CHAPTER 3

SYNTHESIS AND STEREOCHEMISTRY OF MANZAMINE FRAGMENTS VIA OLEFIN METATHESIS REACTION

3.1 Introduction

Every once in a few decades, a novel carbon-carbon bond forming strategy becomes available to synthetic organic chemists, that becomes a favored choice for the synthesis of molecules of complex structural features. For example, not in too distant past, acyloin condensation or intramolecular Wittig olefination were reactions of choice, for construction of medium to large rings. However, due to entropic factors, often yields of the cyclic olefins were low, generally less than 10%. In this context, discovery of olefin metathesis reaction has changed the course of medium to large ring synthesis. Large rings of more than twelve carbons derive their importance, in present day research, because they not only they are structural ingredients of newly isolated natural products, but also form integral part of peptide mimics and crown ethers. The word metathesis is derived from Greek words where meta means change and thesis means position. Olefin metathesis means the inter-exchange of two carbons in an olefin with two carbons of another olefin to generate two new olefins as shown in Scheme 3.1.

\[
\begin{align*}
A = B & \quad + \quad C = D \quad \longrightarrow \quad A = C & \quad + \quad B = D
\end{align*}
\]

Scheme 3.1

Metatheses of terminal olefins become irreversible because of the formation of gaseous ethylene as one of the products (Scheme 3.2).

\[
\begin{align*}
R_1\text{CH=CH}_2 & \quad + \quad R_2\text{CH=CH}_2 \quad \longrightarrow \quad R_1\text{CH}=\text{CHR}_2 & \quad + \quad \text{H}_{2}\text{C}=\text{CH}_2
\end{align*}
\]

Scheme 3.2
When both the terminal alkenes are a part of the same molecule, products from olefin metathesis are cyclic olefins and ethylene (Scheme 3.3). Such a transformation of the acyclic diene moiety to cyclic olefin is referred to as ring closing metathesis (RCM).

\[
\text{CH}_2=\text{CH}-\text{CH}_2-\text{X}-\text{CH}_2-\text{CH}=\text{CH}_2 \xrightarrow{\text{RCM}} \text{X} \quad + \quad \text{H}_2\text{C}=\text{CH}_2
\]

**Scheme 3.3**

Olefin metathesis reaction can also be applied to polymerization of cyclic olefins. Indeed, discovery of olefin metathesis reaction using transition metal complexes began with industrial polymerization of norbornene (Scheme 3.4). Such ring opening polymerizations of cyclic olefins are referred to as ring opening metathesis (ROM).

\[
\text{ROM} \quad \rightarrow \quad \begin{array}{c}
\text{X} \\
\text{H}_2\text{C}=\text{CH}_2
\end{array}
\]

**Scheme 3.4**

In cross metathesis (CM) reaction two terminal olefins join together to a new olefin with the extraction of ethylene, as shown in Scheme 3.5.

\[
\text{R}_1\text{CH} = \text{CH}_2 + \text{R}_2\text{CH} = \text{CH}_2 \xrightarrow{\text{CM}} \text{R}_1\text{CH} = \text{CH}_2 + \text{R}_2\text{CH} = \text{CH}_2
\]

**Scheme 3.5**
Both ring opening and ring closing olefin metathesis reactions are in principle, reversible processes. The thermodynamic stability and physical state of products / reactants determines which product(s) or reactant(s) predominate in the reaction.

3.2 Mechanism of olefin metathesis

Single-pot catalytic olefin metathesis reaction was first reported in 1955 by Anderson and Merckelimg who discovered polymerization of norbornene using titanium (II) complex. However at that time, and up to 1990's both mechanism and scope of olefin metathesis was not well-defined. This situation was primarily due to the fact that the transition metal complexes driving metathesis were not air stable and required glove-box operation for handling them. Moreover, mechanistically, it was thought erroneously that metal brings two olefins together is somewhat like a four-membered transition state to trigger metathesis. Owing due to pioneering efforts of French chemist Chauvin, mechanism for the metathesis of two olefins involving metal carbene complexes became well understood. According to presently accepted and simplified mechanism, as shown in Scheme 3.6, metal carbene complex initially exchanges olefin to form a new metal carbene. The intermediate reacts with one more olefin to eliminate new olefin and regenerate the metal carbene complex. Thus, olefin metathesis can be formally described as inter- or intramolecular exchange of alkylidenes promoted by carbene complexes.
3.3 Catalysts

Generalization of olefin metathesis reaction was driven by the discovery of well-defined functional group tolerant air-stable ruthenium alkylidene complexes (A, A', and B, B') and related catalysts (C, D, E and F); (Fig. 3.1). For the discovery, development and use of metal carbene complexes and for explaining their mechanism of action for the synthesis of olefins, Chauven, Schrock and Grubbs were awarded alkylidene Nobel Prize for Chemistry in 2005.
Molybdenum alkoxyimido alkylidene catalyst E was introduced by Schrock in 1990. This molybdenum based complex is air sensitive, therefore, difficult to prepare and handle. Over the past few years Grubbs ruthenium benzylidene complexes A and B have become very popular for ROM reaction to generate cyclic olefins. The catalysts A, and B, are now referred to as first generation and second generation Grubbs catalysts. While the first generation catalyst A is relatively cheap, it is not very stable and prone to decomposition on heating above 35 °C. Therefore its application is restricted to the use of dichloromethane as a solvent, either at room temperature or at reflux. The second generation catalyst B is relatively stable, primarily due to the presence of two bulky mesityl groups on the imidazolyl ligand. It has one tricyclohexylphosphine ligand and one carbene imidazoyl ligand in the place of two phosphine ligands present in A. Reactions with catalyst B can be conducted in toluene as solvent and reaction temperature can go up to 100 °C. Similar to catalyst A, the catalyst B also tolerates wide range of functional groups, eg, esters, amides, nitrogen and oxygen heterocycles etc.
Hoveyda's ruthenium alkylidene catalyst C is phosphine free, air-stable, robust and displays good catalytic activity. However, presently it is very expensive.

Grubbs\(^2\), Hoveyda and Schrock\(^3\) independently developed chiral version of carbine complexes G-K for enantioselective ring-closing metathesis reaction (Fig. 3.2).

![Diagram of carbine complexes G-K]

Fig. 3.2

Advent of well-defined air stable ruthenium alkylidene catalysts has fuelled wide spread application of olefin metathesis reaction in organic synthesis.\(^4\) Scanning literature revealed that there are more than 500 research publications during the past five years on the application of olefin metathesis reaction in organic synthetic transformations. Since, present research work is on the formation of 13-membered rings, to place present research in right perspective, we have selected examples applicable for this ring formation.

In the earlier two chapters, we have described our studies on the synthesis and stereochemistry of saturated nitrogen heterocycles. Continuing this interest, we desired to construct nitrogen containing 13-member heterocyclic rings as they form part
structure of manzamine group of alkaloids. While working on this project we have also focused to investigate the influence of a remote heteroatom on the stereochemistry of the double bond when a 13-membered ring is constructed from the corresponding open-chain dienes. For this purpose, we conceived of novel 13-membered ring structures with two oxygen atoms and a strategically placed hetero-atom. Furthermore, we reasoned that reduction of the double bond in the products from RCM reaction could deliver 13-member crown ethers.

