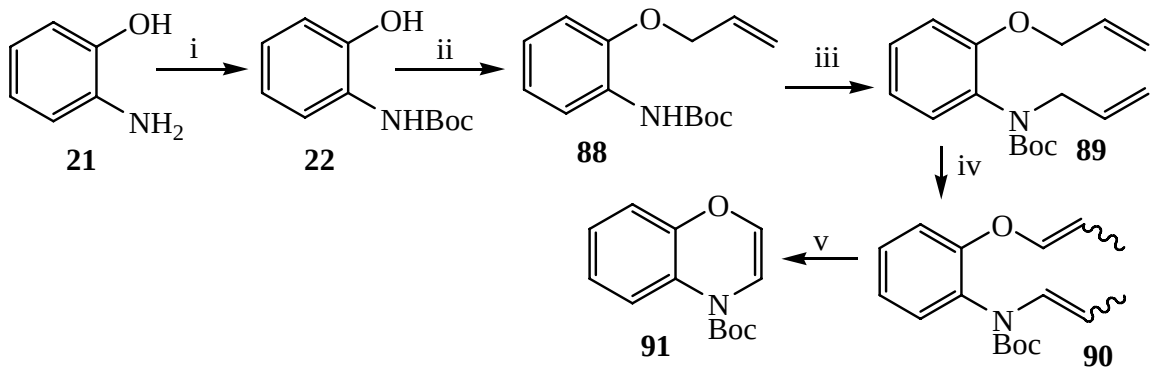
CHAPTER 2. RESULTS AND DISCUSSION

In recent years several research groups have reported RCM approaches to benzo-fused heterocyclic compounds. Bicyclic molecules as a class of compounds are potential pharmacological scaffolds with potential interesting biological activities.[66,67] As mentioned in the introduction, a specific goal for this dissertation is the synthesis of 6-, 7-, 8- and 9-membered benzo-fused heterocyclic compounds. In general, the methodology used was protection of suitable alcohol and amine precursors, allylation, isomerisation followed by RCM for the 6- and 7-membered benzo-fused rings. For the 8- and 9-membered ring, the methodology used was protection, allylation and then RCM.

2.1 SYNTHESIS OF 6-MEMBERED BENZO-FUSED HETEROCYCLIC COMPOUNDS

As described in the introductory section, 6-membered benzo-fused heterocycles are potential pharmaceutical scaffolds. It was thus decided to use an isomerisation-metathesis strategy to synthesize these compounds. The synthesis of 6-membered *N*,*N*- and *N*,*O*-benzo-fused ring systems was attempted using commercially available precursors such as 2-aminophenol and *o*-phenylenediamine with different protecting groups.

2.1.1 SYNTHESIS OF *TERT*-BUTYL 4*H*-1,4-BENZOXAZINE-4-CARBOXYLATE



SCHEME 47

(i) THF, Boc_2O, r.t., 18 hrs, 64%. (ii) Acetone, potassium carbonate, allyl bromide, 60°C, 18 hrs, 92%. (iii) NaH, allyl bromide, THF, 18 hrs 64%. (iv) Catalyst **12**, toluene, 95°C, 18 hrs, 81%. (v) Grubbs II catalyst **4**, toluene, 60°C, 48 hrs, 76%.

The first step in this synthesis was the protection of 2-aminophenol **21** using the Boc protecting group based on the research of Boun and co-workers.[51] This reaction was done at room temperature for 18 hrs after which the crude product was washed with carbon tetrachloride (3 × 100 mL) and dried to afford white crystals of **22** in 64% yield (Scheme 47). The ^{1}H NMR spectrum of **22** showed a singlet at 1.53 ppm, integrating for 9 protons which are characteristic of the three methyl groups attached to the quaternary carbon of the Boc group. Two broad singlets were also visible at 6.66 ppm and 8.12 ppm, each integrating for one proton for the O-H and N-H protons in agreement with data published in the literature.[51]

An allylation reaction was then done on compound **22** at 60°C with allyl bromide in acetone as solvent and using potassium carbonate as the base. The *O*-monoallylated compound **88** was isolated after purification by column chromatography in a yield of 92%. The ^{1}H NMR spectrum showed a doublet at 4.57 ppm for the O-CH_2 which

integrated for two protons. $OCH_2CH=CH_2$ signals were visible at 5.30 ppm and 5.38 ppm as doublets and both integrated for one proton each. The $O-CH_2CH=$ peak was viewed at 5.99-6.12 ppm as a multiplet which integrated for one proton. The ^{13}C NMR spectrum displayed the $O-CH_2$ peak at 69.4 ppm and the $CH=CH_2$ peak at 118.1 ppm. In addition, the high resolution mass spectrum showed a molecular ion peak at *m*/*z* 249.1364 ($C_{14}H_{19}NO_3$ requires 249.1341) and the IR spectrum showed the =C-H peak at 745 cm^{-1}, C-C peak at 1602 cm^{-1} and Ar-O peak at 1157 cm^{-1} which indicated that the compound **88** had formed.

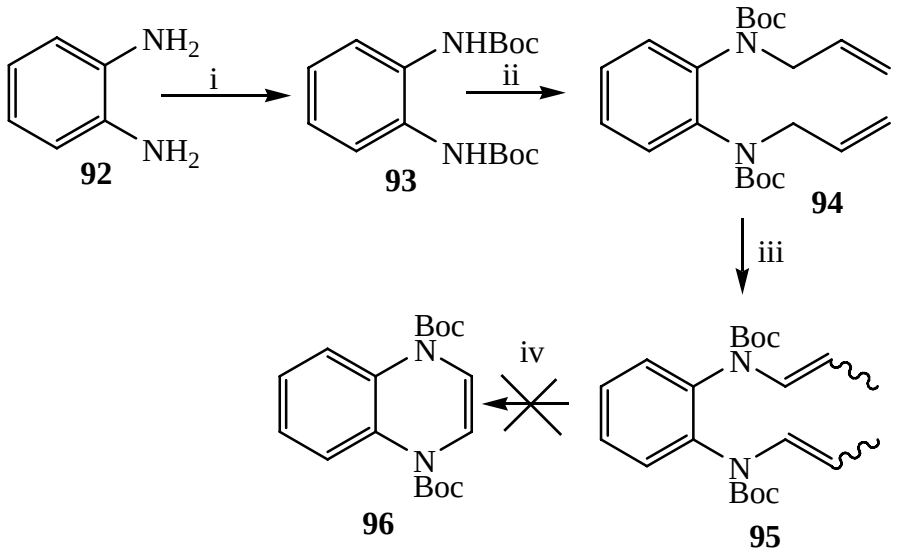
This monoallylated compound **88** was then subjected to a further allylation under the same conditions but did not afford the desired diallylated compound; the monoallylated starting material was re-isolated instead. We then decided to use a stronger base, NaH with THF as solvent in the presence of allyl bromide. The reaction was performed at room temperature for 18 hrs and afforded the diallylated compound **89** in a yield of 64% after column chromatography. The ^1H NMR spectrum of **89** confirmed the disappearance of the N-H peak and a new multiplet was evident at 4.07-4.35 ppm for the new $N–CH_2$ group. In addition, the $NCH_2CH=CH_2$ signal were visible at 5.25 ppm and 5.41 ppm as two doublets of doublets and they both integrated for one proton each. A NCH_2CH signal was visible at 5.81-5.92 ppm as a multiplet. The ^{13}C NMR spectrum displayed the NCH_2 at 52.0 ppm and the $NCH_2CH=CH_2$ peak at 112.5 ppm. The structure was further confirmed by the high resolution mass spectrum which showed a molecular ion peak at *m*/*z* 289.1677 ($C_{14}H_{19}NO_3$ requires 289.1679) and this proved that **89** was our desired compound.

Based on the established methodology, the diallylated compound **89** was then isomerised at a temperature of 95°C for 18 hrs with the ruthenium catalyst **12** to afford an isomerised compound **90** in a yield of 81%. The ^1H NMR of this compound showed the disappearance of the two terminal CH_2 peaks and the appearance of two CH_3 peaks at 1.32 ppm as a singlet and at 1.43 ppm as a doublet of doublets. The structure was further confirmed by a ^{13}C NMR spectrum which showed the new CH_3 peaks at 9.4 ppm and 12.0 ppm which confirmed **90** to be our desired compound. In addition, HRMS showed a

molecular ion peak at *m*/*z* 289.1677 ($C_{14}H_{19}NO_3$ requires 289.1679) and in the IR spectrum, the C=C peak was visible at 1669 cm^{-1}.

The isomerised compound **90** was then treated with Grubbs II catalyst **4** at 60°C for 48 hrs to produce the desired 6-membered compound **91** in a good yield of 76%. The ^1H NMR spectrum showed the disappearance of the OC*H*=C*H*CH_3 and NC*H*=C*H*CH_3 peaks and the appearance of a N-*C*=*H* signal at 5.98 ppm and a O-CH= signal at 6.19 ppm, both peaks occurring as doublets. The structure was further confirmed by a ^{13}C NMR spectrum in which N-*C*=*H* and O-*C*=*H* peaks were visible at 125.5 ppm and 127.7 ppm. In the IR spectrum, the -C=H peak occurred at 851 cm^{-1}. Finally, HRMS showed a molecular ion peak at *m*/*z* 233.1051 ($C_{13}H_{15}NO_3$ requires 233.1047) and it confirmed the structure of our desired compound **91** (Scheme 47).

2.1.2 ATTEMPTED SYNTHESIS OF DI-*TERT*-BUTYL QUINOXALINE-1,4-DICARBOXYLATE



SCHEME 48

(i) Boc_2O, THF, 18 hrs, r.t., 93% (ii) allyl bromide, NaH, DMF, r.t., 18 hrs, 60% (iii) Catalyst **12**, d_8-toluene, 95°C, 98 hrs, 96% (iv) Grubbs II Catalyst **4**, toluene, 80°C, 18 hrs.

As the system of the benzoxazine had been so successfully made, we then attempted the synthesis of di-*tert*-butyl quinoxaline-1,4-dicarboxylate **96** starting from *o*-phenylenediamine **92**. This synthesis had been attempted using the tosyl-protected analogue but it proved unsuccessful and we thought it probably was due to the steric size of the tosyl groups that was preventing the enamines from reacting in a metathetic manner.[58] To investigate this, we decided to use the Boc-protected analogue for the same synthetic strategy. The first step in the synthesis was the protection of the *o*-phenylenediamine using the Boc-protecting group to afford a Boc-protected analogue **93** in a yield of 93%. The ^{1}H NMR spectrum showed a singlet at 1.51 ppm which integrated for 18 protons which is characteristic of the 9 methyl groups attached to the quaternary carbon of the two Boc groups. A broad singlet was visible at 7.45 ppm which integrated for two protons and is a characteristic of the N-H group. The IR spectrum showed the C=O peak at 1731 cm^{-1}. HRMS further proved our structure by the molecular ion peak which was visible at *m*/*z* 308.1736 ($C_{16}H_{24}N_2O_4$ requires 308.1730) indicating our compound.

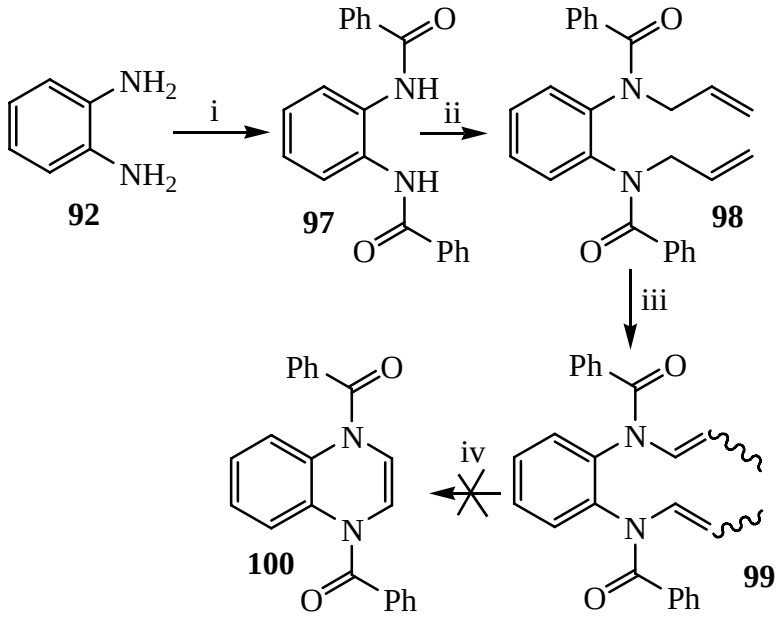
Compound **93** was then subjected to the allylation reaction using NaH as base and allyl bromide with DMF at room temperature for 42 hrs to afford the diallylated compound **94** in a yield of 60%. The ^{1}H NMR spectrum showed the disappearance of the N-H peak and the N-CH_2 signals were seen as broad singlets at 3.63 ppm and 4.47 ppm; NCH_2CH peaks were visible at 5.89-5.91 ppm and occurred as a multiplet and the $NCH_2CH=CH_2$ signals were evident at 5.08-5.11 ppm as a multiplet. In the ^{13}C NMR spectrum, the CH_2 peaks were visible at 51.3 ppm, 52.8 ppm and 117.4 ppm. HRMS showed a molecular ion peak at *m*/*z* 388.2362 ($C_{22}H_{32}N_2O_4$ requires 388.2370), confirming the structure of our compound.

The diallylated compound **94** was then isomerised using the ruthenium catalyst **12** in toluene at 95°C for 28 hrs to afford **95** in a yield of 96%. The ^{1}H NMR spectrum showed the disappearance of the terminal CH_2 peaks and the appearance of the CH_3 peaks which occurred as a multiplet at 1.46-1.49 ppm. In the ^{13}C NMR spectrum, the CH_3 peaks were

visible at 15.0 ppm. The compound was further confirmed on HRMS which showed a molecular ion peak at *m*/*z* 388.2377 ($C_{16}H_{24}N_2O_4$ requires 388.2326).

We then attempted the RCM using Grubbs II catalyst **4** on **95** and to our surprise RCM did not occur. Instead we isolated **95**, the isomerised compound. The failure of the reaction could still be due to steric effects of the two Boc groups (Scheme 48).

2.1.3 ATTEMPTED SYNTHESIS OF 1,4-DIBENZOYL-1,4-DIHYDROQUINOXALINE.



SCHEME 49

(i) Benzoyl chloride, THF, pyridine, 18 hrs, r.t. 88%. (ii) Allyl bromide, NaH, DMSO, r.t., 18 hrs, 80%. (iii) Catalyst **12**, d_8-toluene, 100°C, 18 hrs 94%. (iv) Toluene, Grubbs II catalyst **4**, 18 hrs.

Since the synthesis of the 6-membered benzo-fused nitrogen-containing compounds with the Boc protecting group was unsuccessful, we decided to investigate if the two Boc groups were hindering the RCM. To investigate this, we decided to use a different protecting group on *o*-phenylendiamine. The first step was the protection reaction using

benzoyl chloride in THF with pyridine at room temperature, as described in the literature, to afford **97** in a good yield of 88%**.**[70] The IR spectrum showed the C=O peak at 1643 cm^{-1}. HRMS showed a molecular ion peak at *m*/*z* 316.1211 ($C_{20}H_{16}N_2O_2$ requires 316.1224) and the melting point of the compound was found to be 230°C confirming that we had our compound.

The protected precursor **97** was initially allylated with allyl bromide in DMF at room temperature for 18 hrs but the yield was poor due to poor solubility of our precursor in DMF. We then decided to use DMSO as solvent under the same conditions and we got several products that were visible on the TLC but uncharacterisable. One of the products was our desired compound **98** which was isolated in a good yield of 80%. HRMS showed a molecular ion peak at *m*/*z* 396.1842 ($C_{26}H_{24}N_2O_2$ requires 396.1837). The ^{1}H NMR spectrum displayed the N-CH_2 peaks as a broad multiplet at 3.90-4.20 ppm which integrated for two protons and as a broad singlet at 4.37 ppm which integrated for two protons. The $NCH_2CH=CH_2$ peaks were visible at 5.11 ppm and the $NCH_2CH=$ peaks were visible at 5.86 ppm and both occurred as broad singlets. In addition the structure of the compound was confirmed by ^{13}C NMR in which the CH_2 peaks were seen at 52.1 ppm (NCH_2) and 116.3 ppm ($CH=CH_2$).

An isomerisation reaction was then performed on the compound **98** using ruthenium catalyst **12** in d_8-toluene at 100°C for 18 hrs to afford **99** in a yield of 94% after column chromatography. The ^{1}H NMR spectrum showed the disappearance of the CH_2 peaks and the appearance of the CH_3 peaks, which occurred as multiplets at 1.36-1.62 ppm. The compound structure was further confirmed by HRMS, which showed a molecular ion peak at *m*/*z* 396.1849 ($C_{26}H_{24}N_2O_2$ requires 396.1837).

