CHAPTER 3

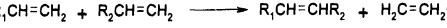
SYNTHESIS AND STEREOCHEMISTRY OF MANZAMINE FRAGMENTS *VIA* OLEFIN METATHESIS REACTION

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,[1] 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.

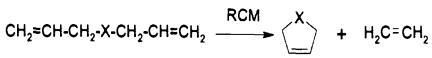
Scheme 3.1

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



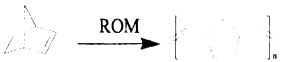
Scheme 3.2

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).



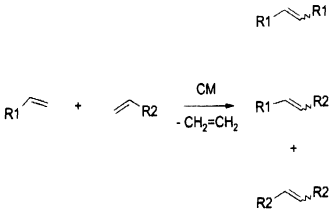
Scheme 3.3

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).



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.

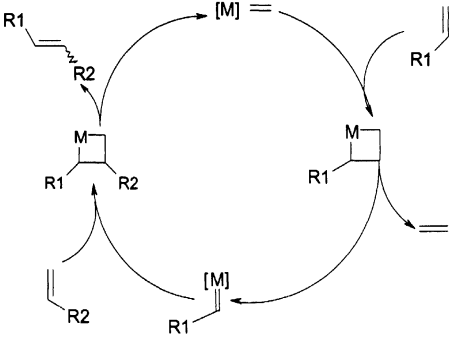


Scheme 3.5

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.



Scheme 3.6

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.

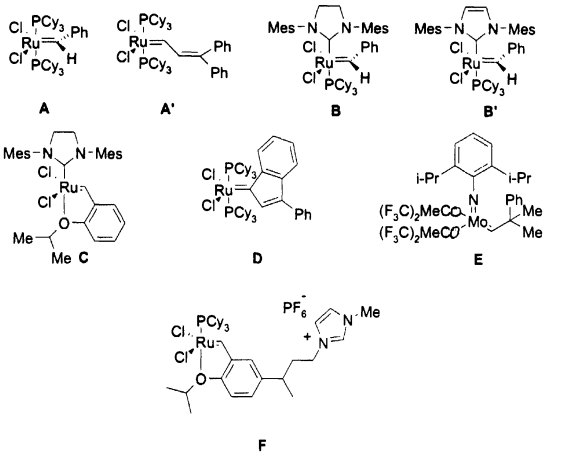


Fig. 3.1

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).

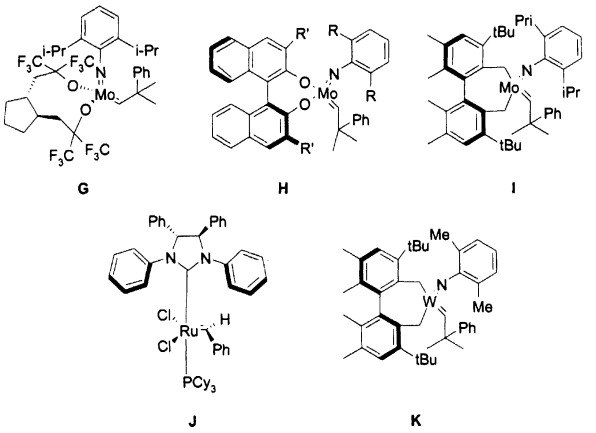


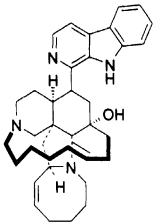
Fig. 3.2

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.

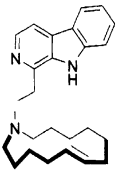
In the earlier two chapters, we have described our studies on the synthesis and stereochemistry of saturated nitrogen heterocycles. Continuing this interest, we desired to construct nitrogen containing 13-member heterocyclic rings as they form part

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.

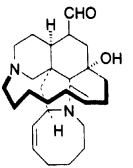
The 13-membered cabocyclic and heterocyclic ring structures are expected to exhibit unique properties different from small and medium ring structures both in terms of conformation and reactivity.[5] Nature selected some molecules with 13-membred heterocyclic rings to impart unique properties. Most famous of the natural products with 13-member rings are manzamine group of alkaloids, eg., **1** and **2** (Fig. 3.3).[6] 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.[7] In addition to manzamines, few more alkaloids from marine sponges like ircinal **3**,[8] madangamine **4**,[9] and motuporamine **5** [10] incorporate 13-membred nitrogen heterocyclic rings. Epilachnene **6**, a 13-membered aza-heterocyclic lactone is a chemical defense agent produced by Mexican beetle.[11]



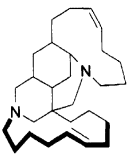
1
Manzamine A



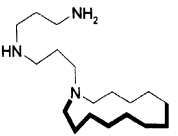
2
Manzamine C



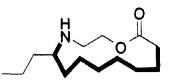
3
Ircinal A



4
Madangamine C



5
Moturopamine A



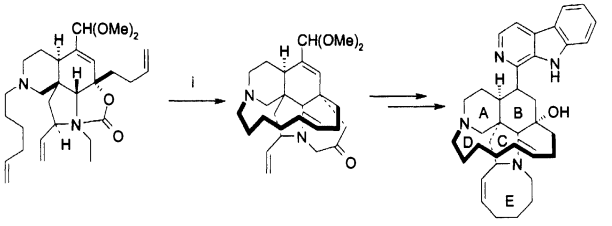
6
Epilachnene

Fig. 3.3

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).[12]

Scheme 3.7

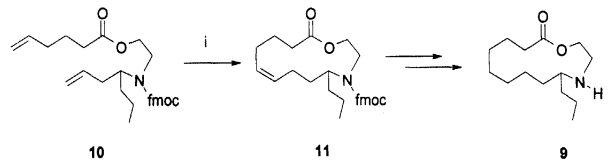


7 8 1

Reagents and conditions: i) Grubbs 1st gen. catalyst **A** (10 mol%), DCM, reflux, 5 h, 67%.