The 13-membered cabocyclic and heterocyclic ring structures are expected to exhibit unique properties different from small and medium ring structures both in terms of conformation and reactivity. Nature selected some molecules with 13-membered heterocyclic rings to impart unique properties. Most famous of the natural products with 13-member rings are manzamine group of alkaloids, eg., 1 and 2 (Fig. 3.3). Manzamines are a class of cytotoxic β-carboline alkaloids that were isolated from Okinawan marine sponges. Biological studies on manzamines have shown that the 13-membered nitrogen heterocyclic ring is crucial for their biological activity. In addition to manzamines, few more alkaloids from marine sponges like ircinal 3, madangamine 4, and motuporamine 5 incorporate 13-membered nitrogen heterocyclic rings. Epilachnene 6, a 13-membered aza-heterocyclic lactone is a chemical defense agent produced by Mexican beetle.
3.4 Recent application of RCM for the synthesis of 13-membered crown ethers

In 1999, Martin and coworkers reported a synthesis of ircinal A and related manzamine alkaloids. For effecting one of the key reactions in the synthesis, the diene 7 was exposed to the Grubbs 1st generation catalyst to furnish a diasteromeric mixture of isomeric cyclic olefins 8 (E/Z = 1:8) in 67% yield (Scheme 3.7).\textsuperscript{12}
In 1999, Seidel and coworkers reported the synthesis of a series of homologous azamacrolides of the type 9 by RCM method. While cyclization of diene 10 catalyzed by Grubbs 1st generation catalyst A surprisingly led to the exclusive formation of Z olefin 11, RCM reaction of its homologous substrate afforded a mixture of Z and E isomeric 14-member cyclic olefins in the ratio of 1:2 (Scheme 3.8). Therefore, it appears that apart from the heteroatom present in the chain, stereochemistry of the cyclic olefin depends on the ring size.

In 2006, McDonald and coworkers reported synthesis of the resorcinyllic macrocycles related to radicicol 12 via ring-closing metathesis. When the diene 13 was
exposed to the 1st generation Grubbs catalyst A, the RCM reaction furnished a mixture of geometric isomers of 14 (Z/E: 8:1) in 60% yield (Scheme 3.9).

Scheme 3.9

Reagents and conditions: i) Grubbs 1st gen. catalyst A (10 mol%), DCM, reflux, 2 h, 60%.

In 2007, Tao and coworkers reported a synthesis of the macrocyclic urea kinase inhibitors of the type 9 via RCM reaction. When the diene 15 was subjected to the Grubbs cyclisation, the reaction provided predominantly Z product 16 and only a minor amount of E olefin compound was detected (Scheme 3.10).

Scheme 3.10

Reagents and conditions: i) Grubbs 2nd gen. catalyst B (10 mol%), DCM, reflux, 24 h, 85%.

In 2007, Ramana and coworkers reported a synthesis of the central core of uprolides D and E 17 by ring closing metathesis (Scheme 3.11). Thus, RCM reaction of the diene 18 gave the 13-membered macrocyclic derivative 19 as an inseparable mixture of E/Z (1:1) isomers mixture in 67% yield.

14
15
16
17
18
19

3.5 Results and discussion

The RCM reaction on dienes can provide cyclic olefins of $E$ or $Z$ stereochemistry. While olefins with only $Z$ stereochemistry are possible in the formation of small rings (5-7), both $E$ and $Z$ double bonds can form in the case of medium and large rings. Till date, there are no systematic studies on the RCM reaction vis à vis stereochemistry of the newly generated double bond, even though it is one of the most explored reactions from mechanistic and synthetic points of view.

In this section, we describe our studies on the RCM reaction on dienes 20-25 to form 13-member cyclic olefins 26-31 and further reduction of the double bond in the newly formed products towards a novel synthesis of the 13-member crown ethers 32-34 (Scheme 3.12).
3.5.1 Synthesis of substrates required for RCM

3.5.1.1 Synthesis and characterization of substituted 6,9,16,17-tetrahydro-15H-dibenzo[6,7][1,6]dioxacyclotridecines

The Claisen-Schmidt condensation between 2-hydroxyacetophenone 37 and substituted 2-hydroxybenzaldehydes (salicylaldehydes) 35-36, which took place readily in the presence of 60% KOH solution, yielded (E)-3-aryl-1-(2-hydroxyphenyl)-2-propen-1-ones (chalcones) 38-39 in moderate yield (Scheme 3.13).
The spectral and analytical data of 38 and 39 matched with the parent unsubstituted chalcone derivative available from the previous studies in our laboratory. Hydrogenative deoxygenation of the enone moiety in 38-39 with Raney nickel lead to double bond and ketone reduced products 40-41. *bis*-Phenols 40-41 were next converted to *bis*-allyl ethers 1-(allyloxy)-2-{3-(allyloxy)aryl]propyl}benzenes 21-22 using allyl bromide, NaH and DMF. The products formed in each transformation were characterized on the basis of IR and NMR spectral data. As an example, the $^1$H NMR spectrum of 21 displayed diagnostic peaks at δ 4.40 (OCH$_2$), 5.03-5.42 (=CH$_2$) and 5.75-5.83 (OCH$_2$CH=CH$_2$) ppm. Aromatic protons appeared in the region between 6.58-7.08 ppm. The $^{13}$C NMR spectrum of 21 exhibited five signals in the aliphatic and sixteen signals in the aromatic region, clearly articulating unsymmetrical nature of the molecule.
3.5.1.2 Synthesis and characterization of 6,9,16,17-tetrahydro-15H-dibenzo[b,g][1,9,5]dioxazacyclotridecine-16-carbaldehyde

Known oxime 43 was prepared by the reaction of salicylaldehyde 42 and hydroxylamine hydrochloride in ethanol. The oxime 43 was treated with HCOONH₄/Pd-C to provide secondary amine 44 (Scheme 3.14). Attempted bis-allylation of 44 with allyl bromide using K₂CO₃ in acetone reflux or NaH in DMF at rt, furnished undesired N-allylated product 45. To circumvent the problem of higher nucleophilicity of the secondary amino group in 44, it was converted into N-formyl derivative 46 by reaction with ethyl formate and formic acid in a mixture of DMF and 1,4-dioxane. Now, bis-allylation of phenolic hydroxyls in 46 with allylbromide, NaH and DMF furnished \(N,N\)-di(2-hydroxybenzyl)acetamide 23 without any problem. The product formation was confirmed by interpreting its IR and \(^1\)H NMR spectra. The IR spectrum did not show a band at about \(\nu = 3320 \text{ cm}^{-1}\) indicating the both the phenolic
hydroxy groups were converted into their allyl ethers. The \(^1\)H NMR spectrum showed multiplets located between \(\delta\) 5.8-5.9 and 5.1-5.4 ppm were accounted for olefinic hydrogens; aromatic hydrogens provided signals in region of \(\delta\) 7.1-6.8 ppm. A sharp signal at \(\delta\) 8.22 ppm was for \(-\text{NCOH}\). The \(^{13}\)C NMR spectrum showed two sets of eleven signals of equal intensity assignable to restricted rotation around amide bond, similar to that of DMF.