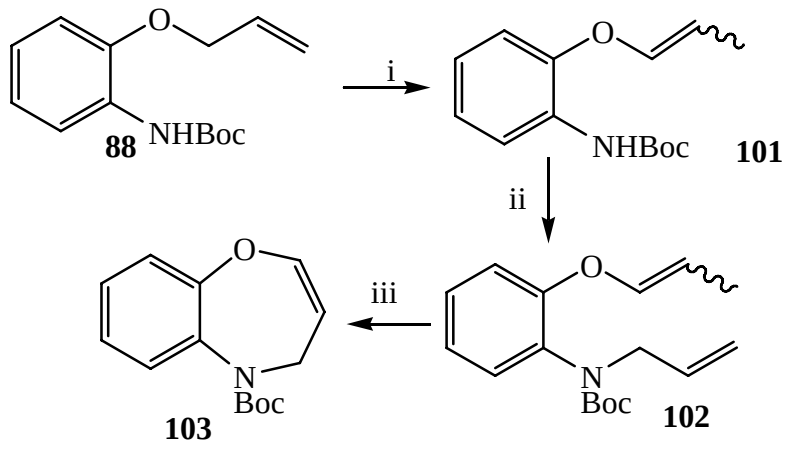
RCM was them attempted on **99** at 80°C for 18 hrs but we only isolated **99**, the isomerised starting material instead of our desired compound **100**. This was proved by TLC and confirmed by ^{1}H NMR (Scheme 49). This supports the view that the size of the two bulky protecting group used in the synthesis creates a steric effect, thereby preventing the enamines from reacting in a metathetic manner whereas, in the cases of

the synthesis of *tert*-butyl 4*H*-1,4-benzoxacine-4-carboxylate, only one protecting group (Boc) was present and as such, there was less steric effect and RCM was not hindered.

2.2 SYNTHESIS OF 7-MEMBERED BENZO-FUSED HETEROCYCLIC COMPOUNDS

Benzoxazepines are biological interesting compounds and they have been investigated extensively due to their biological properties (see introduction). They are found as structural units in natural products[59] and this has prompted the use of various methods for their synthesis, including RCM.

2.2.1 SYNTHESIS OF *TERT*-BUTYL 1,5-BENZOXAZEPINE-5(4*H*)-CARBOXYLATE



SCHEME 50

(i) Catalyst **12,** toluene, 100°C, 18 hrs, 98%. (ii) Allyl bromide, NaH, DMF, r.t., 18 hrs, 92%. (iii) Grubbs II catalyst **4**, toluene, 60°C, 18 hrs, 60%.

The first step in the synthesis was protection of 2-aminophenol **21** using a Boc group to afford **22** which was followed by a mono-allylation using allyl bromide, NaH with THF

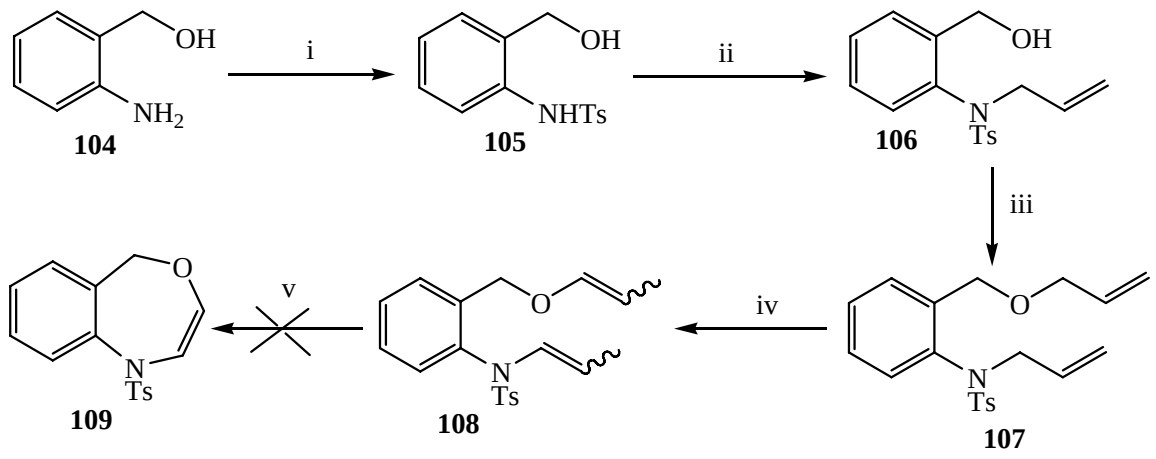
at room temperature for 18 hrs to afford **88** in a yield of 92% as described before (see Scheme 47).

Compound **88** was then subjected to an isomerisation reaction using catalyst **12** at 100°C for 18 hrs to afford **101** in an excellent yield of 98%. The ^{1}H NMR spectrum showed that the compound was a complex mixture of *E*/*Z* isomers. The CH_3 peaks were visible at 1.67 and 1.73 ppm as broad doublets. The ^{13}C NMR spectrum displayed the new CH_3 peaks at 9.4 and 12.1 ppm and the HRMS showed a molecular ion peak at *m*/*z* 249.1364 ($C_{14}H_{19}NO_3$ requires 249.1341) which confirmed the structure of our new compound.

Allylation was then done on compound **101** using NaH as a base and THF as solvent in the presence of allyl bromide at room temperature for 16 hrs to afford **102** in a good yield of 83% after purification by column chromatography. The HRMS showed a molecular ion peak at *m*/*z* 289.1677 ($C_{17}H_{23}NO_3$ requires 289.1669) and the IR spectrum viewed the C-N peak at 1255 cm^{-1}. The ^{1}H NMR spectrum showed the disappearance of the N-H peak and the appearance of the N-CH_2 as a broad singlet at 4.13 ppm; the N-CH_2C*H*= peak was seen at 5.80-5.95 ppm and occurred as a multiplet and the NCH_2CH=CH_2 peaks were visible at 5.02-5.11 ppm. In addition, the ^{1}H NMR spectrum proved that the compound was a 2:1 *E*:*Z* mixture. The compound structure was further confirmed by ^{13}C NMR in which the NCH_2 peak was visible at 52.2 ppm.

The diallylated compound **102** was then subjected to a RCM using Grubbs II catalyst **4** to afford **103** in a yield of 60% (Scheme 43). The ^{1}H NMR showed the O-C*H*=CH peak as a broad singlet at 4.83 ppm and N-CH_2- occurred as a broad singlet at 4.22 ppm while the NCH_2C*H*= proton occurred as a broad doublet at 6.42 ppm. The HRMS showed a molecular ion peak at *m*/*z* 247.1203 ($C_{17}H_{14}NO_3$ requires 247.1208). The compound's structure was further confirmed by ^{13}C NMR spectroscopy in which only one CH_2 peak was visible at 45.2 ppm (Scheme 50). This approach thus successfully gave us the desired 1,5-benzoxazepine structure in a good overall yield. With this success behind us, we decided to attempt the synthesis of another type of 7-membered ring system.

2.2.2 ATTEMPTED SYNTHESIS OF 1-[(4-METHYLPHENYL)SULFONYL]-1,5-DIHYDRO-4,1-BENZOXAZEPINE



SCHEME 51

(i) Pyridine, TsCl (1.0 equiv.), r.t., 18 hrs, 28%. (ii) Acetone, potassium carbonate, allyl bromide, 60°C, 22 hrs, 90%. (iii) THF, allyl bromide, NaH (1.2 equiv.), r.t., 18 hrs, 78%. (iv) Catalyst **12**, d_8-toluene, 70-80°C, 20 hrs, 94%. (v) Grubbs II Catalyst, 60°C, 90-100°C, 18-20 hrs.

The past years have seen intense interest in the RCM reaction. However, not much has been done on the synthesis of 7-membered benzo-fused heterocyclic compounds by RCM from corresponding benzyl-precursors. We attempted the synthesis of 1-[(4-methylphenyl)sulfonyl]-1,5-dihydro-4,1-benzoxazepine **109** using 2-aminobenzyl alcohol **104** as precursor. The first step was the protection of the nitrogen with a tosyl group to afford **105** in a yield of 28% yield.[71] The ^{1}H NMR spectrum showed the methyl group as a singlet at 2.38 ppm which is a characteristic of the methyl group on the tosyl protecting group. In addition, HRMS showed a molecular ion peak at *m*/*z* 277.0765 ($C_{14}H_{15}NO_3S$ required 277.0773) and the melting point was found to be 142-145°C. The IR spectrum showed the O-H peak at 2924 cm^{-1} and the O=S=O stretch was visible at 1158 cm^{-1}. In addition, the ^{13}C NMR spectrum displayed the CH_3 signal on the tosyl group at 21.5 ppm thereby confirming that **105** was our desired compound.

An allylation reaction was then performed on **105** using potassium carbonate with allyl bromide in THF to afford **106** in an excellent yield of 90% which was monoallylated on the nitrogen atom.[72] The compound was then characterized by ^{1}H NMR which showed the presence of O-H peak as a multiplet at 4.99-5.03 ppm together with the $NCH_2CH=CH_2$ peak signals. The NCH_2 peaks were visible as a broad singlet at 3.03 ppm which integrated for one proton and as a multiplet at 3.70-3.76 ppm which integrated for a further one proton. The $NCH_2CH=$ peak was seen as a multiplet at 5.64-5.78 ppm which integrated for one proton. In addition, HRMS showed a molecular ion peak at *m*/*z* 317.1098 ($C_{17}H_{19}NO_3S$ requires 317.1085) and the IR spectrum showed the O-H peak at 3517 cm^{-1} and a C=C stretch was visible at 1598 cm^{-1} thus supporting the structure of our compound.

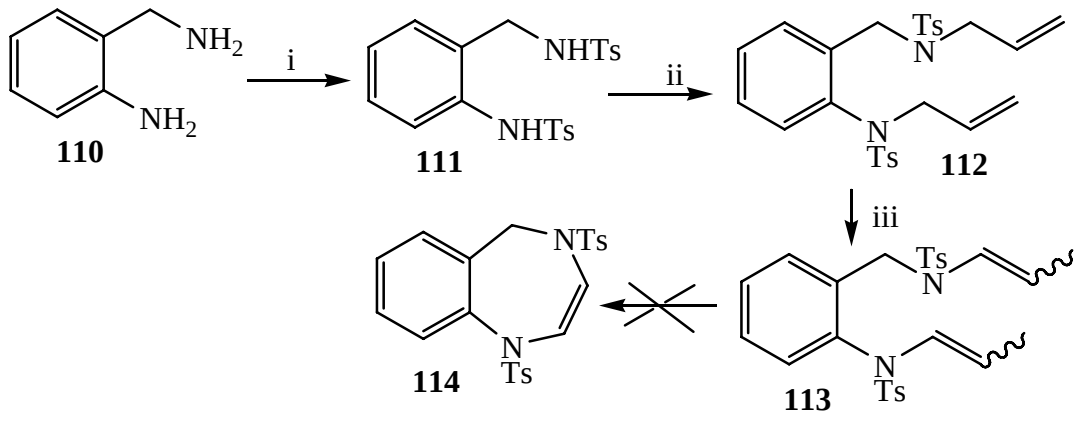
Allylation was next performed on the mono-allylated compound **106** using NaH in THF as solvent with allyl bromide to afford **107** in a good yield of 78% after purification by column chromatography. The ^{1}H NMR spectrum showed the disappearance of the OH signal and the presence of the additional OCH_2 peaks which were visible as broad singlets at 3.85 ppm and 4.35 ppm and integrated for one proton each. The $OCH_2CH=CH_2$ peaks were viewed as a doublet at 5.21 ppm which integrated for one proton and as a doublet of a doublet at 5.33 ppm which integrated for one proton. The $OCH_2CH=$ peak was visible at 5.91-6.04 ppm and it was seen as a multiplet which is a characteristic of the peak. HRMS did not show the molecular ion for the desired compound; instead the fragment peak in which one of the tosyl group had fallen off was visible at 202.1232 ($C_{13}H_{16}NO$ required 202.1223 for M^{+}-Ts). The compound structure was further confirmed by the ^{13}C NMR spectrum in which the two CH_2 signals were seen at 71.5 ppm and 116.8 ppm.

An isomerisation reaction was then performed on **107** using ruthenium catalyst **12** in d_8-toluene to afford our desired isomerised compound **108** in an excellent yield of 94%. The HRMS of **108** displayed a molecular ion peak at *m*/*z* 368.1539 ($C_{24}H_{20}N_2O_4S$ requires 368.1524). The ^{1}H NMR spectrum proved that the compound was a complex mixture of

E/*Z* isomers and it showed the disappearance of the terminal CH_2 and the presence of the new CH_3 peaks as a multiplet at 1.53-1.65 ppm which integrated for 6 protons.

Compound **108** was then subjected to RCM using Grubbs II catalyst **4** in toluene at 60°C but no product **109** was formed. The reaction was then repeated at 90-100°C for 18-24 hrs but once again, RCM did not occur and instead we isolated **108** in a good recovery of 77%. This lack of reactivity could be due to kinetic reason *i.e*. the alkenes could not find each other to react (Scheme 51). However, electronic reasons due to the electron rich nature of the *O*- and *N*-vinyl alkenes could also be sabotaging the formation of **109**.

2.2.3 ATTEMPTED SYNTHESIS OF 1,4-*BIS*[(4-METHYLPHENYL)SULFONYL]-4,5-DIHYDRO-1*H*-1,4-BENZODIAZEPINE



SCHEME 52

(i) THF, TsCl, r.t., 18 hrs, 59%. (ii) Allyl bromide, THF, NaH, r.t., 18 hrs, 83%. (iii) Ruthenium isomerisation catalyst **12**, toluene, 80°C, 48 hrs, 95%. (iv) Grubbs II catalyst **4**, toluene, reflux, 20 hrs.

Since the synthesis of the 7-membered benzo-fused *O,N*-containing compound from benzyl precursors was unsuccessful (possibly due to kinetic reasons), we then decided to investigate this by using a different benzyl precursor, namely 2-aminobenzylamine **110** to

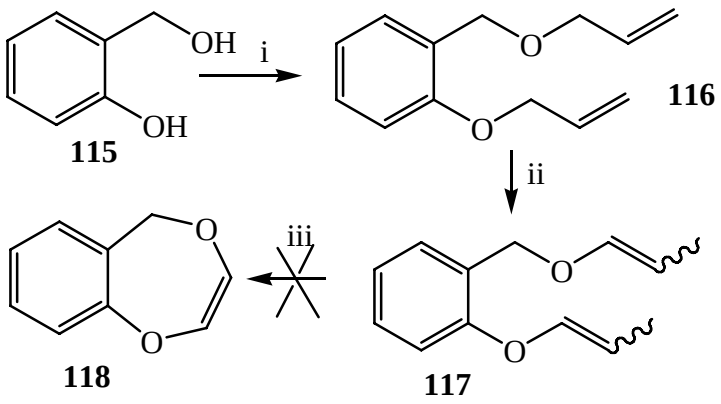
synthesize 1,4-bis[(4-methylphenyl)sulfonyl]-4,5-dihydro-1*H*-1,4-benzodiazepine **114**. The first step in the synthesis was the protection reaction using TsCl and pyridine to afford our desired compound **111** in a yield of 59%.[73] The compound was then characterized by the ^{1}H NMR spectrum in which the methyl groups on the tosyl protecting group were visible at 2.39 ppm and 3.44 ppm as singlets which integrated for three protons each. The N-H peaks were also visible at 5.10-5.14 ppm and appeared as a multiplet.

An allylation reaction was then performed on **111** in acetone with potassium carbonate and allyl bromide to afford **112** in a good yield of 83%. In the ^{1}H NMR spectrum, the NCH_2 signals were viewed as a doublet of doublets at 3.89 ppm and 4.39 ppm and as doublets at 4.51 ppm and 4.76 ppm. The $NCH_2CH=CH_2$ peak was viewed as a multiplet at 4.94-5.07 ppm and the $NCH_2CH=CH_2$ signals were visible as a multiplet at 5.52-5.73 ppm. In addition, the HRMS showed a molecular ion peak at *m*/*z* 511.1680($C_{27}H_{30}N_2O_4S_2$ requires 511.1647) thereby confirming **112** to be our desired compound.

Compound **112** was then subjected to an isomerisation reaction at 80°C for 48 hrs with catalyst **12** to afford **113**, the isomerised compound, in an excellent yield of 95%. HRMS did not show the molecular ion for the desired compound; instead the fragment peak in which one of the tosyl groups had fallen off was visible at *m*/*z* (EI) 355 (M^+- Ts, 100%). The ^{1}H NMR spectrum proved the compound to be a mixture of *E*/*Z* isomers. The CH_3 peaks were visible at 1.53-1.65 ppm as multiplets, but unfortunately the ^{13}C NMR spectrum was complicated and so the product was used in the next RCM reaction without further characterisation.

We then attempted a RCM on **113** at both 50-60° C and at 100-110°C using the Grubbs II catalyst. Unfortunately we isolated our starting material **113** instead of the desired product **114** and we suspect that this could be due to the steric size of the two tosyl groups *i.e.* due to the steric bulk of the tosyl groups, the alkenes were no longer in proximity to allow for the RCM reaction (Scheme 52).

2.2.4 ATTEMPTED SYNTHESIS OF 5*H*-1,4-BENZODIOXEPINE



SCHEME 53

(i) NaH, Allyl bromide, DMF, r.t., 17 hrs, 60%. (ii) Catalyst **12**, Toluene, reflux 80°C, 18 hrs, 72%. (iii) Grubbs II Catalyst **4**, toluene, 80-100°C, 20 hrs.