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).[13] Therefore, it appears that apart from the heteroatom present in the chain, stereochemistry of the cyclic olefin depends on the ring size.

Scheme 3.8



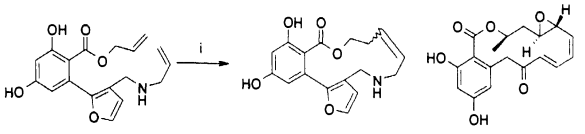
10 11 9

Reagents and conditions: i) Grubbs 1st gen catalyst **A** (10 mol%), DCM, reflux, 20 h, 88%.

In 2006, McDonald and coworkers reported synthesis of the resorcinylic 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).[14]

Scheme 3.9

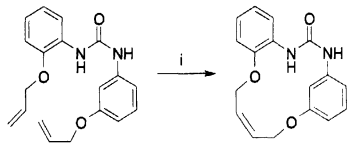


13 **14** **12**

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).[15]

Scheme 3.10

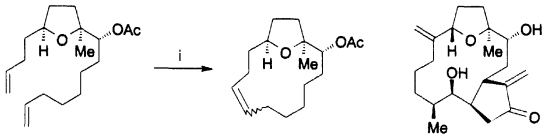


8 **9**

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.[16]

Scheme 3.11



18 **19** **17**

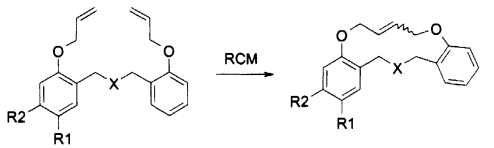
Reagents and conditions: i) Grubbs 1st generation catalyst (5 mol%), DCM, rt, 36 h, 67%

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),[17] 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 a vie* stereochemistry of the newly generated double bond, even though it is one of the most explored reactions from mechanistic and synthetic points of view.

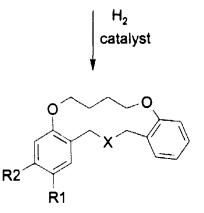
In this section, we describe our studies on the RCM reaction on dienes **20-25** to form 13-member cyclic olefins **26-31** and further reduction of the double bond in the newly formed products towards a novel synthesis of the 13-member crown ethers **32-34** (Scheme 3.12).

Scheme 3.12



20-25 **26-31**

20, **26**, **32**: R1 = R2 = H, X = CH_2
21, **27**: R1 = Cl, R2 = H, X = CH_2
22, **28**: R1 = Cl, R2 = Me, X = CH_2
23, **29**, **33**: R1 = R2 = H, X = NCHO
24, **30**: R1 = R2 = H, X = O
25, **31**, **34**: R1 = R2 = S



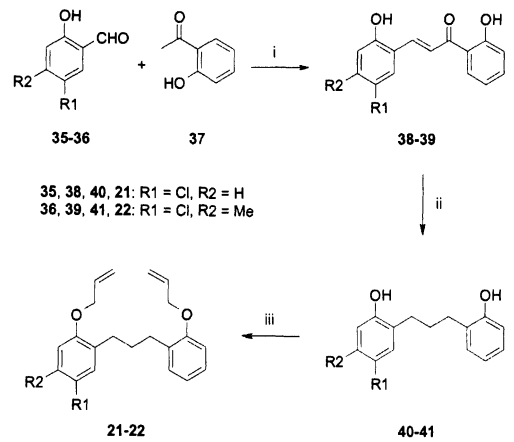
32-34

3.5.1 Synthesis of substrates required for RCM

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

The Claisen-Schmidt condensation between 2-hyroxyacetophenone **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).

Scheme 3.13

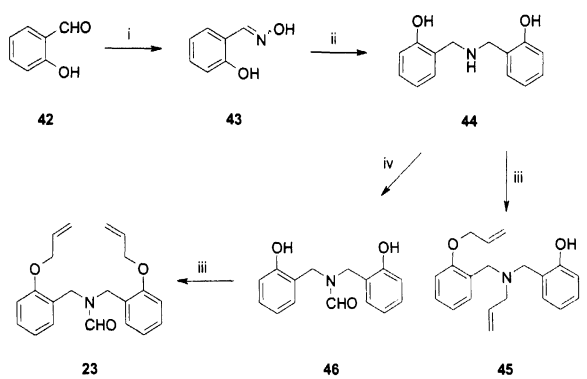


Reagents and conditions: i) 60% aq KOH, 0 °C → rt, 46 h, 45-48%; ii) Raney nickel, i-PrOH, reflux, 16 h, 23-27%; iii) Allyl bromide, NaH, DMF, 0 °C → rt, 75-93%.