3.5.1.3 Synthesis and characterization of 6,9-dihydro-15\(H\),17\(H\)-dibenzo[\(b,g\)][1,5,9]trioxacyclotridecine

The allyl ether of 2-hydroxybenzaldehyde 47 was prepared from 2-hydroxubenzaldehyde 42 by reaction with allyl bromide, NaN\(_2\) in DMF (Scheme 3.15).\(^{19}\) Subsequently, 47 was reduced with NaN\(_2\H\) in MeOH to furnish (2-propoxyphenyl)methanol 48. The benzyl alcohol 48 was transformed into (2-1-(chloromethyl)-2-propoxybenzene 49 with thionyl chloride. The Williamson reaction between the benzylic alcohol 48 and benzylic chloride 49 mediated by sodium hydride in DMF furnished the bis-allyl ether, 1-(allyloxy)-2-(\{2-(allyloxy)benzyl\}oxy)methyl)benzene 24 in near quantitative yield. The \(^1\)H NMR
spectrum of 24 displayed peaks at δ 4.63, 4.53 ppm for -OCH₂ group, δ 6.07-5.97 ppm for -OCH₂CH=CH₂ group and δ 5.75-5.83 ppm for -OCH₂CH₂=CH₂ groups. The aromatic protons appeared in the region between δ 7.4-6.8 ppm. The ¹³C NMR spectrum showed 10 lines out of which those at δ 67.27 and 68.61 ppm were diagnostic for two types of -OCH₂ carbons.

3.5.1.4 Synthesis and characterization of 6,9-dihydro-15H,17H-dibenz[b,g][1,9,5]dioxathiacyclotridecine

![Scheme 3.16](image)

**Reactions and conditions:** i) Na₂S, 70%, NaOH, EtOH, 8 h, 100 °C, 71% or 3-MPA, 50% EtOH, 6.5 h, 36%.

Synthesis of the sulfur incorporated bis-allyl ether, 1-(allyloxy)-2-({2-(allyloxy)benzyl}sulfanyl)methyl)benzene 25 was achieved by the reaction of benzyl chloride 49 with Na₂S or 3-mercaptopropionic acid (3MPA, Scheme 3.16). While the reaction with Na₂S under basic conditions provided the thio-ether 25 in 71% yield, the reaction with 3-MPA, as a sulfur donor, the yield was only 36%. The ¹H NMR spectrum displayed a broad singlet at δ 4.52 ppm for -OCH₂ and a singlet at δ 3.73 ppm for -SCH₂ groups. The ¹³C NMR spectrum along with DEPT and HMBC allowed assignment of peaks at δ 30.43 ppm for -SCH₂ and at δ 68.69 ppm for -OCH₂ carbons respectively. The ¹³C NMR spectrum revealed C₂ symmetric nature of the molecule by exhibiting ten signals.

3.6 RCM Reaction

Earlier in our laboratory, we found that the reaction of the parent bis-allyl ether 20 with 10 mol% of Grubb's 1st generation ruthenium carebene complex in dry
dichlormethane (DCM) reflux for 14 hours yielded \((E)-6,9,16,17\)-tetrahydro-15\(H\)-dibenzo[\(g,l\)][1,6]dioxacyclotridecine 26 as a single isomer in 63% yield (Scheme 3.17).

The cyclic olefin 26 was characterized on the basis of spectral (\(^1\)H, \(^13\)C, DEPT NMR and MS spectra) and analytical data. The \(C_2\) symmetric nature of 26 was evident from its \(^1\)H NMR spectrum, which displayed characteristic singlets at \(\delta 4.54\) (OCH\(_2\)) and 6.05 ppm (C=CH). The \(^13\)C NMR spectrum showed 10 signals with diagnostic peaks located at \(\delta 29.8, 30.4, 67.8\) ppm for the methylenes and \(\delta 111.7\) ppm for the olefinic carbons. The data reported by Ibrahim and coworkers was used to assign \(E\) stereochemistry to the double bond in 26.\(^{25}\) In the \(^1\)H NMR spectrum of the macrocyclic ethers of the type 26, the OCH\(_2\) hydrogens of the \(E\)-isomer appear upfield at about \(\delta 4.6\) ppm as singlets whereas for the \(Z\) isomer they appear relatively downfield at \(\delta 4.7\) ppm as doublet (\(J = 3.7\) Hz). Similarly in the \(^13\)C NMR spectrum corresponding OCH\(_2\) carbon in \(E\)-isomer appear downfield at about \(\delta 69.0\) ppm, whereas in \(Z\)-isomer it appears upfield at about \(\delta 64\) ppm. For the cyclic olefin 26, the OCH\(_2\) hydrogens appeared at \(\delta 4.54\) ppm as singlet in the \(^1\)H NMR spectrum and at \(\delta 67.8\) ppm for the corresponding carbon in the \(^13\)C NMR spectrum. This data enabled us to assign \(E\)-stereochemistry to the olefin.
For generalization of the result, we have now conducted the RCM reaction on 21 and 22 and we observed, again, almost exclusive formation of the $E$-isomeric cyclic olefins 27 and 28 respectively in the RCM reaction. In both the cases OCH$_2$ carbons gave signals at about $\delta$ 68 ppm in their respective $^{13}$C NMR spectra (Table 3.1).

Exclusive arrival of $E$-isomer 26-28 in RCM reaction promoted us to find out if there is any influence of a strategically located hetero-atom on the stereochemistry of the newly generated cyclic alkenes. Accordingly, the bis-allyl ethers 23-25 were subjected to RCM reaction and the results are gathered in Table 1.

Cyclization of the bis-allyl ether with centrally placed NCHO 23 group under RCM conditions provided inseparable diastereomeric mixture of $E/Z$- 6,9,16,17-tetrahydro-15H-dibenzo[b,g][1,9,5]dioxazacyclotricline-16-carbaldehydes 29 in 70% yield in the ratio of 29:71 (Scheme 3.17, entry 3, Table 3.1). Both $^1$H NMR spectrum and $^{13}$C NMR spectrum displayed two sets of signals for each isomer due to restricted rotation in the formamide moiety. Structure of the cyclic olefin 29 was delineated from its spectral data. In addition to the absence of resonances at $\delta$ 5.9 ppm due to terminal olefinic protons, presence of multiplets at $\delta$ 6.2-6.24 and $\delta$ 5.8-5.9 ppm indicated cyclization. The $^1$H NMR spectrum displayed signals for OCH$_2$, NH$_2$ and olefinic CH hydrogens assignable to $E$ and $Z$ isomers, however, as two sets in each case. The $^{13}$C NMR spectrum displayed two sets of signal for olefinic $E/Z$ isomers each one of which was further split into two signals, owing to restricted rotation around amide double bond. Signals at $\delta$ 37.5 and 43.0 ppm were assigned to N-CH$_2$ of the major $Z$ isomer. Signals at $\delta$ 61.9 (double intensity) and 69.5 and 70.83 were assigned to OCH$_2$ carbons belonging to $Z$ and $E$ isomers respectively.

Cyclization of bis-allyl ether with centrally placed extra oxygen 24 with the Grubbs first generation catalyst provided ($E$) 6,9-dihydro-15H,17H-dibenzo[b,g][1,5,9]trioxacyclotricline 30 in 69% yield exclusively (Scheme 3.17, entry 24, Table 3.1). The $^1$H NMR spectrum of the cyclic olefin 30 showed absence of resonances at $\delta$ 6.05-5.99 ppm due to terminal olefinic protons. Instead, it exhibited a doublet at $\delta$ 6.09-6.08 ppm for the olefinic hydrogen. The $^{13}$C NMR spectrum exhibited resonances at $\delta$ 67.39, 67.73 ppm for two types of OCH$_2$ carbons. Presence of OCH$_2$ signal at $\delta$ 67.73 ppm indicated formation of $E$-isomer exclusively.
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<sup>a</sup> Selected $^{13}$C NMR values of allylic OCH<sub>2</sub> carbons in ppm.
Table 3.1 RCM reaction of bis-allylethers to provide E/Z isomers of cyclic olefins.