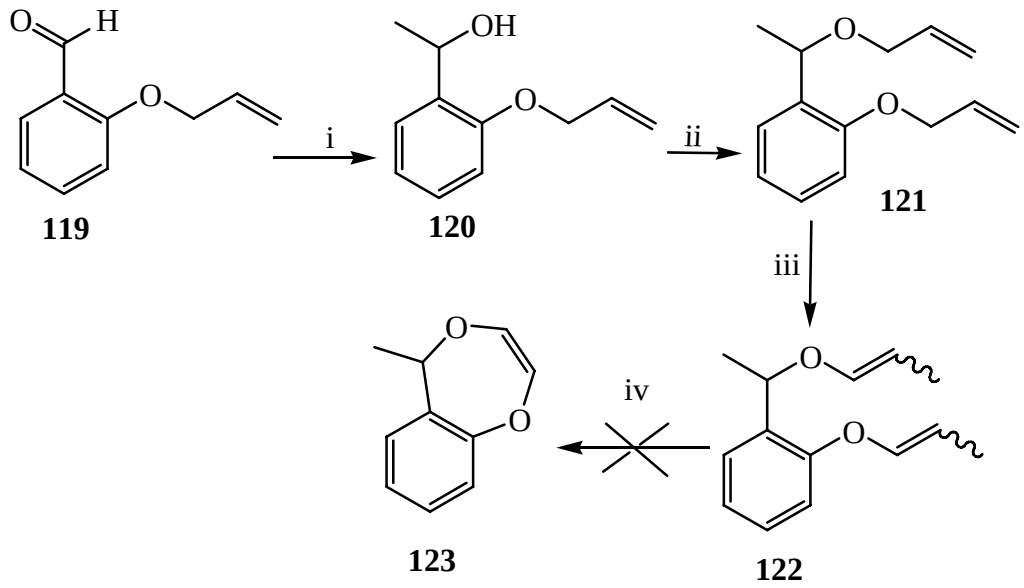
Since we suspected that the steric size of the two tosyl groups was preventing RCM in the synthesis of 7-membered benzo-fused *N*,*N*-compound, we lastly decided to attempt RCM using a different precursor, 2-(hydroxymethyl)phenol **115**. The first step was an allylation reaction using NaH and DMF with allyl bromide to afford **116** in a moderate yield of 60%.[74] The ^{1}H NMR spectrum showed the O-CH_2 peaks as doublets at 4.08 ppm and 4.54 ppm which integrated for two protons each. In addition, the $OCH_2CH=CH_2$ peaks were visible at 5.17-5.43 ppm as multiplets and the $OCH_2CH=$ peaks were visible at 5.91-6.10 ppm and integrated for two protons. In the ^{13}C NMR spectrum, the CH_2 signals were visible at 66.8 ppm, 68.7 ppm, 71.4 ppm, 116.7 ppm and 116.9 ppm thereby confirming **63** to be our desired compound.

Product **116** was then subjected to an isomerisation reaction as before using ruthenium isomerisation catalyst **12** with toluene at reflux for 20 hrs to afford **117** in a good yield of 72%. The mass spectrum showed the molecular ion *m*/z 204.1129 ($C_{13}H_{16}O_3$ required 204.1150). The ^{1}H NMR proved the compound to once again be a complex mixture of

E/*Z* isomers and the CH_3 signals were present as multiplets at 1.54-1.72 ppm which integrated for 6 protons.

We then attempted RCM on **117** at 100°-110°C using the Grubbs II catalyst **4** but unfortunately, we isolated **117** instead of our desired compound **118** (Scheme 53). This approach to the 7-membered benzo-fused ring systems starting from benzylic precursors was thus unsuccessful. The exact reasons for this not forming are not clear as the formation of the compounds 6-membered heterocycles from *O*,*N*-divinyl precursor have been shown to be successful (see Scheme 36, 37 and 38).

2.2.5 ATTEMPTED SYNTHESIS OF 5-METHYL-5*H*-1,4-BENZODIOXEPINE



SCHEME 54

(i) Mg, MeI, diethyl ether, r.t., 18 hrs, 77%. (ii) DMF, NaH, allyl bromide, r.t., 18 hrs, 81%. (iii) Catalyst **12,** d_6-benzene, 100°C, 18 hrs. (iv) Grubbs II catalyst **4**, toluene, 90-100°C, 18 hrs.

Since the attempted synthesis of 7-membered benzo-fused ring systems **109**, **114**, **118** from benzyl-precursors proved to be unsuccessful, perhaps due to the unrestricted

movement of the vinyl groups, we decided to attempt the synthesis of 7-membered benzo-fused ring systems from different precursors. We thought the introduction of steric bulk at the benzylic position might limit the possible conformation of the *O*-vinyl groups, thereby possibly facilitating the RCM reactions.

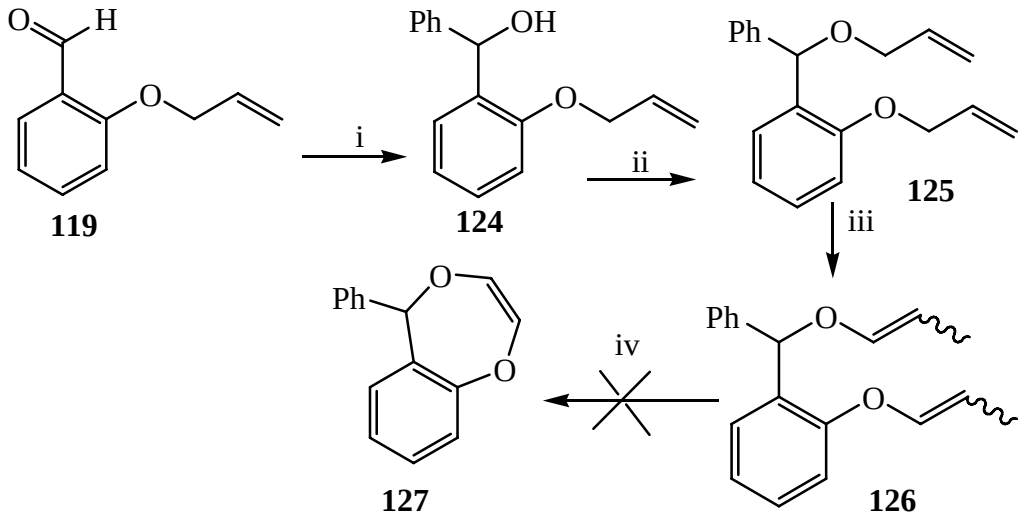
Methylmagnesium iodide was made by dissolving magnesium metal turnings in diethyl ether at 0ºC and methyl iodide was then added when the magnesium metal turning had all dissolved. 2-(Allyloxy)benzaldehyde **119** was thus added drop-wise to a mixture of magnesium metal turnings in diethyl ether and the reaction mixture was stirred at room temperature for 18 hrs after which it was quenched with ammonium chloride to afford **120** in a good yield of 77% after purification by column chromatography. The HRMS showed the molecular ion at 240.1160 ($C_{11}H_{14}O_2$ required 240.1150) and the IR spectrum displayed the new OH peak at 3389 cm^{-1}. The ^1H NMR spectrum showed the methyl group as a doublet at 1.52 ppm which integrated for three protons and the O-H peak as a broad singlet at 2.66 ppm which integrated for one proton. In addition, the ^{13}C NMR spectrum displayed the CH_3 and CHOH signals at 23.8 ppm and 68.7 ppm, respectively.

The compound **120** was then subjected to an allylation reaction using allyl bromide and NaH to afford the desired compound **121** in a good yield of 81%. The HRMS spectrum depicted the molecular ion peak at *m*/*z* 218.1306 ($C_{14}H_{18}O_2$ required 218.1306). The ^1H NMR spectrum showed the disappearance of the OH peak, and the O-CH_2 peak was visible as a multiplet at 3.84-3.92 ppm, the O-CH_2C*H*= peak at 5.87-6.10 ppm (multiplet) and the OCH_2CH=CH_2 signals were present at 5.24-5.28 ppm (multiplet).

Product **121** was then subjected to the usual isomerisation reaction using catalyst **12** in d_6-benzene at 100°C to afford the resultant compound **122**. The ^1H NMR proved that the compound was a complex mixture of *E*/*Z* isomers and the CH_3 peaks were present at 1.61-1.66 ppm as a multiplet which integrated for three protons and at 1.77 ppm as a doublet of doublets integrating for three protons. The crude product **122** was then subjected to RCM at 80-100°C using the Grubbs II catalyst **4** but the desired 7-membered

benzo-fused compound **123** was not isolated. Instead, we isolated the isomerised compound **122** (Scheme 54).

2.2.6 ATTEMPTED SYNTHESIS OF 5-PHENYL-5*H*-1,4-BENZODIOXEPINE



119 **124** **125** **126** **127**

SCHEME 55

(i) Mg, THF, bromobenzene, r.t., 18 hrs, 38%. (ii) NaH, DMF, Allyl bromide, r.t., 18 hrs, 86%. (iii) Catalyst **12**, Toluene, 18 hrs, 80-100°C. (iv) Grubbs II catalyst **4**, 18 hrs, 80-100°C.

The synthesis of 5-methyl-5*H*-1,4-benzodioxepine **123** was unsuccessful and we suspect it could be that the methyl group was sterically too small to force the two vinyloxy groups into close proximity for RCM. To investigate this, we decided to use a different precursor **124** containing the bulkier phenyl group. 2-(Allyloxy)benzaldehyde **119** was thus added drop-wise to a mixture of magnesium metal turnings in THF with bromobenzene. The reaction mixture was stirred at room temperature for 18 hrs after which it was quenched with ammonium chloride. Column chromatography was done on the crude product using 5% ethyl acetate in hexane to afford the product **124** as a colorless oil in a yield of only 38%. HRMS showed the molecular ion *m*/*z* at 240.1160 ($C_{16}H_{16}O_2$ required 240.1150). The IR spectrum showed the new OH peak at 3408 cm^{-1}

and ^{1}H NMR spectrum displayed the O-H peak as a broad doublet at 2.97 ppm. The ^{13}C NMR spectrum further confirmed the structure as the *C*HOH peak was present at 72.3 ppm.

Alcohol **124** was then allylated using NaH with allyl bromide at room temperature for 18 hrs to afford product **125** in a good yield of 86% after column chromatography. The ^{1}H NMR spectrum showed the OCH_2 peak as a doublet at 3.94 ppm (2 protons), the $OCH_2CH=CH_2$ was seen as a multiplet at 5.07-5.30 ppm (4 protons) and $OCH_2CH=$ peak was visible at 5.88-5.91 ppm. In the ^{13}C NMR spectrum the new OCH_2 signal was visible at 69.8 ppm. The HRMS showed the molecular ion *m*/*z* at 280.1458 ($C_{19}H_{20}O_2$ required 280.1463).

The diallyloxy compound **125** was then subjected to an isomerisation reaction using toluene and ruthenium isomerisation catalyst **12** at 80-100°C for 18 hrs to afford **126**. The ^{1}H NMR spectrum showed that the compound was a complex mixture of *E*/*Z* isomers, and confirmed the disappearance of the $=CH_2$ protons and the appearance of two CH_3 groups, which were present as a multiplet at 1.48-1.70 ppm and integrated for 6 protons.

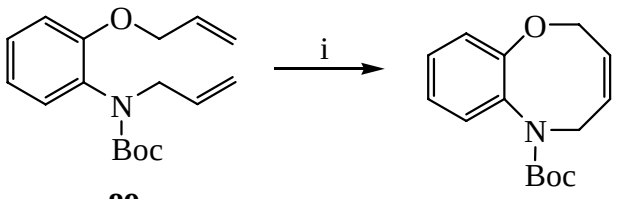
The crude product **126** was then subjected to RCM using Grubbs II catalyst **4** in toluene at 80-100°C for 18 hrs but only **126** was isolated instead of our desired product **127**. We thought the phenyl group would restrict the movement of alkenes thereby allowing RCM but to our surprise RCM did not occur (Scheme 55).

2.3 SYNTHESIS OF 8-MEMBERED BENZO-FUSED HETEROCYCLIC COMPOUNDS

In our laboratories, a variety of 8-membered nitrogen- and oxygen-containing benzo-fused rings have been synthesized through ruthenium-mediated RCM in moderate to good yields (see introductory section). We decided to synthesize other 8-membered benzo-fused ring systems using commercially available precursors with different

protecting groups. The precursors used in this part of the project were 2-aminophenol, *o*-phenylenediamine, 2-aminobenzylalcohol and catechol.

2.3.1 SYNTHESIS OF *TERT*-BUTYL 2,5-DIHYDRO-6*H*-1,6-BENZOXAZOCINE-6-CARBOXYLATE



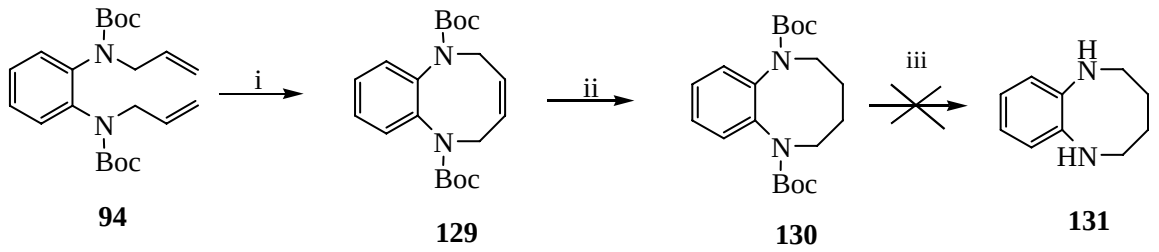
89 **128**

SCHEME 56

(i) Grubbs II catalyst, toluene, r.t., 18 hrs, 69%.

A similar 8-membered ring system to that depicted in the scheme **58** has been prepared by Rambo Khanye, an Honours student, using the tosyl protecting group.[65] We thus decided to prepare the compound with a different protecting group, namely the Boc group to facilitate future deprotection. Compound **89** (synthesis described in Scheme 49) was subjected to RCM using Grubbs II catalyst **4** in toluene to afford the product **128** in a moderate yield of 69% after chromatography. The HRMS showed a molecular ion peak at *m*/*z* 261.1321 ($C_{14}H_{19}NO_3$ requires 261.1364). Furthermore, the ^{1}H NMR showed the OCH_2 peak at 4.71 ppm as a doublet, the NCH_2 peak at 4.34 ppm as a broad singlet and the C*H*=C*H* peaks as multiplet at 5.76-5.92 ppm. The ^{13}C NMR spectrum showed the two CH_2 peaks at 48.9 ppm and 65.1 ppm and this confirmed our desired compound (Scheme 56).

2.3.2 SYNTHESIS OF DI(*TERT*-BUTYL) 2,5-DIHYDRO-1,6-BENZODIAZOCINE-1,6-DICARBOXYLATE



94 **129** **130** **131**

SCHEME 57

(i) Grubbs II catalyst **4**, 60°C, 18 hrs, toluene, 64%. (ii) H_2/Pd, ethanol, 5 bar, 20 hrs, 97%. (iii) Deprotection. (a) THF, TFA, 1-18 hrs. (b) Microwave, 2 mins 30 secs. (c) TFA, $AlCl_3$, DCM, r.t., 15mins – 18 hrs.

Another 8-membered benzo-fused heterocycle, di(*tert*-butyl) 2,5-dihydro-1,6-benzodiazocine-1,6-dicarboxylate **129**, was synthesized from the diallylated compound **94** (see Scheme 48) by RCM using Grubbs II catalyst **4** to afford the 8-membered ring **129** in a moderate yield of 64% after purification by column chromatography (Scheme 57). The HRMS showed the molecular ion *m*/*z* 360.2069 ($C_{20}H_{28}N_2O_4$ required 360.2049). The compound structure was further confirmed by ^{1}H NMR spectrum which showed the N-CH_2 peaks as a broad singlet at 4.08 ppm which integrated for four protons and the CH=CH peak was evident as a broad singlet at 5.86 ppm integrating for two protons. The ^{13}C NMR spectrum displayed the CH_2 signals at 45.7 ppm. Compound **129** was then recrystallized from 20% ethyl acetate in hexane to afford clear crystals, Mp: 113-116ºC and single crystal X-ray diffraction was performed. The crystal structure of **129** belongs to a triclinic crystal system with a P-1 space group. The bond angles and lengths were found to be within the average bond angles and lengths for this type of structure (Figure 5). All the data for this structure are recorded in Appendix A.

We then performed a hydrogenation on the 8-membered benzo-fused ring system **129** using H_2/Pd in ethanol to afford **130** in an excellent yield of 97% (Scheme 50). In the ^{1}H NMR spectrum, the N-$CH_2C\mathit{H}_2$ peak was now visible at 1.67 ppm as a broad singlet (four protons) and the N-$C\mathit{H}_2$ peak was visible at 3.65 ppm as a broad singlet (four protons). The ^{13}C NMR spectrum displayed the NCH_2 signal at 50.9 ppm and the CH_2 signal at 26.5 ppm. The HRMS showed the molecular ion *m*/*z* 362.2203 ($C_{20}H_{30}N_2O_4$ required 362.2206). After recrystallization of the 8-membered benzo-fused ring system from 30% ethyl acetate in hexane, clear crystals (mp 100-103°C) were obtained and X-ray diffraction was performed, confirming that **130** had been formed. This time the crystal structure was found to belong to a monoclinic crystal system with a space group of P21/n. The bond lengths and angles were also found to be within the average bond length and angles expected for this type of structure (Figure 6). All the data for this structure are recorded in Appendix A.

