 °C; IR ν_{max} (cm^{-1}) 3538 (vs, br, O–H stretch), 3014 (vs, C–H stretch), 1575 (s, C=C stretch), 1033 (s, C–O stretch); ^{1}H nmr δ/ppm 7.65 (1H, d, *J* = 8.3 Hz, ArH), 7.36 (1H, dt, *J* = 1.8 Hz, *J* = 7.4 Hz, ArH), 7.29 (1H, d, *J* = 8.3 Hz, ArH), 7.15–7.03 (4H, m, 4 × ArH), 6.68 (1H, s, ArH), 3.99 (3H, s, OCH_3), 3.71 (2H, s, OCH_3), 2.21 (3H, s, CH_3); ^{13}C nmr δ/ppm 152.9 (C), 149.7 (C), 148.9 (C), 133.5 (C), 130.2 (CH), 129.9 (C), 129.2 (CH), 128.6 (C), 127.8 (C), 126.8 (CH), 126.7 (CH), 125.2 (C), 120.6 (CH), 115.4 (CH), 106.4 (CH), 104.1 (CH), 55.7 (OCH_3), 55.4 (OCH_3), 20.1 (CH_3); MS (EI) *m/z* (%). 295 (M+1, 21), 294 (M^+, 100), 264 (4), 221 (3), 189 (3), 94 (2), HRMS calculated for $C_{19}H_{18}O_3$ M^+ 294.1256, found 294.1252.

7.5.2 2-(2-Methyl-naphthalen-1yl)-phenol **(246):**

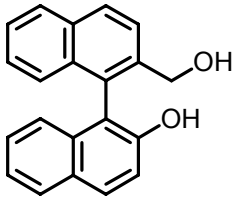


This reaction and the above-mentioned reaction were run concurrently and hence naphthaldehyde **244** (1.00 g, 3.13 mmol) in ethyl acetate (15 ml) was over-reduced to afford product **246** (0.47 g, 68% yield) as a yellowish oil using 10% Pd/C (35 mg, 0.313 mmol).

IR ν_{max} (cm^{-1}) 3411 (s, br, O–H stretch), 3019 (vs, C–H stretch), 1581 (s, C=C stretch), 1125 (s, C–O stretch); ^{1}H nmr δ/ppm 7.83–7.78 (2H, m, 2 × ArH), 7.42–7.31 (5H, m, 5 × ArH), 7.10–6.99 (3H, m, 3 × ArH), 2.22 (3H, s, CH_3); ^{13}C nmr δ/ppm 153.2 (C), 135.5 (C), 132.9 (C), 132.2 (C), 131.4 (C), 130.9 (CH), 129.2 (C), 128.6 (CH), 128.3 (CH), 127.8 (CH), 126.4 (CH), 125.4 (CH), 125.2 (CH), 125.0 (C), 120.5 (CH), 115.5 (CH), 20.6 (CH_3).

7.6 Reduction of aromatic aldehydes

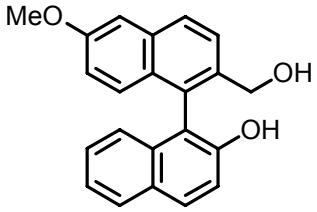
7.6.1 2'-Hydroxymethyl-[1,1']binaphthalenyl-2-ol **(251):**



To a solution of naphthaldehyde **248** (0.77 g, 2.58 mmol) in ethanol (5 ml) was added sodium borohydride (0.12 g, 3.23 mmol) portion-wise. The reaction mixture warmed up and was stirred at room temperature for 5 min before being poured into a separating funnel containing water (50 ml). The mixture was extracted with dichloromethane (3 × 100 ml) and the organic extracts combined, dried ($MgSO_4$) before being filtered throgh a celite plug. Excess dichloromethane was removed on a rotary evaporator and the resultant oil purified by column chromatography using 30-50% ethyl acetate/hexane as an eluent to obtain the diol **251** as cream-white flakes (0.76 g, 99% yield).

mp = 92-96 °C; IR ν_{max} (cm^{-1}) 3321 (s, br, O–H stretch), 3019 (s, C–H stretch), 1579 (s, C=C stretch), 1030 (s, C–H stretch); ^{1}H nmr δ/ppm 7.90–7.82 (4H, m, 4 × ArH), 7.67 (1H, d, *J* = 8.5 Hz, ArH), 7.45–7.41 (1H, m, ArH), 7.31–7.13 (5H, m, 5 × ArH), 6.87 (1H, d, *J* = 8.4 Hz, ArH), 4.31 (2H, s, CH_2OH); ^{13}C nmr δ/ppm 151.1 (C), 138.3 (C), 133.7 (C), 133.3 (CH), 132.9 (C), 129.9 (CH), 129.8 (C), 129.2 (CH), 128.9 (C), 128.1 (2 × CH), 127.4 (C), 126.7 (CH), 126.3 (CH), 126.1 (CH), 125.9 (CH), 124.4 (CH), 123.5 (CH), 117.9 (CH), 116.8 (C), 63.4 (CH_2OH); MS (EI) *m/z* (%) 300 (M^+, 27), 284 (22), 283 (28), 281 (100), 252 (30), 239 (19), 126 (12), 113 (6), 43 (8), HRMS calculated for $C_{21}H_{16}O_2$ M^+ 300.1150, found 300.1164.

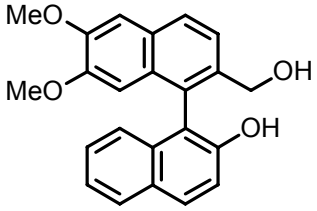
7.6.2 2'-Hydroxymethyl-6'-methoxy-[1,1']binaphthalenyl-2-ol **(252):**



In a similar manner as outlined above naphthaldehyde **249** (0.60 g, 1.83 mmol) in ethanol (5 ml) was reduced to diol **252** (0.55 g, 92% yield), white flakes, using sodium borohydride (0.09 g, 2.28 mmol).

mp = 89-92 °C; IR ν_{max} (cm^{-1}) 3372 (s, br, O–H stretch), 3028 (s, C–H stretch), 1617 (s, C=C stretch), 1036 (s, C–H stretch); ^{1}H nmr δ/ppm 7.89–7.83 (3H, m, 3 × ArH), 7.70 (1H, d, *J* = 8.5 Hz, ArH), 7.33–7.17 (3H, m, 3 × ArH), 7.08 (1H, d, *J* = 9.2 Hz, ArH), 6.94–6.89 (2H, m, 2 × ArH), 4.35 (2H, s, CH_2OH), 3.90 (3H, s, OCH_3); ^{13}C nmr δ/ppm. 157.9 (C), 151.2 (C), 136.2 (C), 134.8 (C), 133.7 (C), 130.0 (CH), 129.7 (CH), 129.0 (C), 128.4 (C), 128.2 (CH), 128.1 (CH), 127.6 (CH), 127.3 (CH), 126.8 (CH), 124.4 (CH), 123.5 (CH), 119.4 (CH), 117.9 (CH), 117.0 (C), 106.2 (CH), 63.6 (CH_2OH), 55.3 (OCH_3); MS (EI) *m/z* (%) 330 (M^+, 18), 312 (100), 311 (70), 239 (15), 113 (5), HRMS calculated for $C_{22}H_{18}O_3$ M^+ 330.1256, found 330.1254.

7.6.3 2'-Hydroxymethyl-6',7'-dimethoxy-[1,1']binaphthalenyl-2-ol (**253**)**:**

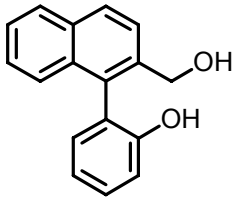


Using the same experimental procedure as described above, aldehyde **250** (0.65 g, 1.81 mmol) in ethanol (5 ml) was reduced to diol **253** (0.64 g, 98% yield) as brownish flakes using sodium borohydride (0.09 g, 2.27 mmol).

mp = 88-90 °C; IR ν_{max} (cm^{-1}) 3319 (s, br, O–H stretch), 3026 (s, C–H stretch), 1581 (s, C=C stretch), 1040 (s, C–H stretch); ^{1}H nmr δ/ppm 7.85 (1H, t, *J* = 8.3 Hz, ArH), 7.76 (1H, d, *J* = 8.3 Hz, ArH), 7.56 (1H, d, *J* = 8.4 Hz, ArH), 7.32–7.15 (4H, m, 4 × ArH), 6.68 (1H, d, *J* = 8.4 Hz, ArH), 6.41 (1H, s, ArH), 4.31 (2H, s, CH_2OH), 3.94 (3H, s,

OCH_3), 3.44 (3H, s, OCH_3); ^{13}C nmr δ/ppm 151.1 (C), 150.1 (C), 149.7 (C), 136.7 (C), 133.5 (C), 129.9 (CH), 129.4 (C), 128.9 (C), 128.8 (C), 128.8 (C), 128.1 (C), 128.0 (CH), 127.6 (CH), 126.7 (CH), 124.9 (CH), 124.3 (CH), 123.5 (CH), 117.9 (CH), 117.1 (C), 106.5 (CH), 104.6 (CH), 63.7 (CH_2OH), 55.8 (OCH_3), 55.4 (OCH_3); MS (EI) *m/z* (%). 361 (M+1, 5), 360 (M^+, 18), 343 (21), 342 (100), 311 (21), 309 (11), 283 (6), 226 (6), 113 (6), HRMS calculated for $C_{23}H_{20}O_4$ M^+ 360.1362, found 360.1362.

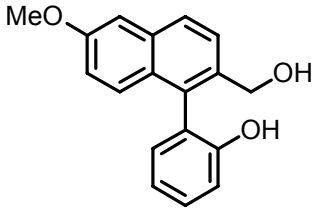
7.6.4 2-(2-Hydroxymethyl-naphthalen-1-yl)-phenol **(254):**



The experimental procedure described in **1.4.1** was followed, but the resultant phenol was not characterized as it always proved to be impure. Hence the yields can be taken as over two steps. Therefore naphthaldehyde **237** (1.00 g, 3.44 mmol) was both deprotected and reduced to diol **254** (0.39 g, 45% yield) initially using aluminum trichloride (0.92 g, 6.89 mmol) in dichloromethane (20 ml) followed by treatment of the resultant phenol with sodium borohydride (16 mg, 4.30 mmol) in ethanol (10 ml).

IR ν_{max} (cm^{-1}) 3324 (s, br, O–H stretch), 3017 (s, C–H stretch), 1575 (s, C=C stretch), 1031 (s, C–H stretch); ^1H nmr δ/ppm 7.83–7.79 (2H, m, 2 × ArH), 7.47–7.26 (3H, m, 3 × ArH), 7.06–7.03 (1H, m, ArH), 6.98 (2H, t, J = 7.9 Hz, 2 × ArH), 6.53 (1H, d, J = 8.5 Hz, ArH), 4.44 (1H, d, J = 12.6 Hz, CH_aH_bOH), 4.39 (1H, d, J = 12.5 Hz, CH_aH_bOH); ^{13}C nmr δ/ppm 153.4 (C), 136.8 (C), 133.3 (C), 132.7 (C), 132.5 (C), 131.4 (CH), 129.6 (CH), 128.8 (CH), 127.9 (CH), 126.5 (CH), 126.4 (CH), 126.1 (2 × CH), 124.4 (C), 120.7 (CH), 116.3 (CH), 63.7 (CH_2OH); MS (EI) *m/z* (%) 250 (M^+, 17), 232 (72), 231 (100), 202 (23), 189 (10), 89 (3), HRMS calculated for $C_{17}H_{14}O_2$ M^+ 250.0994, found 250.0980.

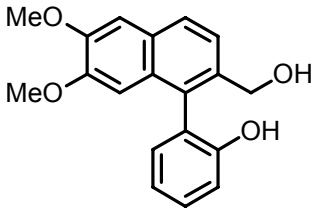
7.6.5 2-(2-Hydroxymethyl-6-methoxy-naphthalen-1-yl)-phenol **(255):**



Using the same procedure as described above, isopropyl ether **238** (1.00 g, 3.57 mmol) was deprotected using aluminum trichloride (0.95 g, 7.14 mmol) in dichloromethane (20 ml) and then reduced to the diol **255** (0.36 g, 41% yield) using sodium borohydride (0.17 g, 4.46 mmol) in ethanol (10 ml). The product was obtained as a white crystalline solid.

mp = 66-68 °C; IR ν_{max} (cm^{-1}) 3316 (s, br, O–H stretch), 3021 (s, C–H stretch), 1624 (s, C=C stretch), 1034 (s, C–H stretch); ^{1}H nmr δ/ppm 7.69 (1H, d, *J* = 8.5 Hz, ArH), 7.49 (1H, d, *J* = 8.4 Hz, ArH), 7.31–7.26 (2H, m, 2 × ArH), 7.10 (1H, d, *J* = 2.4 Hz, ArH), 7.06–6.95 (4H, m, 4 × ArH), 4.42 (1H, d, *J* = 12.4 Hz, C$H_a$$H_b$OH), 4.32 (1H, d, *J* = 13.3 Hz, CH$_a$$H_b$OH), 3.88 (3H, s OCH_3); ^{13}C nmr δ/ppm 157.6 (C), 153.5 (C), 134.6 (C), 134.4 (C), 132.7 (C), 131.4 (CH), 129.4 (CH), 128.1 (C), 127.8 (CH), 127.5 (C), 127.1 (CH), 124.6 (C), 120.5 (CH), 118.9 (CH), 116.3 (CH), 105.9 (CH), 63.6 (CH_2OH), 55.2 (OCH_3); MS (EI) *m/z* (%) 281 (M+1, 5), 280 (M^+, 28), 262 (86), 261 (100), 219 (16), 188 (16), 85 (49), 43 (14), HRMS calculated for $C_{18}H_{16}O_3$ M^+ 280.1099, found 280.1085.

7.6.6 2-(2-Hydroxymethyl-6,7-dimethoxy-naphthalen-1-yl)-phenol (**256**):



In the same manner as outlined above, naphthaldehyde **239** (1.05 g, 3.38 mmol) was treated with aluminum trichloride (0.90 g, 6.77 mmol) in dichloromethane (25 ml) and then with sodium borohydride (0.16 g, 4.22 mmol) in ethanol (10 ml) to give the diol **256** as white flakes (0.46 g, 52% yield).

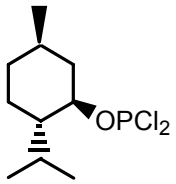
mp = 66-68 °C; IR ν_{max} (cm^{-1}) 3460 (s, br, O–H stretch), 3019 (s, C–H stretch), 1577 (s, C=C stretch), 1029 (s, C–H stretch); ^{1}H nmr δ/ppm 7.71 (1H, d, *J* = 8.4 Hz, ArH), 7.47 (1H, d, *J* = 8.3 Hz, ArH), 7.35 (1H, dt, *J* = 1.6 Hz, *J* = 7.6 Hz, ArH), 7.13 (1H, s, ArH),

7.12 (1H, d, *J* = 6.8 Hz, ArH), 7.05 (2H, d, *J* = 7.7 Hz, 2 × ArH), 6.66 (1H, s, ArH), 4.42 (2H, s, CH_2OH), 3.99 (3H, s OCH_3), 3.69 (3H, s, OCH_3); ^{13}C nmr δ/ppm 153.5 (C), 149.9 (C), 149.7 (C), 135.3 (C), 131.2 (CH), 130.9 (C), 129.7 (CH), 129.3 (C), 128.6 (C), 127.3 (CH), 124.9 (CH), 124.8 (C), 120.8 (CH), 116.4 (CH), 106.4 (CH), 104.7 (CH), 63.9 (CH_2OH), 55.8 (OCH_3), 55.5 (OCH_3); MS (EI) *m/z* (%) 310 (M^+, 15), 292 (34), 291 (29), 263 (18), 218 (100), 149 (10), 130 (27), 68 (77), 41 (11), HRMS calculated for $C_{19}H_{18}O_3$ M^+ 310.1205, found 310.1201.

7.7 Syntheses of phosphite, phosphate, phosphoramidite and phosphoramidate ligands

7.7.1 Syntheses of precursors

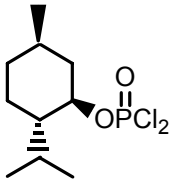
7.7.1.1 Menthyl phosphodichloridite (233):



To a solution of L-menthol (3.00 g, 19.2 mmol) in THF (10 ml) under nitrogen was added phosphorus trichloride (2.64 g, 2 ml, 19.2 mmol) in THF (5 ml) drop-wise. The reaction mixture warmed up and was allowed to stir at room temperature for 1 h after which time an excess solvent was removed *in vacuo*. The resultant yellowish oil was purified by distillation to give product **233** as a colourless oil (bp = 32 °C at 4 mmHg) that was kept under nitrogen for future use.

^{31}P nmr: δ = 176.7 ppm. Literature[8] value, δ = 175.1 ppm; ^1H nmr δ/ppm 4.49 (1H, dq, *J* = 4.6 Hz, *J* = 10.6 Hz, $CHOPCl_2$), 2.39–2.33 (1H, m, C*H*$CH[CH_3]_2$), 2.07 (1H, dseptet, *J*= 2.0 Hz, *J* = 6.9 Hz, $CHCH[CH_3]_2$), 1.73–1.67 (2H, m, CH_2), 1.49–1.34 (2H, m, CH_2), 1.11–1.00 (2H, m, CH_2), 0.94 (3H, d, *J* = 6.6 Hz, CH_3), 0.91 (3H, d, *J* = 7.0 Hz, CH_3), 0.80 (3H, d, *J* = 6.9 Hz, CH_3); ^{13}C nmr δ/ppm 86.6 ($CHOPCl_2$), 48.6 (CH), 43.3 (CH), 33.9 (CH_3), 31.6 (CH_2), 25.0 (CH), 22.9 (CH_2), 22.0 (CH_3), 21.0 (CH_3), 16.0 (CH_2).

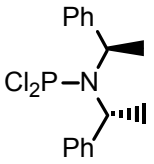
7.7.1.2 Menthyl phosphodichloridate (271):



The same procedure as outlined above was followed but instead of using phosphorus trichloride as a reagent, phosphorus oxychloride was added. The resultant oil was purified by distillation to obtain a colourless oil **271** (bp = 37 °C at 4 mmHg) that was kept under nitrogen for future use.

^{31}P nmr: δ = 7.61 ppm; ^{1}H nmr δ/ppm 4.63 (1H, dq, *J* = 4.6 Hz, *J* = 10.4 Hz, CHOPOCl$_2$), 2.37–2.33 (1H, m, C*H*CH[CH$_3$]$_2$), 2.08 (1H, dseptet, *J*= 2.4 Hz, *J* = 6.9 Hz, CHC*H*[CH$_3$]$_2$), 1.76–1.68 (2H, m, CH$_2$), 1.58–1.29 (3H, m, CH + CH$_2$), 0.96 (6H, dd, *J* = 3.0 Hz, *J* = 6.7 Hz, 2 × CH$_3$), 0.84 (3H, d, *J* = 6.9 Hz, CH$_3$); ^{13}C nmr δ/ppm 86.6 (CHOPOCl$_2$), 48.1 (CH), 42.1 (CH$_2$), 33.6 (CH$_3$), 31.7 (CH$_3$), 25.8 (CH), 22.9 (CH), 21.7 (CH$_3$), 20.6 (CH$_2$), 15.7 (CH$_2$).

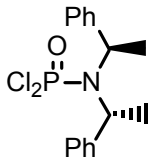
7.7.1.3 *N*-Phosphodichloridite *bis*-(α-methylbenzyl)amine (276):



The above-mentioned procedure was followed as is except that (*R*,*R*)-(+)-*bis*(α-methylbenzyl)amine was used instead of L-menthol. After the *in vacuo* removal of the solvent, product **276** was obtained as a white solid that was stored under nitrogen and used as is.

^{31}P nmr: δ = 166.4 ppm; ^{1}H nmr δ/ppm 7.56 (2H, m, 2 × ArH), 7.46–7.39 (3H, m, 3 × ArH), 7.18–7.16 (3H, m, 3 × ArH), 7.10–7.09 (2H, m, 2 × ArH), 4.96–4.90 (1H, m, C*H*CH$_3$), 3.90–3.84 (1H, m, C*H*CH$_3$), 1.93 (3H, d, *J* = 6.8 Hz, CHC*H$_3$*), 1.77 (3H, d, *J* = 7.1 Hz, CHC*H$_3$*).

7.7.1.4 *N*-Phosphodichloridate *bis*-(α-methylbenzyl)amine (281):



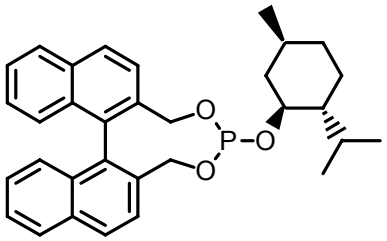
The above-mentioned procedure was followed but phosphorus trichloride was replaced with phosphorus oxychloride to give product **281** as a white solid that was stored under nitrogen and used as is.

^{31}P nmr: δ = 6.529 ppm; ^{1}H nmr δ/ppm 7.55–7.53 (2H, m, 2 × ArH), 7.47–7.39 (3H, m, 3 × ArH), 3.87 (1H, d, *J* =6.6 Hz C*H*CH$_3$), 1.92 (3H, d, *J* = 6.7 Hz, CHC*H*$_3$).

7.7.2 General procedure for the synthesis of ligands

To a solution of diols (**228-232**) and (**251-258**) (1 mmol) in THF under nitrogen was added triethylamine (2 mmol) and the mixture allowed to stirrer at room temperature for 5 min. To this reaction mixture was added drop-wise a solution of menthyl phosphodichloridite **233** (1 mmol) for the synthesis of phosphite ligands or menthyl phosphodichloridate **271** (1 mmol) for the synthesis of phosphate ligands or *N*-phosphodichloridite-*bis*-(α-methylbenzylamine) **276** (1 mmol) for the synthesis of phosphoramidite ligands or *N*-phosphodichloridate-*bis*-(α-methylbenzylamine) **281** (1 mmol) for the synthesis of phosphoramidate ligands in THF. The mixture both warmed-up and turned milky white immediately and was allowed to stirrer at room temperature for 1 h after which time it was filtered through a small pad of celite under nitrogen and excess solvent removed *in vacuo* to give most of the time the products as white to yellowish flakes.

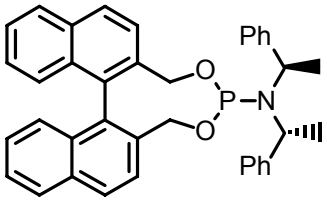
7.7.2.1 13-{[(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl]oxy}-11,15-dihydrodinaphtho[2,1-*e*:1,2-*g*][1,3,2]dioxaphosphonine (221):



Phosphite **221** was obtained as a cream-white foam (0.44 g, 92%).

^{31}P nmr: δ = 151.9 ppm and 149.8 ppm; MS (FAB) *m/z* (%) 501 (MH^+, 1), 363 (10), 283 (36), 221 (19), 139 (100); LRMS calculated for $C_{32}H_{35}O_3P$ M^+ 500.23, found for $C_{32}H_{35}O_3P$ MH^+, 501.1

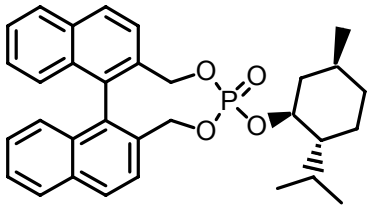
7.7.2.2 *N*-(11,15-Dihydrodinaphtho[2,1-*e*:1,2-*g*][1,3,2]dioxaphosphonin-13-yl)-*N*-[(1*R*)-1-phenylethyl]-*N*-[(1*R*)-1-phenylethyl]amine (222):



Phosphoramidite **222** was obtained as a white foam (0.51 g, 94%).

^{31}P nmr: δ = 149.8 ppm and 149.6 ppm; MS (FAB) *m/z* (%) 568 (MH^+, 14), 279 (16), 226 (100), 154 (11), 105 (97); LRMS calculated for $C_{38}H_{34}NO_2P$ M^+ 567.23, found for $C_{38}H_{35}NO_2P$ MH^+, 568.1

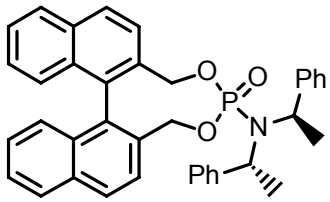
7.7.2.3 13-{[(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl]oxy}-11,15-dihydrodinaphtho[2,1-*e*:1,2-*g*] [1,3,2]dioxaphosphonine 13-oxide (269):



Phosphate **269** was obtained as cream-white flakes (0.49 g, 88% yield).