The spectral and analytical data of **38** and **39** matched with the parent unsubstituted chalcone derivative available from the previous studies in our laboratory.[18] 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.[19] 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_2CH=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-15*H*-dibenzo[b,g][1,9,5]dioxazacyclotridecine-16-carbaldehyde

Scheme 3.14



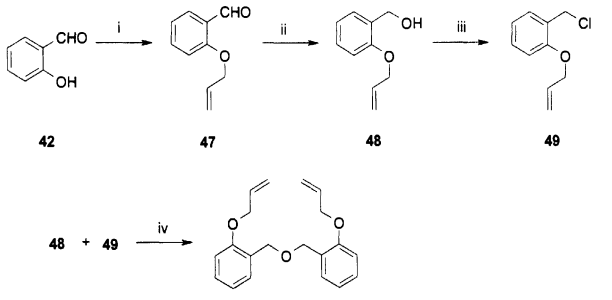
Reagents and conditions: i) $NH_2OH.HCl$, CH_3COONH_4, EtOH, 2 h, 87%; ii) $HCOONH_4$, Pd/C (10%), MeOH, rt, 16 h; iii) allyl bromide, NaH, DMF, 0 °C → rt, 12 h, 79%; iv) HCOOEt, HCOOH, DMF, 0 °C → rt, 10 h, 52%.

Known oxime **43** was prepared by the reaction of salicylaldehyde **42** and hydroxylamine hydrochloride in ethanol.[20] The oxime **43** was treated with $HCOONH_4$/Pd-C to provide secondary amine **44** (Scheme 3.14).[21] Attempted *bis*-allylation of **44** with allyl bromide using K_2CO_3 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.[22] 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 ^1H NMR spectra. The IR spectrum did not show a band at about ν 3320 cm^{-1} indicating the both the phenolic

hydroxy groups were converted into their allyl ethers. The ^{1}H NMR spectrum showed multiplets located between δ 5.8-5.9 and 5.1-5.4 ppm were accounted for olefinic hydrogens; aromatic hydrogens provided signals in region of δ 7.1-6.8 ppm. A sharp signal at δ 8.22 ppm was for –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

Scheme 3.15



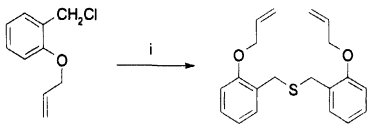
Reagents and conditions: i) Allyl bromide, NaH, DMF, 0 °C → rt, 94%; ii) $NaBH_4$, MeOH, 0 °C → rt, 2h, 92%; iii) $SOCl_2$, reflux, 30 min. 86%; iv) NaH, dry DMF, 12 h, °0 C → rt. 90%.

The allyl ether of 2-hydroxybenzaldehyde **47** was prepared from 2-hydroxubenzaldehyde **42** by reaction with allyl bromide, NaH in DMF (Scheme 3.15).[19] Subsequently, **47** was reduced with $NaBH_4$ 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 -OCH_2 group, δ 6.07-5.97 ppm for –$OCH_2CH{=}CH_2$ group and δ 5.75-5.83 ppm for –$OCH_2CH{=}CH_2$ groups. The aromatic protons appeared in the region between δ 7.4-6.8 ppm. The ^{13}C NMR spectrum showed 10 lines out of which those at δ 67.27 and 68.61 ppm were diagnostic for two types of -OCH_2 carbons.

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

Scheme 3.16



49 **25**

Reactions and conditions: i) Na_2S, 70%, NaOH, EtOH, 8 h, 100 °C, 71% or 3-MPA, 50% EtOH, 6.5 h, 36%.

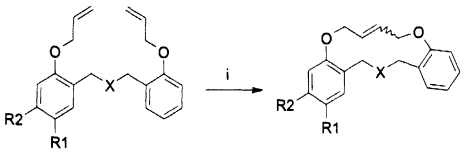
Synthesis of the sulfur incorporated *bis*-allyl ether, 1-(allyloxy)-2-({[2-(allyloxy)benzyl]sulfanyl}methyl)benzene **25** was achieved by the reaction of benzyl chloride **49** with Na_2S or 3-mercapto propionic acid (3MPA, Scheme 3.16). While the reaction with Na_2S under basic conditions[23] provided the thio-ether **25** in 71% yield, the reaction with 3-MPA, as a sulfur donor,[24] the yield was only 36%. The ^1H NMR spectrum displayed a broad singlet at δ 4.52 ppm for -OCH_2 and a singlet at δ 3.73 ppm for –SCH_2 groups. The ^{13}C NMR spectrum along with DEPT and HMBC allowed assignment of peaks at δ 30.43 ppm for -SCH_2 and at δ 68.69 ppm for -OCH_2 carbons respectively. The ^{13}C NMR spectrum revealed C_2 symmetric nature of the molecule by exhibiting ten signals.

3.6 RCM Reaction

Earlier in our laboratory,[18a] 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).