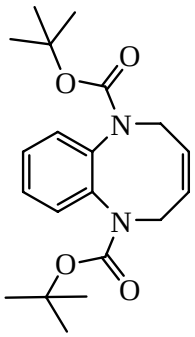
We then attempted deprotection of the Boc groups from compound **130** by the following methods:

METHOD ONE: By using TFA at 0°C and then at room temperature for 1-18 hrs. We discovered that most of our compound had decomposed and we recovered our starting material **130** in a yield of 10%. The structure was confirmed by ^{1}H NMR spectroscopy.

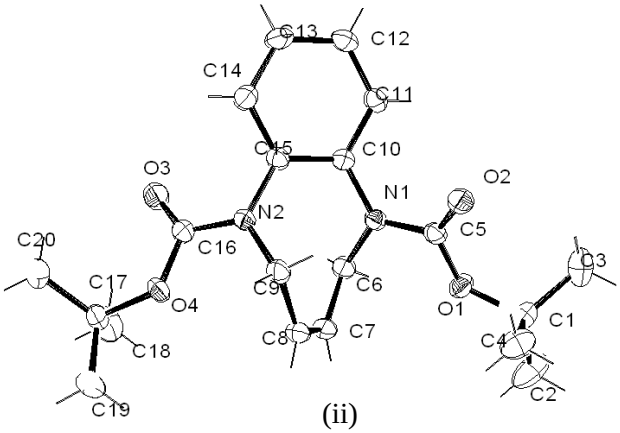
METHOD TWO: A mixture of the 8-membered benzo-fused ring **130** and silica gel was irradiated in a microwave oven (30s irradiation) for a total of 2 mins 30 secs. Column chromatography was then performed to only afford a brown oil which was proved to be the starting material by TLC and ^{1}H NMR spectroscopy instead of our desired compound **131**. The recovery was 39% yield.

METHOD THREE: Since TFA and the microwave method did not deprotect our compound **130**, we then used $AlCl_3$ in CH_2Cl_2 and the reaction mixture was stirred for 15 min at r.t. and then left overnight. Unfortunately, the ^{1}H NMR spectrum of the crude compound isolated was uncharacterisable. We could not give an exact reason why

deprotection proved to be problematic as other groups had been able to successfully deprotect the Boc group from a similar ring system using one of the methods above.



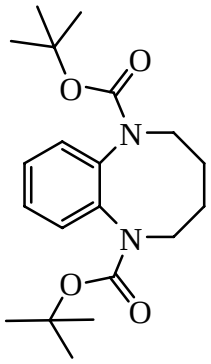
(i)



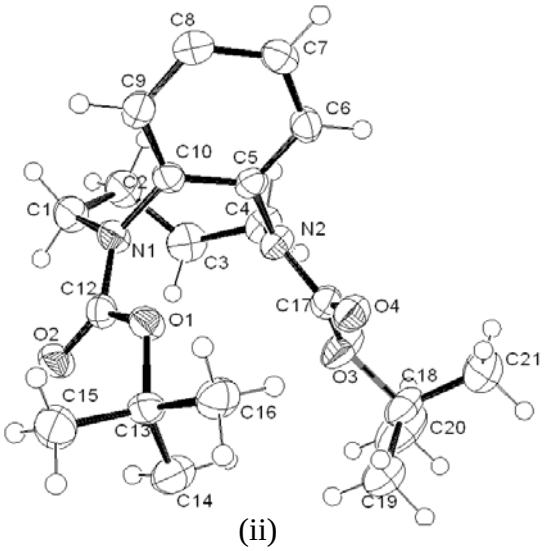
(ii)

FIGURE 5

(i) Molecular structure of **129**. (ii) ORTEP crystal structure of **129**.



(i)

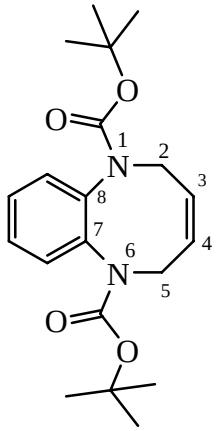
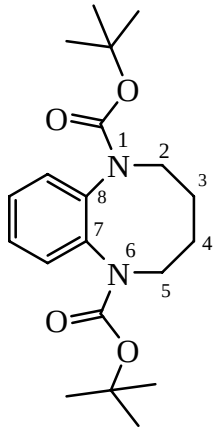


(ii)

FIGURE 6

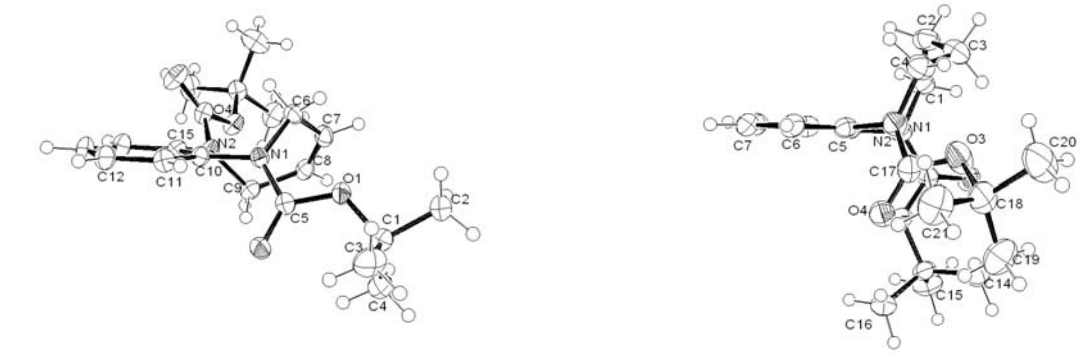
(i) Molecular structure of **130**. (ii) ORTEP crystal structure of **130**.

SOLID STATE STRUCTURE OF **129** AND **130**: The solid-state structures of both compounds were determined by X-ray diffraction. The bond lengths and angles for both structures were found to be consistent except that the bond length of C(3)-C(4) in **129** was found to be shorter than the corresponding bond length in **130** and this would be as a result of the double bond. Thus, C(3)-C(4) in **129** was [1.302(2)Å] while the corresponding bond length in **130** was found to be [1.541(2)Å]. The torsion angles for the heterocyclic portion of both structures differed significantly and this would be as a result of the absence of a double bond in the corresponding structure **130**. The table below shows how some of the torsion angles in the heterocyclic portion of the two compound structures differed.

Torsion angles for structure **129** [°]	Torsion angles for structure **130** [°]
	
1. N(1)-C(2)-C(3)-C(4) = 40.5(2)	1. N(1)-C(2)-C(3)-C(4) = 73.58(19)
2. C(2)-C(3)-C(4)-C(5) = 3.5(3)	2. C(2)-C(3)-C(4)-C(5) = -96.38(18)
3. C(3)-C(4)-C(5)-N(6) = 44.5(2)	3. C(3)-C(4)-C(5)-N(6) = 51.98(19)
4. C(4)-C(5)-N(6)-C(7) = -111.30(6)	4. C(4)-C(5)-N(6)-C(7) = 54.93(19)
5. C(5)-N(6)-C(7)-C(8) = 47.4(2)	5. C(5)-C(6)-N(7)-C(8) = -99.79(15)
6. C(2)-N(1)-C(8)-C(7) = 51.0(2)	6. C(2)-N(1)-C(8)-C(7) = 79.69(16)
7. C(8)-N(1)-C(2)-C(3) = -110.96(16)	7. C(8)-N(1)-C(2)-C(3) = -83.27(17)

If the structures of both compounds are viewed in such a way that the fused-benzene ring of both compounds is flat, the 8-membered rings will show a significant conformational

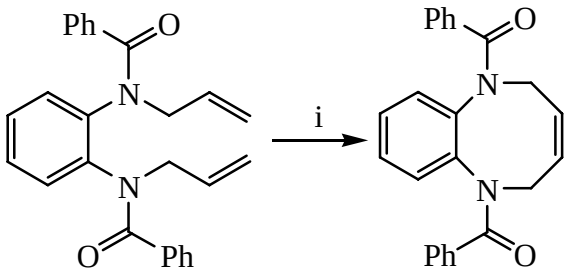
difference. The benzo-fused heterocyclic ring of **130** was found to be bent to an angle of about 90° with the Boc groups pointing downwards but in the case of the benzo-fused heterocyclic compound of **129**, the benzo-fused heterocyclic ring was found to be puckered with one Boc group pointing upward and the second Boc group pointing downward (Figure 7).



129 **130**

Figure 7: Diagram of structures of **129** and **130** when the fused-benzene is viewed flat.

2.3.3 SYNTHESIS OF 1,6-DIBENZOYL-1,2,5,6-TETRAHYDRO-1,6-BENZODIAZOCINE



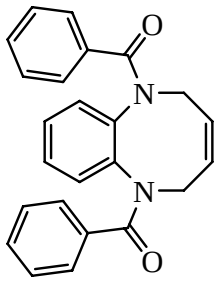
98 **132**

SCHEME 58

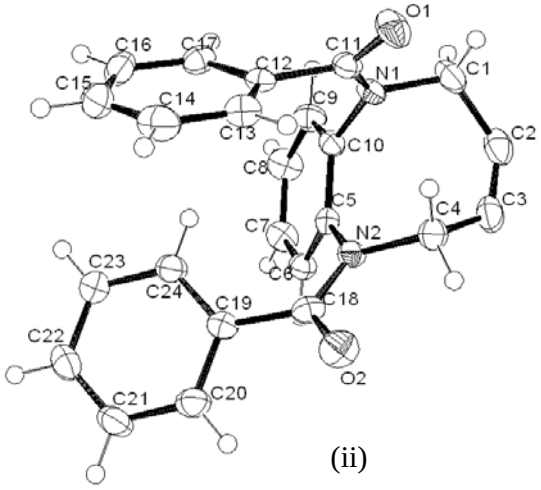
(i) Grubbs II catalyst **4**, PTSA, toluene, 23 hrs, r.t., 97%.

1,6-Dibenzoyl-1,2,5,6-tetrahydro-1,6-benzodiazocine was synthesized from the diallylated compound **98** (prepared in Scheme 51). The diallylated compound **98** was

subjected to RCM using Grubbs II catalyst **4** in toluene and the reaction was then stirred at room temperature for 23 hrs to afford the compound containing the 8-membered ring as a white solid in a good yield of 97% after purification (Scheme 58). The ^{1}H NMR spectrum showed the N-CH_2 peak as a broad singlet at 4.74 ppm which integrated for four protons and the CH=CH peak was evident as a broad singlet at 5.79 ppm which integrated for two protons. The ^{13}C NMR spectrum showed the CH_2 peaks at 45.4 ppm and HRMS showed the molecular ion *m/z* at 368.1539 ($C_{24}H_{20}N_2O_2$ required 368.1524). The compound was recrystallized from 30% ethyl acetate in hexane to afford clear crystals of **132** (mp 195-198°C) and we decided to investigate the compound structure in the solid state by an X-ray diffraction analysis. The bond angles and lengths were found to be within the average bond length and angles expected for this type of structure (Figure 8). All the data for this compound are recorded in Appendix A.



(i)

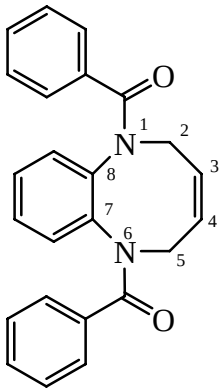
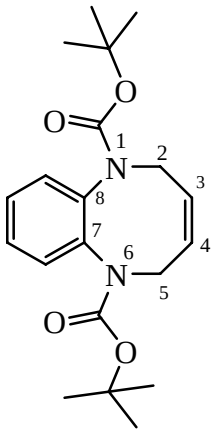


(ii)

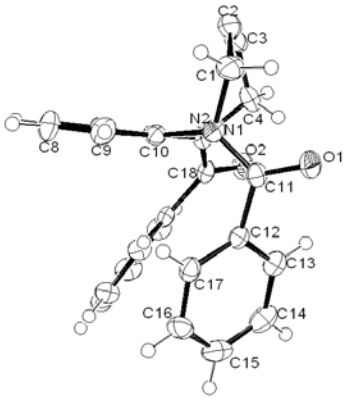
Figure 8

(i) Molecular structure of **132**. (ii) Crystal structure of **132**.

CRYSTAL STRUCTURE OF **132**: An X-ray diffraction was performed to obtain the solid state structure of **132** and the torsion angles of compound **132** was compared with the similar 8-membered nitrogen containing compound **129** which had a different protecting group. The torsion angles within the 8-membered ring were to differ as a result of the different protecting groups present in both compounds. The table for some of the corresponding torsion angles in the heterocyclic portion of the compound that differs in both compounds is given below.

Torsion angles for compound **132** [°]	Torsion angles for compound **129** [°]
	
1. C(2)-N(1)-C(8)-C(7) = 96.36(18)	1. C(2)-N(1)-C(8)-C(7) = 51.0(2)
2. C(7)-N(6)-C(5)-C(4) = -27.7(2)	2. C(7)-N(6)-C(5)-C(4) = -111.30(16)
3. C(8)-N(1)-C(2)-C(3) = -58.9(2)	3. C(8)-N(1)-C(2)-C(3) = -110.96(16)
4. N(1)-C(2)-C(3)-C(4) = -23.6(3)	4. N(1)-C(2)-C(3)-C(4) = 40.5(2)
5. C(5)-C(4)-C(3)-C(2) = -6.5(3)	5. C(5)-C(4)-C(3)-C(2) = 3.5(3)
6. N(6)-C(5)-C(4)-C(3) = 83.1(2)	6. N(6)-C(5)-C(4)-C(3) = 44.5(2)

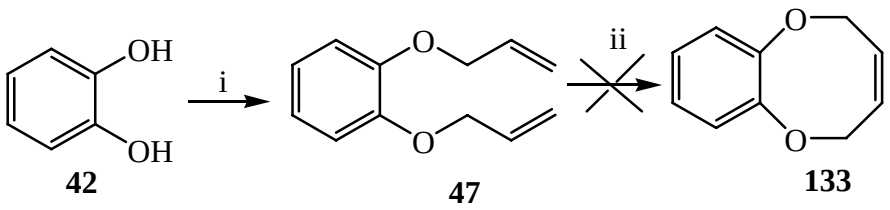
When the fused-benzene ring of the crystal structure of **132** was viewed flat, the benzo-fused heterocyclic ring was found to be bent to an angle of nearly 90° just as in the case of **129** and the two protecting groups were found to be pointing downward (Figure 9).



132

Figure 9: Diagram for the structure of **132** when the benzene ring is viewed as flat.

2.3.4 ATTEMPTED SYNTHESIS OF 2,5-DIHYDRO-1,6-BENZODIOXACINE



42 **47** **133**

SCHEME 59

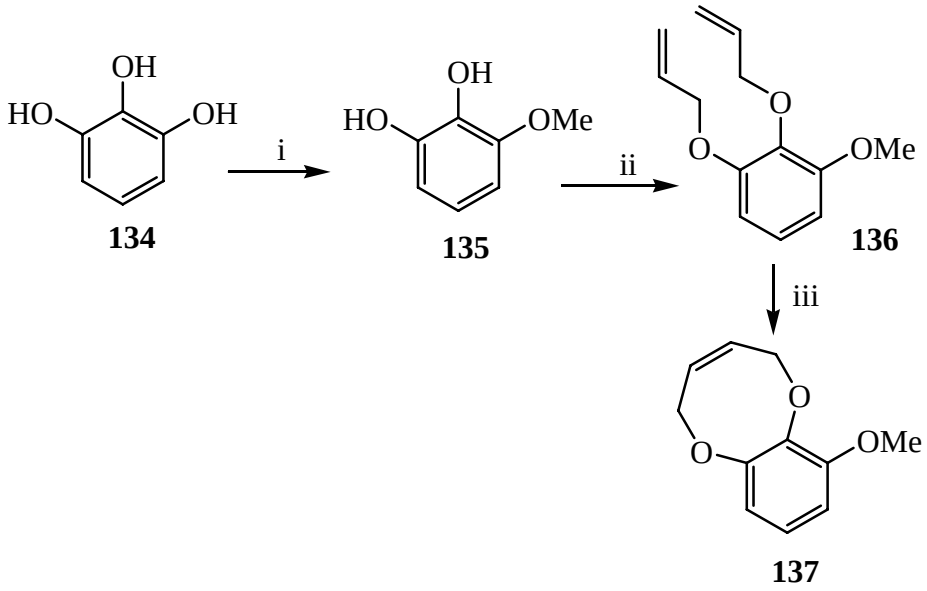
(i) Acetone, potassium carbonate, allyl bromide, 20 hrs, 60°C, 92%. (ii) Grubbs II catalyst **4**, toluene, 80-100°C.