Finally, the bis-allyl ether 25 was subjected to RCM reaction to provide (E/Z)6,9-dihydro-15H,17H-dibenzo[b,g][1,9,5]dioxathiacyclotridecine 31 in 72% yield in the ratio of 57:43 (Scheme 3.17). The $^1$H NMR spectrum did not show signals between $\delta$ 6.2 to 6.0 ppm for terminal olefinic hydrogens. Instead, it showed two olefinic proton triplets at $\delta$ 6.19 ($J = 2.0$ Hz) and 6.07 ($J = 1.0$ Hz) ppm weak coupling with adjacent CH$_2$ is characteristic of olefins present in 13-membered ring matrix. The OCH$_2$ appeared as two doublets at $\delta$ 4.65 and 4.53 ppm. Two singlets for SCH$_2$ appeared at $\delta$ 3.80 and $\delta$ 3.77 ppm for E and Z isomers. The $^{13}$C NMR spectrum showed two sets of signals accounting for E and Z isomers present in almost equal ratio. Integration of relevant signal located at $\delta$ 71.0 and 64.0 ppm showed E and Z olefinic isomer ratio was 57:43.

3.7 Synthesis of 13-membred crown ethers

With cyclic olefins 26-31 in hand, we performed hydrogenation of the double bond with an intention to generate corresponding dibenzo-13-crown ethers. Reduction of the cyclic olefin 26 with H$_2$, Pd/C (10%) was uneventful and it provided the crown ether, 6,7,8,9,16,17-hexahydro-15H-dibenzo[g,l][1,6]dioxacyclotridecine 32 in 86% yield (Scheme 3.18).

![Scheme 3.18](image)

Reagents and conditions: i) H$_2$, Pd/C (10%), EtOH, 8h, 86%

The $^1$H NMR spectrum of 32 showed did not show signal for olefin at $\delta$ 6.0 ppm, which indicates that the reduction of the olefin 32 has taken place. New peaks at $\delta$ 1.92 ppm indicate product formation, OCH$_2$ peaks appeared as broad doublet at $\delta$ 3.99
ppm and aromatic ring attached CH$_2$ peaks appeared as triplet at $\delta$ 2.63 ppm with $J = 16$ Hz. In $^{13}$C NMR spectrum there were ten signals out of which four were in the aliphatic region.

Similar reduction of the cyclic olefin 30 with H$_2$, Pd/C (10%) resulted in a mixture of products, possibly arising out of competing debenzylation. However, the hydrogenation of 29 and 31 worked nicely with H$_2$ in presence of Wilkinson catalyst to furnish crown-ethers 33 and 34 in good yield.

The reduction of cyclic olefin 29 provided 6,7,8,9,16,17-hexahydro-15$H$-dibenzo[b,g][1,9,5]dioxazacycloadecine-16-carbaldehyde 33 (Scheme 3.19)\textsuperscript{26}. Besides absence of resonances for olefinic protons in $^1$H NMR spectrum at $\delta$ 6.31-6.24 ppm and $\delta$ 5.90-5.88 ppm, presence of two quartets at $\delta$ 2.18-2.10 ppm confirmed assigned structure 33. In $^{13}$C NMR spectrum (Fig 3.19) a pairs of nine signals for 33 confirmed assigned structure.

In the case of amide 33 similar to that of dimethyl formamide (DMF), the spectra displayed two sets of signals owing to restricted rotation around of the amide bond. To clarify the spectrum the amide 33 was reduced with LAH to get quantitative yield of cryptand 50 (Scheme 3.20). After reduction, the $^{13}$C NMR spectrum showed anticipated 10 line spectrum.
Reduction of cyclic olefin 30 with oxygen in the tether with hydrogen in presence of a variety of catalyst like 5% Pd/C, 10% Pd/C and Wilkinson catalyst led the cleavage. We need to pursue this reaction further to achieve reduction of the double bond without concomitant ring opening.

The reduction of cyclic olefin 31 with H₂/Wilkinson catalyst resulted 6,7,8,9-tetrahydro-15H,17H dibenzo[b,g][1,9,5]dioxathiacyclotridecine 34 (Scheme 3.21).

Unlike cyclic olefin 31, the ¹H NMR spectrum of 34 was very clear. The ¹H NMR spectrum was clean exhibiting three singlets in the aliphatic region of equal intensity. Interestingly OCH₂ hydrogen did not appear as triplet with of customary coupling of about 7 Hz. This aspect of coupling is common to OCH₂ hydrogen present as a part of medium sized rings. A nine-line ¹³C NMR spectrum with three signals in the aliphatic and six in the aromatic region confirmed assigned structure.

In the Table 3.2 we have gathered the all the saturated 13-membred crown ethers 32, 33 and 34 prepared under this study Table 3.2.
3.8 Summary

In summary, we have studied the influence of remote heteroatom during Grubbs RCM to form 13-membered cyclic ether with at least two oxygen atoms. This study shows that the heteroatom has profound influence on the olefin forming step possibly complexing with ruthenium. While $E$ olefin is formed as a major product with CH$_2$ in position, with sulfur it was almost 57:43. Further reduction of cyclic olefin provided 13-membered crown ethers. For reduction we needed to use H$_2$/Wilkinson catalyst in some cases.

3.9 Experimental Section

General:

For general details about experimental conditions see Chapter-1. The 2-hydroxybenzaldehydes 35 and 36 required for this study were made via Reimer-Tiemann reaction according to literature procedure,

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</table>
Representative procedure for the synthesis of (E)-1,3-di(2-hydroxyaryl)-2-propen-1-ones (chalones): (E)-1-(4-Chloro-2-hydroxy-5-methylphenyl)-3-(2-hydroxyphenyl)-2-propen-1-one 38:

To a solution of 2-hydroxyacetophenone 37 (1.30 g, 9.5 mmol), 5-chloro-2-hydroxybenzaldehyde 35 (1.50 g, 9.5 mmol) in 10 mL EtOH. 60% aqueous KOH (11.2 g in 18 mL water) solution was added drop-wise at 0 °C for 30 min. The reaction mixture was stirred at rt for 30 h. by which time the reaction was complete (TLC). The reaction mixture was neutralized with 2N aqueous HCl (20 mL) and the aqueous medium was extracted with ethyl acetate (4 × 25 mL). The combined organic layer was washed with water (2 × 30 mL) and brine (15 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude residue was purified by CC using hexanes/ethyl acetate (70:30) as the eluent to give pure (E)-1-(4-Chloro-2-hydroxy-5-methylphenyl)-3-(2-hydroxyphenyl)-2-propen-1-one 38 as Yellow color solid;¹⁸ Yield = 1.62 g (62%); Rf = 0.23 (30% EtOAc- hexanes); IR (KBr) ν 3441, 3028, 2861, 1644, 1594, 1243, 749 cm⁻¹; ¹H NMR (60 MHz, CCl₄) δ 7.8-6.93 (m) ppm. GC MS 274 (38%, M⁺), 260 (37%), 232 (100%), 192 (43%), 164 (20%), 151 (41%), 124 (13%), 91 (21%), 39 (12%); Anal. Calcd. for C₁₃H₁₁ClO₃; C, 65.59; H, 4.04; Found: C, 65.57, H, 4.02.