^{31}P nmr: δ = 0.286 ppm and 0.107 ppm; MS (FAB) *m/z* (%) 515 (MH^+, 2), 479 (4), 377 (12), 279 (48), 201 (12); LRMS calculated for $C_{32}H_{35}O_4P$ M^+ 514.23, found for $C_{32}H_{36}O_4P$ MH^+, 515.4.

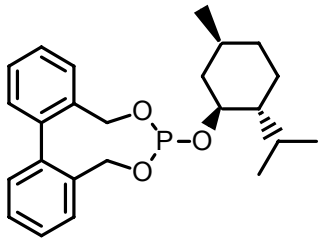
7.7.2.4 *N*-(13-Oxido-11,15-dihydrodinaphtho[2,1-*e*:1,2-*g*][1,3,2]dioxaphosphonin-13-yl)-*N*-[(1*R*)-1-phenylethyl]-*N*-[(1*R*)-1-phenylethyl]amine (279):



Phosphoramidate **279** was obtained as yellowish flakes (0.48 g, 93%).

^{31}P nmr: δ = 0.432 ppm and −0.858 ppm; MS (FAB) *m/z* (%) 584 (MH^+, 3), 462 (4), 279 (38), 267 (24), 226 (89), 154 (26), 105 (100); LRMS calculated for $C_{38}H_{34}NO_3P$ M^+ 583.23, found for $C_{38}H_{35}NO_3P$ MH^+, 584.3.

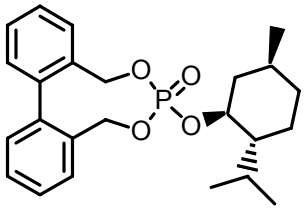
7.7.2.5 7-{[(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl]oxy}-5,9-dihydrodibenzo[*e*,*g*][1,3,2]dioxaphosphonine (266):



Phosphite **266** was produced as thick yellowish oil (0.53 g, 82%).

^{31}P nmr: δ = 149.2 ppm and 147.2 ppm; MS (EI) *m/z* (%) 398 (M^+, 0.6), 261 (57), 225 (63), 197 (43), 179 (100), 165 (43), 139 (29), 91 (23), 83 (20), 55 (15); HRMS calculated for $C_{24}H_{31}O_3P$ M^+ 398.2011, found 398.2008.

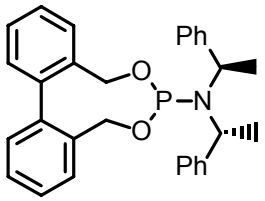
7.7.2.6 7-{[(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl]oxy}-5,9-dihydrodibenzo[*e*,*g*][1,3,2]dioxaphosphonine 7-oxide (270):



Phosphate **270** was obtained as thick brown oil (0.46 g, 79%).

^{31}P nmr: δ = 1.207 ppm and 0.967 ppm; MS (FAB) *m/z* (%) 412 (MH^+, 8), 230 (44), 229 (78), 136 (16), 105 (100); LRMS calculated for $C_{24}H_{31}O_4P$ M^+ 411.19, found for $C_{24}H_{32}O_4P$ MH^+, 412.1.

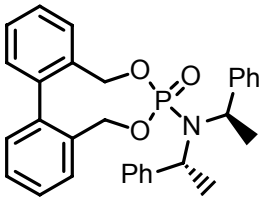
7.7.2.7 *N*-(5,9-Dihydrodibenzo[*e*,*g*][1,3,2]dioxaphosphonin-7-yl)-*N*-[(1*R*)-1-phenylethyl]-*N*-[(1*R*)-1-phenylethyl]amine (275):



Phosphoramidite **275** was produced as white flakes (0.53 g, 82%).

^{31}P nmr: δ = 149.4 ppm and 147.8 ppm; MS (FAB) *m/z* (%) 464 (MH^+, 3), 447 (4), 265 (21), 226 (100), 154 (33), 105 (91); LRMS calculated for $C_{30}H_{30}NO_2P$ M^+ 463.23, found for $C_{30}H_{31}NO_2P$ MH^+, 464.1.

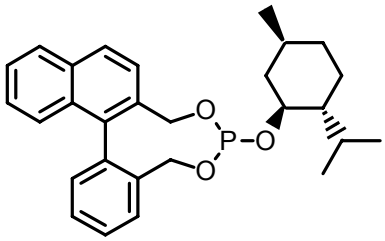
7.7.2.8 *N*-(7-Oxido-5,9-dihydrodibenzo[*e*,*g*][1,3,2]dioxaphosphonin-7-yl)-*N*-[(1*R*)-1-phenylethyl]-*N*-[(1*R*)-1-phenylethyl]amine (280):



Phosphoramidate **280** was obtained as a thick light-brown oil (0.63 g, 93%).

^{31}P nmr: δ = −4.511 ppm.

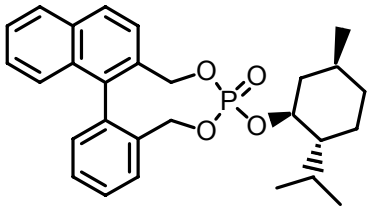
7.7.2.9 3-{[(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl]oxy}-1,5-dihydronaphtho[2,1-*f*][2,4,3]benzodioxaphosphonine (262):



Product **262** was obtained as yellow flakes (0.43 g, 84%).

^{31}P nmr: δ = 152.4 ppm, 150.4 ppm, 149.6 ppm and 147.5 ppm.

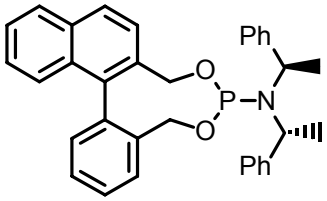
7.7.2.10 3-{[(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl]oxy}-1,5-dihydronaphtho[2,1-*f*][2,4,3]benzodioxaphosphonine-3-oxide (268):



Phosphate **268** was obtained as thick light-brown oil (0.63 g, 90% yield).

^{31}P nmr: δ = 4.072 ppm.

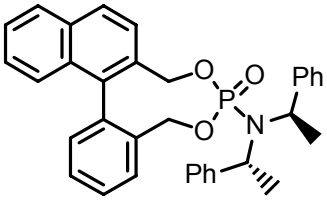
7.7.2.11 *N*-(1,5-Dihydronaphtho[2,1-*f*][2,4,3]benzodioxaphosphonin-3-yl)-*N*-[(1*R*)-1-phenylethyl]-*N*-[(1*R*)-1-phenylethyl]amine (272):



Product **272** was produced as white flakes (0.59 g, 87% yield).

^{31}P nmr: δ = 149.7 ppm and 148.7 ppm; MS (FAB) *m/z* (%) 518 (MH^+, 3), 447 (2), 307 (4), 290 (6), 226 (98), 217 (18), 154 (40), 105 (100); LRMS calculated for $C_{34}H_{32}NO_2P$ M^+ 517.21, found for $C_{34}H_{33}NO_2P$ MH^+, 518.2.

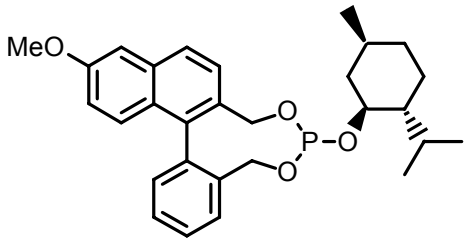
7.7.2.12 *N*-(3-Oxido-1,5-dihydronaphtho[2,1-*f*][2,4,3]benzodioxaphosphonin-3-yl)-*N*-[(1*R*)-1-phenylethyl]-*N*-[(1*R*)-1-phenylethyl]amine (277):



Phosphoramidate **277** was obtained as a thick yellow oil (0.57 g, 93% yield).

^{31}P nmr: δ = −5.115 ppm; MS (FAB) *m/z* (%) 534 (MH^+, 6), 518 (6), 307 (24), 289 (21), 229 (56), 154 (100), 136 (88), 105 (58); LRMS calculated for $C_{34}H_{32}NO_3P$ M^+ 533.21, found for $C_{34}H_{33}NO_3P$ MH^+, 534.5.

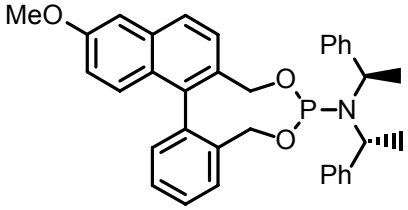
7.7.2.13 3-{[(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl]oxy}-1,5-dihydronaphtho[2,1-*f*][2,4,3]benzodioxaphosphonin-9-ylmethyl ether (263):



Phosphite **263** was obtained as white flakes (0.43 g, 88%).

^{31}P nmr: δ = 149.6 ppm, 149.5 ppm, 149.2 ppm and 148.5 ppm; MS (FAB) *m/z* (%) 479 (MH^+, 3), 465 (5), 356 (12), 335 (7), 259 (100), 247 (37), 200 (33), 139 (29); LRMS calculated for $C_{29}H_{35}O_4P$ M^+ 478.22, found for $C_{29}H_{36}O_4P$ MH^+, 479.2.

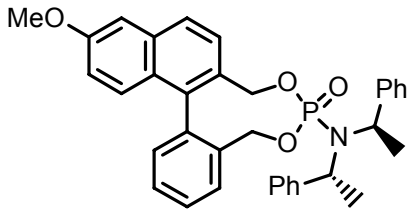
7.7.2.14 *N*-(9-Methoxy-1,5-dihydronaphtho[2,1-*f*][2,4,3]benzodioxaphosphonin-3-yl)-*N*-[(1*R*)-1-phenylethyl]-*N*-[(1*R*)-1-phenylethyl]amine (273):



Phosphoramidite **273** was obtained as thick yellow oil (0.26 g, 70%).

^{31}P nmr: δ = 152.6 ppm, 150.4 ppm, 149.8 ppm and 147.8 ppm.

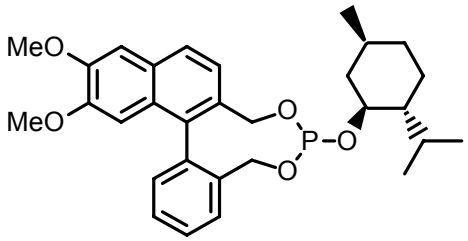
7.7.2.15 *N*-(9-Methoxy-3-oxido-1,5-dihydronaphtho[2,1-*f*][2,4,3]benzodioxaphosphonin-3-yl)-*N*-[(1*R*)-1-phenylethyl]-*N*-[(1*R*)-1-phenylethyl]amine (278):



Phosphoramidate **278** was produced as thick yellowish oil (0.62 g, 94%).

^{31}P nmr: δ = −4.358 ppm and −6.213 ppm.

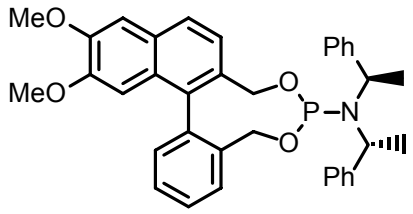
7.7.2.16 3-{[(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl]oxy}-1,5-dihydronaphtho[2,1-*f*][2,4,3]benzodioxaphosphonin-9-yl methyl ether (264):



Phosphite **264** was synthesized as thick yellow oil (0.42 g, 89%).

^{31}P nmr: δ = 152.0 ppm and 151.3 ppm; MS (FAB) *m/z* (%) 509 (MH^+, 5), 387 (14), 371 (28), 289 (86), 139 (100), 102 (55); LRMS calculated for $C_{30}H_{37}O_5P$ M^+ 508.24, found for $C_{30}H_{38}O_3P$ MH^+, 509.4.

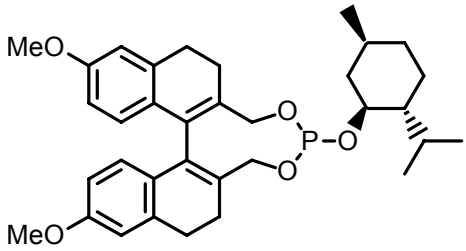
7.7.2.17 *N*-(9,10-Dimethoxy-1,5-dihydronaphtho[2,1-*f*][2,4,3] benzodioxaphosphonin-3-yl)-*N*-[(1*R*)-1-phenylethyl]-*N*-[(1*R*)-1-phenylethyl]amine (274):



Phosphoramidite **274** was synthesized as yellowish flakes (0.45 g, 85%).

^{31}P nmr: δ = 149.6 ppm and 149.5 ppm; MS (FAB) *m/z* (%) 578 (MH^+, 16), 306 (12), 289 (13), 226 (100), 154 (43), 105 (80); LRMS calculated for $C_{36}H_{36}NO_4P$ M^+ 577.24, found for $C_{36}H_{37}NO_4P$ MH^+, 578.4.

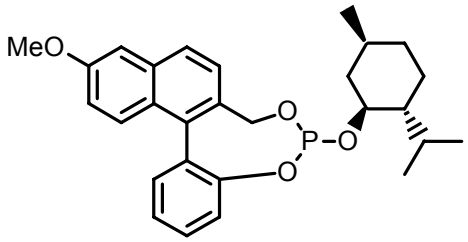
7.7.2.18 13-{[(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl]oxy}-2,7-dimethoxy-9,10,11,15,16,17-hexahydrodinaphtho[2,1-*e*:1,2-*g*][1,3,2] dioxaphosphonine (265):



Phosphite **265** was obtained as a white foam (0.22 g, 73%).

^{31}P nmr: δ = 154.6 ppm and 153.2 ppm.

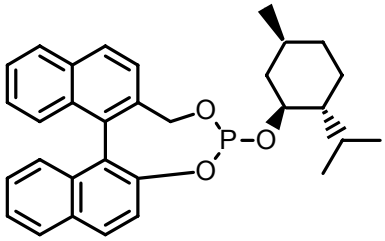
7.7.2.19 2-{[(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl]oxy}-4*H*-naphtho[2,1-*e*][1,3,2]benzodioxaphosphocin-8-yl methyl ether (267):



Phosphite **267** was obtained as white flakes (0.31 g, 91% yield).

^{31}P nmr: δ = 105.7 ppm and 104.2 ppm.

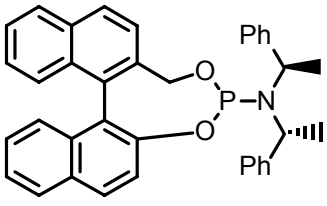
7.7.2.20 12-{[(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl]oxy}-14*H*-dinaphtho[2,1-*d*:1,2-*f*][1,3,2]dioxaphosphocine (223):



Product **223** was produced as white flakes (0.41 g, 85%).

^{31}P nmr: δ = 144.0 ppm, 142.9 ppm, 142.5 ppm and 140.4 ppm.

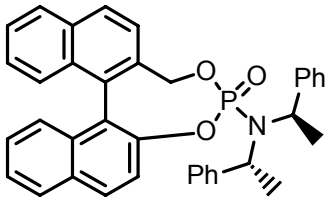
7.7.2.21 *N*-(14*H*-Dinaphtho[2,1-*d*:1,2-*f*][1,3,2]dioxaphosphocin-12-yl)-*N*-[(1*R*)-1-phenylethyl]-*N*-[(1*R*)-1-phenylethyl]amine (224):



Phosphoramidite **224** was obtained as white flakes (0.38 g, 83%).

^{31}P nmr: δ = 109.9 ppm and 108.2 ppm; MS (FAB) *m/z* (%) 556 (MH^+, 3), 477 (2), 339 (3), 200 (21), 179 (22), 102 (100); LRMS calculated for $C_{37}H_{32}NO_2P$ M^+ 555.21, found for $C_{37}H_{33}NO_2P$ MH^+, 556.3.

7.7.2.22 *N*-(14*H*-Dinaphtho-12-oxido-[2,1-*d*:1,2-*f*][1,3,2]dioxaphosphocin-12-yl)-*N*-[(1*R*)-1-phenylethyl]-*N*-[(1*R*)-1-phenylethyl]amine (282):



Phosphoramidate **282** was obtained as thick yellowish oil (0.57 g, 86% yield).

^{31}P nmr: $\delta = -16.27$ ppm.

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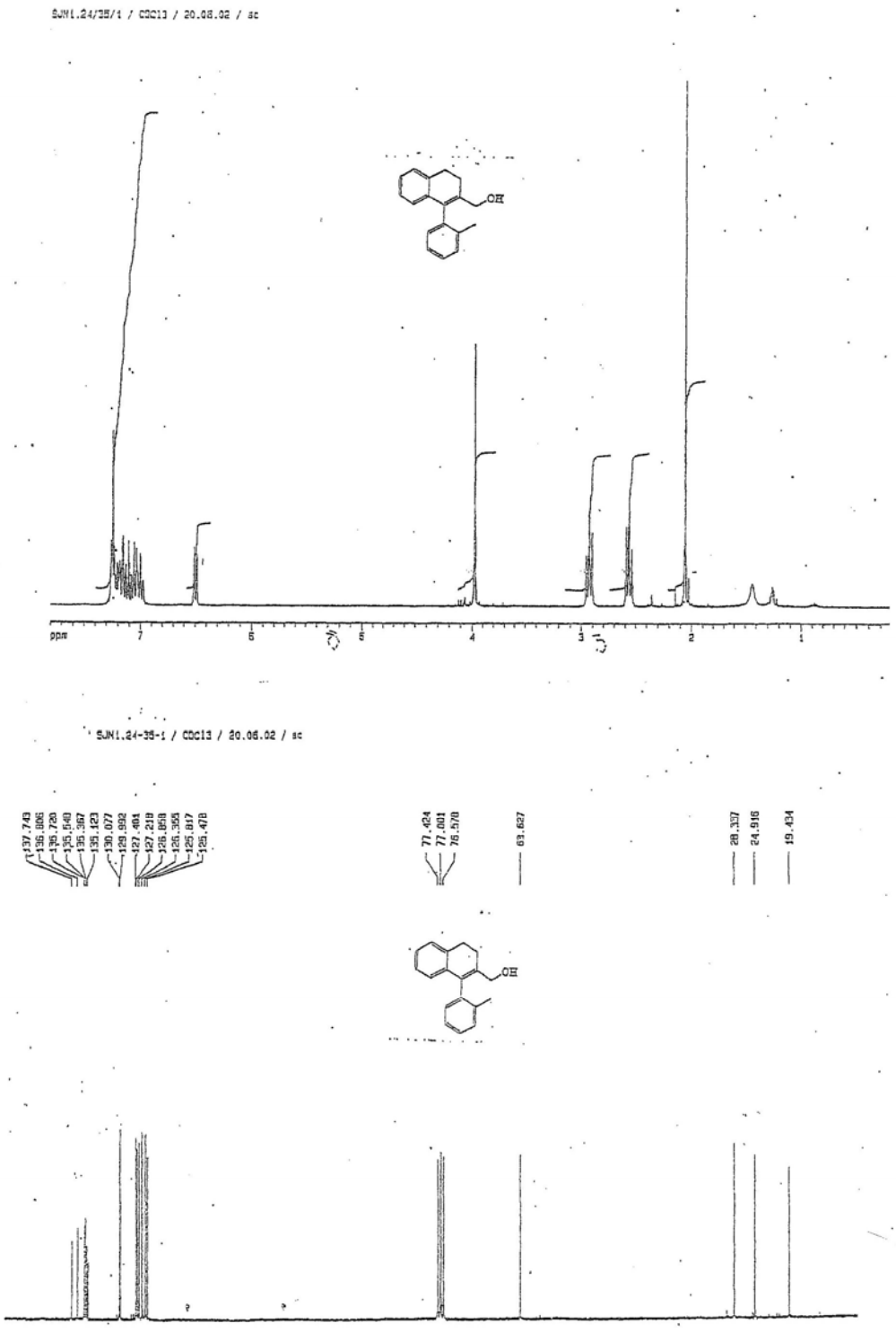
Appendices

Appendix 1: Selected ^{1}H , ^{13}C and ^{31}P nmr spectra

Compound	Page
[1-(*o*-Tolyl)-3,4-dihydronaphthalen-2-yl]methanol (**79**)	201
[1-(*o*-Tolyl)-3,4-dihydronaphthalen-2-yl]methyl acetate (**82**)	202
[6,7-Dimethoxy-1-(1-naphthyl)-3,4-dihydronaphthalen-2-yl]methyl acetate (**96**)	203
[1-(3,4,5-Trimethoxyphenyl)naphthalen-2-yl]methyl acetate (**58**)	204
6,7-Dimethoxy-1-phenyl-3,4-dihydro-2-naphthaldehyde (**89**)	205
[6,7-Dimethoxy-1-(3,4,5-trimethoxyphenyl)naphthalen-2-yl]methyl acetate (**95**)	206
(6,7-Dimethoxy-1-phenylnaphthalen-2-yl)methyl acetate (**97**)	207
7b-(3,4,5-Trimethoxyphenyl)-1a,2,3,7b-tetrahydro-1*H*-cyclopropa-[*a*]naphthalene (**125**)	208
1-(2-Formylnaphthyl)-2-naphthaldehyde **(231)**	209
1-(2-Formylphenyl)-6-methoxy-2-naphthaldehyde (**226**)	210
1-(2-Isopropoxyphenyl)-6-methoxy-2-naphthaldehyde (**238**)	211
(2'-Hydroxymethyl-[1,1']binaphthyl-2-yl)-methanol (**251**)	212
[1-(2-Hydroxymethyl-phenyl)-2-naphthyl]-methanol (**254**)	213
[1-(2-Hydroxymethyl-phenyl)-6-methoxynaphthalen-2-yl]-methanol (**255**)	214
2'-Hydroxymethyl-6'-methoxy-[1,1']binaphthalenyl-2-ol (**252**)	215
2'-Hydroxymethyl-6',7'-dimethoxy-[1,1']binaphthalenyl-2-ol (**253**)	216
13-{[(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl]oxy}-11,15-dihydrodinaphtho[2,1-*e*:1,2-*g*][1,3,2]dioxaphosphonine (**221**)	217
13-{[(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl]oxy}-11,15-dihydrodinaphtho[2,1-*e*:1,2-*g*] [1,3,2]dioxaphosphonine 13-oxide (**270**)	218