Recently Guillaumet and co-workers showed how RCM can be applied to afford 2,5-dihydro-1,6-benzodiazocine compounds.[60] We attempted the synthesis of 2,5-dihydro-1,6-benzodiaoxacine **133** starting from a commercially available precursor catechol **42** based on the Guillaumet and co-workers methodology.[60] The first step in the synthesis was the allylation of the precursor **42** and this was done using acetone, allyl bromide with potassium carbonate to afford **47** in a good yield of 92%. The IR spectrum showed the C-O peak at 1124 cm^{-1} and a new C=C peak at 1648 cm^{-1}. The ^{1}H NMR spectrum showed the O-CH_2 peak as a doublet at 4.59 ppm which integrated for four protons,

$OCH_2CH=CH_2$ were evident as a doublet of a doublets at 5.26 ppm and 5.41 ppm (two protons each) and the $OCH_2CH=$ peak was visible at 6.01-6.14 ppm as a multiplet. ^{13}C NMR spectroscopy showed the OCH_2 at 69.8 ppm and the $=CH_2$ peak at 114.3 ppm and HRMS showed the molecular ion *m/z* 190.0990 ($C_{12}H_{14}O_2$ required 190.0994), thereby confirming the compound's structure.

Diallylated compound **47** was then subjected to RCM using Grubbs II catalyst **4** in toluene and the reaction was attempted at room temperature, 50-70^{0}C and at 80-100°C. Inexplicably we only isolated **47** instead of the desired compound **133** (Scheme 59). We also attempted the RCM using the Hoveyda-Grubbs catalyst **5** in toluene for 20 hrs but only isolated our starting material. We then decided to use DCM instead of toluene with Grubbs II catalyst **4** for 18 hrs but only isolated the diallylated compound **47**. The result was a surprise to us as other groups have managed to make this type of ring system. Our aim was to investigate if internal isomerisation is applicable on the expected 8-membered heterocycle **133**.

2.3.5 SYNTHESIS OF 7-METHOXY-2,5-DIHYDRO-1,6-BENZODIOXOCINE



134 **135** **136** **137**

SCHEME 60

(i) Ethanol, $Na_2B_4O_7.10H_2O$, H_2O, K_2CO_3, $(CH_3)_2SO_4$, 18 hrs, 60%. (ii) Acetone, allyl bromide, potassium carbonate, 60°C, 18 hrs, 76%. (iii) Grubbs II catalyst **4**, toluene, reflux, 48 hrs, 66%.

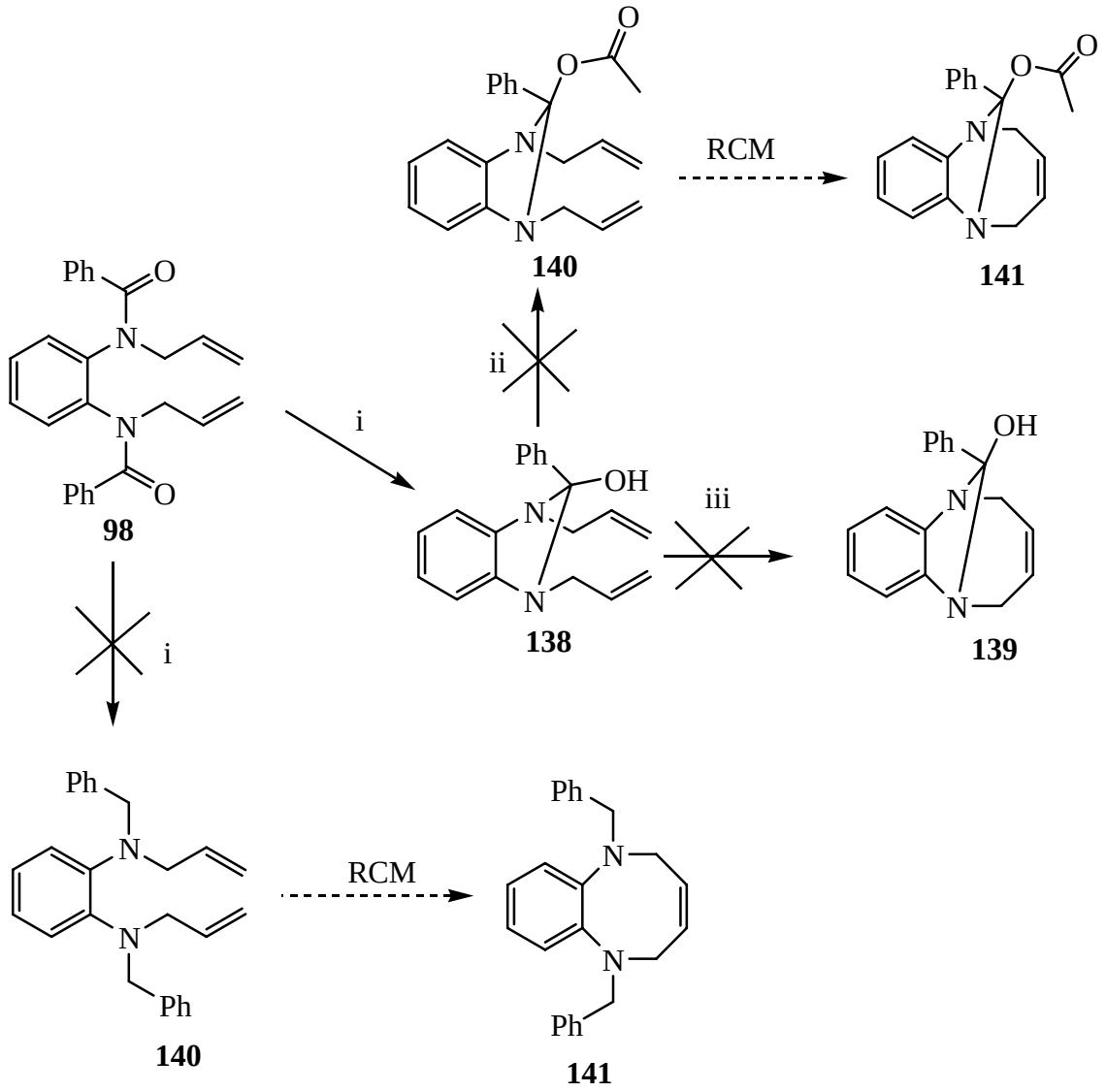
Since the synthesis of 8-membered benzo-fused oxygen-containing heterocylic compound based on catechol was unsuccessful, we decided to synthesize 7-methoxy-2,5-dihydro-1,6-benzodioxocine from commercially available pyrogallol **134**. We hoped that the methoxy group adjacent to the two allyloxy groups would constrain the freedom of the alkenes and thereby promote the RCM. The first step of this short synthesis was based on the research of Jing and co-workers in which compound **134** in ethanol was added drop- wise to a solution of $Na_2B_4O_7.10H_2O$ in water. Potassium carbonate and $(CH_3)_2SO_4$ were then added and reaction was left to stirred overnight to afford **135**. [75]

Diphenol **135** was then subjected to allylation using acetone, potassium carbonate with allyl bromide at 60°C for 18 hrs to afford our product **136** as a yellow oil in a yield of 76%. The HRMS showed the molecular ion *m*/*z* 220.1098 ($C_{13}H_{16}O_3$ required 220.1099). The ^{1}H NMR spectrum displayed the O-CH_2 peak as doublets at 4.53 ppm and 4.57 ppm

which integrated for two protons respectively, the $OCH_2CH=C\mathit{H}_2$ peaks were visible as multiplet at 5.16-5.44 ppm (four protons) and the $OCH_2C\mathit{H}$ signals were displayed at 5.99-6.18 ppm as a multiplet. In the ^{13}C NMR spectrum, the OCH_2 signals were seen at 69.8 ppm and 74.0 ppm and $=CH_2$ peaks were visible at 105.4 ppm and 107.1 ppm. In addition, the IR spectrum showed the C=C peak at 1647 cm^{-1}.

Compound **136** was then subjected to RCM using Grubbs II catalyst **4** in toluene at reflux for 48 hrs to afford the desired 8-membered oxygen-containing benzo-fused compound **137** in a moderate yield of 66%. This reaction worked possibly due to the restricted movement of the allyl groups. The HRMS spectrum showed the molecular ion *m*/*z* at 192.0785 ($C_{11}H_{12}O_3$ required 192.0786). In addition, the ^1H NMR spectrum displayed the CH=CH peaks as a multiplet at 5.88-5.91 ppm which integrated for two protons and the ^{13}C NMR spectrum showed the disappearance of the terminal CH_2 and the presence of the new CH= peaks at 105.1 and 113.6 ppm, thereby confirming the structure of compound **137** (Scheme 60).

2.3.6 ATTEMPTED SYNTHESIS OF 13-PHENYL-1,8-DIAZATRICYCLO[6.4.1.$0^{2,7}$]TRIDECA-2,4,6,10-TETRAEN-13-OL

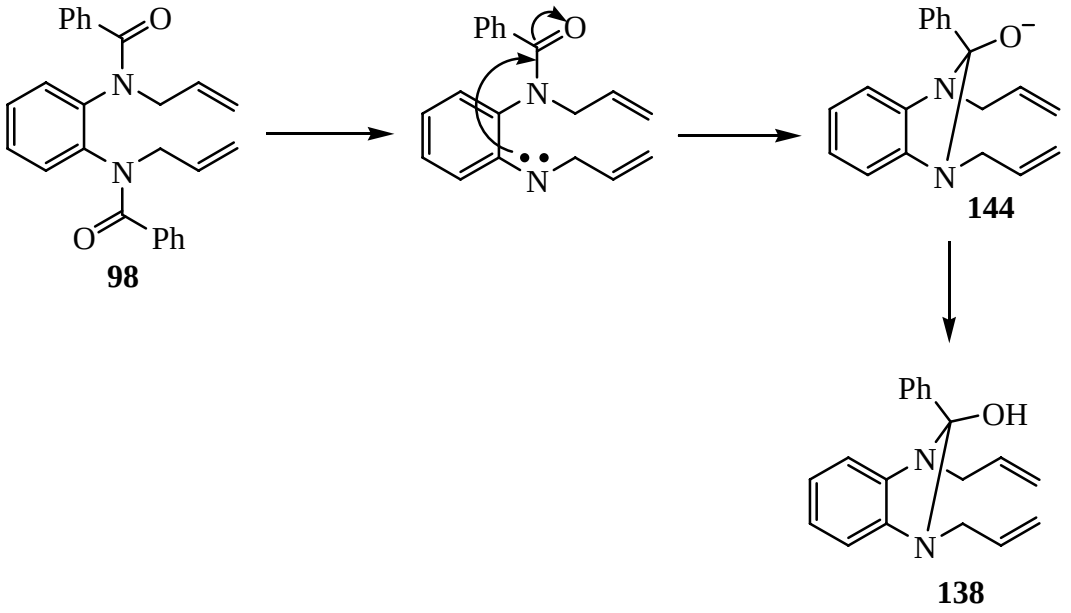


SCHEME 61

(i) $LiAlH_4$, THF, 18 hrs, 25%. (ii) Acetic anhydride, pyridine, r.t., 18 hrs. (iii) Grubbs II catalyst **4**, toluene, 18 hrs.

Since the synthesis of 1,6-dibenzoyl-1,2,5,6-tetrahydro-1,6-benzodiazocine **130** was successful, we decided to synthesize an 8-membered nitrogen-containing compound with an alkyl protecting group on the nitrogen atom. We thus envisaged the synthesis of compound **140** leading to the formation of **141**. We thus attempted the reduction of the

amides in compound **98** to amines using $LiAlH_4$ at room temperature but to our surprise we isolated compound **138**. The compound proved to be very unstable and decomposed very readily in our hands. The HRMS showed molecular peak at *m*/*z* 292.1583 ($C_{19}H_{20}N_2O$ required 292.1575). The ^{1}H NMR spectrum was very complex and the NCH_2 peaks were visible as multiplets at 3.41-3.50 ppm and 3.64-3.61 ppm and both integrated for two protons each. In addition, the OH peak was seen at 5.56 ppm and occurred as a singlet. In the ^{13}C NMR spectrum, the C-OH peak was present at 87.8 ppm and in the IR spectrum the OH signal was visible at 3730 cm^{-1}. We suspect a deprotection of one of the protecting group had occurred and the electron pair on the nitrogen then attacked the carbonyl group to produce **144** which during the work up process with water, generated **138** (Scheme 62).

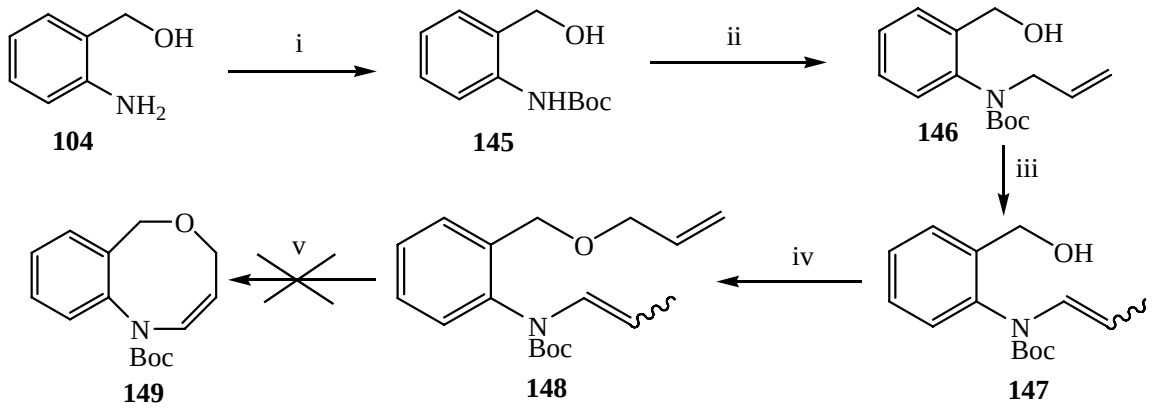


SCHEME 62

Since the expected amine **142** was not isolated, we decided to subject **138** to RCM conditions but we isolated a mixture of compounds that proved uncharacterisable instead of **139**. This was probably due to the fact that **138** was very unstable. We suspected the compound was unstable due to the presence of the benzylic OH group. To investigate this, we tried to protect the OH group with acetic anhydride to isolate **140** so as to attempt a RCM. However, when we performed the protection reaction on **138**, we isolated a

compound that was also uncharacterisable in our hands (Scheme 61). In retrospect, it probably would have been better to attempt a $LiAlH_4$ reduction on the cyclized compound **132** with the benzamide protecting groups but due to time constraints, this was not attempted.

2.3.7 ATTEMPTED SYNTHESIS OF *TERT*-BUTYL 1,4-DIHYDRO-6*H*-5,1-BENZOXAZOCINE-1-(6*H*)-CARBOXYLATE



SCHEME 63

(i) THF, $(Boc)_2O$, r.t., 20 hrs, 76%. (ii) Allyl bromide, Potassium carbonate, Acetone, 60°C, 18 hrs, 67%. (iii) Isomerisation catalyst **12**, toluene, 60°C, 18 hrs, 90%. (iv) Allyl bromide, NaH, DMF, r.t., 18 hrs, 80%. (v) Grubbs II catalyst **4**, toluene, 80-100°C, 18 hrs.

The synthesis of *tert*-butyl 1,4-dihydro-6*H*-5,1-benzoxazocine-1-(6*H*)-carboxylate was attempted using 2-aminobenzyl alcohol **104** as the initial precursor for the synthesis. The first step of the synthesis was protection of the precursor **104** using the Boc-protecting group to afford the mono-protected product **145** in a yield of 76%. HRMS showed the molecular ion *m*/*z* 223.1356 ($C_{12}H_{17}NO_3$ required 223.1208). The ^1H NMR spectrum showed the peak for the CH_3 group on the Boc as a singlet at 1.52 ppm which is characteristic of the methyl group and the N-H peak was viewed at 2.96 ppm. In addition, the OH signal was visible at 7.70 ppm as broad singlet. The IR spectrum showed the OH

peak at 3360 cm^{-1}, the C=O peak was visible at 1704 cm^{-1} and NH peak was seen at 1590 cm^{-1}.

Compound **145** was then monoallylated using allyl bromide and potassium carbonate to afford the product **146** in a moderate yield of 67%. HRMS showed the molecular ion *m/z* 263.1533 ($C_{15}H_{21}NO_3$ required 263.1521). The ^{1}H NMR spectrum displayed the N-CH_2 as a doublet at 3.99 ppm which integrated for two protons, the N-CH_2CH=CH_2 signals were seen as doublets at 5.24 ppm and 5.32 ppm which both integrated for one proton each and the NCH_2CH peak was visible at 5.87-6.00 ppm and integrated for one proton. The ^{13}C NMR spectrum showed the CH_2 signals at 70.4 ppm, 71.0 ppm and 117.1 ppm. The IR spectrum showed the presence of the OH peak at 3372 cm^{-1} and the absence of the NH peak thereby confirming the compound structure.

Compound **146** was then subjected to an isomerisation reaction using ruthenium isomerisation catalyst **12** in toluene at 60°C for 18 hrs to afford **141** in a good yield of 90%. The ^{1}H NMR spectrum proved the compound to consist of approximately a 65:35 complex mixture of *E*/*Z* isomers. The terminal CH_3 peaks were present as a multiplet at 1.53-1.63 ppm which integrated for three protons, the NC*H*=CH signal was viewed as a multiplet at 6.97-7.03 ppm and the NCH=C*H* peak was viewed as a multiplet at 4.47-4.56 ppm which integrated for one proton respectively. The high resolution mass spectrum showed the molecular ion *m/z* 263.1533 ($C_{15}H_{21}NO_3$ required 263.1521). Finally, the ^{13}C NMR spectrum showed the terminal CH_3 peaks at 9.3 ppm for the *E* isomer and at 12.1 ppm for the *Z* isomer.