(E)-1-(4-Chloro-2-hydroxy-5-methylphenyl)-3-(2-hydroxyphenyl)-2-propen-1-one 39:

Following the general procedure described above the reaction of 2-hydroxyacetophenone 37 (623 mg, 3.6 mmol) with 4-chloro-2-hydroxy-5-methylbenzaldehyde 36 (500 mg, 3.67) in 20 mL ethanol and 60% aqueous KOH (3.9 g, in 8 mL) resulted 1-(4-chloro-2-hydroxy-5-methylphenyl)-3-(2-hydroxyphenyl)-2-propen-1-one 39 after purification by CC. Yellow color solid, mp 124-126 °C; Yield = 486 mg (46%); Rf = 0.21 (30% EtOAc- hexanes); IR (KBr) ν 3378, 3081, 1650, 1602, 833 cm⁻¹; ¹H NMR (60 MHz, CCl₄) δ 7.95-6.94 (m, 8H), 2.2 (s, 3H) ppm. GC MS 288 (24%, M⁺), 236 (37%), 210 (100%), 178 (43%), 166 (20%), 141 (41%), 124 (13%), 91 (21%); Anal. Calcd for C₁₆H₁₃ClO₃; C, 66.56; H, 4.54; Found: C, 66.55, H, 4.48.
Chapter 3

Representative procedure for the synthesis of 2-(3-(2-hydroxy aryl) propyl) phenols: 4-Chloro-2-[3-(2-hydroxyphenyl)propyl]phenol 40:

To a solution of 1-(4-chloro-2-hydroxyphenyl)-3-(2-hydroxyphenyl)-2-propen-1-one 38 (600 mg, 3.8 mmol), Raney nickel (6 g) in isopropanol (50 mL) was added and the resulting mixture was refluxed for 16 h. After completion of the reaction (TLC) Raney nickel was filtered through celite. Solvent from filtrate was removed under reduced pressure and the residue was charged on silica gel CC. Eluting with hexanes/EtOAc (70:30) provided a colorless solid 4-Chloro-2-[3-(2-hydroxyphenyl)propyl]phenol 40, which was recrystallized from 10% DCM in hexanes. Colorless solid, mp 104-106 °C; Yield = 309 mg (54%); Rf = 0.18 (30% EtOAc/hexanes); IR (KBr) ν 3541, 3441, 2929, 1594, 1444, 1112, 924 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.99-6.72 (m, 7H), 5.8 (br s, 2H), 2.66-2.63 (m, 4H), 1.93-1.89 (m, 2H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 153.35 (2C), 130.21, 129.79, 127.38, 127.15, 127.08, 126.90, 120.76, 120.58, 116.49, 115.34, 30.04, 29.71, 29.57 ppm GC MS 263 (100%, M⁺), 221 (13%), 202 (28%), 132 (14%), 117 (84%), 103 (16%), 91 (43%); Anal. Calcd for C₁₅H₁₅ClO₂; C, 68.57; H, 5.75; Found: C, 68.59, H, 5.76.

4-chloro-2-[3-(2-hydroxyphenyl)propyl]-5-methylphenol 41:

Following the general procedure described above the reaction of 1-(4-chloro-2-hydroxy-5-methylphenyl)-3-(2-hydroxyphenyl)-2-propen-1-one 39 (400 mg, 1.3 mmol) Raney nickel (4 g) in isopropanol (40 mL) resulted in 5-chloro-2-[3-(2-hydroxyphenyl)propyl]-4-methylphenol 41 after purification by CC. Colorless solid, mp 110-112 °C; Yield = 260 mg (68%); Rf = 0.16 (30% EtOAc/hexanes); IR (KBr) ν 3347, 3266, 2944, 1219, 748 cm⁻¹; ¹H NMR (60 MHz, CDCl₃) δ 7.10-6.54 (m, 6H), 4.85 (br s, 2H), 2.64-2.52 (m, 4H), 2.2 (s, 3H), 1.25-1.10 (m, 2H) ppm; GC MS 277 (18%, M⁺), 264 (100%), 202 (30%), 132 (13%), 117 (86%), 115 (21%), 103 (18%), 91 (34%), 77 (16%); Anal. Calcd for C₁₆H₁₇ClO₂; C, 69.44; H, 6.19; Found: C, 69.03, H, 5.91.
Representative procedure for the synthesis of 1-allyloxy(2-(3-2(allyloxyaryl) propyl)phenols: 1-(Allyl oxy)-2-{3-[2-(allyloxy)phenyl]propyl}-4-chlorobenzene 21:

To a solution of 4-chloro-2-[3-(2-hydroxyphenyl)propyl]phenol 40 (200 mg, 0.7 mmol) in 10 mL dry DMF, NaH (45 mg, 60% oil dispersion in mineral oil, 1.9 mmol) was added under a blanket of dry nitrogen and stirred at 0 °C for 30 min. Then allyl bromide (228 mg, 1.9 mmol) was added drop-wise and continued the stirring for 8 h. at rt. After completion of the reaction (TLC) the reaction mixture was diluted with ice-cooled water (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layer was washed with water (2 × 25 mL), brine solution (20 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to obtain crude product. Purification of the crude product on silica gel (100-200 mesh) CC using hexane/EtOAc (95:05) as eluent provided 1-(allyloxy)-2-{3-[2-(allyloxy)phenyl]propyl}-4-chlorobenzene 21. as colorless liquid, Yield = 208 mg (80%); R₇ = 0.76 (5% EtOAc/hexanes); IR (KBr) v 2925, 2825, 1594, 1456, 1241, 913, 743 cm⁻¹; ¹H NMR (60 MHz, CCl₄) δ 7.11-6.63 (m, 7H), 6.30-5.97 (m, 2H), 5.34 (m, 4H), 4.4 (d, J = 3 Hz, 4H), 2.64 (m, 4H), 2.12-1.73 (m, 2H) ppm; GC MS 343 (41%, M⁺), 330 (22%), 284 (100%), 196 (16%), 168 (11%), 144 (18%), 120 (11%), 91 (18%), 77 (16%). Anal. Calcd for C₂₁H₂₃ClO₂: C, 73.57; H, 6.76; Found: C, 73.08, H, 6.51.

1-(Allyloxy)-2-{3-[2-(allyloxy)phenyl]propyl}-5-chloro-4-methylbenzene 22:

Following the general procedure, the reaction of 4-chloro-2-[3-(2-hydroxyphenyl)propyl]-5-methylphenol 41 (400 mg, 1.4 mmol) allyl bromide (350 mg, 2.8 mmol) and NaH (70 mg, 2.8 mmol) in dry DMF (18 mL), resulted 1-(allyloxy)-2-{3-[2-(allyloxy)phenyl]propyl}-4-chloro-5-methylbenzene 22 after purification by CC. Colorless liquid, Yield = 480 mg (93%); R₇ = 0.72 (5% EtOAc-hexanes); IR (KBr) v 3071, 3028, 2927, 2852, 1487, 1456, 1237, 918, 743 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.13-7.08 (m, 3H), 6.86-6.63 (m, 4H), 6.04-5.97 (m, 2H), 5.40-5.21 (m, 4H), 4.50 (d, J = 3 Hz, 4H, OCH₂), 2.73-2.30 (m, 2H), 2.22 (s, 3H), 1.97-1.82 (m, 2H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 157.78, 153.96, 137.52, 133.71, 133.55, 133.24, 129.87, 12972, 126.68, 122.61, 120.61, 116.77, 116.54, 111.30, 68.77,
68.40, 31.87, 30.62, 22.64, 20.02 ppm; GC MS 357 (62%, M'), 344 (57%), 282 (100%), 198 (12%), 164 (25%), 117 (10%), 77 (28%); Anal. Calcd for C_{22}H_{25}ClO_{2}; C, 74.04; H, 7.06; Found: C, 73.86, H, 6.74.