Scheme 3.17



20-25 **26-31**

20, **26**: R1 = R2 = H, X = CH_2; **21**, **27**: R1 = Cl, R2 = H, X = CH_2
22, **28**, R1 = Cl, R2 = CH_3, X = CH_2; **23**, **29**: R1 = R2 = H, X = N-CHO
24, **30**: R1 = R2 = H, X = O; **25**, **31**: R1 = R2 = H, X = S

Reagents and conditions: i) Grubbs catalyst A 10 mol%, dry DCM, reflux, 14-24 h, 63-73%

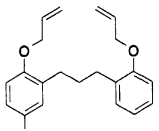
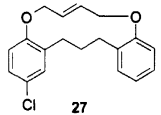
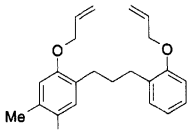
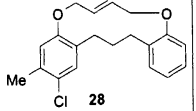
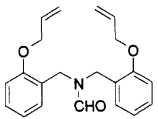
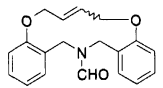
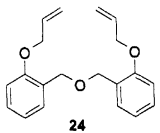
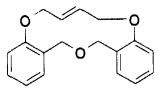
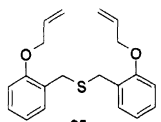
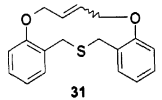
The cyclic olefin **26** was characterized on the basis of spectral (^{1}H, ^{13}C, DEPT NMR and MS spectra) and analytical data. The C_2 symmetric nature of **26** was evident from its ^{1}H NMR spectrum, which displayed characteristic singlets at δ 4.54 (OCH_2) and 6.05 ppm (C=CH). The ^{13}C NMR spectrum showed 10 signals with diagnostic peaks located at δ 29.8, 30.4, 67.8 ppm for the methylenes and δ 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 up field at about δ 4.6 ppm as singlets whereas for the *Z* isomer they appear relatively downfield at δ 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 δ 69.0 ppm, whereas in *Z*-isomer it appears up field at about δ **64** ppm. For the cyclic olefin **26**, the OCH_2 hydrogens appeared at δ 4.54 ppm as singlet in the ^{1}H NMR spectrum and at δ 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 δ 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-15*H*-dibenzo[*b,g*][1,9,5]dioxazacyclotridecine-16-carbaldehydes **29** in 70% yield in the ratio of 29:71 (Scheme 3.17, entry 3, Table 3.1). Both ^1H 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 δ 5.9 ppm due to terminal olefinic protons, presence of multiplets at δ 6.2-6.24 and δ 5.8-5 9 ppm indicated cyclization. The ^1H 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 δ 37.5 and 43.0 ppm were assigned to N-CH_2 of the major *Z* isomer. Signals at δ 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-15*H*,17*H*-dibenzo[*b,g*][1,5,9]trioxacyclotridecine **30** in 69% yield exclusively (Scheme 3.17, entry 24, Table 3.1). The ^1H NMR spectrum of the cyclic olefin **30** showed absence of resonances at δ 6.05-5.99 ppm due to terminal olefinic protons. Instead, it exhibited a doublet at δ 6.09-6.08 ppm for the olefinic hydrogen. The ^{13}C NMR spectrum exhibited resonances at δ 67.39, 67.73 ppm for two types of OCH_2 carbons. Presence of OCH_2 signal at δ 67.73 ppm indicated formation of *E*-isomer exclusively.

Entry	Substrate	Product (Yield %)	^{13}C NMR spectral values[a] *E*	^{13}C NMR spectral values[a] *Z*	*E*/*Z* ratio
	 **21**	 **27** 73	68.18	----	100:0
	 **22**	 **28** 71	68.27	----	100:0
	 **23**	 **29** 70	70.83 69.65	61.90	29:71
	 **24**	 **30** 69	67.73	----	100:0
	 **25**	 **31** 72	71:36	64.60	57:43

[a] Selected ^{13}C NMR values of allylic OCH_2 carbons in ppm.

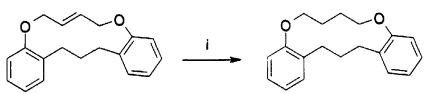
Table 3.1 RCM reaction of *bis*-allylethers to provide *E*/*Z* isomers of cyclic olefins.

Finally, the *bis*-allyl ether **25** was subjected to RCM reaction to provide (*E*/*Z*)6,9-dihydro-15*H*,17*H*-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 δ 6.2 to 6.0 ppm for terminal olefinic hydrogens. Instead, it showed two olefinic proton triplets at δ 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 δ 4.65 and 4.53 ppm. Two singlets for SCH_2 appeared at δ 3.80 and δ 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 δ 71.0 and 64.0 ppm showed *E* and *Z* olefinc 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-15*H*-dibenzo[*g*,*l*][1,6]dioxacyclotridecine **32** in 86% yield (Scheme 3.18).