The *E/Z* mixture of **147** was then allylated using NaH with allyl bromide and the reaction was stirred at room temperature for 19 hrs to afford **148** as a yellow oil in a yield of 80%. The high resolution mass spectrum showed the molecular ion *m/z* 303.1838 ($C_{18}H_{25}NO_3$ required 303.1834). The ^{1}H NMR spectrum proved the compound to be a complex mixture of *E*/*Z* isomers with the ratio being difficult to determine. The O-CH_2 peak was seen as a multiplet at 4.63-4.90 ppm and OCH_2CH=CH_2 peak was visible at 5.87-5.98

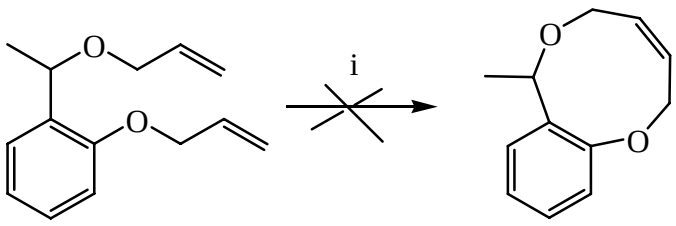
ppm as a multiplet. The ^{13}C NMR spectrum displayed the presence of new CH_2 peaks at 52.8 ppm, 52.9 ppm, 67.0 ppm and 69.2 ppm.

Precursor **148** was then subjected to RCM using Grubbs II catalyst **4** in toluene at 90-100°C for 20 hrs and we isolated the starting material **148** instead of our desired product **149**. This was confirmed by TLC; once again this could be as a result of a kinetic effect *i.e*. the two alkenes are pointing away from each other thereby hindering RCM or an electronic effect due to the electron rich *N*-vinyl alkene (Scheme 63).

2.4 ATTEMPTED SYNTHESIS OF 9-MEMBERED BENZO-FUSED HETEROCYCLIC COMPOUNDS

We attempted the synthesis of various 9-membered benzo-fused heterocyclic compounds and we met with failures which could be due to kinetic effect *i.e*. the alkenes can not find each other because they were far apart. Therefore, we decided to introduce bulky groups to the ring systems.

2.4.1 ATTEMPTED SYNTHESIS OF 7-METHYL-2,5-DIHYDRO-7*H*-1,6-BENZODIOXONINE



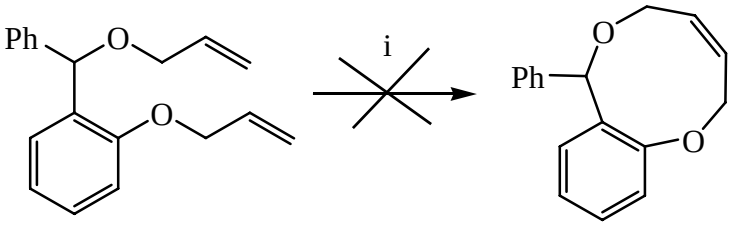
121 **150**

SCHEME 64

(i) Grubbs II catalyst **4**, toluene, 90-100°C, 18 hrs.

We attempted the synthesis of 7-methyl-2,5-dihydro-7*H*-1,6-benzodioxonine **150** from a diallylated precursor **121.** It was subjected to RCM using Grubbs II catalyst with toluene at 80-100°C for 18 hrs but we recovered **121** in a yield of 80% instead of our desired product **150** which was proved by TLC and ^{1}H NMR spectrum (Scheme 64).

2.4.2 ATTEMPTED SYNTHESIS OF 7-PHENYL-2,5-DIHYDRO-7*H*-1,6-BENZODIOXONINE



125 **151**

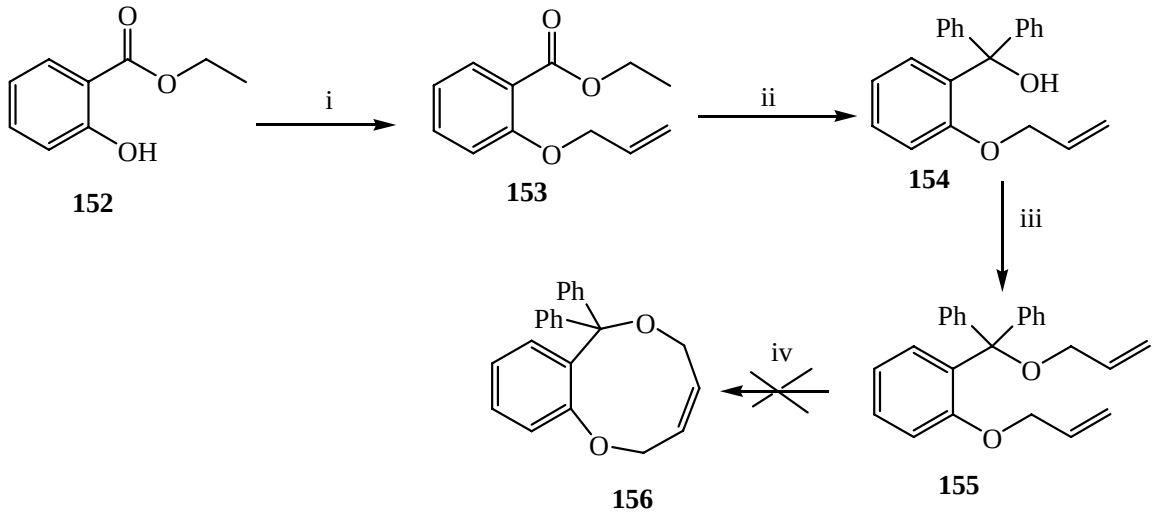
SCHEME 65

(i) Grubbs II catalyst **4**, toluene, 18 hrs, 80-100°C.

We attempted the synthesis of 7-phenyl-2,5-dihydro-7*H*-1,6-benzodioxonine **151** using the diallylated precursor **125.** Compound **125** was thus subjected to RCM using Grubbs II catalyst in toluene and reaction was heated at 80-100°C for 18 hrs. Unfortunately, we only isolated the starting material **125** (44%) instead of **151** (Scheme 65).

It appeared as the steric bulk of the phenyl group was not enough to force the two allyloxy groups together for RCM. We thus decided to synthesize one more substrate, this time containing two benzylic phenyl groups, to see if we could encourage RCM to occur.

2.4.3 ATTEMPTED SYNTHESIS OF 7,7-DIPHENYL-2,5-DIHYDRO-7*H*-1,6-BENZODIOXONINE



SCHEME 66

(i) Acetone, potassium carbonate, allyl bromide, reflux, 18 hrs, 96%. (ii) Mg, bromobenzene, THF, r.t., 18 hrs, 44%. (iii) DMF, NaH, allyl bromide, 18 hrs, r.t., 63%. (iv) Grubbs II catalyst **4**, toluene, reflux, 18 hrs.

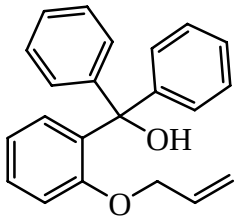
We started the synthesis of 7,7-diphenyl-2,5-dihydro-7*H*-1,6-benzodioxonine **156** using ethyl 2-hydroxybenzoate **152**, which is commercially available, as our precursor. The first step was allylation of precursor **152** using allyl bromide with potassium carbonate as base at 60°C for 18 hrs to afford the product **153** in a yield of 96%. The HRMS spectrum showed the expected molecular ion *m*/*z* 206.0993 for the product ($C_{12}H_{14}O_3$ requires 206.0943). The ^{1}H NMR spectrum showed the O-C*H*$_2$CH peak as a doublet of doublets at 4.61 ppm, the OCH$_2$CH=C*H*$_2$ peaks were visible at 5.29 ppm and 5.51 ppm as two doublets both integrating for one proton each. The OCH$_2$C*H*= peak was visible at 6.01-6.07 ppm as a multiplet. In the IR spectrum, the C=O peak was seen at 1726 cm^{-1} and the C=C stretch was observed at 1601 cm^{-1}. Finally, the ^{13}C NMR spectrum displayed the CH$_2$ peaks at 69.3 ppm and 113.5 ppm.

Ester **153** was then reacted with the Grignard reagent performed from magnesium and bromobenzene at room temperature for 18 hrs to afford the product as a white solid **154** in a yield of 44% after chromatography. The HRMS spectrum showed a molecular ion at *m*/*z* 316.1467 ($C_{22}H_{20}O_2$ required 316.1463) and the IR spectrum showed the new OH peak at 3515 cm^{-1}. The ^1H NMR spectrum showed the disappearance of the OCH_2CH_3 peak and the presence of the O-H peak as a singlet at 5.25 ppm. The new aromatic protons were visible at 6.53 ppm as a doublet and at 7.26-7.32 ppm as multiplet. After recrystallization of **154** from 10% ethyl acetate in hexane we isolated clear crystals of **154** (mp: 99-101°C). X-ray diffraction was performed on a suitable crystal confirming that **154** had formed. The crystal structure belongs to the monoclinic crystal system with a space group of P2/c. The bond angles and lengths were found to be within the required bond length and angles for this type of ring system (Figure 10). The data for the structure are recorded in Appendix A.

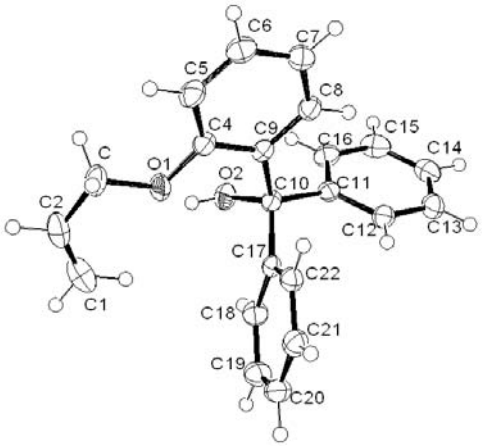
Benzyl alcohol **154** was then subjected to an allylation reaction using NaH and allyl bromide for 18 hrs to afford **155** as a crystalline solid in a moderate yield of 63%. The melting point of the compound was found to be 98-100°C. The HRMS spectrum showed the expected molecular ion at *m*/*z* 356.1772 ($C_{25}H_{24}O_2$ required 356.1776). The ^1H NMR spectrum showed the O-CH_2 peak as a doublet at 3.55 ppm and the OCH_2CH peak as a multiplet at 5.36-5.51 ppm. X-ray diffraction was then performed on the crystals of **155** and the structure was found to belong to a triclinic crystal system with a space group of P-1. The bond angles and bond lengths were within the average bond angles and lengths for this type of ring system (Figure 11). All the data for this ring system is recorded in Appendix A.

Bisallyloxy compound **155** was then subjected to RCM at 80-100°C using Grubbs II catalyst **4** in toluene for 18 hrs but frustratingly, we isolated **155** (9% yield) instead of our desired product **156** (Scheme 66). From the crystal structure of **155** it is evident that the two alkenes are pointing away from each other which suggests that this could be why the RCM did not occur. What is rather unexpected in the crystal structure of **154**, the monoallylated compound, is that the alcohol group and allyloxy group are in reasonable

proximity, but that upon allylation the two allyl groups prefer to be far apart. This interesting observation begs to be investigated further. Techniques such as molecular modeling (to compare energies of the different conformers) and variable temperature NMR spectroscopy (to measure barriers to rotation) could be very useful in understanding why the RCM reactions were not occurring. They were however not done due to time constraints but could be pursued in future projects.

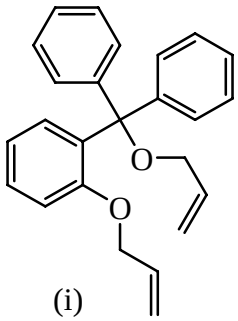


(i)

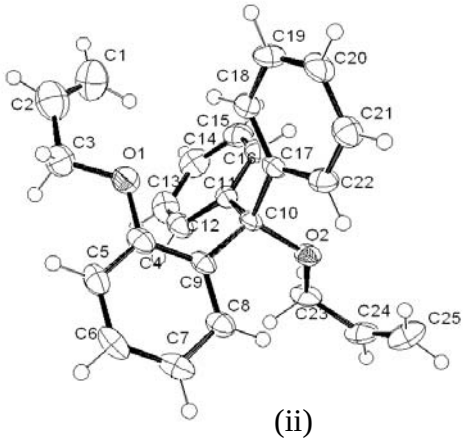


(ii)

FIGURE 10: (i) Molecular structure of **154**. (ii) ORTEP crystal structure of **154**.



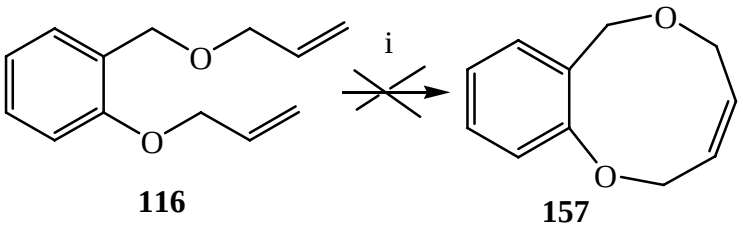
(i)



(ii)

FIGURE 11: (i) Molecular structure of **155**. (ii) ORTEP crystal structure of **155**.

2.4.4 ATTEMPTED SYNTHESIS OF 2,5-DIHYDRO-7*H*-1,6-BENZODIOXONINE



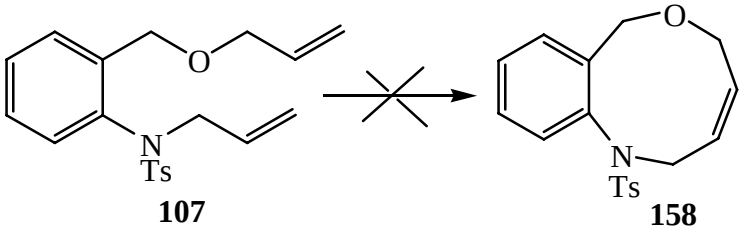
116 **157**

SCHEME 67

(i) Grubbs II catalyst **4**, toluene, 100-110°C, 20 hrs.

Nine-membered heterocycles are challenging to make using RCM, we thus decided to try to synthesize 2,5-dihydro-7*H*-1,6-benzodioxonine **157** from the previously prepared diallylated precursor **116**. RCM was performed on this compound using Grubbs II catalyst **4** in toluene at 100-110°C. The desired 9-membered benzo-fused ring **157** was not isolated after chromatography. Instead the diallylated starting material (30% yield) was isolated. This was probably due to kinetic reasons *i.e.* the alkenes could not find each other (Scheme 67).

2.4.5 ATTEMPTED SYNTHESIS OF 1-[(4-METHYLPHENYL)SULFONYL]-1,2,5,7-TETRAHYDRO-6,1-BENZOXAZONINE



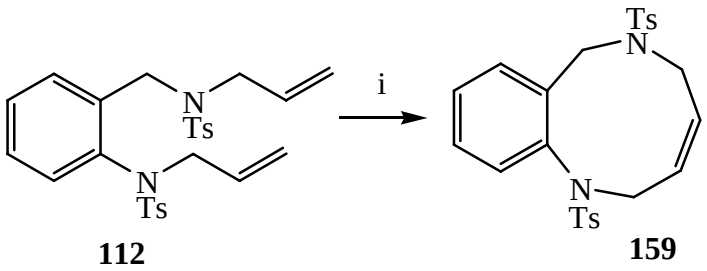
107 **158**

SCHEME 68

(i) Grubbs II Catalyst **4**, 60°C, 90-100°C, 18-20 hrs.

We also attempted the synthesis of 1-[(4-methylphenyl)sulfonyl]-1,2,5,7-tetrahydro-6,1-benzoxazonine **158** from the diallylated precursor **107**. This would have given us the 9-membered 6,1-benzoxazonine system containing a nitrogen and oxygen atom, analogous to the 1,6-benzodioxonine system **158** above. RCM was thus performed on **107** using Grubbs II catalyst **4** in toluene at 60°C and at 100°C but we isolated a compound that could not be characterized instead of our desired product **158**. We suspect that polymerization may have taken place instead of RCM due to unrestricted movement of the allyl group (Scheme 68). This is a common side reaction which can occur in reactions where the RCM is sluggish.

2.4.6 THE SYNTHESIS OF 1,6-BIS[(4-METHYLPHENYL)SULFONYL]-2,5,6,7-TETRAHYDRO-1*H*-1,6-BENZODIAZONINE



112 **159**

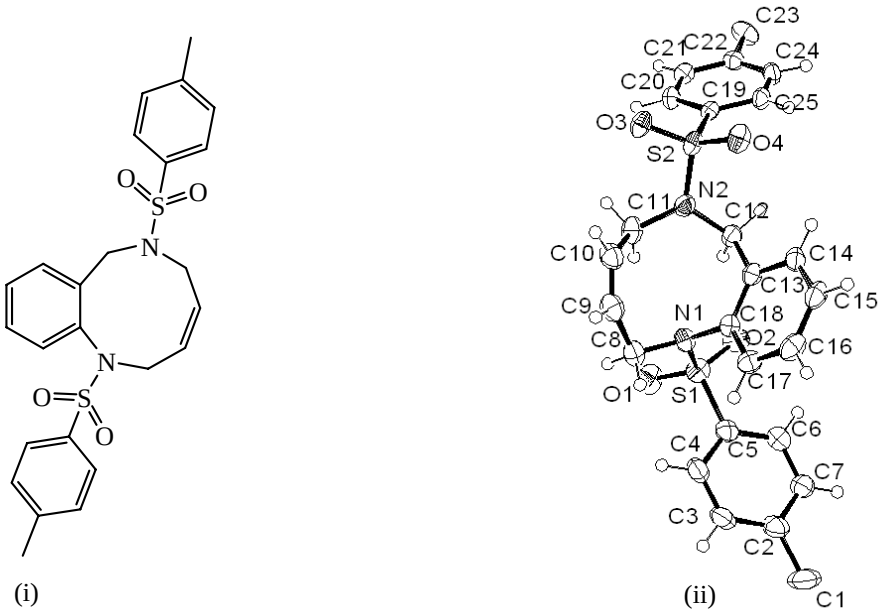
SCHEME 69

(i) Grubbs II catalyst **4**, toluene, 60°C, 20 hrs, 96%.