3-{[(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl]oxy}-1,5-dihydronaphtho[2,1-*f*][2,4,3]benzodioxaphosphonine-3-oxide (**269**)	219
N-(3-Oxido-1,5-dihydronaphtho[2,1-*f*][2,4,3]benzodioxaphosphonin-3-yl)-*N*-[(1*R*)-1-phenylethyl]-*N*-[(1*R*)-1-phenylethyl]amine (**280**)	220
7-{[(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl]oxy}-5,9-dihydrodibenzo[*e*,*g*][1,3,2]dioxaphosphonine (**266**)	221
7-{[(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl]oxy}-5,9-dihydrodibenzo[*e*,*g*][1,3,2]dioxaphosphonine 7-oxide (**271**)	222
N-(5,9-Dihydrodibenzo[*e*,*g*][1,3,2]dioxaphosphonin-7-yl)-*N*-[(1*R*)-1-phenylethyl]-*N*-[(1*R*)-1-phenylethyl]amine (**277**)	223
N-(7-Oxido-5,9-dihydrodibenzo[*e*,*g*][1,3,2]dioxaphosphonin-7-yl)-*N*-[(1*R*)-1-phenylethyl]-*N*-[(1*R*)-1-phenylethyl]amine (**283**)	224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6
5
4
3
2
1
SJN1.24-35-1 / CDCl3 / 20.06.02 / sc
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136.726
135.540
135.367
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127.404
127.219
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125.817
125.478
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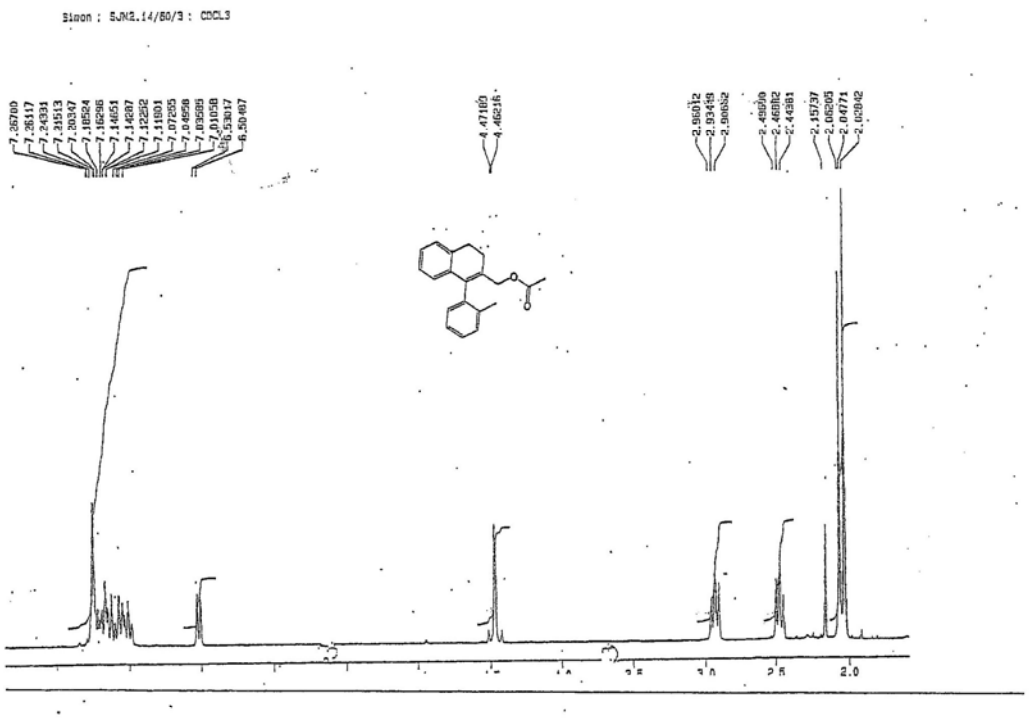
77.001
76.578
63.627
28.357
24.916
19.434
OH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7.14651
7.14087
7.12282
7.11801
7.07295
7.04556
7.03589
7.01058
6.53017
6.50467
4.47169
4.46216
2.96012
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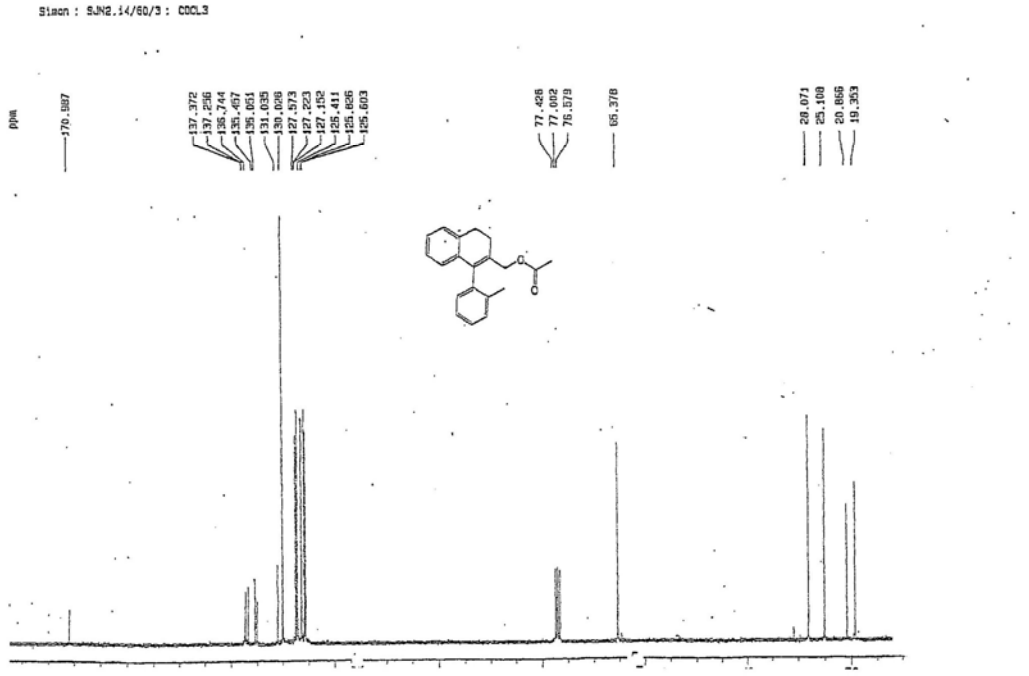
2.03842
2.0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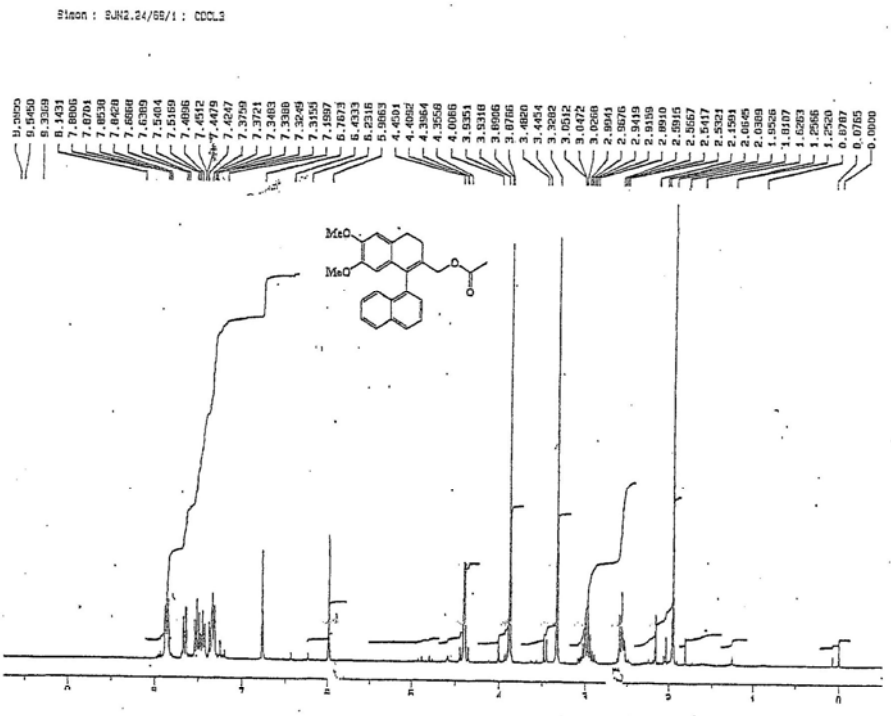
19.353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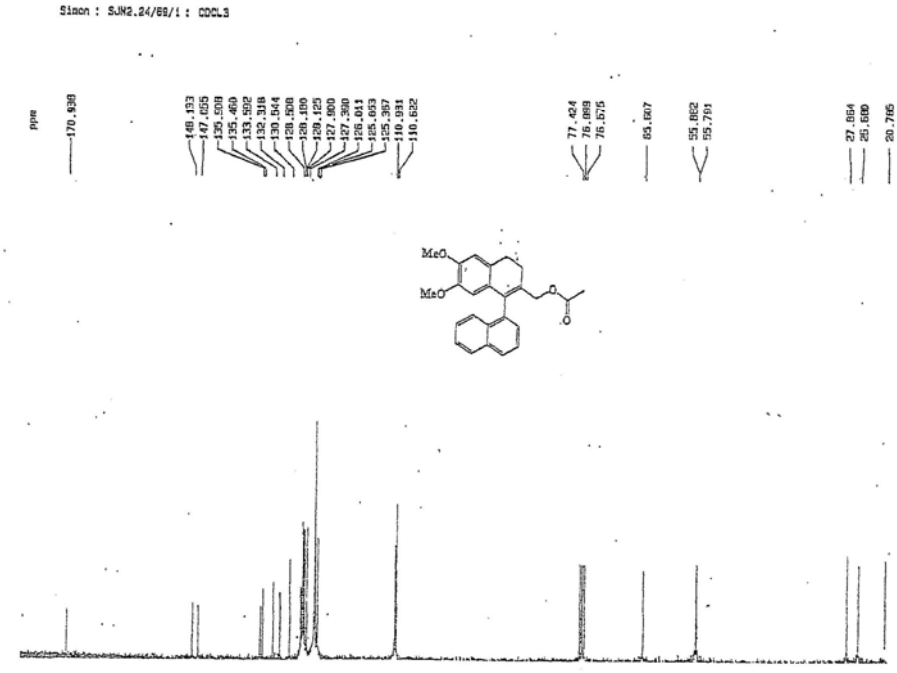
MeO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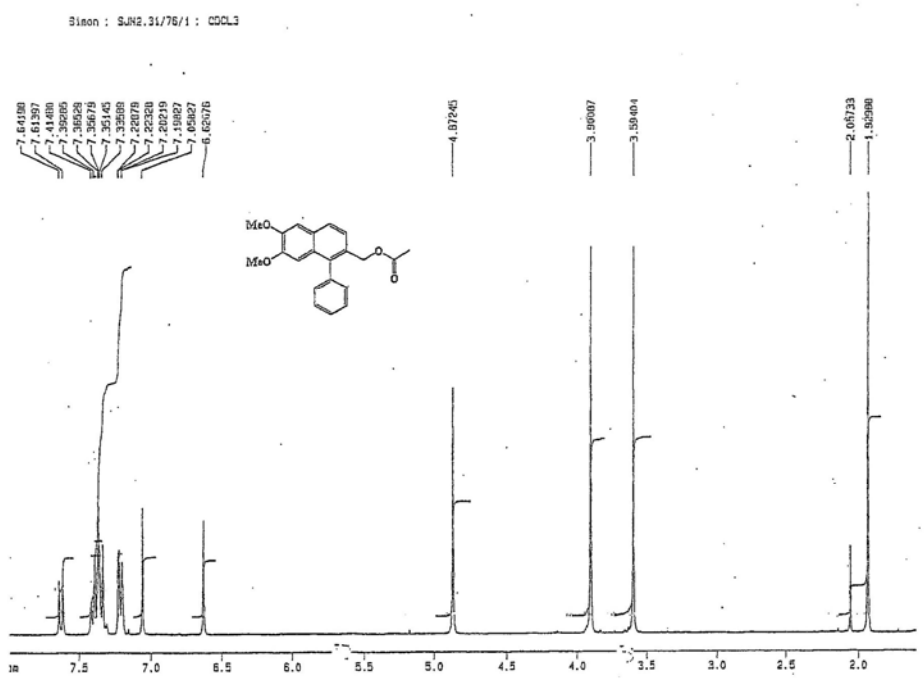
ppm
MeO
MeO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7.33588
7.22879
7.22328
7.20219
7.19827
7.05827
6.62676
4.87245
3.90007
3.59404
2.05733
1.92988
MeO
MeO
O
O
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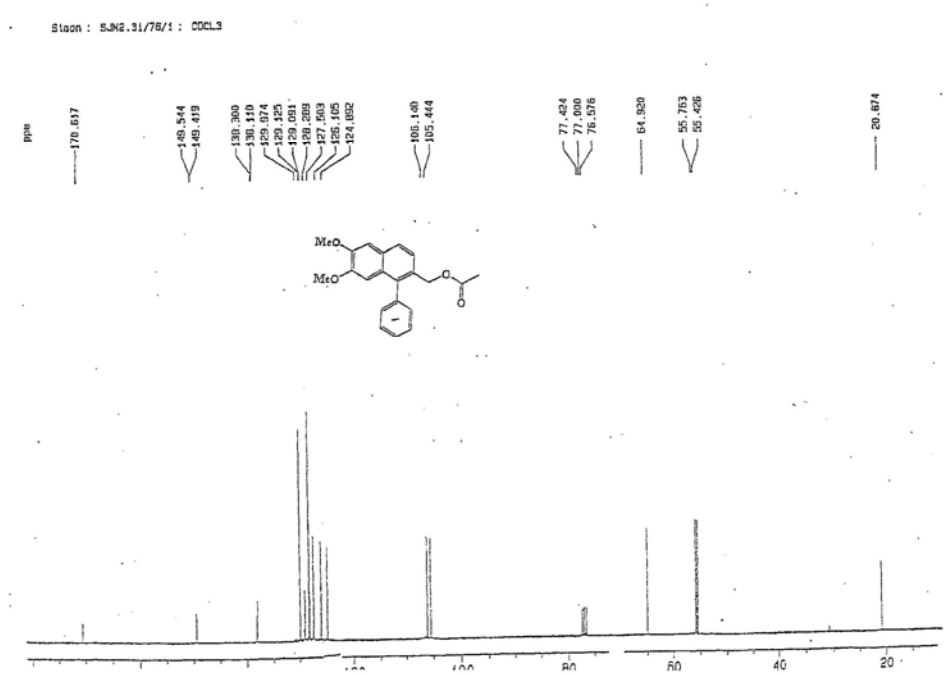
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0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129.091
128.289
127.503
126.105
124.892
106.140
105.444
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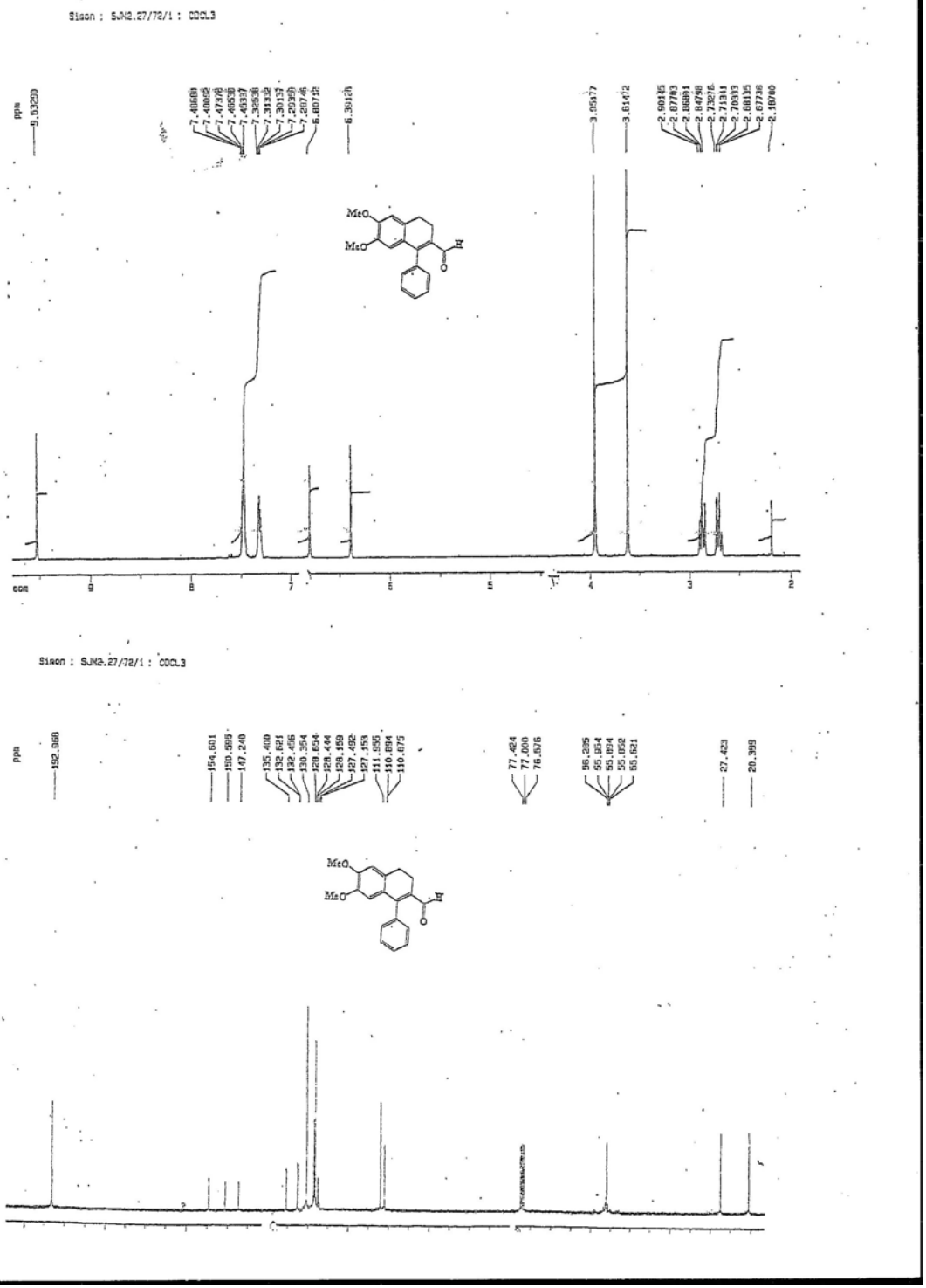
77.000
76.576
64.920
55.763
55.426
20.674
MeO
MeO
O
O
80
60
40
20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7.32536
7.31332
7.30137
7.29329
7.26746
6.80712
6.39126
3.85177
3.61472
2.90125
2.87783
2.86891
2.84768
2.73276
2.71341
2.70333
2.68135
2.67738
2.18780
MeO
MeO
H
O
ppm
9
8
7
6
5
4
3
2
Sisan : SJM2.27/72/1 : CDCL3
ppm
192.868
154.601
150.599
147.240
135.409
132.621
132.456
130.354
128.654
128.444
128.159
127.492
127.153
111.995
110.894
110.675
77.424
77.000
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56.285
55.954
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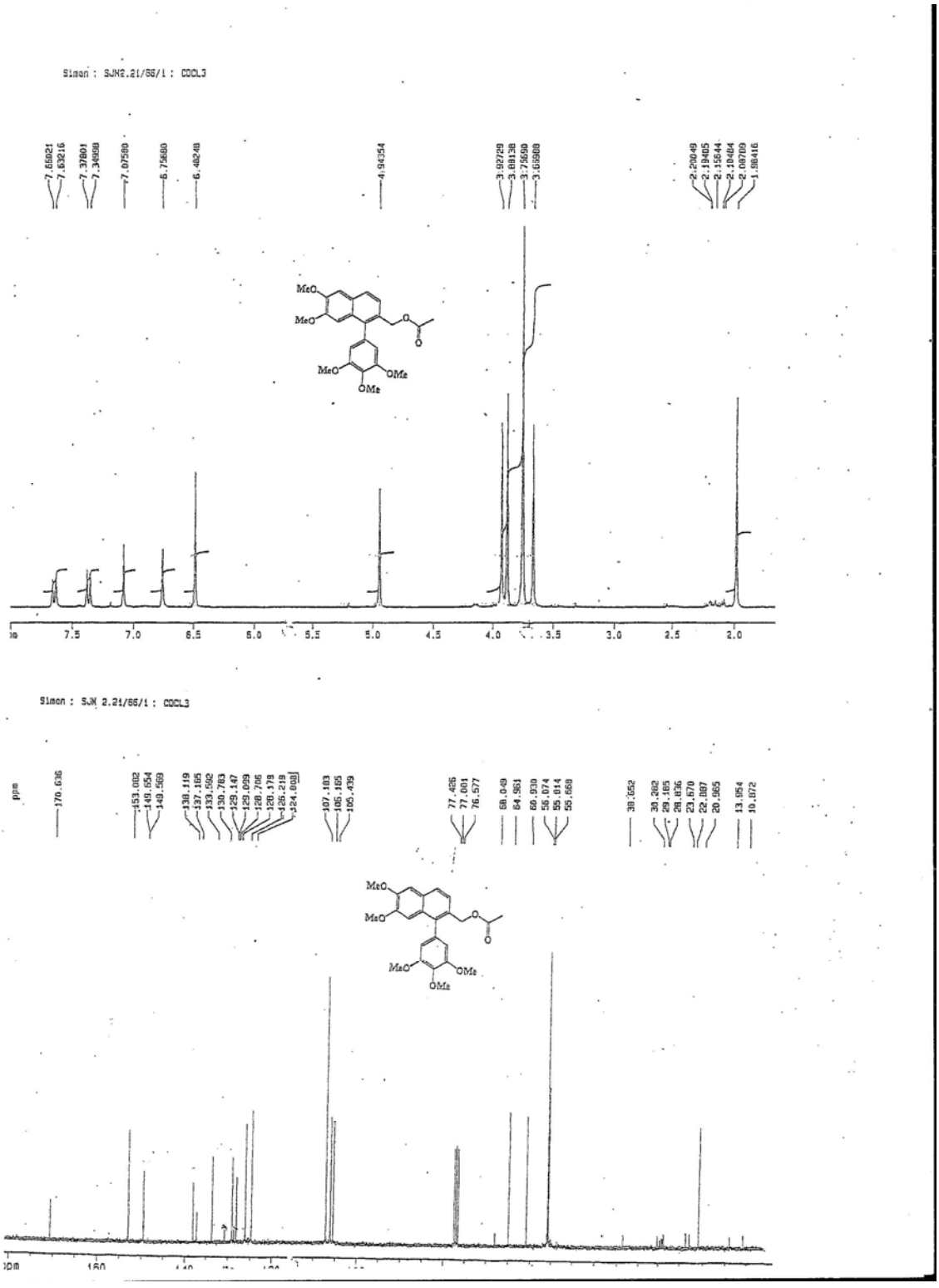
55.852
55.621
27.423
20.399
MeO
MeO
H
O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7.37801
7.34999
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6.75680
6.48248
4.94054
3.92729
3.88138
3.75690
3.65988
2.20049
2.19405
2.15644
2.10404
2.08709
1.98416
MeO
MeO
MeO
OMe
OMe
O
O
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
Simon : SJM 2.21/66/1 : CDCL3
ppm
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149.654
149.569
138.119
137.165
133.592
130.783
129.147
129.099
128.706
128.179
126.219
124.698
107.183
105.165
105.439
77.426
77.001
76.577
60.049
64.961
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55.914
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38.652
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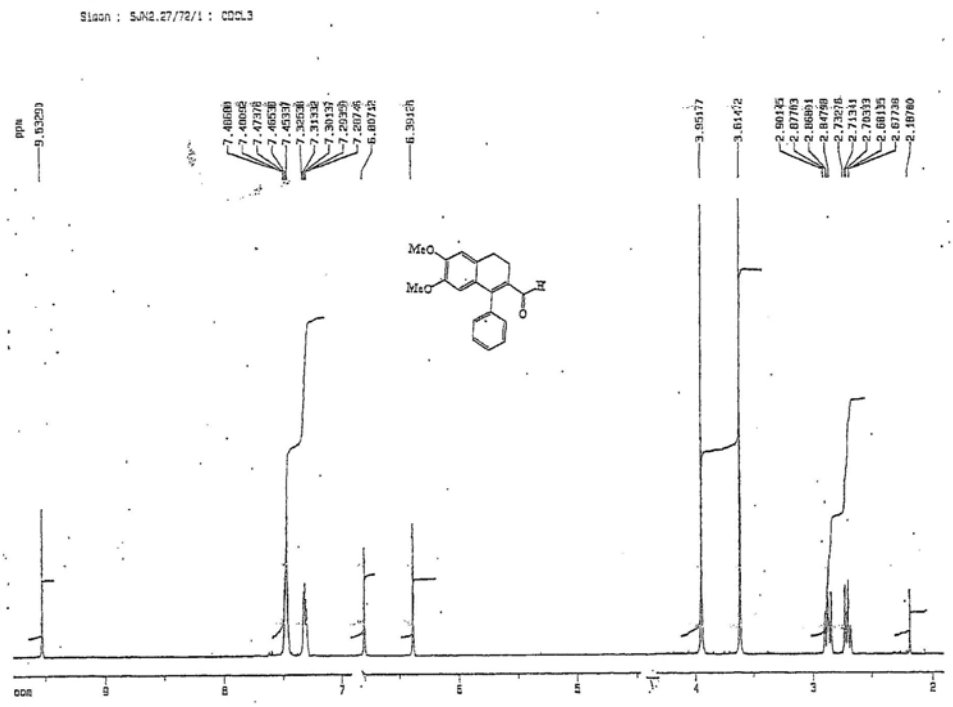
13.954
10.072
MeO
MeO
MeO
OMe
OMe
O
O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7.32538
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7.30137
7.29399
7.28746
6.80712
6.39128
3.95177
3.61472
2.90125
2.87783
2.86891
2.84798
2.73276
2.71341
2.70333
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2.67738
2.18780
MeO
MeO
H
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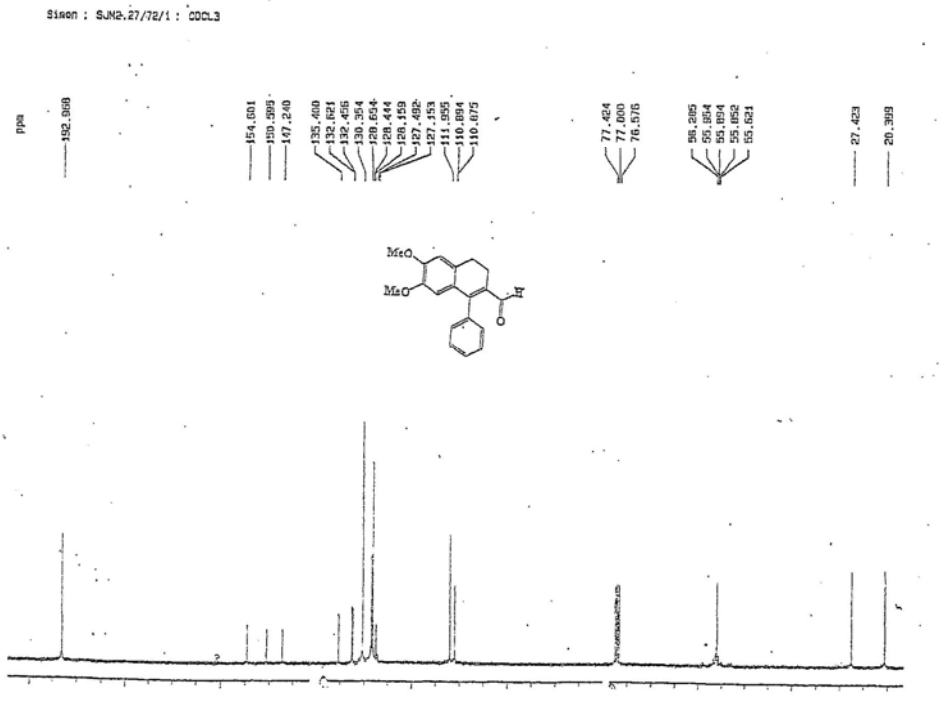
7
6
5
4
3
2