Scheme 3.18



26 **32**

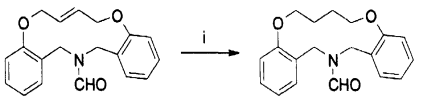
Reagents and conditions: i) H_2, Pd/C (10%), EtOH, 8h, 86%

The ^{1}H NMR spectrum of **32** showed did not show signal for olefin at δ 6.0 ppm, which indicates that the reduction of the olefin **32** has taken place. New peaks at δ 1.92 ppm indicate product formation, OCH_2 peaks appeared as broad doublet at δ 3.99

ppm and aromatic ring attached CH_2 peaks appeared as triplet at δ 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

Scheme 3.19



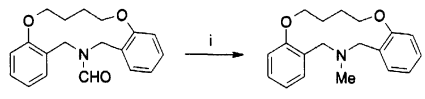
29 **33**

Reagents and conditions: i) Wilkinson catalyst (12%), C_6H_6: MeOH, 10 h, 56%

The reduction of cyclic olefin **29** provided 6,7,8,9,16,17-hexahydro-15*H*-dibenzo[b,g][1,9,5]dioxazacyclotridecine-16-carbaldehyde **33** (Scheme 3.19)[26]. Besides absence of resonances for olefinic protons in ^1H NMR spectrum at δ 6.31-6.24 ppm and δ 5.90-5.88 ppm, presence of two quartets at δ 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.

Scheme 3.20



29 **50**

Reagents and conditions: i) LAH, THF, -78 °C-rt, 45 min., 93%

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 H_2/Wilkinson catalyst resulted 6,7,8,9-tetrahydro-15*H*,17*H*dibenzo[b,g][1,9,5]dioxathiacyclotridecine **34** (Scheme 3.21).

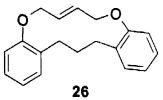
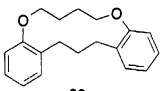
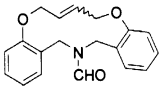
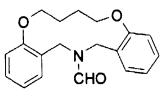
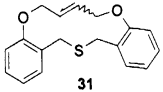
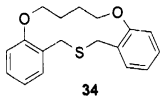
Scheme 3.21

31 **34**

Reagents and conditions: i) Wilkinson catalyst (12%), C_6H_6: MeOH, 24 h, 75%

Unlike cyclic olefin **31**, the ^{1}H NMR spectrum of **34** was very clear. The ^{1}H NMR spectrum was clean exhibiting three singlets in the aliphatic region of equal intensity. Interestingly OCH_2 hydrogen did not appear as triplet with of customary coupling of about 7 Hz. This aspect of coupling is common to OCH_2 hydrogen present as a part of medium sized rings. A nine-line ^{13}C 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.

Entry	Substrate	Product	Yield %
1	 **26**	 **32**	86
2	 **29**	 **33**	57
3	 **31**	 **34**	75

3.8 Summary

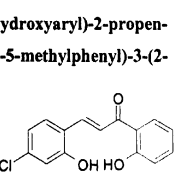
In summary, we have studied the influence of remote heteroatom during Grubbs RCM to form 13-membered cyclic ether with at least two oxygen atoms. This study shows that the heteroatom has profound influence on the olefin forming step possibly complexing with ruthenium. While *E* olefin is formed as a 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:

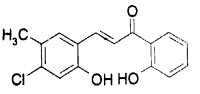
For general details about experimental conditions see Chapter-1. The 2-hydroxybenzaldehydes **35** and **36** required for this study were made *via* Reimer-Tiemann reaction according to literature procedure,[27] Grubbs catalyst was purchased from Sigma-Aldrich.

Representative procedure for the synthesis of (*E*)-1,3-di(2-hydroxyaryl)-2-propen-1-ones (chalcones): (*E*)-1-(4-Chloro-2-hydroxy-5-methylphenyl)-3-(2-hydroxyphenyl)-2-propen-1-one 38:



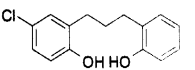
To a solution of 2-hydroxyacetophenone **37** (1.30 g, 9.5 mmol), 5-chloro-2-hydroxybenzaldehyde **35** (1.50 g, 9.5 mmol) in 10 mL EtOH. 60% aqueous KOH (11.2 g in 18 mL water) solution was added drop-wise at 0 °C for 30 min. The reaction mixture was stirred at rt for 30 h. by which time the reaction was complete (TLC). The reaction mixture was neutralized with 2*N* 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. Na_2SO_4, 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;[28] Yield = 1.62 g (62%); R_f = 0.23 (30% EtOAc- hexanes); IR (KBr) ν 3441, 3028, 2861, 1644, 1594, 1243, 749 cm^{-1}; ^1H NMR (60 MHz, CCl_4) 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 $C_{15}H_{11}ClO_3$; 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:



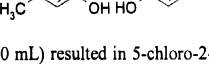
Following the general procedure described above the reaction of 2-hydroxyacetophenone **37** (623 mg, 3.6 mmol) with 4-chloro-2-hydroxy-5-methylbenzaldehyde **36** (500 mg, 3.67) in 20 mL ethanol and 60% aqueous KOH (3.9 g, in 8 mL) resulted 1-(4-chloro-2-hydroxy-5-methylphenyl)-3-(2-hydroxyphenyl)-2-propen-1-one **39** after purification by CC. Yellow color solid, mp 124-126 °C; Yield = 486 mg (46%); R_f = 0.21 (30% EtOAc- hexanes); IR (KBr) ν 3378, 3081, 1650, 1602, 833 cm^{-1}; ^1H NMR (60 MHz, CCl_4) 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 $C_{16}H_{13}ClO_3$; C, 66.56; H, 4.54; Found: C, 66.55, H, 4.48.