Finally in this section, we attempted to make the 1,6-benzodiazonine system **159** containing two *N*-heteroatoms even though the synthesis of the benzodioxonine and benzoxazonine systems had been unsuccessful. To this end the diallylated precursor **112** was subjected to RCM using Grubbs II catalyst **4** in toluene at 60°C. Surprisingly, after column chromatography the desired product **159** was isolated in an excellent yield of 96%. The HRMS spectrum of this compound showed the molecular ion at *m*/*z* 482.1338 ($C_{25}H_{26}N_2O_4S_2$ required 482.1334). The ^{1}H NMR spectrum showed the new NCH_2CH=C*H* protons as a multiplet at 5.56-5.59 ppm (two protons) (Scheme 69). After recrystallization from 20% ethyl acetate in hexane, clear crystals of **159** were isolated (mp: 84-89°C). X-ray diffraction was performed and the X-ray crystal structure was found to be a monoclinic crystal system in a space group of P21/c. The bond angles and

lengths were found to be within the required bond angles and lengths for this type of ring system thereby confirming the structure of our compound **159** (Figure 12). All the data for this structure are recorded in Appendix A.

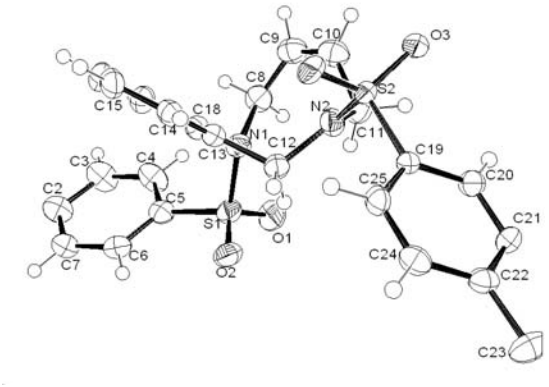
It is not clear why the 1,6-benzodiazonine system should form so readily while the other 9-membered rings did not form at all in our hands. It might be that the tosyl protecting group on the nitrogen in position 6 of the final ring system might be responsible for forcing the two allyl groups into close proximity for RCM. This observation needs to be investigated further.



(i) (ii)

FIGURE 12: (i) Molecular structure of **159**. (ii) ORTEP crystal structure of **159**.

When the fused-benzene ring was viewed as flat, the heterocyclic ring was found to be puckered conspicuously with the tosyl protecting groups pointing sidewards in opposite directions (Figure 13).



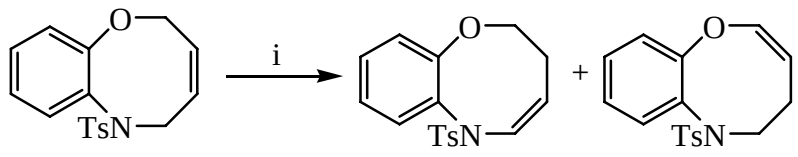
159

FIGURE 13: The crystal structure of **159** when the fused-benzene ring is viewed as flat.

2.5 INTERNAL ISOMERISATION OF THE 8- AND 9-MEMBERED BENZO-FUSED HETEROCYCLIC COMPOUNDS.

Very little research has been done on the internal isomerisation of benzo-fused compounds. Internal isomerisation on benzo-fused ring systems could be of interest in that, with minimal manipulations, a new compound with the alkenes in a different position could be made. Further utilization of these internal alkenes would then offer analogues with new functional groups in different positions, a characteristic specifically useful in the pharmaceutical industry when compounds with slight differences are useful in probing and evaluating biological activities. We thus decided to attempt internal isomerisation on various 8- and 9-membered benzo-fused *N,N*-, *N,O*-, *S,N*- and *O,O*-heterocyclic ring systems that we had prepared before. The isomerisation reactions were performed under concentrated conditions and at a high temperature.

2.5.1 SYNTHESIS OF A MIXTURE OF 6-[(4-METHYLPHENYL)SULFONYL]-3,6-DIHYDRO-2*H*-1,6,-BENZOXAZOCINE AND 6-[(4-METHYLPHENYL)SULFONYL]-5,6-DIHYDRO-4*H*-1,6,-BENZOXAZOCINE



160 **161** **162**

SCHEME 70

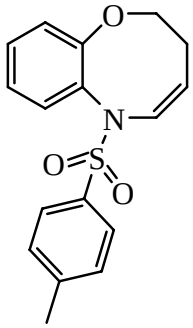
(i) d_8-toluene, ruthenium isomerisation catalyst **12**, 60-70°C, 18 hrs, 77% yield (1:1).

Compound **160** was dissolved in d_8-toluene at room temperature and ruthenium isomerisation catalyst **12** was added and the reaction was monitored in an NMR tube at 60-70°C for a further 18 hrs. Column chromatography then afforded the isomerised compound as a mixture of regioisomers, **161** and **162** in a combined yield of 77%. The regio isomers had similar R_F and could not be separated by column chromatography but were observed in a ratio of (50:50).

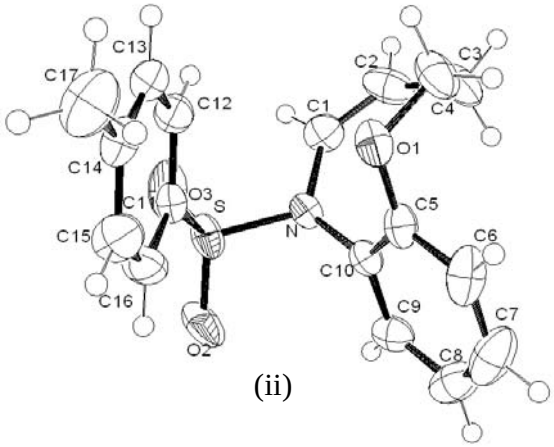
The melting point of the regioisomers was found to be 101-104 °C and the HRMS spectrum showed the molecular ion peak at 315.0914 ($C_{17}H_{17}NO_3S$ required 315.0929). The ^{1}H NMR spectrum showed the O-CH_2 or N-CH_2 peak as a triplet at 3.42 ppm, the O-CH_2CH_2 or N-CH_2CH_2 as a triplet at 3.73 ppm and the N-CH=*CH* peak as a doublet of a doublets at 4.46 ppm and the OCH=*CH* peak as a doublet of a doublets at 4.84 ppm (Scheme 70).

After recrystallization of **161** (Figure 14) and **162** (Figure 15) from methanol, crystals were obtained. From the collection of crystals, two different crystal habitats were observed and we managed to obtain examples of both suitable, for single crystal diffraction studies. An X-ray diffraction was then performed on both crystals and to our delight proved to give the solid state structures of the two possible regioisomers **161** and

162 from the isomerisation reaction. Both regioisomers were found to have a monoclinic crystal system in a space system of P21/n. All data for these structures are recorded in Appendix A.

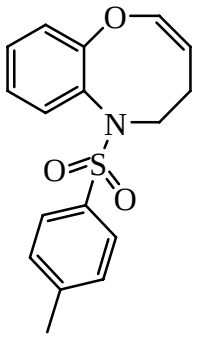


(i)

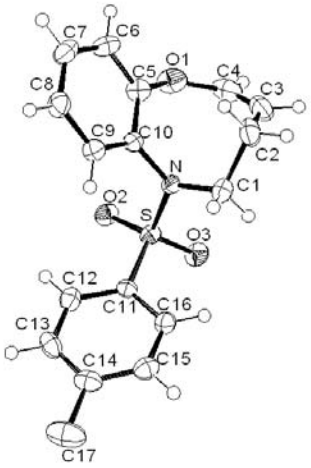


(ii)

FIGURE 14: (i) Molecular structure of **161**. (ii) ORTEP crystal structure of **161**.



(i)

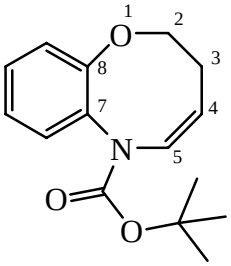
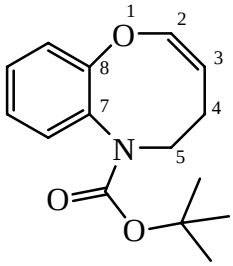


(ii)

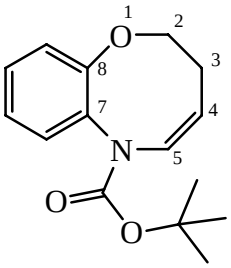
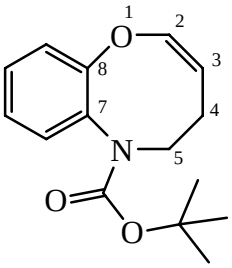
FIGURE 15: (i) Molecular structure of **162**. (ii) ORTEP crystal structure of **162**.

CRYSTAL STRUCTURES OF **161** AND **162**: The bond lengths and angles of both compound structures were found to be consistent but differed in a few cases probably due to the shift in the double bond within the 8-membered ring system. The difference in

corresponding bond lengths and angles of the compound structures of **161** and **162** are given below.

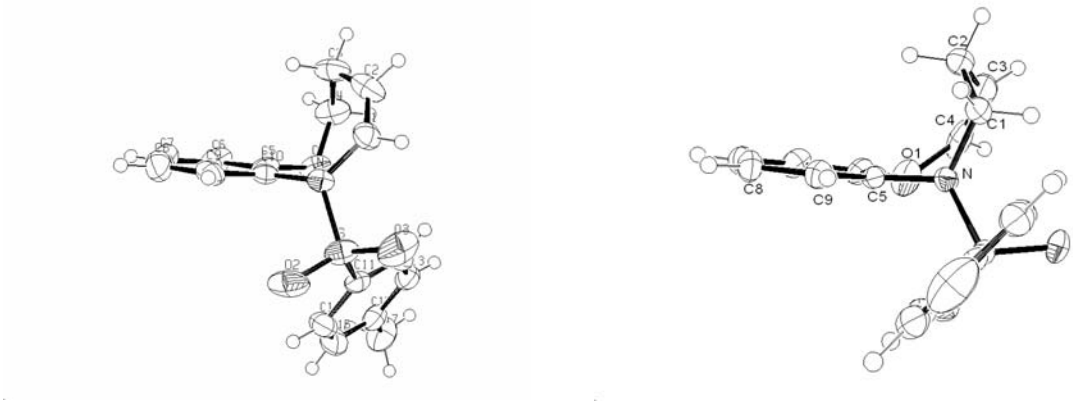
Bond lengths for compound **161** [Å]	Bond lengths for compound **162** [Å]
	
1. N-C(5) = 1.422(2)	1. N-C(5) = 1.474(3)
2. C(4)-C(5) = 1.325(3)	2. C(4)-C(5) = 1.530(4)
3. C(2)-C(3) = 1.512(3)	3. C(2)-C(3) = 1.314(4)

The corresponding torsion angles within the heterocyclic ring of both compounds were found to be slightly different. The table for the difference in the corresponding torsion angles for both compound structures is below:

Torsion angles for compound **161** [°]	Torsion angles for compound **162** [°]
	
1. N-C(5)-C(4)-C(3) = -13.0(4)	1. N-C(5)-C(4)-C(3) = -58.0(3)
2. C(2)-C(3)-C(4)-C(5) = -58.3(3)	2. C(2)-C(3)-C(4)-C(5) = 70.7(4)
3. C(8)-O(1)-C(2)-C(3) = 49.0(2)	3. C(8)-O(1)-C(2)-C(3) = 0.4(5)
4. O(1)-C(2)-C(3)-C(4) = 55.6(3)	4. O(1)-C(2)-C(3)-C(4) = 7.7(5)
5. C(5)-N-C(7)-C(8) = 60.0(2)	5. C(5)-N-C(7)-C(8) = 92.7(5)
6. C(2)-O(1)-C(8)-C(7) = -99.4(2)	6. C(2)-O(1)-C(8)-C(7) = -58.6(4)

7. N-C(7)-C(8)-O(1) = -0.5(3)	7. N-C(7)-C(8)-O(1) =10.1(4)
8. C(7)-N-C(5)-C(4) = -6.5(3)	8. C(7)-N-C(5)-C(4) = -50.3(3)

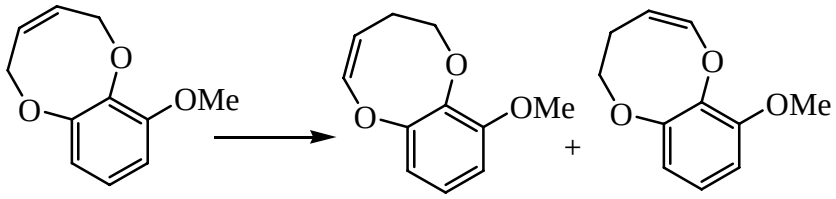
When the fused-benzene ring was viewed as flat, the crystal structures of **161** and **162** were found to be bent to an angle of nearly 90° with the tosyl protecting group pointing downward (Figure 16).



161 **162**

FIGURE 16: The crystal structure of **161** and **162** when the fused-benzene ring is viewed as flat.

2.5.2 SYNTHESIS OF A MIXTURE OF 10-METHOXY-2,3-DIHYDRO-1,6-BENZODIOXOCINE AND 7-METHOXY-2,3-DIHYDRO-1,6-BENZODIAXOCINE



137 **163** **164**

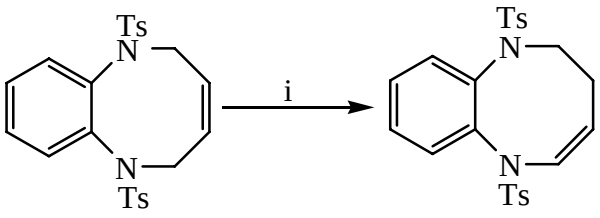
SCHEME 71

(i) Toluene, ruthenium isomerisation catalyst **12**, 90-100°C, 48 hrs, 63% yield.

We attempted an isomerisation on a 1,6-benzodiaxocine compound which has two oxygen atoms in the 8-membered ring. 7-Methoxy-2,5-dihydro-1,6-benzodioxocine[61] **137**

was thus dissolved in toluene and 5 mol% ruthenium isomerisation catalyst **12** was used to afford a mixture after purification of regioisomers with ratio that was difficult to determine in a combined yield of 63%. The regioisomers had similar R_F and could not be separated by column chromatography. The ^{1}H NMR spectrum showed the O-$CH_2C\mathit{H}_2$ peak as a multiplet at 2.18-2.29 ppm, the O-CH_2 protons were viewed as triplets at 4.04 and 4.18 ppm, OCH=C*H* peaks were seen as multiplets at 4.57-4.69 and 4.75-4.81 ppm and OC*H*=CH peaks were seen as doublets 6.36 and 6.47ppm. The ^{13}C NMR showed two CH_2 peaks at 66.0 and 68.6 ppm. The compound was further confirmed by HRMS in which the molecular ion was visible *m*/*z* at 192.0781 ($C_{11}H_{12}O_3$ required 192.0786) (Scheme 71).

2.5.3 SYNTHESIS OF 1,6-*BIS*[(4-METHYLPHENYL)SULFONYL]-1,2,3,6-TETRAHYDRO-1,6-BENZODIAZOCINE



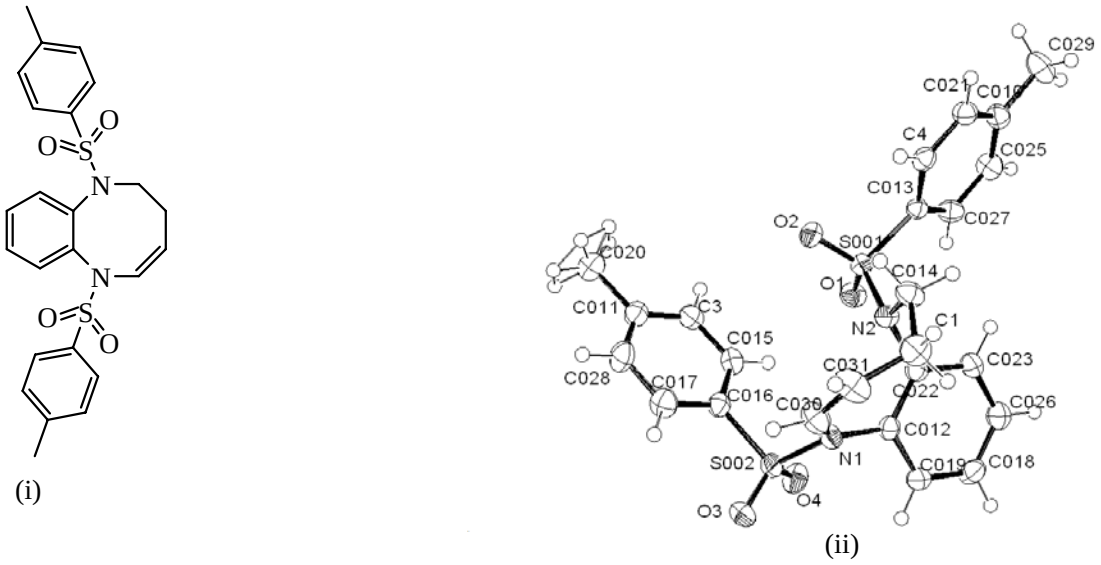
165 **166**

SCHEME 72

(i) Toluene, ruthenium isomerisation catalyst **12**, 100°C, 20 hrs, 60% yield.