Simon : SJM2.27/72/1 : CDCL3
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132.621
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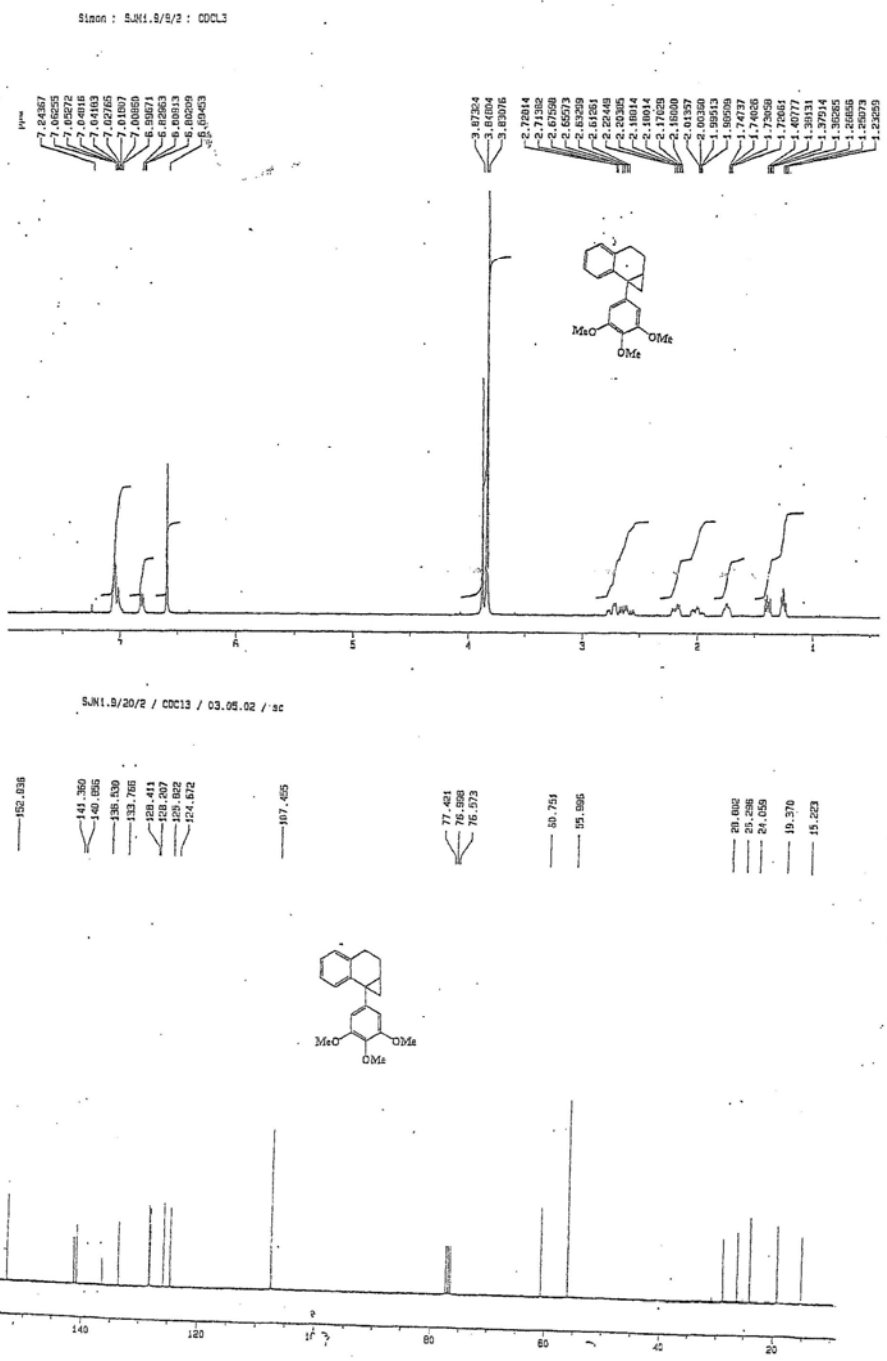
130.354
128.654
128.444
128.159
127.492
127.153
111.955
110.894
110.875
77.424
77.000
76.576
56.285
55.854
55.894
55.852
55.621
27.423
20.389
MeO
MeO
H
O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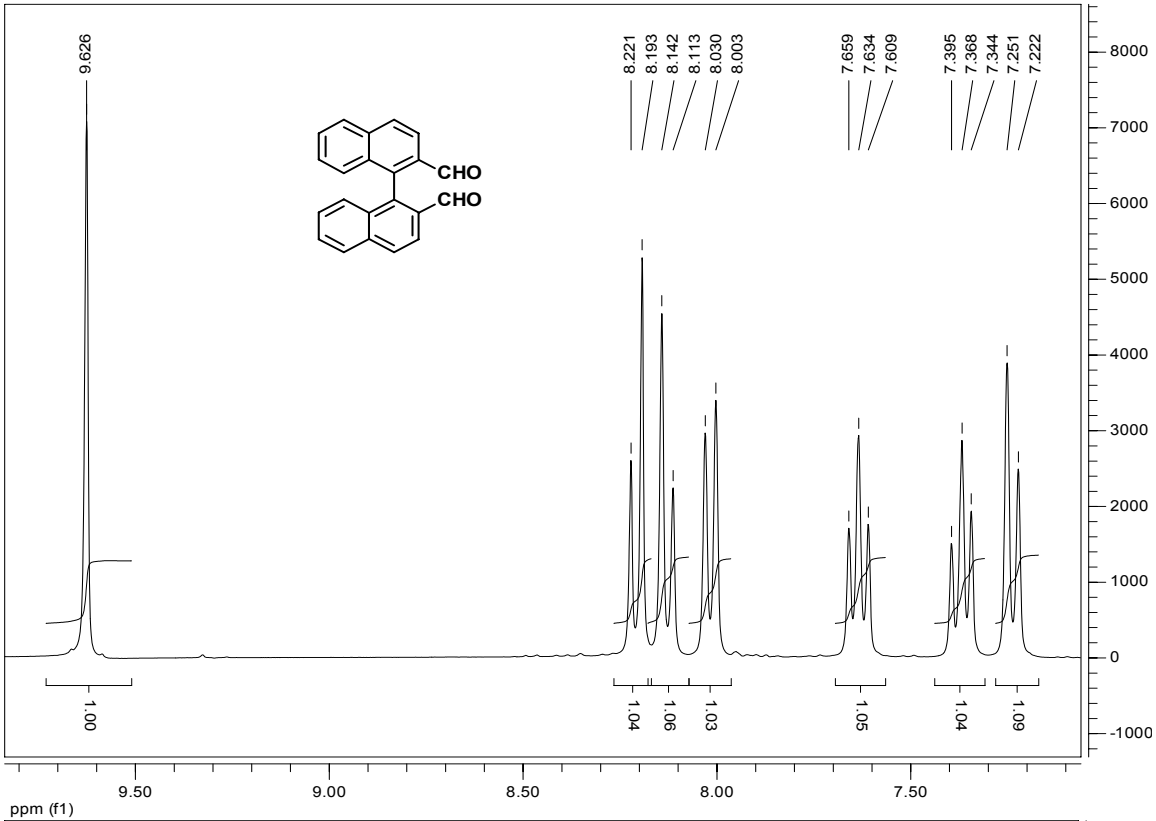
SJN1.9/20/2 / CDCl3 / 03.05.02 / sc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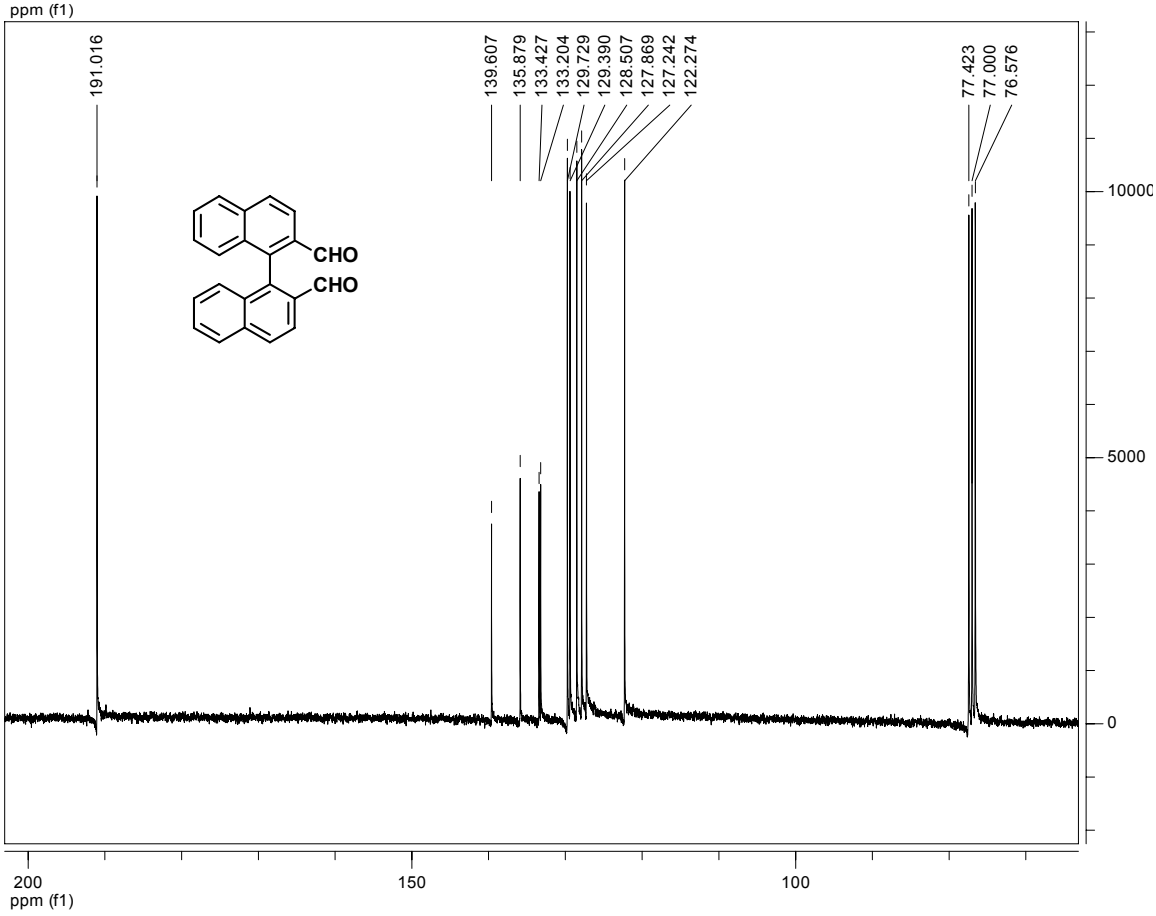
7.344
7.251
7.222
CHO
CHO
1.00
1.04
1.06
1.03
1.05
1.04
1.09
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
9.50
9.00
8.50
8.00
7.50
ppm (f1)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77.000
76.576
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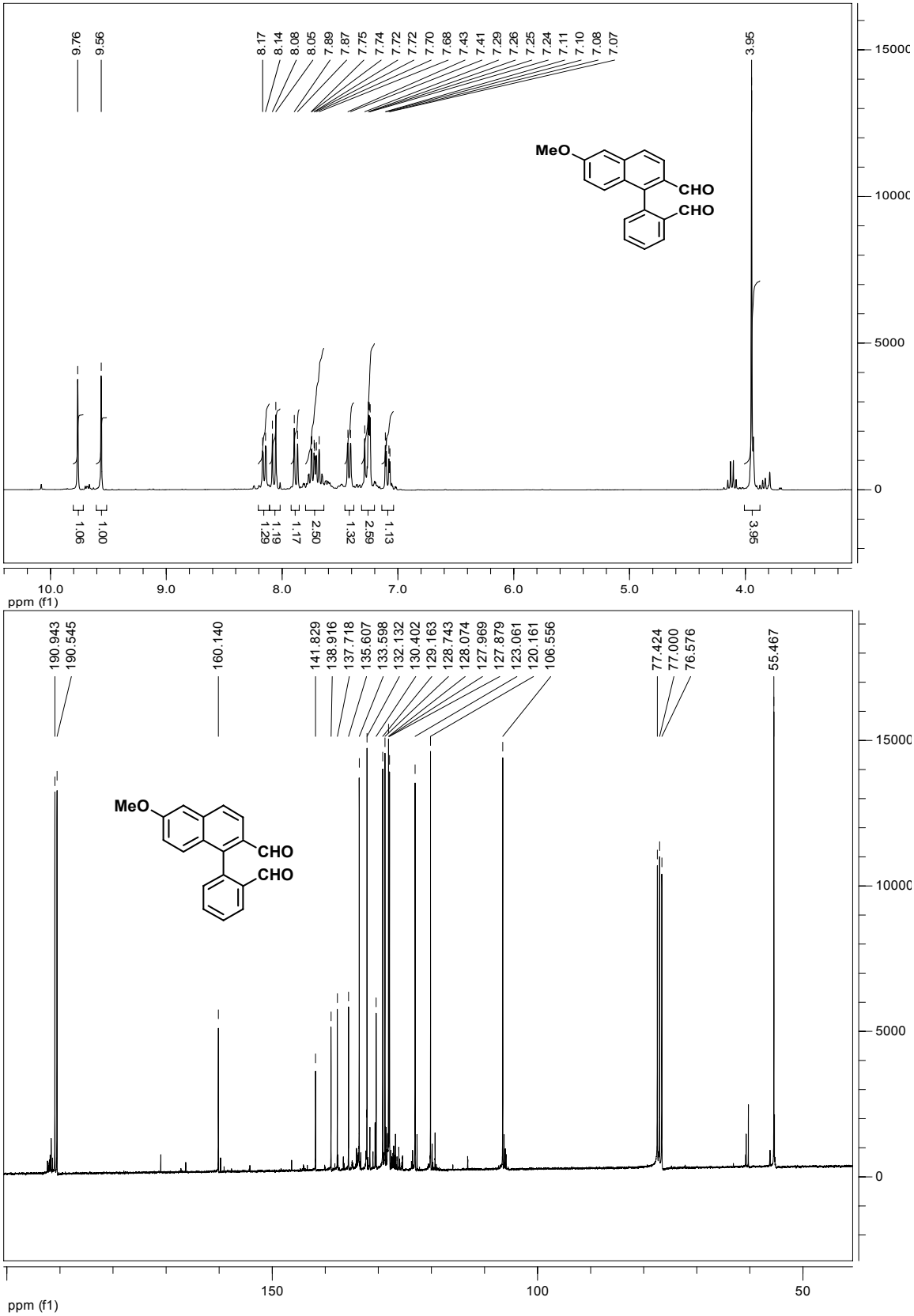
CHO
10000
5000
0
200
150
100
ppm (f1)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8.08
8.05
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7.87
7.75
7.74
7.72
7.72
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7.68
7.43
7.41
7.29
7.26
7.25
7.24
7.11
7.10
7.08
7.07
3.95
MeO
CHO
CHO
1.06
1.00
1.29
1.19
1.17
2.50
1.32
2.59
1.13
3.95
15000
10000
5000
0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
ppm (f1)
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190.545
160.140
141.829
138.916
137.718
135.607
133.598
132.132
130.402
129.163
128.743
128.074
127.969
127.879
123.061
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106.556
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5000
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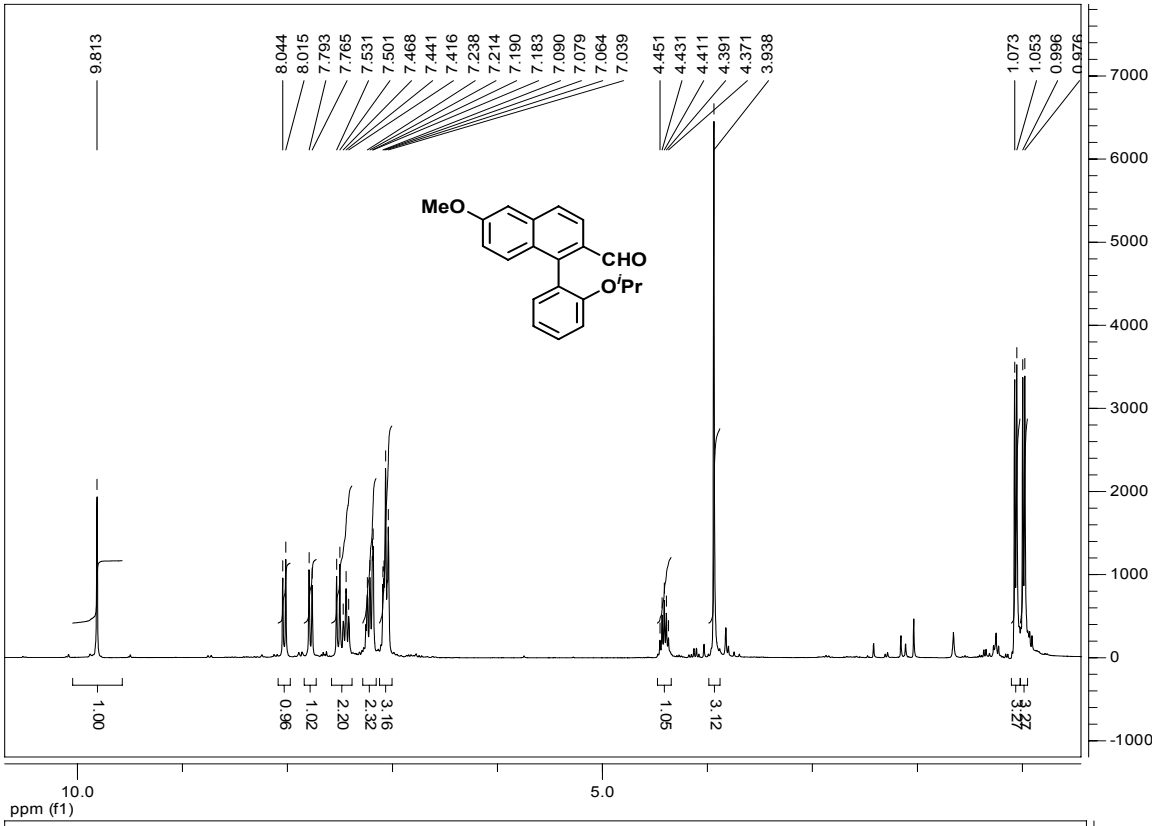
100
50
ppm (f1)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7.416
7.238
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7.190
7.183
7.090
7.079
7.064
7.039
4.451
4.431
4.411
4.391
4.371
3.938
1.073
1.053
0.996
0.976
MeO
CHO
O^{i}Pr
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0.96
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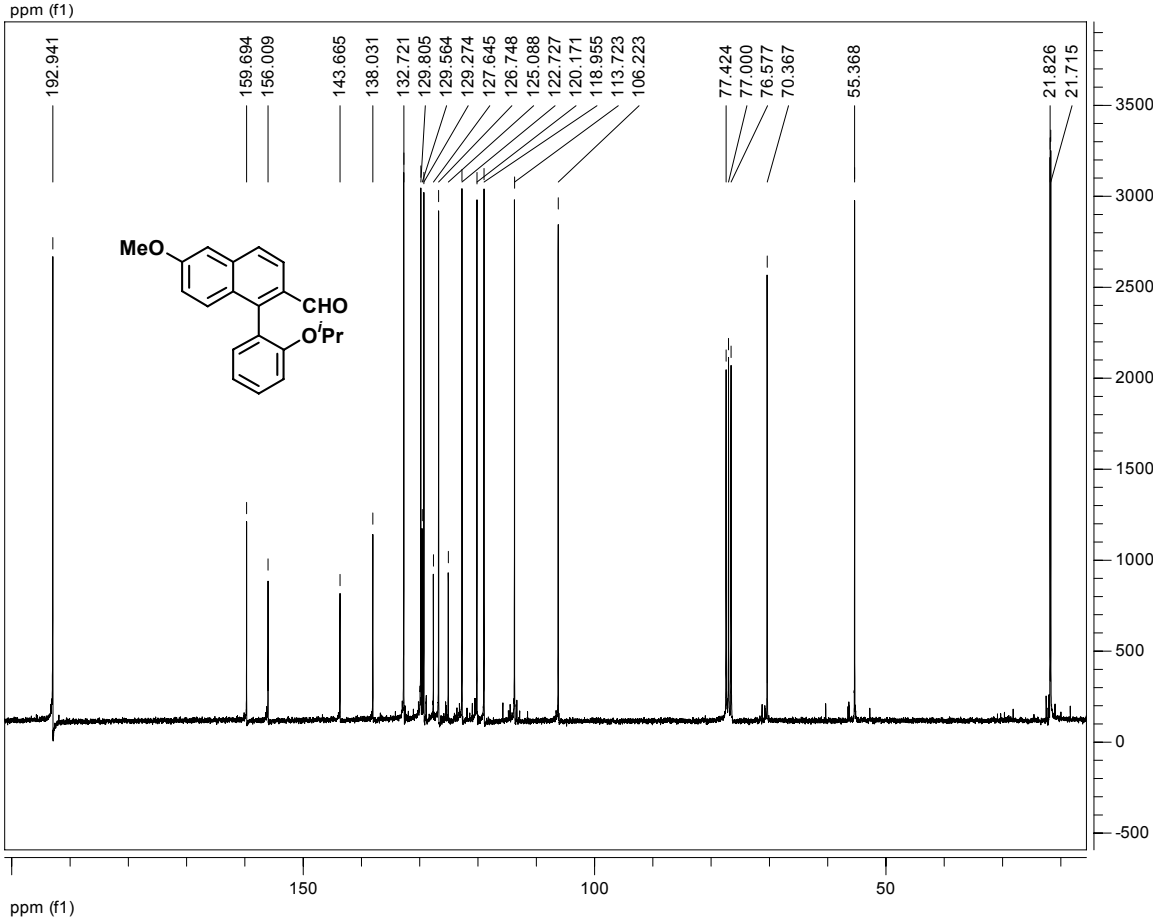
2.32
3.16
1.05
3.12
3.27
10.0
5.0
ppm (f1)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122.727
120.171
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113.723
106.223
77.424
77.000
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55.368
21.826
21.715
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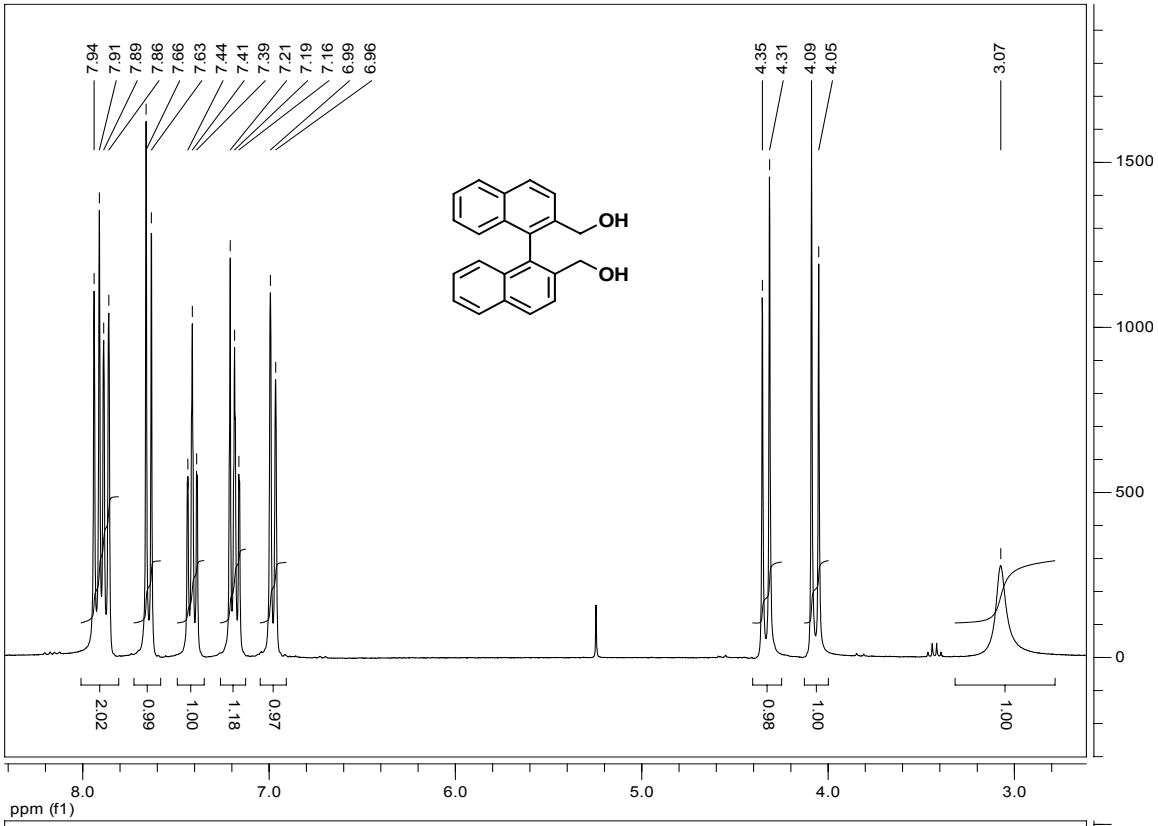
CHO
O^{i}Pr
150
100
50
ppm (f1)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7.89
7.86
7.66
7.63
7.44
7.41
7.39
7.21
7.19
7.16
6.99
6.96
4.35
4.31
4.09
4.05
3.07
OH
OH
2.02
0.99
1.00
1.18
0.97
0.98
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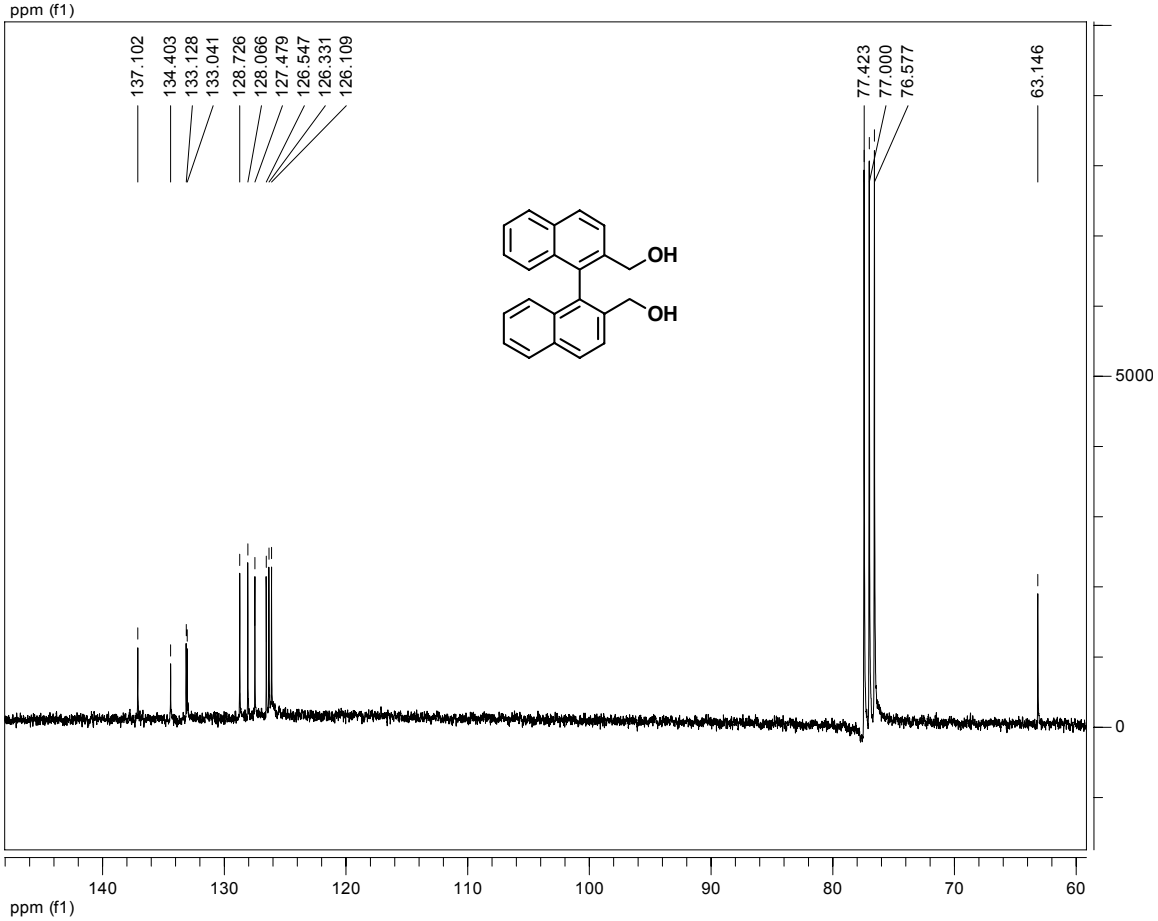
1500
1000
500
0
8.0
7.0
6.0
5.0
4.0
3.0
ppm (f1)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126.109
77.423
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76.577
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OH
OH
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0
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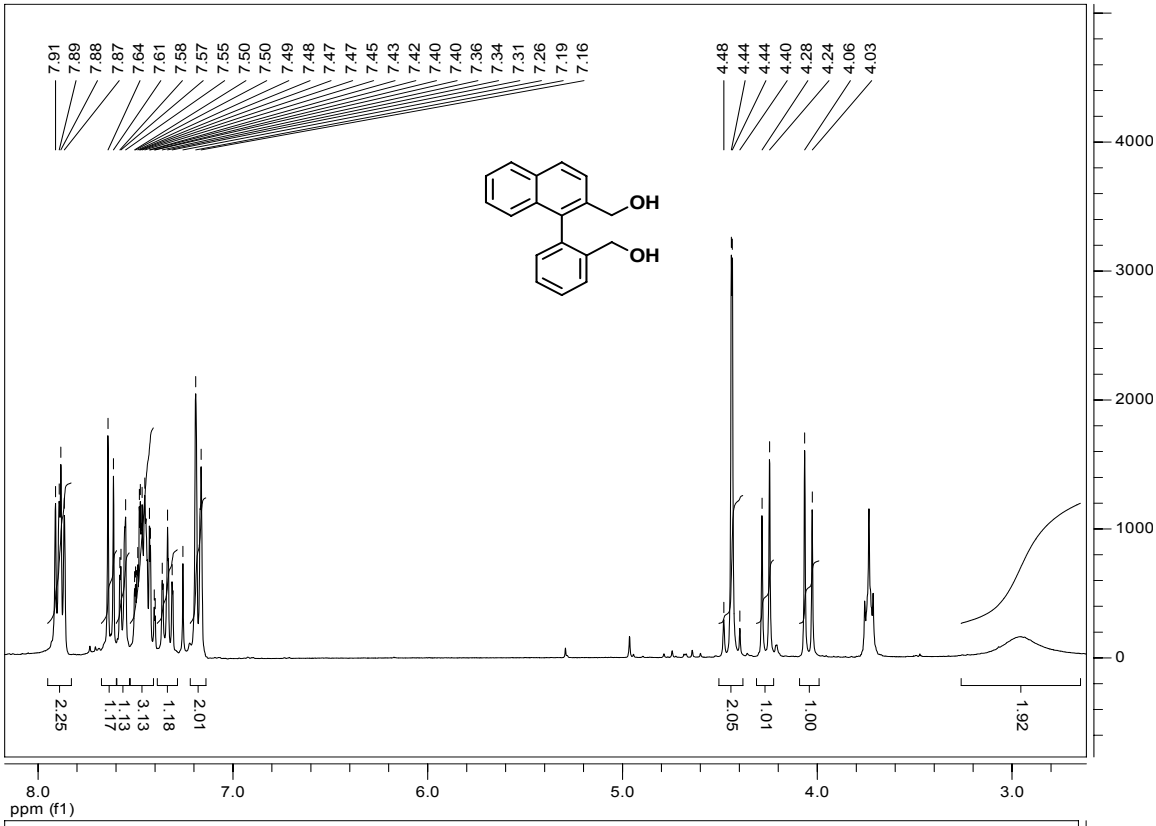
130
120