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



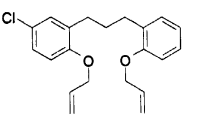
To a solution of 1-(4-chloro-2-hydroxyphenyl)-3-(2-hydroxyphenyl)-2-propen-1-one **38** (600 mg, 3.8 mmol), Raney nickel (6 g) in isopropanol (50 mL) was added and the resulting mixture was refluxed for 16 h.. After completion of the reaction (TLC) Raney nickel was filtered through celite. Solvent from filterate 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 recrystalized from 10% DCM in hexanes. Colorless solid, mp 104-106 °C; Yield = 309 mg (54%); R_f = 0.18 (30% EtOAc/hexanes); IR (KBr) ν 3541, 3441, 2929, 1594, 1444, 1112, 924 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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; ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{15}H_{15}ClO_2$; C, 68.57; H, 5.75; Found: C, 68.59, H, 5.76.

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



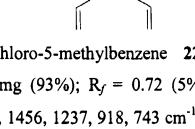
Following the general procedure described above the reaction of 1-(4-chloro-2-hydroxy-5-methylphenyl)-3-(2-hydroxyphenyl)-2-propen-1-one **39** (400 mg, 1.3 mmol) Raney nickel (4 g) in isopropanol (40 mL) resulted in 5-chloro-2-[3-(2-hydroxyphenyl)propyl]-4-methylphenol **41** after purification by CC. Colorless solid, mp 110-112 °C; Yield = 260 mg (68%); R_f = 0.16 (30% EtOAc/hexanes); IR (KBr) ν 3347, 3266, 2944, 1219, 748 cm^{-1}; ^1H NMR (60 MHz, CCl_4) 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 $C_{16}H_{17}ClO_2$; C, 69.44; H, 6.19; Found: C, 69.03, H, 5.91.

Representative procedure for the synthesis of 1-allyloxy(2-(3-2(allylloxyaryl) propyl) phenols: 1-(Allyloxy)-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 Na_2SO_4 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%); R_f = 0.76 (5% EtOAc/hexanes); IR (KBr) ν 2925, 2825, 1594, 1456, 1241, 913, 743 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 7.11-6.63 (m, 7H), 6.30-5.97 (m, 2H), 5.34 (m, 4H), 4.4 (d, J = 3Hz, 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 $C_{21}H_{23}ClO_2$; C, 73.57; H, 6.76; Found: C, 73.08, H, 6.51.

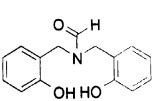
1-(Allyloxy)-2-{3-[2-(allyloxy)phenyl]propyl}-5-chloro-4-methylbenzene 22:



Following the general procedure, the reaction of 4-chloro-2-[3-(2-hydroxyphenyl)propyl]-5-methylphenol **41** (400 mg, 1.4 mmol) ally 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%); R_f = 0.72 (5% EtOAc-hexanes); IR (KBr) ν 3071, 3028, 2927, 2852, 1487, 1456, 1237, 918, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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, OCH_2), 2.73-2.30 (m, 4H), 2.22 (s, 3H), 1.97-1.82 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 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,

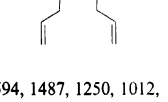
68.40, 31.87, 30.62, 22.64, 20.02 ppm; GC MS 357 (62%, M^+), 344 (57%), 282 (100%), 198 (12%), 164 (25%), 117 (10%), 77 (28%); Anal. Calcd for $C_{22}H_{25}ClO_2$; C, 74.04; H, 7.06; Found: C, 73.86, H, 6.74.

***N,N*-Di(2-hydroxybenzyl)formamide[29] 46:**



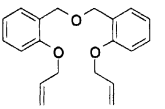
To a solution of 2-{[(2-hydroxybenzyl)amino] methyl}phenol **44** (1 g, 4.3 mmol) in 5 mL 1,4-dioxane, ethyl formate (1.61 g, 21.8 mmol) in 10 mL DMF and formic acid (3 mL) and the mixture is refluxed for 8 h. After completion of the reaction (TLC) reaction mixture was cooled to rt and the organic volatiles 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 × 50 mL). The organic layer was washed with water (2 × 20 mL) followed by brine solution (15 mL) and dried over by anhydrous Na_2SO_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, 8H), 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:**



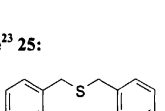
Following the general procedure the reaction of *N,N*-di(2-hydroxybenzyl)acetamide **46** (1g, 3.8 mmol) (20 mL) ally bromide (1 g, 8.5 mmol) and NaH (205 mg, 8.5 mmol) in dry DMF resulted *N,N*-di[2-(allyloxy)benzyl]acetamide **23** after purification by CC. Colorless liquid, Yield = 1.07 mg (79%); 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 Na_2SO_4 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, $CDCl_3$) 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; ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{20}H_{22}O_3$; C, 77.39; H, 7.14; Found: C, 77.03, H, 6.97.