*N,N-Di(2-hydroxybenzyl)formamide* Rai 46:

To a solution of 2-[(2-hydroxybenzyl)amino]methyl]phenol 44 (1 g, 4.3 mmol) in 5 mL 1,4-dioxane, ethyl formate (1.61 g, 21.8 mmol) in 10 mL DMF and formic acid (3 mL) and the mixture is refluxed for 8 h. After completion of the reaction (TLC) reaction mixture was cooled to rt and the organic volatiles were removed under reduced pressure. To the residue methanol (8 mL) was added and stirred 30 min. at rt. The mixture was diluted with ice-cold water (25 mL), and aqueous layer was extracted with diethyl ether (2 x 50 mL). The organic layer was washed with water (2 x 20 mL) followed by brine solution (15 mL) and dried over by anhydrous Na_{2}SO_{4}. Removal of solvent under reduced pressure followed by CC with hexanes/EtOAc as the eluent provided *N,N-Di(2-hydroxybenzyl)acetamide* 46 as colorless solid. mp 138-140 °C; Yield = 583 mg (52%); R_f = 0.16 (30% EtOAc/hexanes); IR (KBr) ν 3318, 3078, 3015, 2818, 1648, 1486, 926, 755 cm^{-1}; ^1H NMR (60 MHz, CCl_{4}) δ 8.23 (s, 1H), 7.24-6.71 (m, 5H), 4.33-4.24 (m, 4H) ppm; GC MS 258 (38%, M'), 244 (37%), 232 (100%), 192 (43%), 164 (20%), 151 (41%), 124 (13%), 91 (21%), 39 (12%).

*N,N-Di[2-(allyloxy)benzyl]formamide* 23:

Following the general procedure the reaction of *N,N-di(2-hydroxybenzyl)acetamide* 46 (1g, 3.8 mmol) (20 mL) ally bromide (1 g, 8.5 mmol) and NaH (205 mg, 8.5 mmol) in dry DMF resulted *N,N-di[2-(allyloxy)benzyl]acetamide* 23 after purification by CC. Colorless liquid, Yield = 1.07 mg (79%); R_f = 0.4 (20% EtOAc/hexanes); IR (KBr) ν 3071, 2918, 1651, 1594, 1487, 1250, 1012, 743 cm^{-1}; ^1H NMR (60 MHz, CCl_{4}) δ 8.23 (s, 1H), 7.14-6.80 (m, 8H), 5.89-5.76 (m, 2H), 5.40-5.14 (m, 4H), 4.42 (s, 4H), 4.27 (s, 4H) ppm; GC MS 338 (41%, M'), 308 (12%) 260 (100%), 232 (18%), 165 (41%), 151 (41%), 119 (18%), 77 (27%); Anal. Calcd for C_{21}H_{23}NO_{3}; C, 74.75; H, 6.87; N, 4.15; Found: C, 74.76, H, 6.90, N, 4.14.
1-(Allyloxy)-2-({[2-(allyloxy)benzyl]oxy}methyl)benzene 24:

A stirred solution of [2-(allyloxy)phenyl]methanol 48 (290 mg, 1.7 mmol) in dry DMF (15 mL) NaH (42 mg, 60% suspension in mineral oil, 1.7 mmol) was added at 0-5 °C under a blanket of dry nitrogen atmosphere and stirred for 30 min. To the suspension 1-(allyloxy)-2-(chloromethyl)benzene 49 (400 mg, 1.7 mmol) was added drop-wise during 10 min. and continued stirring at rt. for 10 h. After completion of the reaction (TLC) the reaction mixture was diluted with ice-cold water (20 mL) and extracted with diethyl ether (3 × 25 mL). The combined organic layer was washed with water (2 × 30 mL) and brine solution (25 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by CC on silica gel (100-200 mesh) using hexane/EtOAc as eluent to obtain 1-(allyloxy)-2-({[2-(allyloxy)benzyl]oxy}methyl)benzene 24 as a colorless solid, mp 92-94 °C; Yield = 497 mg (90%); R_f = 0.69 (5% EtOAc-hexanes); IR (KBr) ν 2915, 1487, 1256, 993, 736 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.49 (d, J = 7.2 Hz, 2H), 7.17 (t, J = 8.0 Hz, 3H), 6.94 (t, J = 7.2 Hz 3H), 6.81 (d, J = 8.0 Hz, 2H), 6.07-5.97 (m, 2H), 5.38 (d, J = 6.4 Hz, 2H), 5.23 (d, J = 9.2 Hz, 2H), 4.69 (s, 4H), 4.53 (d, J = 2 Hz, 4H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 155.81, 133.33, 128.61, 128.10, 127.37, 120.57, 116.99, 111.21, 68.61, 67.27 ppm; GC MS 311 (31%, M⁺), 298 (51%), 262 (100%), 184 (22%), 158 (11%), 120 (13%), 104 (23%), 91 (18%); Anal. Calcd for C₂₀H₂₂O₃; C, 77.39; H, 7.14; Found: C, 77.03, H, 6.97.

1-(Allyloxy)-2-({[2-(allyloxy)benzyl]sulfanyl}methyl)benzene 25:

To a solution of 1-(allyloxy)-2-(chloromethyl)benzene 49 (300 mg, 1.6 mmol) in 12 mL ethanol, sodium sulfide (638 mg, 8.2 mmol) was added and the reaction mixture was heated reflux for 10 min. Subsequently aqueous 70% NaOH (5 mL) was added drop-wise and reaction was continued for 10h. After completion of the reaction (TLC) the reaction mixture was cooled to rt and diluted with ice-cold water (20 mL), neutralized with 5N HCl, and extracted with diethyl ether (3 × 20 mL). The combined organic layer was washed with water (2 × 20 mL) and brine solution (15 mL), dried over anhydrous Na₂SO₄ and
concentrated under reduced pressure to obtain a light yellow color liquid, which was purified by CC, hexanes/EtOAc as the eluent, to obtain 1-(allyloxy)-2-{[2-(allyloxy)benzyl]sulfanylmethyl}benzene 25. Yield = 381 mg (71%); \( R_f = 0.70 \) (5% EtOAc-hexanes); IR (KBr) \( \nu = 3021, 2927, 1600, 1494, 1256, 1224, 1011, 749, 667 \) cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta = 7.17 \) (d, \( J = 7 \) Hz, 2H), 7.13 (t, \( J = 6.4 \) Hz, 3H), 6.88 (t, \( J = 7 \) Hz, 3H), 6.79 (d, \( J = 6.8 \) Hz, 2H), 6.05-5.96 (m, 2H), 5.40 (dd, \( J = 16 \) Hz, 2 Hz, 2H), 5.21 (dd, \( J = 10 \) Hz, 3 Hz, 2H), 4.52 (d, \( J = 2 \) Hz, 2H), 3.73 (s, 4H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta = 156.23, 133.27, 130.25, 128.20, 127.33, 120.48, 116.93, 111.54, 68.69, 30.43 \) ppm; GC MS 327 (43%), 313 (100%), 281 (22%), 264 (38%), 180 (11%), 151 (22%), 138 (37%), 91 (16%), 77 (10%). Anal. Calcd for C\(_{20}\)H\(_{20}\)S: C, 73.59; H, 6.79; Found: C, 73.16, H, 6.21.