110
100
90
80
70
60
ppm (f1)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7.50
7.50
7.49
7.48
7.47
7.47
7.45
7.43
7.42
7.40
7.40
7.36
7.34
7.31
7.26
7.19
7.16
4.48
4.44
4.44
4.40
4.28
4.24
4.06
4.03
OH
OH
2.25
1.17
1.13
3.13
1.18
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1.00
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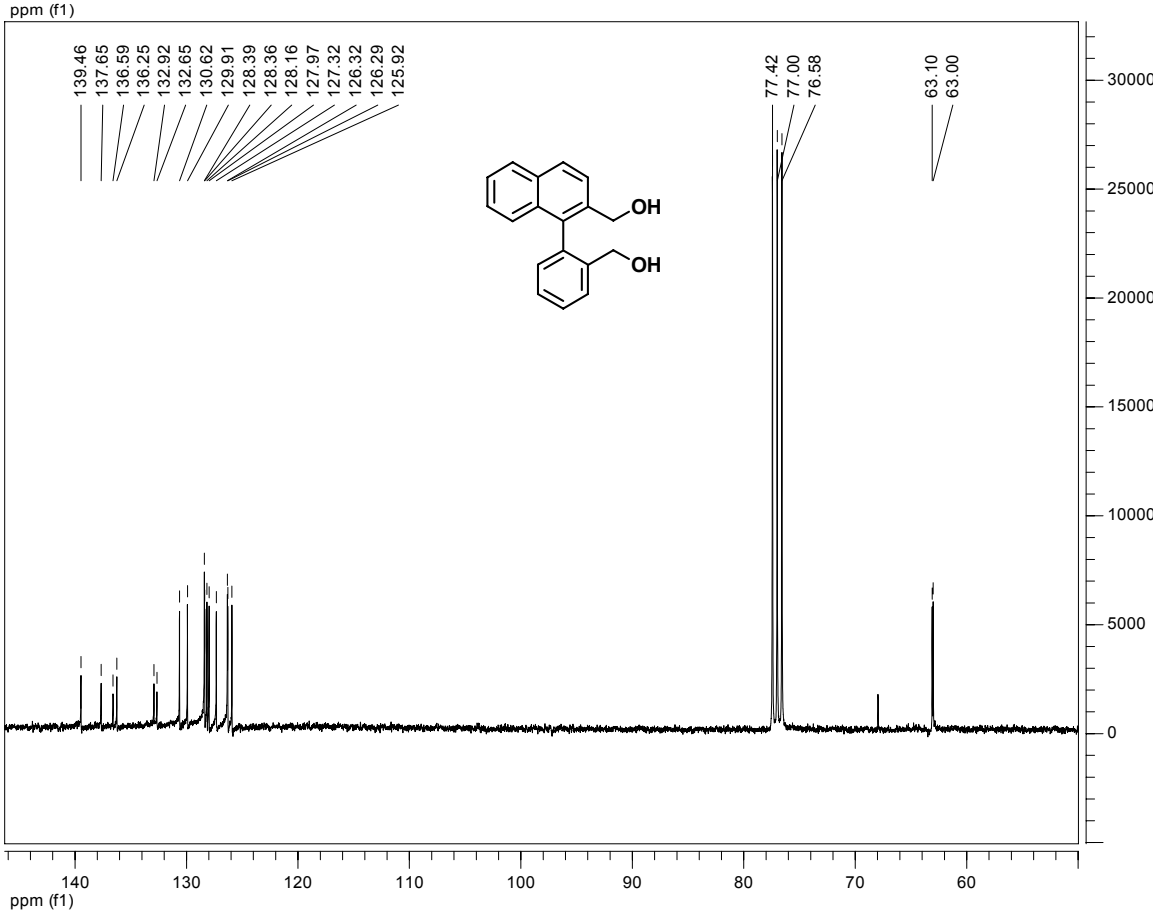
ppm (f1)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127.32
126.32
126.29
125.92
77.42
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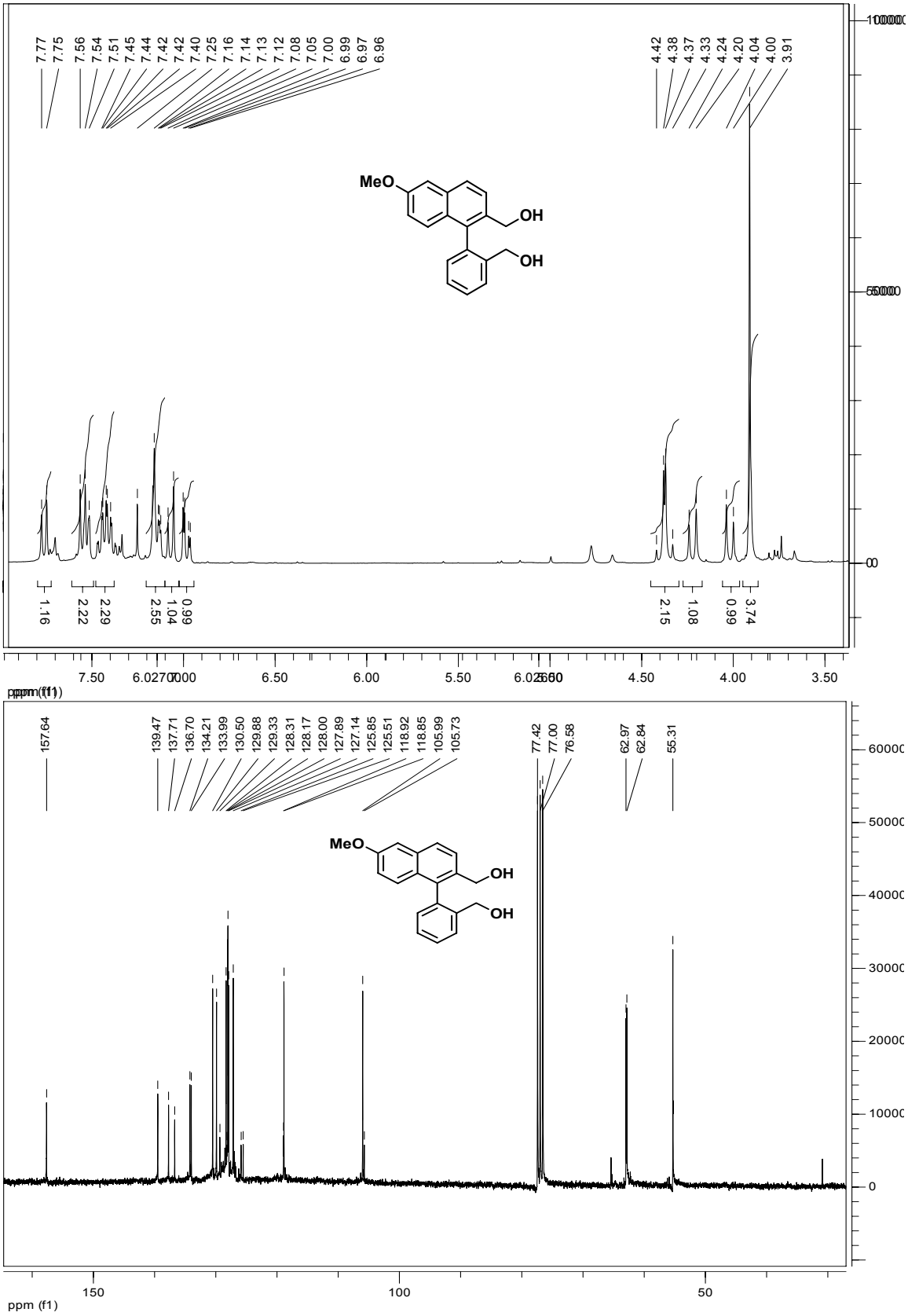
76.58
63.10
63.00
OH
OH
140
130
120
110
100
90
80
70
60
ppm (f1)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7.40
7.25
7.16
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7.13
7.12
7.08
7.05
7.00
6.99
6.97
6.96
4.42
4.38
4.37
4.33
4.24
4.20
4.04
4.00
3.91
MeO
OH
OH
1.16
2.22
2.29
2.55
1.04
0.99
2.15
1.08
0.99
3.74
7.50
6.50
6.00
5.50
4.50
4.00
3.50
ppm (f1)
157.64
139.47
137.71
136.70
134.21
133.99
130.50
129.88
129.33
128.31
128.17
128.00
127.89
127.14
125.85
125.51
118.92
118.85
105.99
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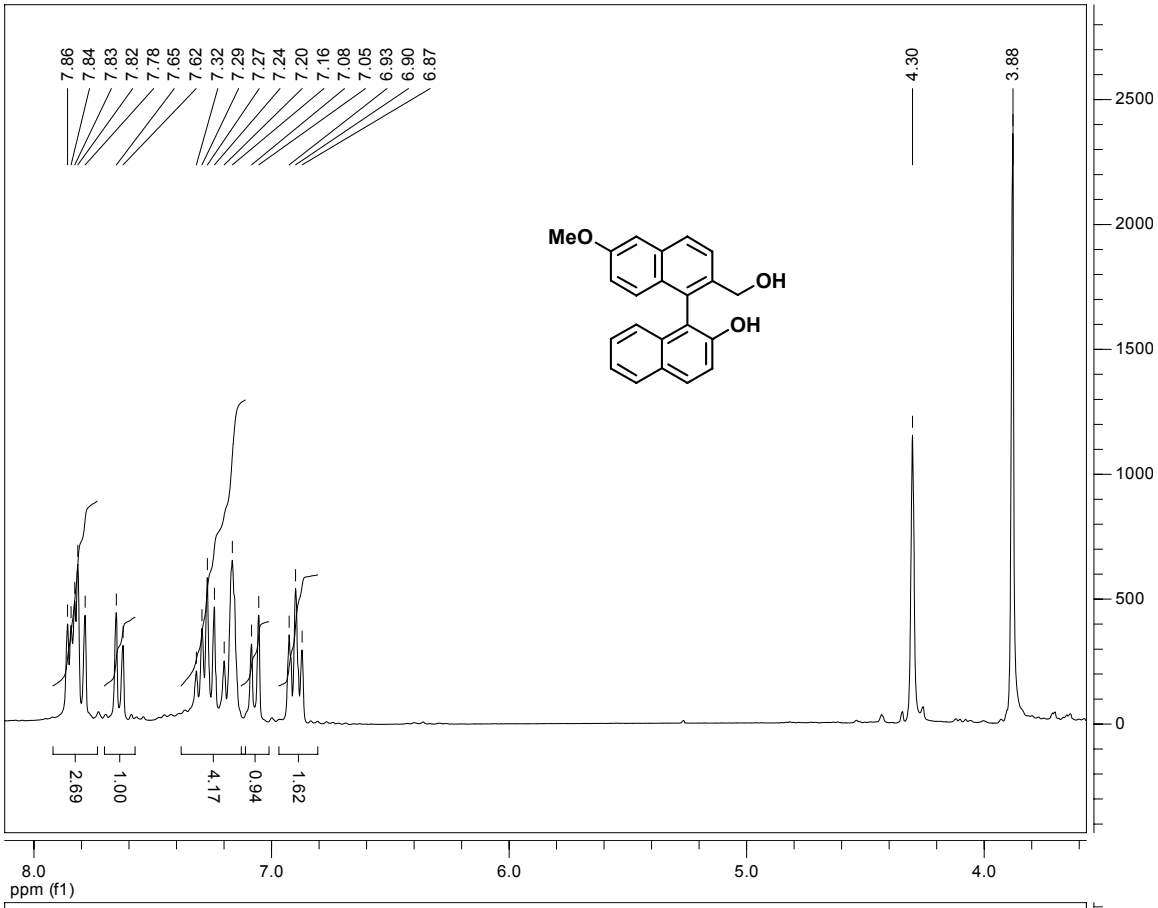
76.58
62.97
62.84
55.31
MeO
OH
OH
150
100
50
ppm (f1)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7.78
7.65
7.62
7.32
7.29
7.27
7.24
7.20
7.16
7.08
7.05
6.93
6.90
6.87
4.30
3.88
MeO
OH
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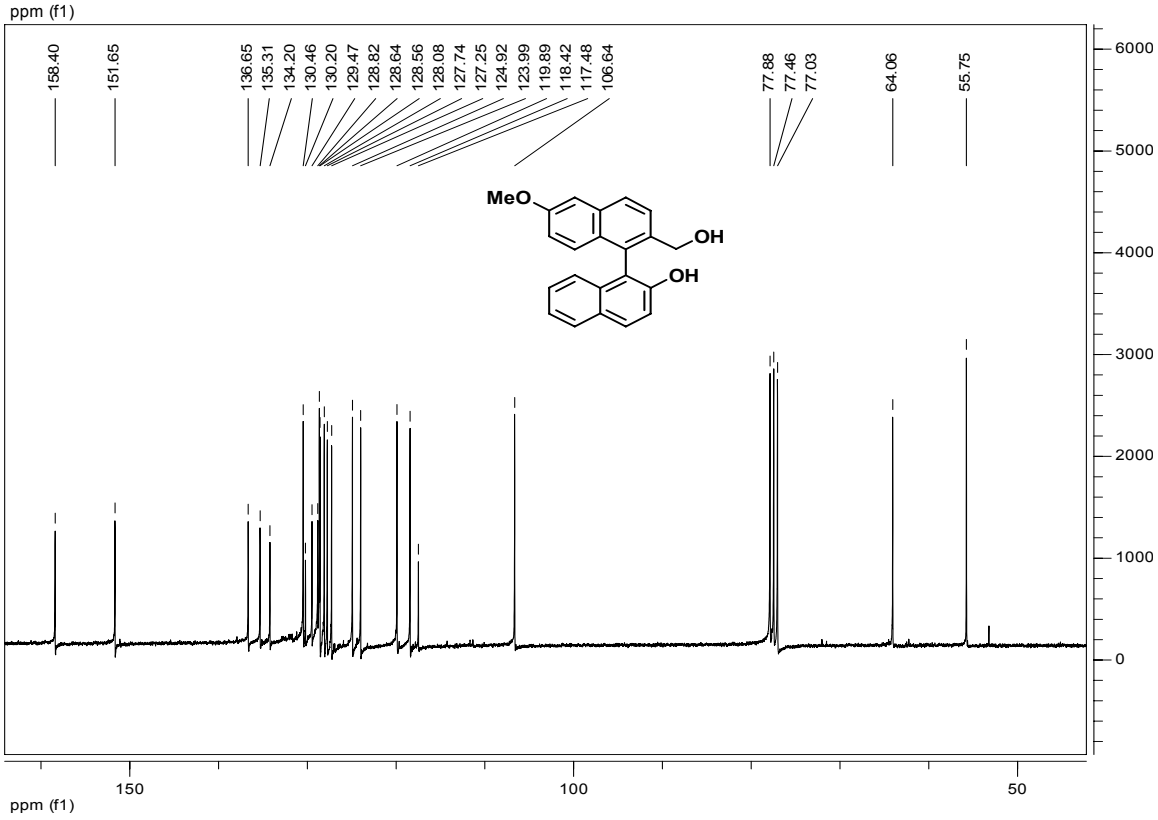
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127.25
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123.99
119.89
118.42
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OH
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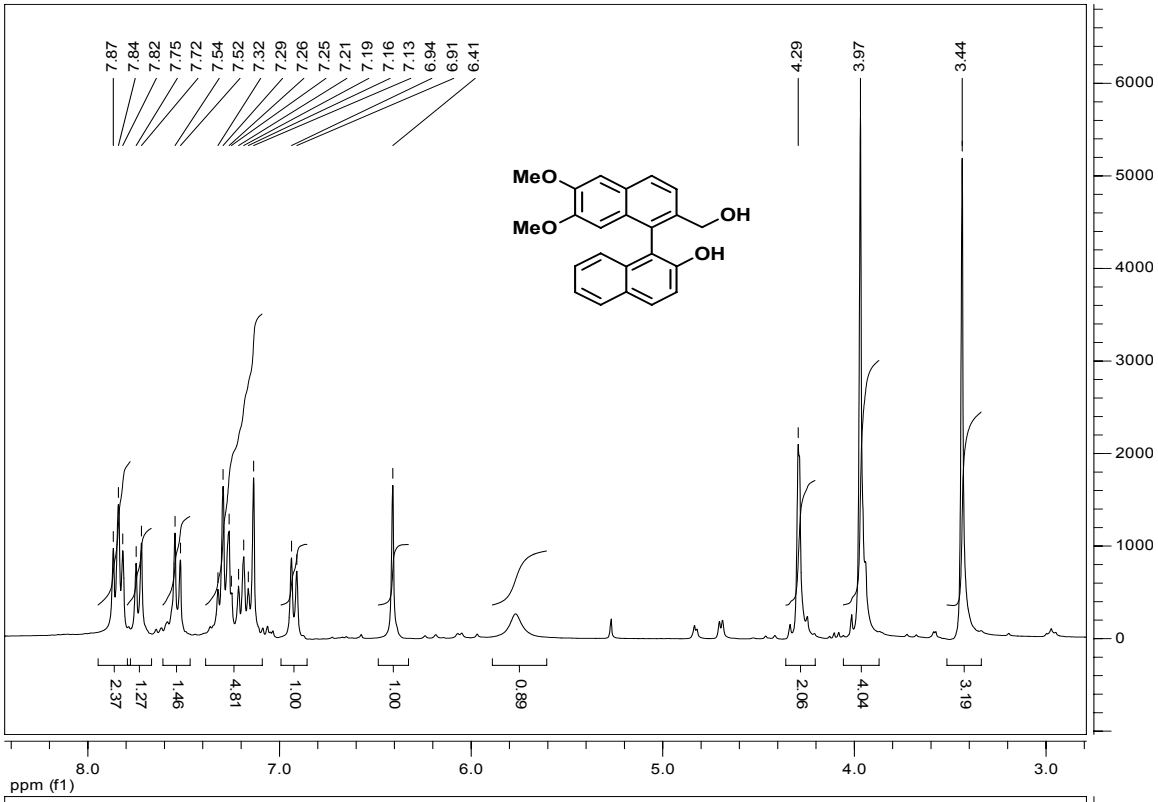
50
ppm (f1)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4.29
3.97
3.44
MeO
MeO
OH
OH
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1.27
1.46
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1.00
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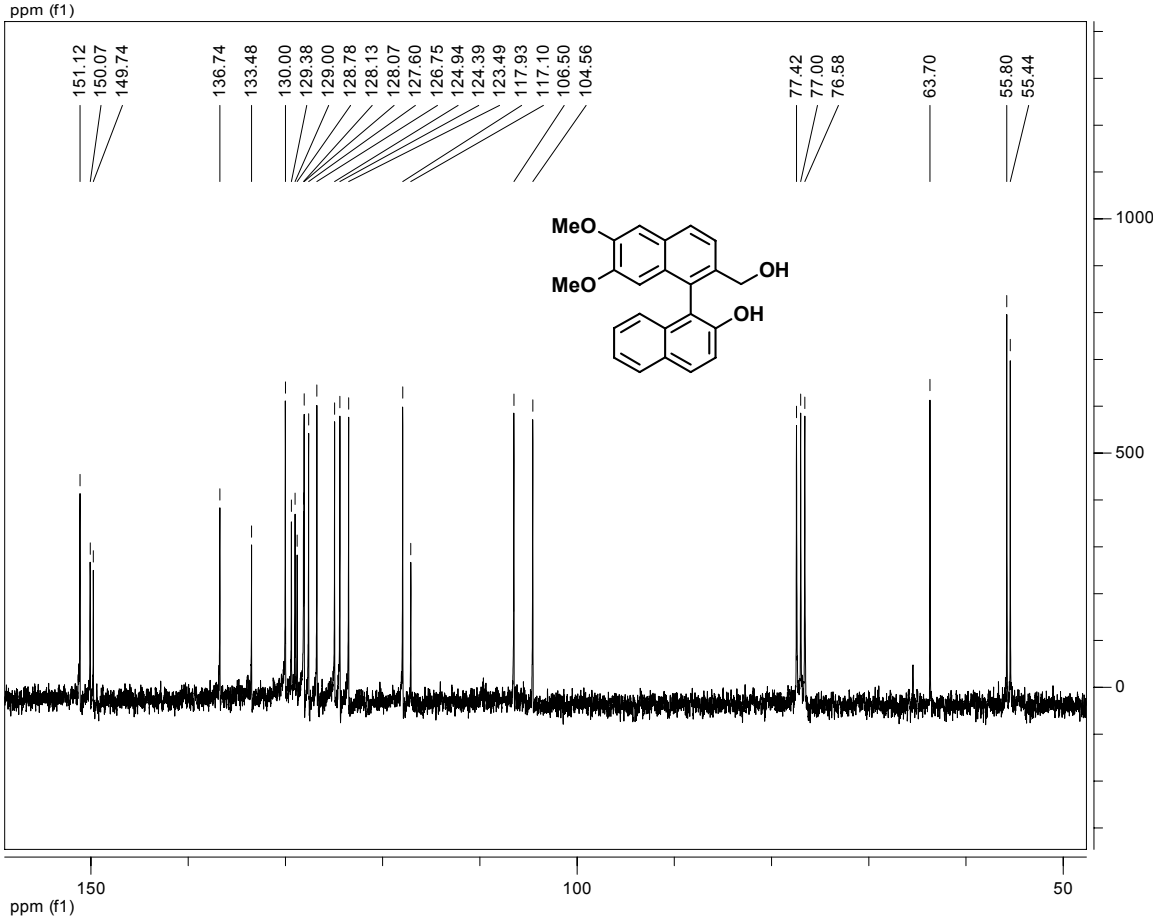
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117.93
117.10
106.50
104.56
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OH
OH
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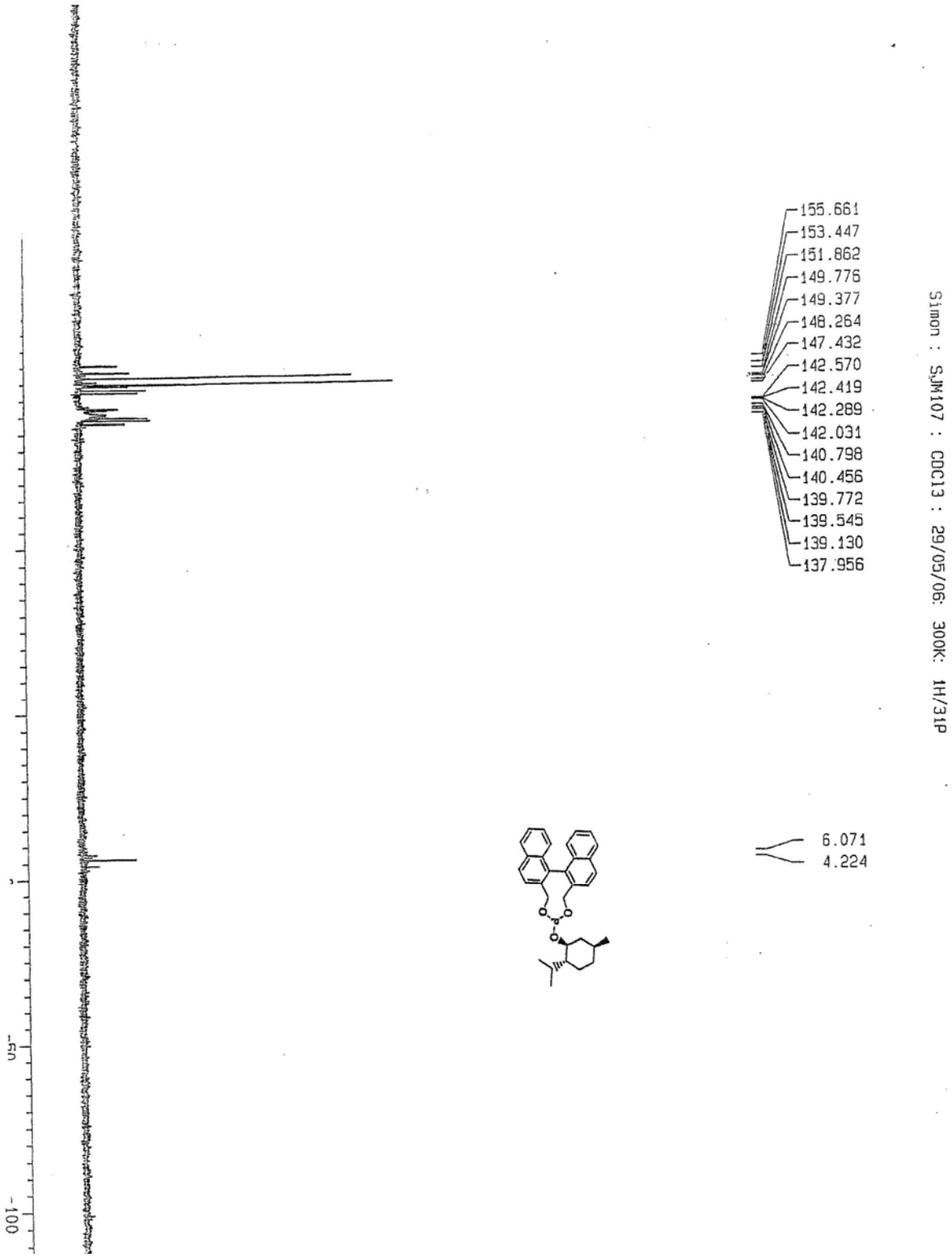
50
ppm (f1)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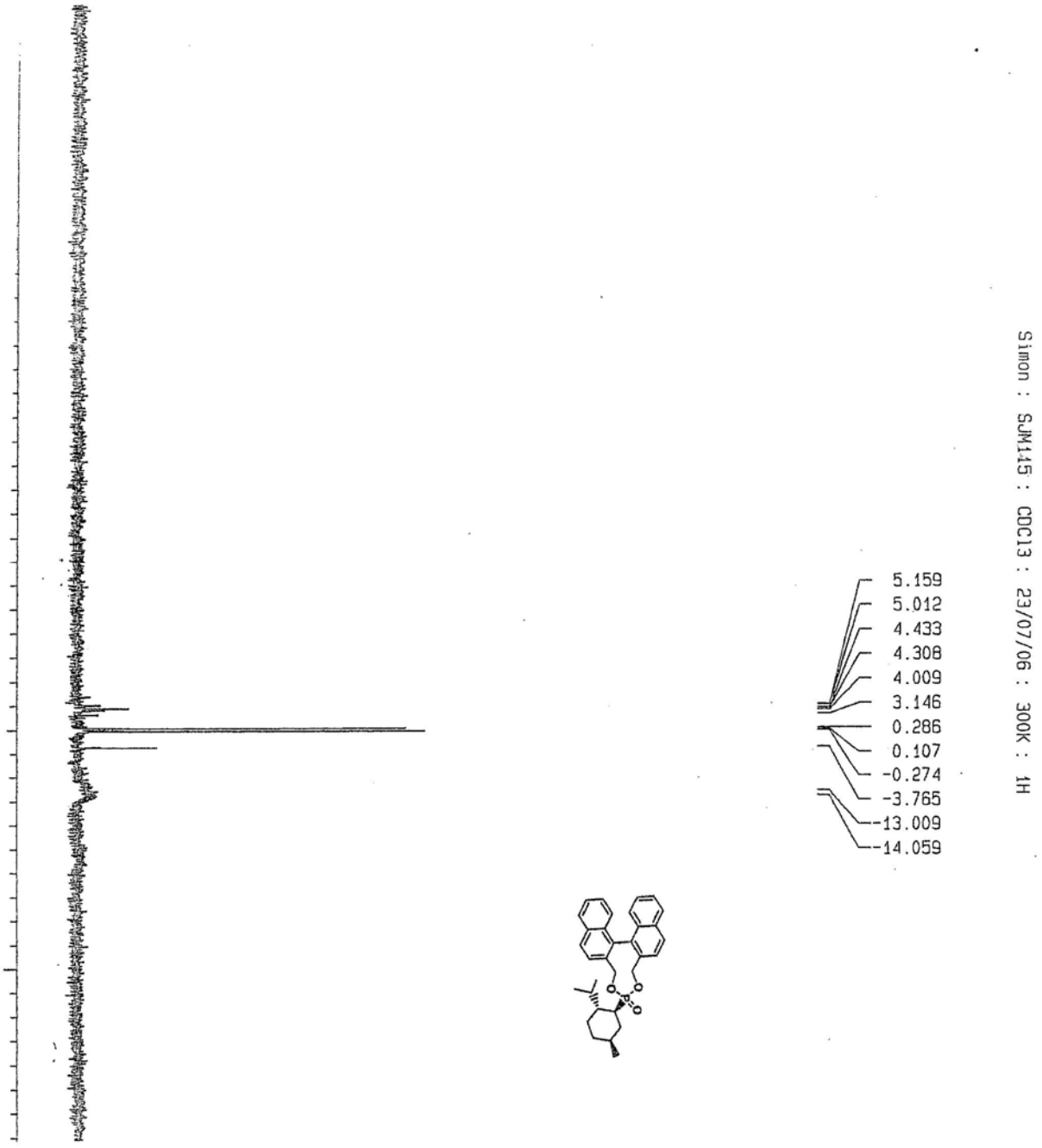
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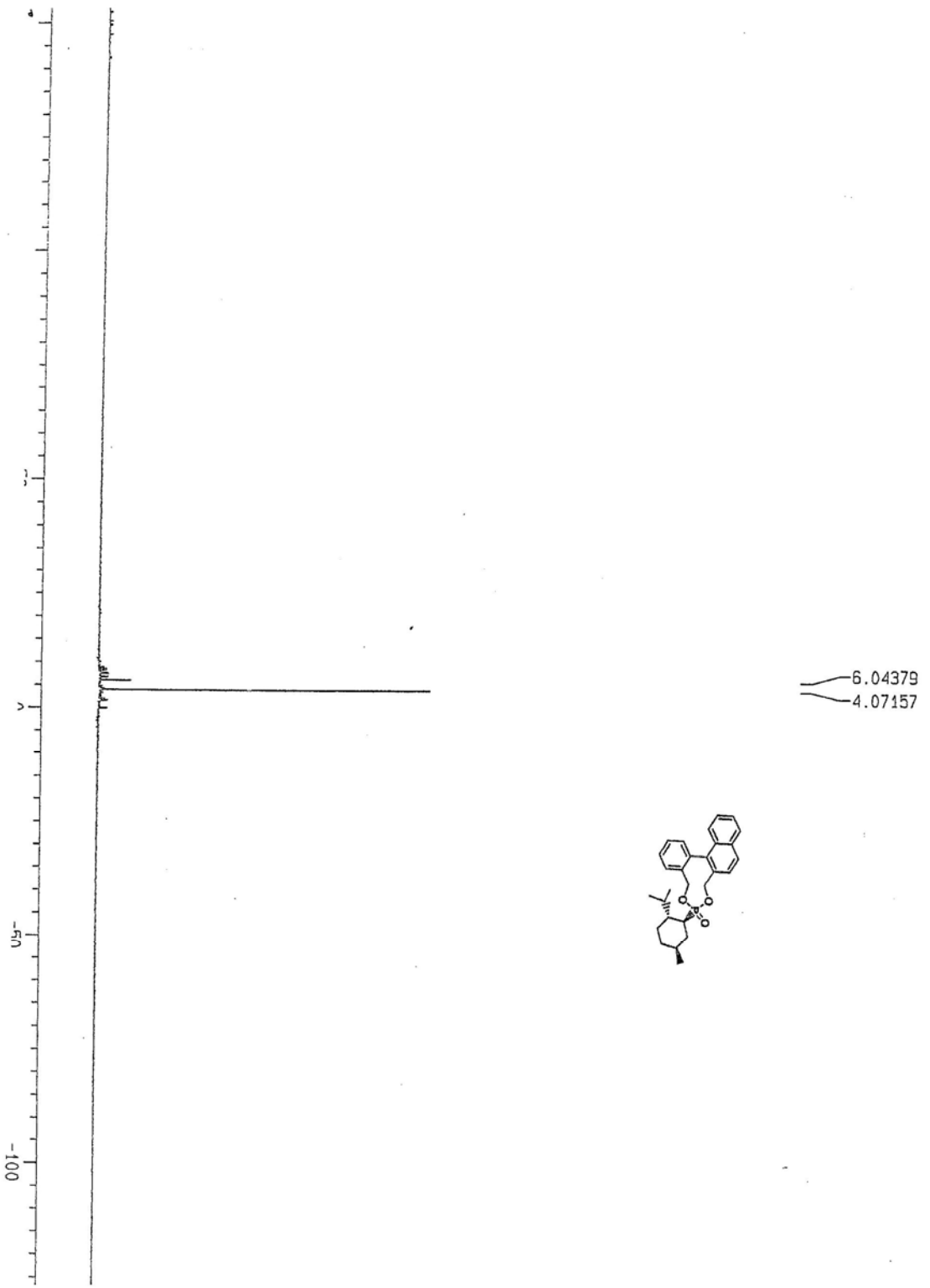
-13.009
-14.059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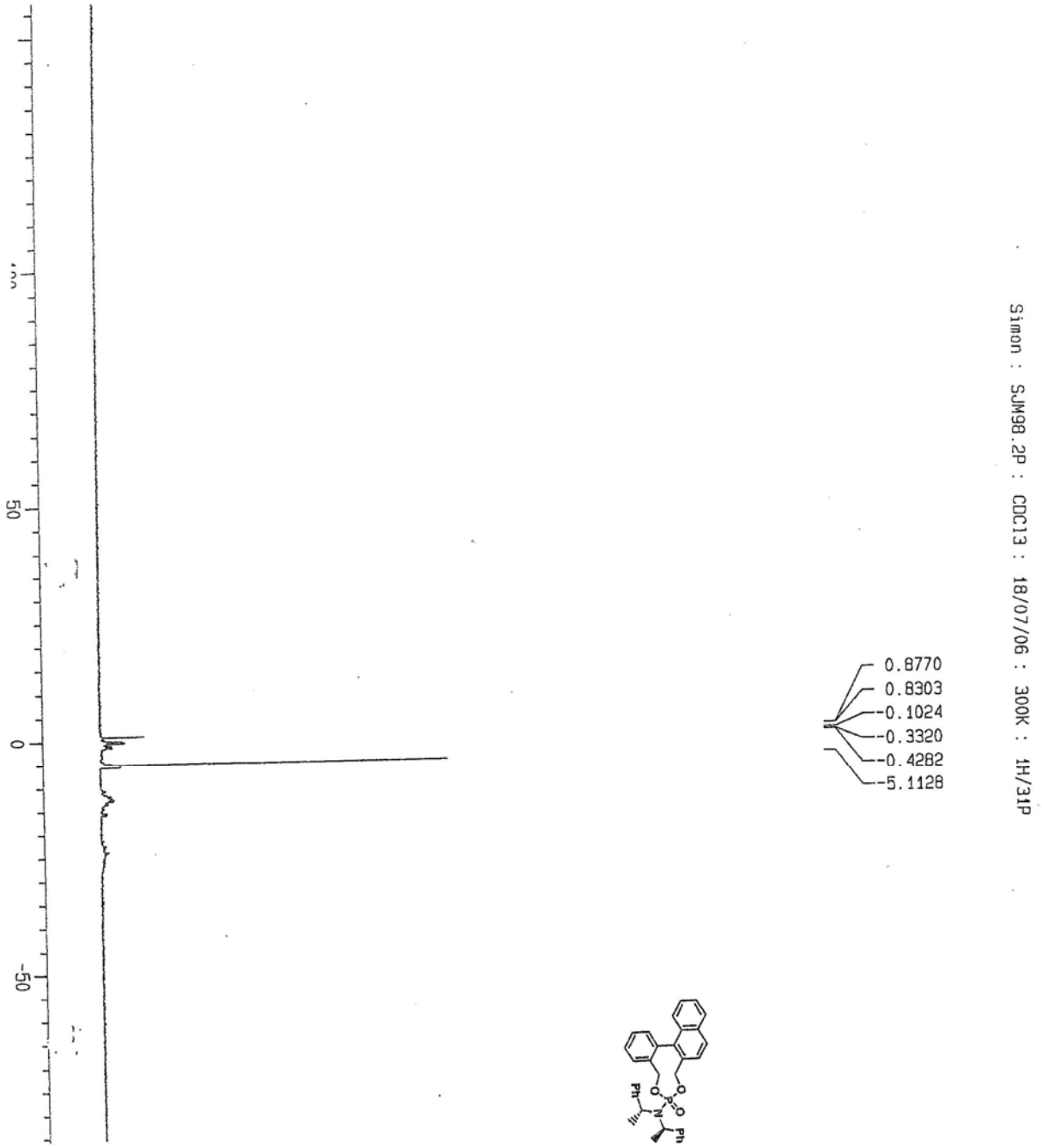
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-50
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-0.1024
-0.3320
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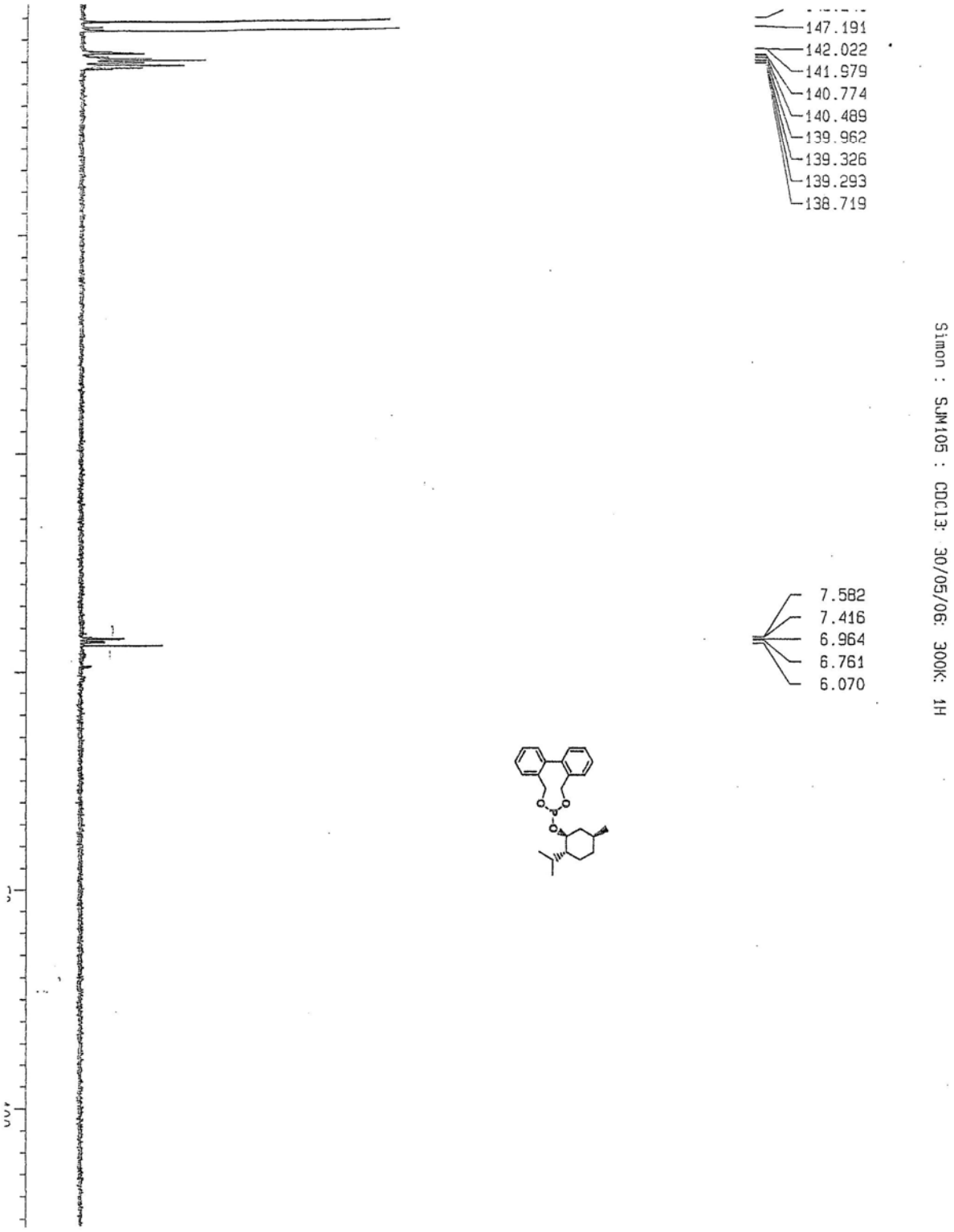
Simon : SJM98.2P : CDCl3 : 18/07/06 : 300K : 1H/31P
Ph
Ph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141.979
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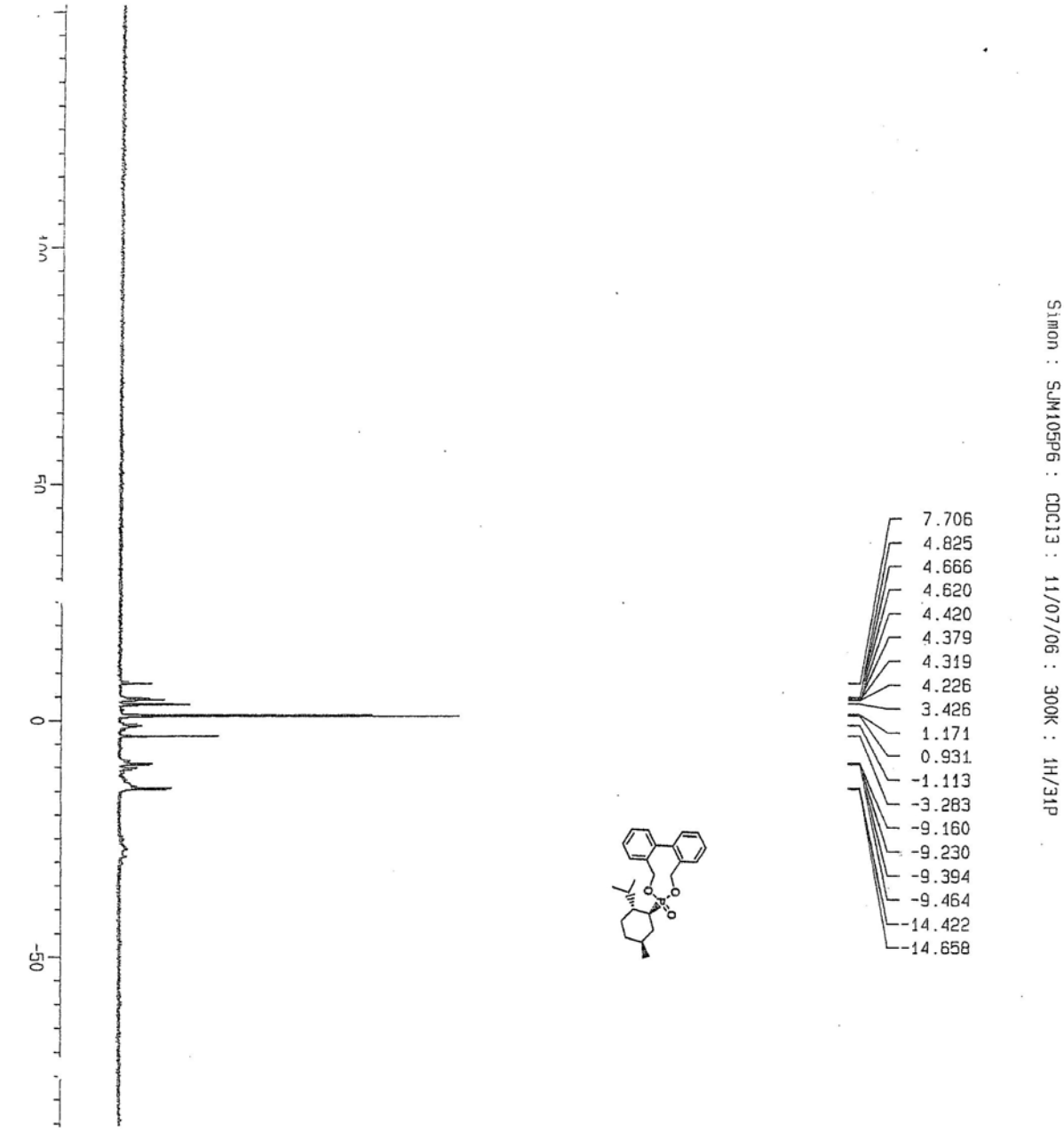
139.962
139.326
139.293
138.719
7.582
7.416
6.964
6.761
6.070
Simon : SJM105 : CDCl3: 30/05/06: 300K: 1H