1-(Allyloxy)-2-({[2-(allyloxy)benzyl]sulfanyl}methyl)benzene[23] 25:

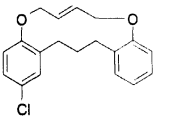


To a solution of 1-(allyloxy)-2-(chloromethyl)benzene **49** (300 mg, 1.6 mmol) in 12 mL ethanol, sodium sulfide (638 mg, 8.2mmol) was added and the reaction mixture was heated reflux for 10 min. Subsequently aqueous 70% NaOH (5 mL) was added drop-wise and reaction was continued for 10h. After completion of the reaction (TLC) the reaction mixture was cooled to rt and diluted with ice-cold water (20 mL), neutralized with 5*N* 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 Na_2SO_4 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) ν 3021, 2927, 1600, 1494, 1456, 1256, 1224, 1011, 749, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 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, 4H), 3.73 (s, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 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%, M^+), 313 (100%), 281 (22%), 264 (38%), 180 (11%), 151 (22%), 138 (37%), 91 (16%), 77 (10%). Anal. Calcd for $C_{20}H_{22}O_2S$; C, 73.59; H, 6.79; Found: C, 73.16, H, 6.21.

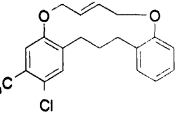
General procedure for ring closing metathesis (RCM) reaction: (*E*)-6,9,16,17-Tetrahydro-15*H*-dibenzo[*g,l*] [1,6]dioxacyclotridecine

(*E*)-2-Chloro-6,9,16,17-tetrahydro-15*H*-dibenzo[*g,l*][1,6]dioxacyclotridecine 27:



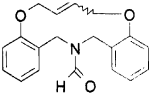
To a solution of bis-allyl product 1-(allyloxy)-2-{3-[2-(allyloxy)phenyl]propyl}-4-chlorobenzene **21** (200 mg, 0.5 mmol) in dry DCM (40 mL) a solution of bis(tricyclohexylphosphine)-benzylideneruthenium dichloride (1st generation Grubbs catalyst **A**, 21 mg, 10 mol%) in dry DCM (8 mL) was added drop-wise. 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-15*H*-dibenzo[*g,l*][1,6]dioxacyclo-tridecine **27** as a single diasteromer. Colorless solid, mp 121-123 °C; Yield = 133 mg (73%); R_f = 0.80 (5% EtOAc-hexanes); IR (KBr) ν 3048, 2908, 1603, 1443, 758 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ7.05-7.16 (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, $CDCl_3$) δ 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 $C_{19}H_{19}ClO_2$; C, 72.49; H, 6.08; Found: C, 72.50, H, 6.06.

(*E*)-2-Chloro-3-methyl-6,9,16,17-tetrahydro-15*H*-dibenzo[*g,l*][1,6]dioxacyclo Tridecine 28:



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 20h. resulted in (*E*)-2-chloro-3-methyl-6,9,16,17-tetrahydro-15*H*-dibenzo[*g,l*][1,6]dioxacyclotridecine **28** after purification by CC as a colorless solid. MP 108-110 °C; Yield = 116 mg (71%); R_f = 0.76 (5% EtOAc-hexanes); IR (KBr) ν 3021, 2924, 2861, 1597, 1241, 751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 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; ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.90, 129.66, 127.68, 127.37, 126.86, 126.74, 126.00, 120.67, 114.39, 111.76, 109.37, 68.27, 67.82, 30.61, 29.92, 29.10 ppm; Anal. Calcd for $C_{20}H_{21}ClO_2$; C, 73.05; H, 6.44; Found: C, 73.02, H, 6.46.

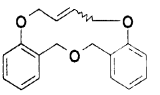
(*E/Z*)-6,9,16,17-Tetrahydro-15*H*-dibenzo[*b,g*][1,9,5]dioxazacyclotridecine-16-carbaldehyde 29:



Following general procedure described above the reaction of *N,N*-di[2-(allyloxy)benzyl]formamide **23** (100 mg, 0.8 mmol) with Grubbs catalyst **A** (12 mg, 10 mol%) in dry DCM (26 mL) at 40 °C for 18 h resulted in (*E/Z*)-6,9,16,17-tetrahydro-15*H*-dibenzo[*b,g*][1,9,5]dioxazacyclotridecine-16-carbaldehyde **29** in the ratio of 29:71 after purification by CC. Colorless solid, mp 133-135 °C; Yield = 66 mg (70%); R_f = 0.66 (5% EtOAc-hexanes); IR (KBr) ν 2930, 1669, 1385, 1303, 1179, 997, 763 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.37 (s, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.35-7.08 (m, 3H), 7.05-6.89 (m 4H), 6.34-6.21 (m, 3H), 5.97-5.81 (m, 1H), 4.70 (d, J = 6Hz, 1H), 4.63 (d, J = 6.6 Hz, 1H), 4.56-4.47 (m, 2H), 4.39 (s, 2H), 4.27 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.32 (CH), 132.24 (CH), 131.70 (C), 131.32 (C), 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 (CH_2), 69.65 (CH_2), 61.90 (CH_2), 44.68 (CH_2),

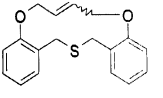
43.00 (CH_2), 38.90 (CH_2), 37.50 (CH_2) ppm; Anal. Calcd. for $C_{19}H_{19}NO_3$; C, 73.77; H, 6.19; N, 4.53; Found: C, 72.82, H, 6.76, N, 4.91.