Compound **165** was dissolved in toluene at room temperature and 4 mol% ruthenium isomerisation catalyst **12** was added. The reaction was then performed for 20 hrs at 100°C to afford the desired isomerised compound **166** as a brown solid in a yield of 60% after purification by column chromatography. The high resolution mass spectrum of the product showed the molecular ion at *m*/*z* 468.1172 ($C_{24}H_{24}N_2O_4S_2$ required 468.1177). The ^{1}H NMR spectrum showed the new NC$H_2C\mathit{H}_2$ peak as a multiplet at 1.72-1.78 ppm, the N-CH_2 peak was visible as a triplet at 3.18 ppm (two protons). In addition, the NCH=C*H* peak was observed as a doublet of triplets at 4.66 ppm which integrated for two protons and the N-C*H*=CH peak was seen as a doublet at 6.69 ppm which integrated

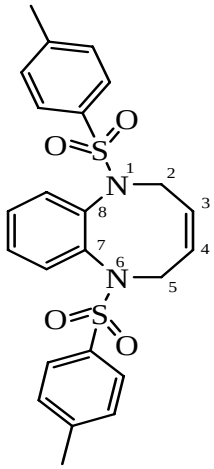
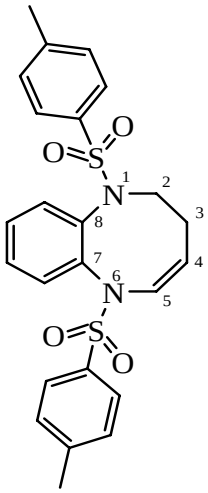
for one proton. The ^{13}C NMR spectrum contained the two CH_2 peaks at 22.0 ppm and 48.7 ppm and the melting point of the isomerised compound was found to be 134-138°C (Scheme 72). An X-ray diffraction experiment was performed on a suitable crystal of **166** and the structure was found to have a monoclinic crystal system in a P21/c space group. The bond angles and lengths were found to be within the average bond angles and length for this type of ring system (Figure 17). All data for this structure are recorded in Appendix A.



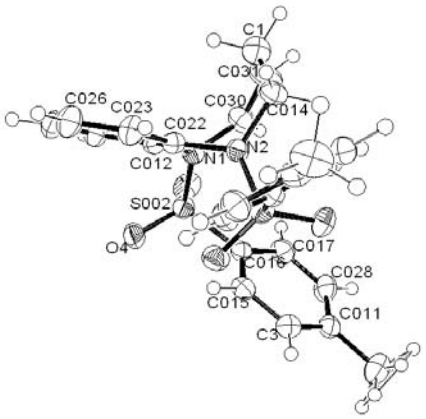
(i) (ii)

FIGURE 17: (i) Molecular structure of **166**. (ii) Crystal structure of **166**.

CRYSTAL STRUCTURE OF COMPOUND **166**: We compared the torsion angles of structure **165** and **166**. We observed that the torsion angles differed in both structures which is expected due to the shift in the double bond. The differences in the torsion angles for both compounds are given below.

Torsion angles for compound **165** [°]	Torsion angles for compound **166** [°]
	
1. N(1)-C(2)-C(3)-C(4) = -30.0(3)	1. N(1)-C(2)-C(3)-C(4) = -59.6(4)
2. C(5)-C(4)-C(3)-C(2) = -4.6(3)	2. C(5)-C(4)-C(3)-C(1) = 63.3(5)
3. N(6)-C(5)-C(4)-C(3) = 89.3(2)	3. N(6)-C(5)-C(4)-C(3) = 12.1(6)
4. C(7)-N(6)-C(5)-C(4) = -36.6(2)	4. C(7)-N(6)-C(5)-C(4) = 3.0(5)
5. C(5)-N(6)-C(7)-C(8) = -39.1(2)	5. C(5)-N(6)-C(7)-C(8) = -56.1(4)
6. C(8)-N(1)-C(2)-C(3) = -55.5(2)	6. C(8)-N(1)-C(2)-C(3) = -47.3(3)
7. N(6)-C(7)-C(8)-N(1) = -0.5(2)	7. N(6)-C(7)-C(8)-N(1) = 1.4(4)
8. C(2)-N(1)-C(8)-C(7) = 101.98(18)	8. C(2)-N(1)-C(8)-C(7) = 95.5(3)

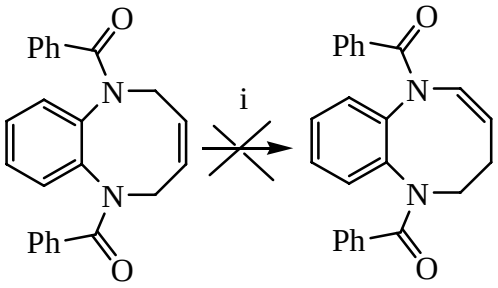
When the fused-benzene was viewed side-on, the heterocyclic ring was found to be bent with the tosyl protecting groups pointing in opposite directions. The heterocyclic ring was pointing upward (Figure 18).



166

FIGURE 18: The crystal structure of **166** when the fused-benzene ring is viewed from the side.

2.5.4 ATTEMPTED SYNTHESIS OF 1,6-DIBENZOYL-1,2,3,6-TETRAHYDRO-1,6-BENZODIAZOCINE



132 **167**

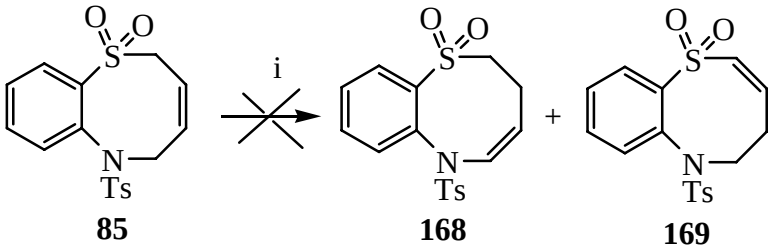
SCHEME 73

(i) Toluene, ruthenium isomerisation catalyst **12**, 70-100°C, 20 hrs.

Having successfully isomerised the ditosyl compound **165** we wished to see if we could do the same for the diamide system **132.** We thus attempted the synthesis of 1,6-dibenzoyl-1,2,3,6-tetrahydro-1,6-benzodiazocine **167** from an 8-membered benzo-fused heterocyclic compound, 1,6-dibenzoyl-1,2,5,6-tetrahydro-1,6-benzodiazocine **132**. The reaction was done as before using ruthenium catalyst **12** at 70-100°C for 20 hrs.

However, the ^{1}H NMR spectrum of the isolated compound was very broad and difficult to interpret so this reaction was not taken any further (Scheme 73).

2.5.5 ATTEMPTED SYNTHESIS OF 6-[(4-METHYLPHENYL)SULFONYL]-3,6-DIHYDRO-2*H*-1,6-BENZOTHIAZOCINE 1,1-DIOXIDE OR 6-[(4-METHYLPHENYL)SULFONYL]-5,6-DIHYDRO-4*H*-1,6-BENZOTHIAZOCINE 1,1-DIOXIDE



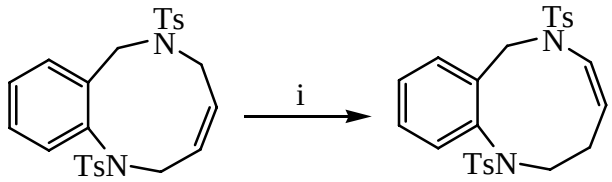
85 **168** **169**

SCHEME 74

(i) DCM, ruthenium isomerisation catalyst **12**, reflux, 20 hrs.

Finally in this section concerning the isomerisation of alkenes in 8-membered benzo-fused heterocyclic rings, we decided to try the internal isomerisation on a system containing a sulfone group. We thus attempted the synthesis of 6-[(4-methylphenyl)sulfonyl]-3,6-dihydro-2*H*-1,6-benzothiazocine 1,1-dioxide[59] **168** or 6-[(4-methylphenyl)sulfonyl]-5,6-dihydro-4*H*-1,6-benzothiazocine 1,1-dioxide **169** from the 8-membered benzo-fused heterocyclic 6-[(4-methylphenyl)sulfonyl]-5,6-dihydro-2*H*-1,6-benzothiazocine 1,1-dioxide **85** which we had in hand from a previous project (see Scheme 45). This synthesis was attempted using toluene as solvent initially but compound **85** proved to be insoluble. We then decided to use DCM as solvent with ruthenium isomerisation catalyst **12**. The reaction mixture was heated at in an oil bath at 80-100°C for 20 hrs. The ^{1}H NMR spectrum of the isolated compound after reaction showed that we isolated **85** instead of the desired compound **168** and **169** (Scheme 74). At this point we were unable to explain why the alkene did not isomerize as allyl sulfone have been successfully isomerised using $RuCl(CO)PPh_3$.[80]

2.5.6 SYNTHESIS OF 1,6-*BIS*[(4-METHYLPHENYL)SULFONYL]-2,3,6,7-TETRAHYDRO-1*H*-1,6-BENZODIAZONINE



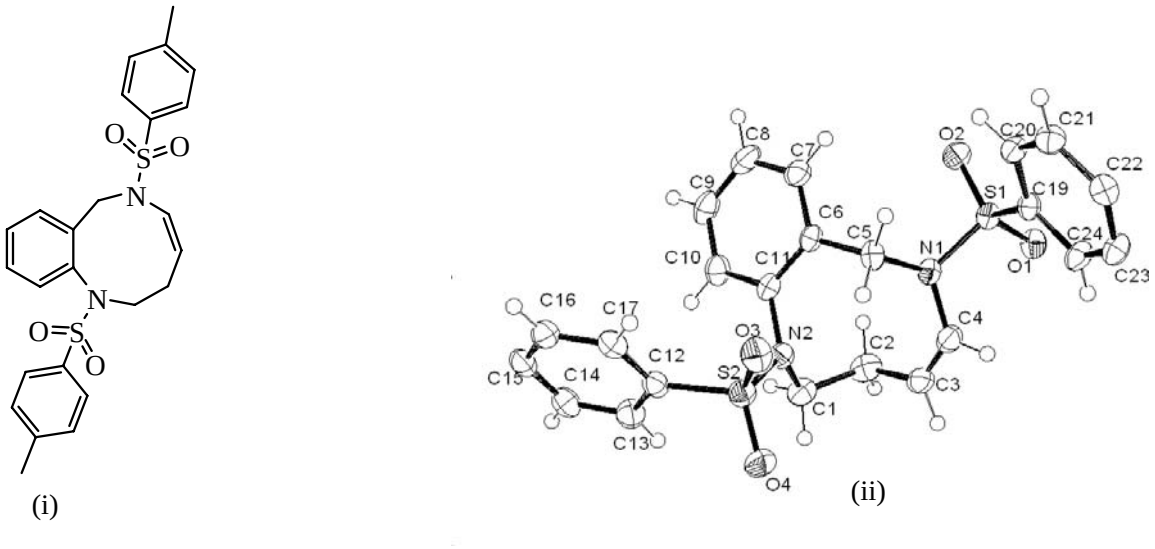
159 **170**

SCHEME 75

(i) d_6-benzene, ruthenium isomerisation catalyst **12**, 90°C, 40 hrs, 97% yield.

1,6-*bis*[(4-Methylphenyl)sulfonyl]-2,5,6,7-tetrahydro-1*H*-1,6-benzodiazonine **159** was dissolved in d_6-benzene and ruthenium isomerisation catalyst **12** was added. The reaction mixture was then heated at 90°C for 40 hrs and the reaction was monitored in a NMR tube. Column chromatography then afforded the product as a brown solid **170** in a good yield of 97%. The ^{1}H NMR spectrum showed the new NCH_2CH_2 peak as two multiplets at 1.76-1.99 ppm and 2.04-2.17 ppm, the N-CH_2CH_2 protons were evident at 3.05 ppm and at 3.95 ppm. In addition, the NCH=C*H* peak was observed as a multiplet at 5.61-5.65 ppm and the NC*H*=CH peak was viewed as doublet at 6.09 ppm. Lastly, HRMS showed the molecular ion *m*/*z* at 482.1341 ($C_{25}H_{26}N_2O_4S_2$ required 482.1334) (Scheme 75).

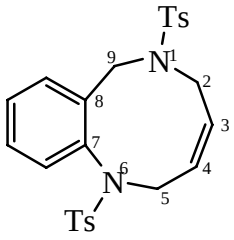
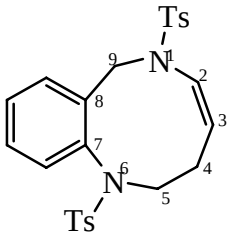
After recrystallization from 20% ethyl acetate in hexane, crystals of **170** were isolated (mp; 192-196°C). A single crystal X-ray structure was successfully determined and the bond angles and lengths were found to be within the required bond lengths and angles for this type of ring system, confirming the structure of compound **170**. The structure belongs to a monoclinic crystal system with a space of P21/c (Figure 19). All data of this structure are recorded in Appendix A.



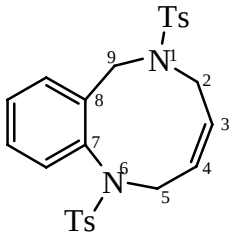
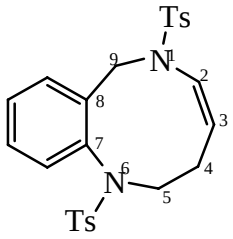
(i) (ii)

FIGURE 19: (i) Molecular structure of **170**. (ii) ORTEP crystal structure of **170**.

CRYSTAL STRUCTURES OF **159** AND **170**: We compared the bond lengths and angles of compounds **159** and **170** and we observed that the shift in the double bond within the ring system has affected the bond lengths and angles of both compounds. The corresponding bond lengths and angles for both compounds were found to be comparable except in the few cases given below:

Bond length for compound **159** [Å]	Bond length for compound **170** [Å]
	
1. C(2)-C(3) = 1.507(4)	1. C(2)-C(3) = 1.303(3)
2. C(3)- C(4) = 1.311(4)	2. C(3)-C(4) = 1.500(3)
3. C(4)-C(5) = 1.496(4)	3. C(4)-C(5) = 1.534(3)

The corresponding torsion angles for both compounds were also found to differ and this is as a result of the shift in the double bonds. The table for the difference in the corresponding torsion angles is given below.

Torsion angles for compound **159** [°]	Torsion angles for compound **170** [°]
	
1. N(6)-C(5)-C(4)-C(3) = 39.1(4)	1. N(6)-C(5)-C(4)-C(3) = 65.0(2)
2. C(5)-C(4)-C(3)-C(2) = 1.2(5)	2. C(5)-C(4)-C(3)-C(2) = -101.0(3)
3. C(4)-C(3)-C(2)-N(1) = -99.7(3)	3. C(4)-C(3)-C(2)-N(1) = 1.9(3)
4. C(3)-C(2)-N(1)-C(9) = 95.2(3)	4. C(3)-C(2)-N(1)-C(9) = 81.7(2)
5. C(7)-N(6)-C(5)-C(4) = 61.1(3)	5. C(7)-N(6)-C(5)-C(4) = 65.7(2)
6. C(8)-C(9)-N(1)-C(2) = -81.7(3)	6. C(8)-C(9)-N(1)-C(2) = -107.06(19)
7. C(8)-C(7)-N(6)-C(5) = -118.4(3)	7. C(8)-C(7)-N(6)-C(5) = -109.98(19)
8. N(1)-C(9)-C(8)-C(7) = 82.7(3)	8. N(1)-C(9)-C(8)-C(7) = 86.0(2)
9. C(9)-C(8)-C(7)-N(6) = -2.6(3)	9. C(9)-C(8)-C(7)-N(6) = 1.0(3)

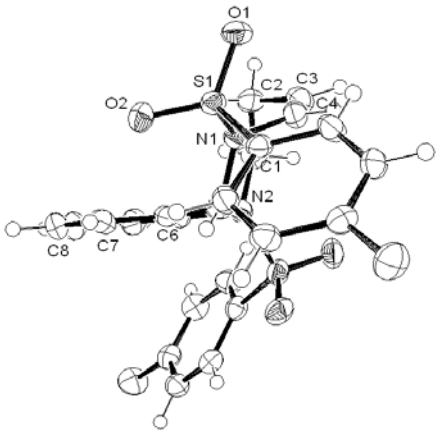


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FIGURE 20: The crystal structure of **170** when the fused-benzene ring was viewed as flat

When the benzene ring was viewed from the side, the heterocyclic ring was found to be puckered with one of the tosyl group pointing upward and the second tosyl group pointing downward (Figure 20).