Simon : SJM105P6 : CDCl3 : 11/07/06 : 300K : 1H/31P
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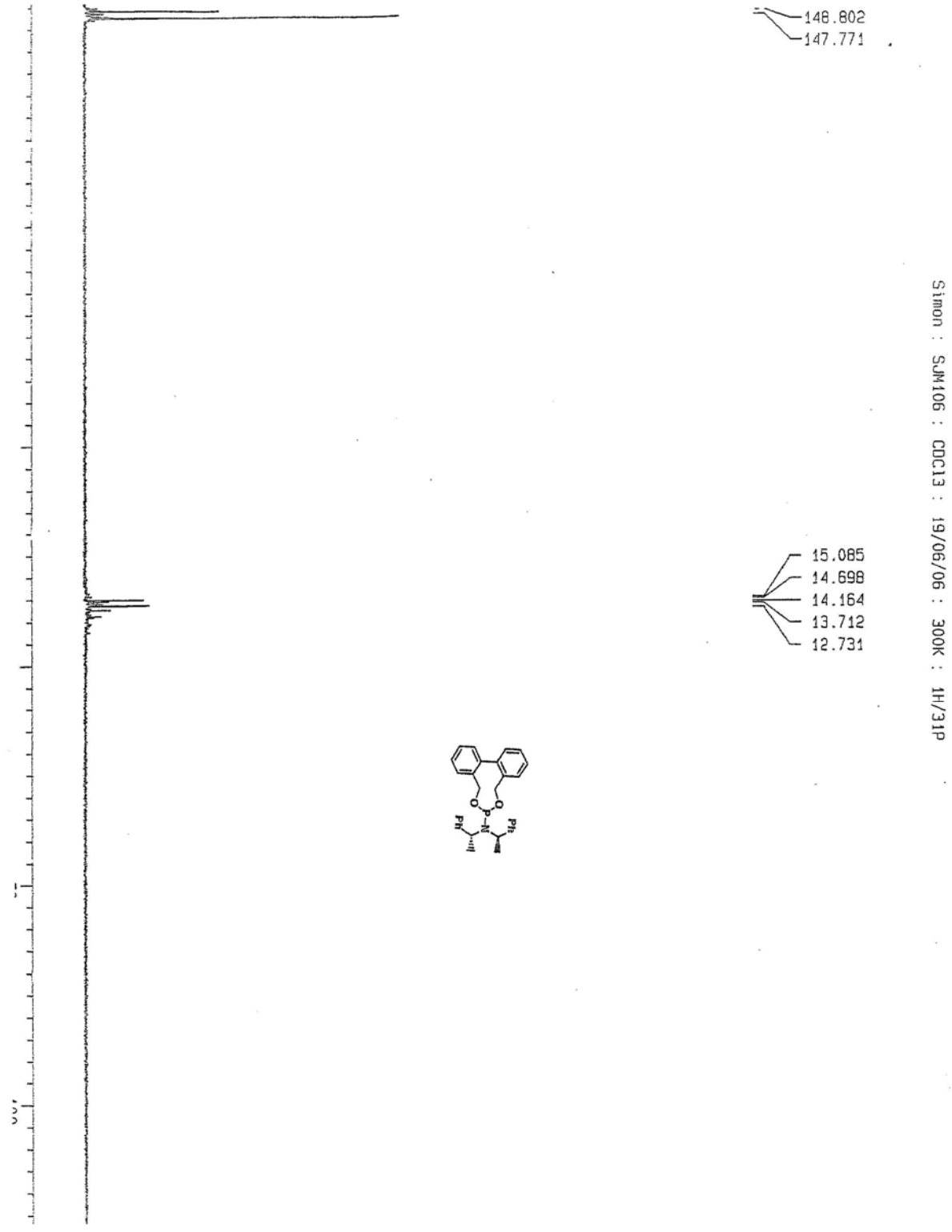
4.825
4.666
4.620
4.420
4.379
4.319
4.226
3.426
1.171
0.931
-1.113
-3.283
-9.160
-9.230
-9.394
-9.464
-14.422
-14.658
50
0
-50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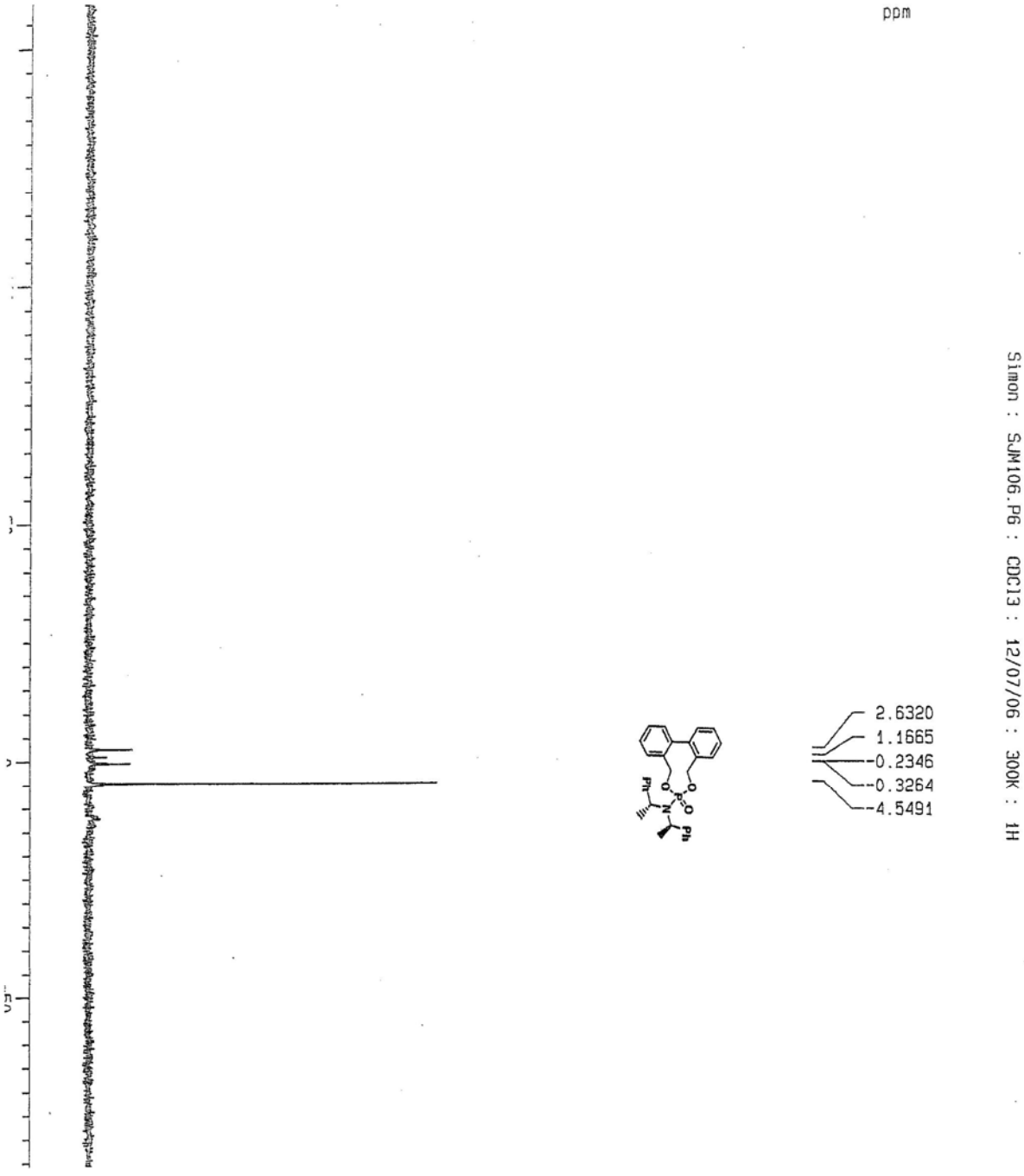
147.771
15.085
14.698
14.164
13.712
12.731
Simon : SJM106 : CDCl3 : 19/06/06 : 300K : 1H/31P