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



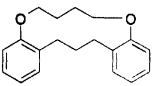
Following general procedure described above the reaction of 1-(allyloxy)-2-({[2-(allyloxy)benzyl]oxy}methyl)benzene **24** (300 mg, 1 mmol) with Grubbs catalyst **A** (26 mg, 10 mol%) in dry DCM (50 mL) at 40 °C for 10 h resulted in (E/Z) 6,9-dihydro-15*H*,17*H*-dibenzo[*b*,*g*][1,5,9]trioxacyclotridecine **30** after purification by CC. Colorless solid, mp 127-129 °C; Yield = 195 mg (69%); R_f = 0.80 (5% EtOAc-hexanes); IR (KBr) ν 3040, 2921, 2852, 1597, 1453, 1287, 1243, 1087, 1011, 753 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 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; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.66, 128.31, 128.13, 127.75, 120.87, 111.32, 67.73 (CH_2), 67.39 (CH_2) ppm; Anal. Calcd for $C_{18}H_{18}O_3$; C, 76.57; H, 6.43; Found: C, 76.56, H, 6.39.

(*E/Z*)-6,9-Dihydro-15*H*,17*H*-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-15*H*,17*H*-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%); R_f = 0.74 (5% EtOAc-hexanes); IR (KBr) ν 2921, 2857, 1600, 1487, 1231, 749 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 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; ^{13}C NMR (75 MHz, $CDCl_3$) 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 (CH_2), 64.60 (CH_2), 31.63 (CH_2), 30.61 (CH_2) ppm; Anal. Calcd for $C_{18}H_{18}SO_2$; C, 72.45; H, 6.08; Found: C, 72.92, H, 6.38.

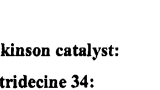
6,7,8,9,16,17-Hexahydro-15*H*-dibenzo[*g,l*][1,6]dioxacyclotridecine 32:



To a solution of 6,9,16,17-tetrahydro-15*H*-dibenzo[*g,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 H_2 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-15*H*-dibenzo[*g,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%); R_f = 0.67 (20% EtOAc/hexanes); IR (KBr) ν 3024, 2927, 2865, 1494, 1456, 1375, 1251, 1087, 1018, 799, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 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; ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.80, 131.32, 131.15, 129.80, 126.73, 120.21, 111.17, 111.05, 67.51 (OCH_2), 67.28 (OCH_2), 30.09 (2 × CH_2), 26.45 (CH_2), 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 $C_{19}H_{22}O_2$; 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-15*H*,17*H*-dibenzo[*b,g*][1,9,5]dioxathiacyclotridecine 34:

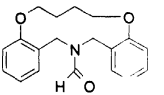


A solution of 6,9-dihydro-15*H*,17*H*-dibenzo[*b,g*][1,9,5] dioxathiacyclotridecine **31** (50 mg, 0.4 mmol) in a mixture of dry benzene and methanol (15 mL 1:1) was stirred in an atmosphere of hydrogen at rt for 24 h. with *tris* (triphenylphosphine)rhodium(I) chloride (7 mg, 12 mol%) catalyst. After 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-15*H*,17*H*-dibenzo[b,g][1,9,5]dioxathiacyclotridecine **34**. Colorless solid, mp 71-73 °C; Yield = 37 mg (75%); R_f = 0.86 (5% EtOAc-hexanes); IR (KBr) ν 2912, 2833, 1610, 1510, 1244, 1174, 1035, 833 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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; ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{18}H_{20}SO_2$; C, 71.97; H, 6.71; Found: C, 71.96, H, 6.73.

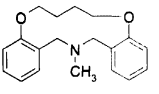
6,7,8,9,16,17-Hexahydro-15*H*-dibenzo[*b,g*][1,9,5]dioxazacyclotridecine-16-carbaldehyde 33:

Following general procedure described above, the reduction of 6,9,16,17-tetrahydro-15*H*-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-15*H*-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}; ^1H 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 $C_{19}H_{21}NO_3$; 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-15*H*-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-15*H*-dibenzo[*b,g*][1,9,5]dioxaza cyclotridecine-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 × 10 mL). The ether layer was



separated, washed with brine and dried over anhydrous Na_2SO_4. 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-15*H*-dibenzo[*b*,*g*][1,9,5]dioxaza cyclotridecine-16-carbaldehyde **50**. Colorless liquid, Yield = 26 mg (93%); R_f = 0.82 (5% EtOAc-hexanes); IR (KBr) ν 2975, 2866, 1604, 1507, 1460, 1237, 1032, 824, 771 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 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; ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.77 (C), 132.10 (CH), 129.15 (C), 128.85 (CH), 121.12 (CH), 116.33 (CH), 71.07 (CH_2), 59.60 (CH_2), 39.85 (CH_3), 27.18 (CH_2) ppm; HRMS: Calcd. for $C_{19}H_{23}NO_2$; 297.40; Found 298.18.

3.10 References

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