General procedure for ring closing metathesis (RCM) reaction: (E)-6,9,16,17-Tetrahydro-15H-dibenzo[g,l][1,6]dioxacyclotridecine

To a solution of bis-allyl product 1-(allyloxy)-2-{3-[2-(allyloxy)phenyl]propyl}-4-chlorobenzene 21 (200 mg, 0.5 mmol) in dry DCM (40 mL) a solution of bis(tricyclohexylphosphine)-benzylideneruthenium dichloride (1st generation Grubbs catalyst A, 21 mg, 10 mol%) in dry DCM (8 mL) was added drop-wise. The resulting solution was allowed to stir at 40 °C for 24 h. After completion of the reaction (TLC) the solvent was removed in vacuo and the residue was purified by silica gel CC using EtOAc/hexanes (5:95) as eluent to afford the cyclic olefin (E)-2-chloro-6,9,16,17-tetrahydro-15H-dibenzo[g,l][1,6]dioxacyclotridecine 27 as a single diasteromer. Colorless solid, mp 121-123 °C; Yield = 133 mg (73%); \( R_f = 0.80 \) (5% EtOAc-hexanes); IR (KBr) \( \nu = 3048, 2908, 1603, 1443, 758 \) cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta = 7.05-7.16 \) (m, 4H), 6.90-6.81 (m, 3H), 6.05-6.02 (m, 2H), 4.54 (s, 4H), 2.73-2.63 (m, 4H), 1.96-1.88 (m, 2H) ppm; \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta = 156.52, 131.56, 129.92, 127.14, 126.35, 120.71, 111.76, 68.18 \) (CH\(_2\)), 67.82 (CH\(_2\)), 30.30 (2 × CH\(_2\)), 29.59 (CH\(_2\)) ppm; Anal. Calcd for C\(_{19}\)H\(_{16}\)ClO\(_2\): C, 72.49; H, 6.08; Found: C, 72.50, H, 6.06.
Following general procedure described above, the reaction of 1-(allyloxy)-2-{3-[2-(allyloxy)phenyl]propyl}-4-chloro-5-methylbenzene 22 (170 mg, 0.4 mmol) with Grubbs catalyst A (15 mg, 10 mol%) in 39 mL of dry DCM at 40 °C for 20 h resulted in (E)-2-chloro-3-methyl-6,9,16,17-tetrahydro-15H-dibenzog,f][1,6]dioxacyclotridecine 28 after purification by CC as a colorless solid. MP 108-110 °C; Yield = 116 mg (71%); Rf = 0.76 (5% EtOAc-hexanes); IR (KBr) v 3021, 2924, 2861, 1597, 1241, 751 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.35-6.98 (m, 3H), 6.87-6.64 (m, 3H), 6.03 (br s, 2H), 4.53 (s, 4H), 2.68 (m, 4H), 2.30 (s, 3H), 1.87 (m, 2H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 132.32 (CH), 132.24 (CH), 131.70 (CH), 131.32 (CH), 131.25 (CH), 129.67 (C), 128.98 (C), 128.88 (CH), 128.70 (CH), 128.60 (CH), 127.11 (CH), 126.15, 125.59, 123.26, 122.63, 121.40 (CH), 121.33 (CH), 118.78 (CH), 116.43 (CH), 112.78 (CH), 111.73 (CH), 70.83 (CH₂), 69.65 (CH₂), 61.90 (CH₂), 44.68 (CH₂).
43.00 (CH₂), 38.90 (CH₂), 37.50 (CH₂) ppm; Anal. Calcd. for C₁₉H₁₉NO₃; C, 73.77; H, 6.19; N, 4.53; Found: C, 72.82, H, 6.76, N, 4.91.

*(E/Z)-6,9-Dihydro-15H,17H-dibenzo[b,g][1,5,9]trioxacyclotridecine 30:*

Following general procedure described above the reaction of 1-(allyloxy)-2-([2-(allyloxy)benzyl]oxy)methyl)benzene 24 (300 mg, 1 mmol) with Grubbs catalyst A (26 mg, 10 mol%) in dry DCM (50 mL) at 40 °C for 10 h resulted in (E/Z)-6,9-dihydro-15H,17H-dibenzo[b,g][1,5,9]trioxacyclotridecine 30 after purification by CC. Colorless solid, mp 127-129 °C; Yield = 195 mg (69%); Rᵣ = 0.80 (5% EtOAc-hexanes); IR (KBr) v 3040, 2921, 2852, 1597, 1453, 1287, 1243, 1087, 1011, 753 cm⁻¹; 

¹H NMR (500 MHz, CDCl₃) δ 7.57-7.55 (m, 2H), 7.27-7.23 (m, 4H), 7.02-6.98 (m, 4H), 6.88-6.86 (m, 2H), 4.76 (s, 4H), 4.76 (s, 4H), 4.55 (s, 4H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 155.66, 128.31, 128.13, 127.75, 120.87, 111.32, 67.73 (CH₂), 67.39 (CH₂) ppm; Anal. Calcd for C₁₉H₁₉O₃; C, 76.57; H, 6.43; Found: C, 76.56, H, 6.39.

*(E/Z)-6,9-Dihydro-15H,17H-dibenzo[b,g][1,9,5]dioxathiacyclotridecine 31:*

Following general procedure described above the reaction of 1-(allyloxy)-2-([2-(allyloxy)benzyl]sulfanyl)methyl)benzene 25 (160 mg, 0.4 mmol) with Grubbs catalyst A (15 mg, 10 mol%) in dry DCM (50 mL) at 40 °C for 13 h resulted in (E/Z)-6,9-dihydro-15H,17H-dibenzo[b,g][1,9,5]dioxathiacyclotridecine 31 in the ratio of 57:43 after purification by CC. Colorless solid, mp 93-95 °C; Yield = 111 mg (72%); Rᵣ = 0.74 (5% EtOAc-hexanes); IR (KBr) v 3021, 2927, 2857, 1600, 1487, 1231, 749 cm⁻¹; 

¹H NMR (300 MHz, CDCl₃) δ 7.36-7.15 (m, 4H), 6.98-6.80 (m, 4H), 6.24-6.18 (m, 1H), 6.08-6.06 (m, 1H), 4.67-4.62 (d, 2H), 4.54-4.52 (m, 2H), 3.77 (s, 2H), 3.74 (s, 2H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 156.86 (C), 156.29 (C), 130.91 (CH), 130.69 (CH), 130.41 (CH), 129.34 (C), 128.98 (C), 128.01 (CH), 122.35 (CH), 121.66 (CH), 117.89 (CH), 114.39 (CH), 71.36 (CH₂), 64.60 (CH₂), 31.63 (CH₂), 30.61 (CH₂) ppm; Anal. Calcd for C₁₈H₁₈SO₂; C, 72.45; H, 6.08; Found: C, 72.92, H, 6.38.
6,7,8,9,16,17-Hexahydro-15H-dibenzog,l][1,6]dioxacyclotridecine 32:

To a solution of 6,9,16,17-tetrahydro-15H-dibenzog,l][1,6]dioxacyclotridecine 26 (30 mg, 0.09 mmol) in methanol (5 mL) Pd/C (4 mg, 10 mol%) was added and allowed the reaction mixture to stir in H₂ atmosphere for 8 hours. After completion of the reaction (TLC) the reaction mixture was filtered through celite. The filtrate was concentrated by vacuo to obtain 6,7,8,9,16,17-hexahydro-15H-dibenzog,l][1,6]dioxacyclotridecine 32 after purification by CC on silica gel (100-200 mesh) with hexane/EtOAc (7:3) as the eluent. Colorless solid, mp 134-136 °C; Yield = 21 mg (86%); Rf = 0.67 (20% EtOAc/hexanes); IR (KBr) ν 3024, 2927, 2865, 1494, 1456, 1375, 1291, 1283, 1215, 1184, 1087, 1018, 799, 743 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.23-7.07 (m, 4H), 6.88-6.73 (m, 4H), 3.99 (d, 4H), 2.63 (t, J = 16 Hz, 4H), 1.95 (br d, 4H), 1.55 (s, 1H), 1.33 (s, 1H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 156.80, 131.32, 131.15, 129.80, 126.73, 120.21, 111.17, 111.05, 67.51 (OCH₃), 67.28 (OCH₂), 30.09 (2 × CH₂), 26.45 (CH₂), 26.25 ppm; GC MS 282 (36%, M⁺), 256 (29%), 206 (430%), 191 (100%), 163 (17%), 147 (33%), 121 (10%), 91 (23%), 77 (12%); Anal. Calcd. for C₁₉H₂₂O₂; C, 80.82; H, 7.85; Found: C, 80.79, H, 7.84.

Representative procedure for reduction of double bond by Wilkinson catalyst:

6,7,8,9-Tetrahydro-15H,17H-dibenzob,g][1,9,5]dioxathiacyclotridecine 34:

A solution of 6,9-dihydro-15H,17H-dibenzob,g][1,9,5]dioxathiacyclotridecine 31 (50 mg, 0.4 mmol) in a mixture of dry benzene and methanol (15 mL 1:1) was stirred in an atmosphere of hydrogen at rt for 24 h. with tris (triphenylphosphine)rhodium(I) chloride (7 mg, 12 mol%) catalyst. After completion of the reaction (TLC) the solvent was removed by vacuo. The residue was purified by silica gel CC and eluting with hexanes/ethyl acetate (1:1) to provide 6,7,8,9-tetrahydro-15H,17H-dibenzob,g][1,9,5]dioxathiacyclotridecine 34. Colorless solid, mp 71-73 °C; Yield = 37 mg (75%); Rf = 0.86 (5% EtOAc-hexanes); IR (KBr) ν 2912, 2833, 1610, 1510, 1244, 1174, 1035, 833 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.32 (d, J = 8 Hz, 2H), 7.25 (t, J = 6.4 Hz, 2H), 6.98 (t, J = 8.2 Hz, 4H), 4.18 (s, 4H), 2.13 (s, 4H), 2.13 (s, 4H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 157.11, 130.50, 129.45, 127.98, 121.23.
113.84, 69.54, 31.53, 26.53 ppm; GC MS 302 (21%, M'), 280 (19%), 280 (19%), 259 (13%), 194 (100%), 185 (9%), 107 (76%), 78 (11%), 39 (14%); Anal. Calcd. for C_{18}H_{20}O_{2}; C, 71.97; H, 6.71; Found: C, 71.96, H, 6.73.

6,7,8,9,16,17-Hexahydro-15H-dibenzo[b,g][1,9,5]dioxazacyclotridecine-16-carbaldehyde 33:

Following general procedure described above, the reduction of 6,9,16,17-tetrahydro-15H-dibenzo[b,g][1,9,5]dioxazacyclotridecine-16-carbaldehyde 29 (80 mg, 0.1 mmol) with tris (triphenyl phosphine)rhodium(I) chloride (5 mg, 12 mol%) in dry benzene and methanol (10 mL 1:1) in an atmosphere of hydrogen at rt for 10 h resulted 6,7,8,9,16,17-hexahydro-15H-dibenzo[b,g][1,9,5]dioxazacyclotridecine-16-carbaldehyde 33 after purification by CC. Colorless solid, mp 108-110 °C; Yield = 45 mg (57%); R_f = 0.70 (5% EtOAc-hexanes); IR (KBr) ν 2979, 1637, 1608, 1349, 1157, 1018, 842, 744 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 8.39 (s, 1H), 7.67 (d, J = 7.2 Hz, 1H), 7.36-7.24 (m, 3H), 7.04 (d, J = 7.2 Hz, 1H), 7.0-6.92 (m, 3H), 4.68 (s, 2H), 4.53 (s, 2H), 4.22 (t, J = 4.8 Hz, 2H), 4.15 (t, J = 5.2 Hz, 2H), 2.18(q, 2H), 2.11 (q, 2H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ 163.49, 157.49, 157.34, 133.07, 129.73, 129.38, 129.04, 127.39, 126.37, 121.94, 120.92, 115.00, 111.80, 70.33, 68.91, 45.68, 41.37, 26.90, 26.19 ppm; GC MS 312 (53%, M'), 302 (16%), 271 (13%), 228 (100%), 148 (51%), 135 (36%), 107 (81%), 91 (76%), 77 (24%), 39 (43%); Anal. Calcd. for C\(_{19}\)H\(_{21}\)N\(_2\)O\(_3\); C, 73.29; H, 6.80; N, 4.50; Found: C, 72.92, H, 6.38, N, 4.53.

16-Methyl-6,7,8,9,16,17-hexahydro-15H-dibenzo[b,g][1,9,5]dioxazacyclotridecine 50:

To a cold (0 °C), magnetically stirred solution of the 6,7,8,9,16,17-hexahydro-15H-dibenzo[b,g][1,9,5]dioxazacyclotridecine-16-carbaldehyde 33 (30 mg, 0.09 mmol) in dry THF (5 mL) LiAlH\(_4\) (18 mg 0.01 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 1 h. and allowed to warm up to rt a period of 30 min. Ethyl acetate (1 mL) was carefully introduced to consume the excess reagent and the reaction was quenched with ice-cold water (5 mL). The solution was filtered through a sintered funnel and the residue thoroughly washed with ether (3 x 10 mL). The ether layer was
separated, washed with brine and dried over anhydrous Na₂SO₄. The solvent was evaporated and the residue was purified on a silica gel (100-200 mesh) CC using EtOAc/hexanes (5:95) as eluent to furnish the 6,7,8,9,16,17-hexahydro-15H-dibenz[o][1,9,5]dioxaza cyclotridecine-16-carbaldehyde 50. Colorless liquid, Yield = 26 mg (93%); Rf = 0.82 (5% EtOAc-hexanes); IR (KBr) ν 2975, 2866, 1604, 1507, 1460, 1237, 1032, 771 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.26-7.17 (m, 4H), 6.96-6.88 (m, 4H), 4.21 (br s, 4H), 3.82-3.66 (m, 4H), 2.07-2.04 (m, 2H), 2.00 (s, 3H), 1.67-1.63 (m, 2H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 158.77 (C), 132.10 (CH), 129.15 (C), 128.85 (CH), 121.12 (CH), 116.33 (CH), 71.07 (CH₂), 59.60 (CH₂), 39.85 (CH₃), 27.18 (CH₂) ppm; HRMS: Calcd. for C₁₉H₂₃NO₂: 297.40; Found 298.18.

3.10 References


18 a) Rathesh Kumar, P. M. Phil., dissertation submitted to the Pondicherry University, Pondicherry, 2005.