ppm
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1.1665
-0.2346
-0.3264
-4.5491
Simon : SJM106.P6 : CDCl3 : 12/07/06 : 300K : 1H

*Appendix 2: Crystal structure solution and refinement of 7b-(3,4,5-trimethoxyphenyl)-1a,2,3,7b-tetrahydro-1*H*-cyclopropa[a]naphthalene (125)*

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+* (Bruker, 1999a) and absorption corrections were made using the program *SADABS* (Sheldrick, 1996).

The crystal structure was solved by direct methods using *SHELXTL* (Bruker, 1999b). Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares calculation based on F^2 using *SHELXTL*. Hydrogen atoms were positioned geometrically and allowed to ride on their respective parent atoms. Diagrams and publication material were generated using SHELXTL and PLATON (Spek, 1990).

References

Bruker (1999). *SAINT+*. Version 6.02 (includes XPREP and SADABS). Bruker AXS Inc., Madison, Wisconsin, USA.
Sheldrick, G. M. (1996). *SADABS.* University of Göttingen, Germany.
Bruker (1999). SHELXTL. Version 5.1. (includes XS, XL, XP, XSHELL) Bruker AXS Inc., Madison, Wisconsin, USA.
Spek, A. L. (1990). *Acta Cryst.* A**46**, C-34.

Table 1. Crystal data and structure refinement for 7b-(3,4,5-Trimethoxyphenyl)-1a,2,3,7b-tetrahydro-1*H*-cyclopropa[*a*]naphthalene (**117**)

Identification code	2msm01_s
Empirical formula	$C_{20}H_{22}O_3$
Formula weight	310.38
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P\ 2_12_12_1$
Unit cell dimensions	a = 7.7343(12) Å □ = 90°
	b = 17.203(3) Å □ = 90°
	c = 25.074(4) Å □ = 90°
Volume	3336.2(9) Å^3
Z	8
Density (calculated)	1.236 Mg/m^3
Absorption coefficient	0.082 mm^{-1}
F(000)	1328
Crystal size	0.45 mm × 0.11 mm × 0.09 mm
Theta range for data collection	1.44 to 26.00°
Index ranges	-9 <= h <= 9
	-21 <= k <= 18
	-30 <= l <= 30
Reflections collected	19823
Independent reflections	6582 [R(int) = 0.0546]
Completeness to theta = 26.00°	100.0%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9927 and 0.9641
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6582 / 0 / 422
Goodness-of-fit on F^2	0.954
Final R indices [I>2□(I)]	R_1 = 0.0467, wR_2 = 0.0910
R indices (all data)	R_1 = 0.1159, wR_2 = 0.1103
Absolute structure parameter	1.0(11)
Extinction coefficient	0.0050(6)
Largest diff. signal and hole	0.131 and -0.139 e.Å^{-3}

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for 7b-(3,4,5-trimethoxyphenyl)-1a,2,3,7b-tetrahydro-1*H*-cyclopropa[*a*]naphthalene (**117**). U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	*y*	*z*	U_{eq}
C(1)	3658(4)	1990(2)	2994(1)	75(1)
C(2)	1408(4)	1005(2)	2626(1)	95(1)
C(3)	1933(4)	476(2)	3087(1)	95(1)
C(4)	4206(6)	-542(2)	3196(1)	91(1)
C(5)	5843(7)	-832(2)	3145(1)	96(1)
C(6)	7119(5)	-375(2)	2911(1)	76(1)
C(7)	6690(4)	360(2)	2735(1)	59(1)
C(11)	-980(3)	85(2)	4181(1)	64(1)
C(12)	-3561(4)	951(2)	4482(1)	92(1)
C(13)	-2974(5)	1566(2)	4087(1)	90(1)
C(14)	-886(6)	2685(2)	4108(1)	93(1)
C(15)	714(7)	3003(2)	4206(1)	98(1)
C(16)	1984(5)	2555(2)	4433(1)	83(1)
C(17)	1638(4)	1795(2)	4560(1)	60(1)
C(1')	5819(3)	1851(1)	2226(1)	50(1)
C(2')	7121(3)	2327(1)	2421(1)	52(1)
C(3')	8248(4)	2702(1)	2075(1)	52(1)
C(4')	8073(4)	2609(1)	1529(1)	52(1)
C(5')	6782(4)	2122(1)	1331(1)	53(1)
C(6')	5660(3)	1747(1)	1678(1)	54(1)
C(7')	9792(4)	3292(2)	2789(1)	79(1)
C(8')	10665(5)	2657(2)	1047(1)	84(1)
C(9')	5409(5)	1588(2)	556(1)	92(1)
C(11')	875(3)	302(1)	5026(1)	45(1)
C(12')	2204(3)	-202(1)	4890(1)	52(1)
C(13')	3315(4)	-481(1)	5277(1)	53(1)
C(14')	3100(4)	-264(1)	5809(1)	53(1)
C(15')	1772(4)	244(1)	5945(1)	50(1)
C(16')	668(3)	523(1)	5556(1)	51(1)
C(17')	4830(4)	-1289(2)	4660(1)	89(1)
C(18')	5735(4)	-277(2)	6280(1)	85(1)
C(19')	231(4)	840(2)	6653(1)	78(1)
C(1A)	2688(4)	1641(2)	2540(1)	73(1)
C(3A)	3768(4)	190(2)	3026(1)	65(1)
C(7A)	5035(4)	658(1)	2789(1)	50(1)
C(11A)	-2171(4)	370(2)	4606(1)	69(1)
C(13A)	-1237(4)	1915(2)	4219(1)	68(1)
C(17A)	32(4)	1459(2)	4458(1)	51(1)
C(7B)	4583(3)	1459(1)	2603(1)	53(1)
C(17B)	-304(3)	633(1)	4610(1)	48(1)
O(1')	9561(2)	3180(1)	2231(1)	65(1)
O(2')	9102(3)	3027(1)	1183(1)	64(1)
O(3')	6735(3)	2063(1)	788(1)	71(1)
O(11')	4651(3)	-981(1)	5185(1)	72(1)
O(12')	4086(3)	-605(1)	6203(1)	70(1)
O(13')	1672(3)	421(1)	6476(1)	72(1)

Table 3. Bond lengths [Å] and angles [°] for 7b-(3,4,5-trimethoxyphenyl)-1a,2,3,7b-tetrahydro-1*H*-cyclopropa[*a*]naphthalene (**117**).

C(1)-C(1A)	1.491(4)	C(6')-H(6')	0.9300
C(1)-C(7B)	1.519(3)	C(7')-O(1')	1.424(3)
C(1)-H(1B)	0.9700	C(7')-H(7'1)	0.9600
C(1)-H(1C)	0.9700	C(7')-H(7'2)	0.9600
C(2)-C(1A)	1.492(4)	C(7')-H(7'3)	0.9600
C(2)-C(3)	1.525(4)	C(8')-O(2')	1.408(3)
C(2)-H(2A)	0.9700	C(8')-H(8'1)	0.9600
C(2)-H(2B)	0.9700	C(8')-H(8'2)	0.9600
C(3)-C(3A)	1.510(4)	C(8')-H(8'3)	0.9600
C(3)-H(3A)	0.9700	C(9')-O(3')	1.434(3)
C(3)-H(3B)	0.9700	C(9')-H(9'1)	0.9600
C(4)-C(5)	1.367(5)	C(9')-H(9'2)	0.9600
C(4)-C(3A)	1.372(4)	C(9')-H(9'3)	0.9600
C(4)-H(4)	0.9300	C(11')-C(12')	1.387(3)
C(5)-C(6)	1.390(5)	C(11')-C(16')	1.392(3)
C(5)-H(5)	0.9300	C(11')-C(17B)	1.498(3)
C(6)-C(7)	1.379(4)	C(12')-C(13')	1.383(3)
C(6)-H(6)	0.9300	C(12')-H(12')	0.9300
C(7)-C(7A)	1.386(4)	C(13')-O(11')	1.364(3)
C(7)-H(7)	0.9300	C(13')-C(14')	1.395(3)
C(11)-C(11A)	1.491(4)	C(14')-O(12')	1.379(3)
C(11)-C(17B)	1.522(3)	C(14')-C(15')	1.391(3)
C(11)-H(11B)	0.9700	C(15')-O(13')	1.368(3)
C(11)-H(11C)	0.9700	C(15')-C(16')	1.383(3)
C(12)-C(11A)	1.500(4)	C(16')-H(16')	0.9300
C(12)-C(13)	1.518(4)	C(17')-O(11')	1.424(3)
C(12)-H(12A)	0.9700	C(17')-H(17A)	0.9600
C(12)-H(12B)	0.9700	C(17')-H(17B)	0.9600
C(13)-C(13A)	1.509(4)	C(17')-H(17C)	0.9600
C(13)-H(13A)	0.9700	C(18')-O(12')	1.407(3)
C(13)-H(13B)	0.9700	C(18')-H(18A)	0.9600
C(14)-C(15)	1.376(5)	C(18')-H(18B)	0.9600
C(14)-C(13A)	1.380(4)	C(18')-H(18C)	0.9600
C(14)-H(14)	0.9300	C(19')-O(13')	1.400(3)
C(15)-C(16)	1.371(5)	C(19')-H(19A)	0.9600
C(15)-H(15)	0.9300	C(19')-H(19B)	0.9600
C(16)-C(17)	1.373(3)	C(19')-H(19C)	0.9600
C(16)-H(16)	0.9300	C(1A)-C(7B)	1.507(4)
C(17)-C(17A)	1.394(4)	C(1A)-H(1A)	0.9800
C(17)-H(17)	0.9300	C(3A)-C(7A)	1.401(4)
C(1')-C(2')	1.387(3)	C(7A)-C(7B)	1.495(3)
C(1')-C(6')	1.392(3)	C(11A)-C(17B)	1.513(4)
C(1')-C(7B)	1.504(3)	C(11A)-H(11A)	0.9800
C(2')-C(3')	1.389(3)	C(13A)-C(17A)	1.392(4)
C(2')-H(2')	0.9300	C(17A)-C(17B)	1.494(3)
C(3')-O(1')	1.364(3)	C(1A)-C(1)-C(7B)	60.10(17)
C(3')-C(4')	1.386(3)	C(1A)-C(1)-H(1B)	117.8
C(4')-O(2')	1.380(3)	C(7B)-C(1)-H(1B)	117.8
C(4')-C(5')	1.394(3)	C(1A)-C(1)-H(1C)	117.8
C(5')-O(3')	1.367(3)	C(7B)-C(1)-H(1C)	117.8
C(5')-C(6')	1.387(3)	H(1B)-C(1)-H(1C)	114.9

C(1A)-C(2)-C(3)	111.8(3)
C(1A)-C(2)-H(2A)	109.3
C(3)-C(2)-H(2A)	109.3
C(1A)-C(2)-H(2B)	109.3
C(3)-C(2)-H(2B)	109.3
H(2A)-C(2)-H(2B)	107.9
C(3A)-C(3)-C(2)	111.6(3)
C(3A)-C(3)-H(3A)	109.3
C(2)-C(3)-H(3A)	109.3
C(3A)-C(3)-H(3B)	109.3
C(2)-C(3)-H(3B)	109.3
H(3A)-C(3)-H(3B)	108.0
C(5)-C(4)-C(3A)	122.3(3)
C(5)-C(4)-H(4)	118.9
C(3A)-C(4)-H(4)	118.9
C(4)-C(5)-C(6)	119.4(3)
C(4)-C(5)-H(5)	120.3
C(6)-C(5)-H(5)	120.3
C(7)-C(6)-C(5)	118.8(3)
C(7)-C(6)-H(6)	120.6
C(5)-C(6)-H(6)	120.6
C(6)-C(7)-C(7A)	122.0(3)
C(6)-C(7)-H(7)	119.0
C(7A)-C(7)-H(7)	119.0
C(11A)-C(11)-C(17B)	60.26(17)
C(11A)-C(11)-H(11B)	117.7
C(17B)-C(11)-H(11B)	117.7
C(11A)-C(11)-H(11C)	117.7
C(17B)-C(11)-H(11C)	117.7
H(11B)-C(11)-H(11C)	114.9
C(11A)-C(12)-C(13)	112.6(3)
C(11A)-C(12)-H(12A)	109.1
C(13)-C(12)-H(12A)	109.1
C(11A)-C(12)-H(12B)	109.1
C(13)-C(12)-H(12B)	109.1
H(12A)-C(12)-H(12B)	107.8
C(13A)-C(13)-C(12)	113.5(3)
C(13A)-C(13)-H(13A)	108.9
C(12)-C(13)-H(13A)	108.9
C(13A)-C(13)-H(13B)	108.9
C(12)-C(13)-H(13B)	108.9
H(13A)-C(13)-H(13B)	107.7
C(15)-C(14)-C(13A)	121.5(3)
C(15)-C(14)-H(14)	119.2
C(13A)-C(14)-H(14)	119.2
C(16)-C(15)-C(14)	119.6(3)
C(16)-C(15)-H(15)	120.2
C(14)-C(15)-H(15)	120.2
C(15)-C(16)-C(17)	119.5(3)
C(15)-C(16)-H(16)	120.2
C(17)-C(16)-H(16)	120.2
C(16)-C(17)-C(17A)	121.7(3)
C(16)-C(17)-H(17)	119.1
C(17A)-C(17)-H(17)	119.1
C(2')-C(1')-C(6')	119.2(2)
C(2')-C(1')-C(7B)	120.2(2)
C(6')-C(1')-C(7B)	120.5(2)
C(1')-C(2')-C(3')	120.6(2)
C(1')-C(2')-H(2')	119.7
C(3')-C(2')-H(2')	119.7
O(1')-C(3')-C(4')	115.2(2)
O(1')-C(3')-C(2')	124.6(2)
C(4')-C(3')-C(2')	120.2(2)
O(2')-C(4')-C(3')	120.3(2)
O(2')-C(4')-C(5')	120.2(2)
C(3')-C(4')-C(5')	119.4(2)
O(3')-C(5')-C(6')	125.0(2)
O(3')-C(5')-C(4')	114.7(2)
C(6')-C(5')-C(4')	120.3(2)
C(5')-C(6')-C(1')	120.3(2)
C(5')-C(6')-H(6')	119.9
C(1')-C(6')-H(6')	119.9
O(1')-C(7')-H(7'1)	109.5
O(1')-C(7')-H(7'2)	109.5
H(7'1)-C(7')-H(7'2)	109.5
O(1')-C(7')-H(7'3)	109.5
H(7'1)-C(7')-H(7'3)	109.5
H(7'2)-C(7')-H(7'3)	109.5
O(2')-C(8')-H(8'1)	109.5
O(2')-C(8')-H(8'2)	109.5
H(8'1)-C(8')-H(8'2)	109.5
O(2')-C(8')-H(8'3)	109.5
H(8'1)-C(8')-H(8'3)	109.5
H(8'2)-C(8')-H(8'3)	109.5
O(3')-C(9')-H(9'1)	109.5
O(3')-C(9')-H(9'2)	109.5
H(9'1)-C(9')-H(9'2)	109.5
O(3')-C(9')-H(9'3)	109.5
H(9'1)-C(9')-H(9'3)	109.5
H(9'2)-C(9')-H(9'3)	109.5
C(12')-C(11')-C(16')	119.4(2)
C(12')-C(11')-C(17B)	121.2(2)
C(16')-C(11')-C(17B)	119.4(2)
C(13')-C(12')-C(11')	120.4(2)
C(13')-C(12')-H(12')	119.8
C(11')-C(12')-H(12')	119.8
O(11')-C(13')-C(12')	124.8(2)
O(11')-C(13')-C(14')	114.9(2)
C(12')-C(13')-C(14')	120.3(2)
O(12')-C(14')-C(15')	120.0(2)
O(12')-C(14')-C(13')	120.3(2)
C(15')-C(14')-C(13')	119.4(2)
O(13')-C(15')-C(16')	125.1(2)
O(13')-C(15')-C(14')	114.9(2)
C(16')-C(15')-C(14')	120.0(2)
C(15')-C(16')-C(11')	120.5(2)
C(15')-C(16')-H(16')	119.7
C(11')-C(16')-H(16')	119.7
O(11')-C(17')-H(17A)	109.5
O(11')-C(17')-H(17B)	109.5
H(17A)-C(17')-H(17B)	109.5
O(11')-C(17')-H(17C)	109.5

H(17A)-C(17')-H(17C)	109.5	C(12)-C(11A)-C(17B)	119.1(3)
H(17B)-C(17')-H(17C)	109.5	C(11)-C(11A)-H(11A)	115.1
O(12')-C(18')-H(18A)	109.5	C(12)-C(11A)-H(11A)	115.1
O(12')-C(18')-H(18B)	109.5	C(17B)-C(11A)-H(11A)	115.1
H(18A)-C(18')-H(18B)	109.5	C(14)-C(13A)-C(17A)	119.3(3)
O(12')-C(18')-H(18C)	109.5	C(14)-C(13A)-C(13)	120.8(3)
H(18A)-C(18')-H(18C)	109.5	C(17A)-C(13A)-C(13)	119.9(3)
H(18B)-C(18')-H(18C)	109.5	C(13A)-C(17A)-C(17)	118.3(3)
O(13')-C(19')-H(19A)	109.5	C(13A)-C(17A)-C(17B)	121.5(3)
O(13')-C(19')-H(19B)	109.5	C(17)-C(17A)-C(17B)	120.2(2)
H(19A)-C(19')-H(19B)	109.5	C(7A)-C(7B)-C(1')	117.4(2)
O(13')-C(19')-H(19C)	109.5	C(7A)-C(7B)-C(1A)	116.9(2)
H(19A)-C(19')-H(19C)	109.5	C(1')-C(7B)-C(1A)	117.3(2)
H(19B)-C(19')-H(19C)	109.5	C(7A)-C(7B)-C(1)	117.6(2)
C(1)-C(1A)-C(2)	121.2(3)	C(1')-C(7B)-C(1)	115.8(2)
C(1)-C(1A)-C(7B)	60.89(18)	C(1A)-C(7B)-C(1)	59.02(17)
C(2)-C(1A)-C(7B)	118.5(3)	C(17A)-C(17B)-C(11')	115.6(2)
C(1)-C(1A)-H(1A)	115.2	C(17A)-C(17B)-C(11A)	116.6(2)
C(2)-C(1A)-H(1A)	115.2	C(11')-C(17B)-C(11A)	118.2(2)
C(7B)-C(1A)-H(1A)	115.2	C(17A)-C(17B)-C(11)	117.9(2)
C(4)-C(3A)-C(7A)	119.2(3)	C(11')-C(17B)-C(11)	117.8(2)
C(4)-C(3A)-C(3)	120.0(3)	C(11A)-C(17B)-C(11)	58.85(17)
C(7A)-C(3A)-C(3)	120.9(3)	C(3')-O(1')-C(7')	117.2(2)
C(7)-C(7A)-C(3A)	118.3(3)	C(4')-O(2')-C(8')	114.29(19)
C(7)-C(7A)-C(7B)	121.8(2)	C(5')-O(3')-C(9')	117.7(2)
C(3A)-C(7A)-C(7B)	119.9(3)	C(13')-O(11')-C(17')	117.6(2)
C(11)-C(11A)-C(12)	120.9(2)	C(14')-O(12')-C(18')	115.4(2)
C(11)-C(11A)-C(17B)	60.89(17)	C(15')-O(13')-C(19')	117.9(2)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 \times 10^3$) for 7b-(3,4,5-trimethoxyphenyl)-1a,2,3,7b-tetrahydro-1*H*-cyclopropa[*a*]naphthalene (**117**). 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}
C(1)	59(2)	75(2)	91(2)	-19(2)	14(2)	0(2)
C(2)	44(2)	138(3)	104(3)	-23(2)	7(2)	-12(2)
C(3)	77(3)	112(3)	94(2)	-12(2)	30(2)	-40(2)
C(4)	133(4)	71(2)	69(2)	7(2)	2(2)	-34(3)
C(5)	166(4)	56(2)	65(2)	8(2)	-31(3)	-7(3)
C(6)	94(3)	62(2)	72(2)	-11(2)	-28(2)	14(2)
C(7)	58(2)	56(2)	61(2)	-7(1)	-4(1)	-4(2)
C(11)	64(2)	66(2)	61(2)	-7(1)	-8(2)	-3(2)
C(12)	47(2)	148(3)	81(2)	-29(2)	-9(2)	4(2)
C(13)	82(3)	116(3)	73(2)	-11(2)	-23(2)	30(2)
C(14)	142(4)	72(2)	65(2)	11(2)	-12(2)	39(2)
C(15)	168(4)	54(2)	73(2)	11(2)	-4(3)	-2(3)
C(16)	114(3)	64(2)	69(2)	6(2)	1(2)	-24(2)
C(17)	76(2)	52(2)	52(2)	2(1)	-1(2)	-1(2)
C(1')	45(2)	45(1)	60(2)	3(1)	7(1)	3(1)
C(2')	50(2)	50(2)	57(2)	-1(1)	1(1)	0(1)
C(3')	48(2)	43(1)	64(2)	1(1)	3(2)	-5(1)
C(4')	57(2)	38(1)	59(2)	6(1)	4(2)	-2(1)
C(5')	67(2)	41(1)	52(2)	2(1)	0(2)	2(2)
C(6')	54(2)	43(1)	65(2)	1(1)	-2(1)	-9(1)
C(7')	68(2)	95(2)	73(2)	-19(2)	4(2)	-25(2)
C(8')	88(3)	78(2)	88(2)	5(2)	30(2)	-5(2)
C(9')	125(3)	84(2)	67(2)	-10(2)	-7(2)	-38(2)
C(11')	45(2)	43(1)	49(2)	3(1)	-2(1)	-5(1)
C(12')	54(2)	53(2)	48(1)	2(1)	5(1)	-1(2)
C(13')	51(2)	43(1)	63(2)	1(1)	4(2)	1(1)
C(14')	55(2)	53(2)	51(2)	10(1)	-7(1)	-4(2)
C(15')	54(2)	50(2)	47(2)	-2(1)	-1(1)	0(2)
C(16')	49(2)	51(2)	52(2)	-3(1)	-2(1)	-1(1)
C(17')	77(2)	83(2)	108(3)	-35(2)	5(2)	17(2)
C(18')	72(2)	93(2)	91(2)	5(2)	-23(2)	9(2)
C(19')	76(2)	101(2)	58(2)	-15(2)	10(2)	8(2)
C(1A)	46(2)	88(2)	85(2)	4(2)	2(2)	5(2)
C(3A)	75(2)	71(2)	48(2)	-6(2)	7(2)	-24(2)
C(7A)	50(2)	55(2)	44(1)	-4(1)	1(1)	-8(2)
C(11A)	50(2)	94(2)	63(2)	-3(2)	-2(2)	-12(2)
C(13A)	80(2)	78(2)	45(2)	-3(2)	-7(2)	23(2)
C(17A)	53(2)	60(2)	40(1)	-5(1)	-2(1)	8(2)
C(7B)	40(2)	57(2)	63(2)	-3(1)	8(1)	-2(1)
C(17B)	47(2)	55(2)	43(1)	-3(1)	0(1)	-3(1)
O(1')	62(1)	70(1)	62(1)	-4(1)	1(1)	-21(1)
O(2')	74(1)	49(1)	71(1)	15(1)	10(1)	-11(1)
O(3')	92(2)	62(1)	57(1)	2(1)	-4(1)	-20(1)
O(11')	74(2)	68(1)	74(1)	-2(1)	4(1)	21(1)
O(12')	70(1)	71(1)	67(1)	21(1)	-12(1)	1(1)
O(13')	77(2)	95(1)	45(1)	-8(1)	-5(1)	11(1)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for 7b-(3,4,5-trimethoxyphenyl)-1a,2,3,7b-tetrahydro-1*H*-cyclopropa[*a*]naphthalene (**117**).

	x	*y*	*z*	U_{eq}
H(1B)	3426	1791	3349	90
H(1C)	3914	2542	2979	90
H(2A)	1310	698	2303	114
H(2B)	284	1229	2701	114
H(3A)	1827	759	3420	114
H(3B)	1156	34	3101	114
H(4)	3360	-852	3352	110
H(5)	6102	-1329	3266	115
H(6)	8241	-562	2875	91
H(7)	7538	664	2575	70
H(11B)	-1128	292	3824	76
H(11C)	-618	-454	4196	76
H(12A)	-3918	1204	4809	110
H(12B)	-4556	681	4337	110
H(13A)	-2917	1335	3734	108
H(13B)	-3830	1977	4076	108
H(14)	-1751	2995	3963	111
H(15)	933	3520	4120	118
H(16)	3071	2765	4499	99
H(17)	2498	1496	4719	72
H(2')	7240	2395	2787	63
H(6')	4799	1425	1543	65
H(7'1)	8827	3577	2930	118
H(7'2)	10838	3578	2851	118
H(7'3)	9865	2796	2963	118
H(8'1)	11307	2544	1365	127
H(8'2)	11333	2992	821	127
H(8'3)	10419	2181	861	127
H(9'1)	5580	1057	660	138
H(9'2)	5463	1628	174	138
H(9'3)	4298	1763	678	138
H(12')	2349	-353	4536	62
H(16')	-221	861	5649	61
H(17A)	3759	-1522	4552	134
H(17B)	5727	-1674	4658	134
H(17C)	5125	-877	4418	134
H(18A)	6347	-270	5947	128
H(18B)	6366	-582	6534	128
H(18C)	5614	244	6411	128
H(19A)	195	1335	6476	118
H(19B)	313	919	7031	118
H(19C)	-804	554	6573	118
H(1A)	2408	2001	2249	88
H(11A)	-2473	-15	4878	83

Table 6. Torsion angles [°] for 7b-(3,4,5-trimethoxyphenyl)-1a,2,3,7b-tetrahydro-1*H*-cyclopropa[*a*]naphthalene (**117**).

C(1A)-C(2)-C(3)-C(3A)	-51.7(4)	C(17B)-C(11)-C(11A)-C(12)	108.4(3)
C(3A)-C(4)-C(5)-C(6)	-0.2(5)	C(13)-C(12)-C(11A)-C(11)	-38.5(4)
C(4)-C(5)-C(6)-C(7)	-0.2(4)	C(13)-C(12)-C(11A)-C(17B)	33.1(4)
C(5)-C(6)-C(7)-C(7A)	0.7(4)	C(15)-C(14)-C(13A)-C(17A)	2.8(5)
C(11A)-C(12)-C(13)-C(13A)	-47.5(4)	C(15)-C(14)-C(13A)-C(13)	-177.3(3)
C(13A)-C(14)-C(15)-C(16)	-1.7(5)	C(12)-C(13)-C(13A)-C(14)	-146.2(3)
C(14)-C(15)-C(16)-C(17)	-0.3(5)	C(12)-C(13)-C(13A)-C(17A)	33.7(4)
C(15)-C(16)-C(17)-C(17A)	1.1(4)	C(14)-C(13A)-C(17A)-C(17)	-2.0(4)
C(6')-C(1')-C(2')-C(3')	0.6(4)	C(13)-C(13A)-C(17A)-C(17)	178.1(2)
C(7B)-C(1')-C(2')-C(3')	-178.8(2)	C(14)-C(13A)-C(17A)-C(17B)	177.1(2)
C(1')-C(2')-C(3')-O(1')	179.9(2)	C(13)-C(13A)-C(17A)-C(17B)	-2.8(4)
C(1')-C(2')-C(3')-C(4')	0.5(4)	C(16)-C(17)-C(17A)-C(13A)	0.0(4)
O(1')-C(3')-C(4')-O(2')	-4.6(3)	C(16)-C(17)-C(17A)-C(17B)	-179.1(2)
C(2')-C(3')-C(4')-O(2')	174.9(2)	C(7)-C(7A)-C(7B)-C(1')	16.3(3)
O(1')-C(3')-C(4')-C(5')	179.1(2)	C(3A)-C(7A)-C(7B)-C(1')	-163.9(2)
C(2')-C(3')-C(4')-C(5')	-1.5(4)	C(7)-C(7A)-C(7B)-C(1A)	163.5(2)
O(2')-C(4')-C(5')-O(3')	4.4(3)	C(3A)-C(7A)-C(7B)-C(1A)	-16.7(4)
C(3')-C(4')-C(5')-O(3')	-179.2(2)	C(7)-C(7A)-C(7B)-C(1)	-129.3(3)
O(2')-C(4')-C(5')-C(6')	-175.0(2)	C(3A)-C(7A)-C(7B)-C(1)	50.5(3)
C(3')-C(4')-C(5')-C(6')	1.4(4)	C(2')-C(1')-C(7B)-C(7A)	-92.4(3)
O(3')-C(5')-C(6')-C(1')	-179.7(2)	C(6')-C(1')-C(7B)-C(7A)	88.2(3)
C(4')-C(5')-C(6')-C(1')	-0.3(4)	C(2')-C(1')-C(7B)-C(1A)	120.5(3)
C(2')-C(1')-C(6')-C(5')	-0.7(4)	C(6')-C(1')-C(7B)-C(1A)	-58.9(3)
C(7B)-C(1')-C(6')-C(5')	178.7(2)	C(2')-C(1')-C(7B)-C(1)	53.7(3)
C(16')-C(11')-C(12')-C(13')	-0.2(3)	C(6')-C(1')-C(7B)-C(1)	-125.7(3)
C(17B)-C(11')-C(12')-C(13')	177.9(2)	C(1)-C(1A)-C(7B)-C(7A)	107.6(3)
C(11')-C(12')-C(13')-O(11')	179.6(2)	C(2)-C(1A)-C(7B)-C(7A)	-4.3(4)
C(11')-C(12')-C(13')-C(14')	0.6(3)	C(1)-C(1A)-C(7B)-C(1')	-105.2(3)
O(11')-C(13')-C(14')-O(12')	-6.0(3)	C(2)-C(1A)-C(7B)-C(1')	142.9(3)
C(12')-C(13')-C(14')-O(12')	173.1(2)	C(2)-C(1A)-C(7B)-C(1)	-111.9(3)
O(11')-C(13')-C(14')-C(15')	-180.0(2)	C(1A)-C(1)-C(7B)-C(7A)	-106.3(3)
C(12')-C(13')-C(14')-C(15')	-0.8(3)	C(1A)-C(1)-C(7B)-C(1')	107.6(3)
O(12')-C(14')-C(15')-O(13')	6.1(3)	C(13A)-C(17A)-C(17B)-C(11')	-158.8(2)
C(13')-C(14')-C(15')-O(13')	-180.0(2)	C(17)-C(17A)-C(17B)-C(11')	20.2(3)
O(12')-C(14')-C(15')-C(16')	-173.3(2)	C(13A)-C(17A)-C(17B)-C(11A)	-12.9(3)
C(13')-C(14')-C(15')-C(16')	0.7(4)	C(17)-C(17A)-C(17B)-C(11A)	166.1(2)
O(13')-C(15')-C(16')-C(11')	-179.5(2)	C(13A)-C(17A)-C(17B)-C(11)	54.1(3)
C(14')-C(15')-C(16')-C(11')	-0.2(4)	C(17)-C(17A)-C(17B)-C(11)	-126.8(2)
C(12')-C(11')-C(16')-C(15')	0.0(3)	C(12')-C(11')-C(17B)-C(17A)	-103.4(3)
C(17B)-C(11')-C(16')-C(15')	-178.1(2)	C(16')-C(11')-C(17B)-C(17A)	74.6(3)
C(7B)-C(1)-C(1A)-C(2)	107.5(3)	C(12')-C(11')-C(17B)-C(11A)	111.3(3)
C(3)-C(2)-C(1A)-C(1)	-33.1(4)	C(16')-C(11')-C(17B)-C(11A)	-70.7(3)
C(3)-C(2)-C(1A)-C(7B)	38.3(4)	C(12')-C(11')-C(17B)-C(11)	43.7(3)
C(5)-C(4)-C(3A)-C(7A)	0.3(5)	C(16')-C(11')-C(17B)-C(11)	-138.3(2)
C(5)-C(4)-C(3A)-C(3)	179.4(3)	C(11)-C(11A)-C(17B)-C(17A)	107.9(2)
C(2)-C(3)-C(3A)-C(4)	-145.7(3)	C(12)-C(11A)-C(17B)-C(17A)	-3.3(4)
C(2)-C(3)-C(3A)-C(7A)	33.4(4)	C(11)-C(11A)-C(17B)-C(11')	-107.1(2)
C(6)-C(7)-C(7A)-C(3A)	-0.6(4)	C(12)-C(11A)-C(17B)-C(11')	141.7(2)
C(6)-C(7)-C(7A)-C(7B)	179.2(2)	C(12)-C(11A)-C(17B)-C(11)	-111.3(3)
C(4)-C(3A)-C(7A)-C(7)	0.1(4)	C(11A)-C(11)-C(17B)-C(17A)	-105.8(3)
C(3)-C(3A)-C(7A)-C(7)	-178.9(3)	C(11A)-C(11)-C(17B)-C(11')	107.9(3)
C(4)-C(3A)-C(7A)-C(7B)	-179.7(2)	C(4')-C(3')-O(1')-C(7')	-179.9(2)
C(3)-C(3A)-C(7A)-C(7B)	1.3(4)	C(2')-C(3')-O(1')-C(7')	0.6(3)

C(3')-C(4')-O(2')-C(8')	90.0(3)	C(14')-C(13')-O(11')-C(17')	173.6(2)
C(5')-C(4')-O(2')-C(8')	-93.6(3)	C(15')-C(14')-O(12')-C(18')	-102.5(3)
C(6')-C(5')-O(3')-C(9')	1.0(4)	C(13')-C(14')-O(12')-C(18')	83.6(3)
C(4')-C(5')-O(3')-C(9')	-178.3(2)	C(16')-C(15')-O(13')-C(19')	8.0(4)
C(12')-C(13')-O(11')-C(17')	-5.4(4)	C(14')-C(15')-O(13')-C(19')	-171.3(2)

Symmetry transformations used to generate equivalent atoms:

ORTEP Diagrams (50% probability level):

