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On the stereochemistry of the olefinic double bond in 13-membered heterocyclic rings accessible by ring-closing metathesis reaction

H. Surya Prakash Rao *, Shaik Rafi †, P. Ratish Kumar, C. Guravaiah, Nandurka Muthanna

Department of Chemistry, Pondicherry University, Pondicherry 605 014, India

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ABSTRACT

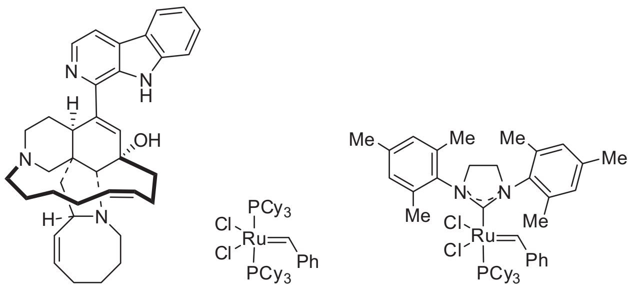
13-Membered heterocyclic ring analogs of the core structure of manzamine alkaloids were synthesized by ring closing metathesis (RCM) reaction. The influence of a remote heteroatom (N, O, S) on *E*/*Z* stereochemistry of the olefinic double bond formed in RCM reaction using Grubbs 1st and 2nd generation ruthenium carbene complexes was evaluated. Studies show that RCM reaction is kinetically controlled and the hetero atoms influence the double bond stereochemistry.

The 13-membered carbocyclic and heterocyclic ring structures are expected to exhibit unique properties different from small and medium ring structures both in terms of conformation and reactivity.[1] Nature selected some molecules with 13-membred heterocyclic rings to impart unique properties for example, manzamine group of alkaloids represented by manzamine A **1** (Fig. 1).[2] Biological studies on manzamines have shown that the 13-membered nitrogen containing heterocyclic ring is crucial for their biological activity.[3]

The ring-closing metathesis reaction (RCM) on dienes and ene ynes with ruthenium carbene complexes like Grubbs 1st (**2**) and 2nd (**3**) generation catalysts (Fig. 1) has emerged in recent years as the most potent tool for the synthesis of cyclic compounds, particularly those with medium and large rings.[4] 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 experimental studies on the RCM reaction to form macrocyclic rings vis a 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. It is to be noted that in the construction of the 13-membered heterocyclic rings as found in manzamine alkaloids mixtures of *E* and *Z* isomers of varying ratios were realized.[5]

In continuation of our earlier studies on synthesis and stereochemistry of nitrogen heterocycles,[6] we wanted to prepare hetero-atom substituted 13-membered rings by RCM reaction. In this regard we set to investigate the influence of a remote hetero-atom on the stereochemistry of the double bond when a 13-membered ring is constructed from the corresponding open-chain dienes when RCM reaction is conducted with Grubbs 1st and 2nd generation catalysts. For this purpose, we conceived of novel 13-membered ring structures (**11–17**) with two oxygen atoms and a strategically placed hetero-atom derivable from the corresponding open chain bis-allyl ethers **4–10** (Scheme 1).

Claisen–Schmidt condensation between 2-hydroxyacetophenone **21** and 2-hydroxybenzaldehydes (salicylaldehydes) **18–20** provided corresponding chalcones **22**–**24** (Scheme 2).[7] Hydrogenative deoxygenation of chalcones **22–24** with Raney nickel furnished corresponding reduced products[8] which on reaction



1 2 3

Figure 1. Structures of manzamine A **1**, Grubbs 1st (**2**), and 2nd (**3**) generation catalysts.

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* Corresponding author. Tel.: +91 413 2654411; fax: +91 413 2655987.
E-mail addresses: hspr.che@pondiuni.edu.in, hspr@yahoo.com (H. Surya Prakash Rao).
† Present address: Cosmic Discoveries, Institute of Life Sciences, University of Hyderabad Campus, Hyderabad 500 042, India.

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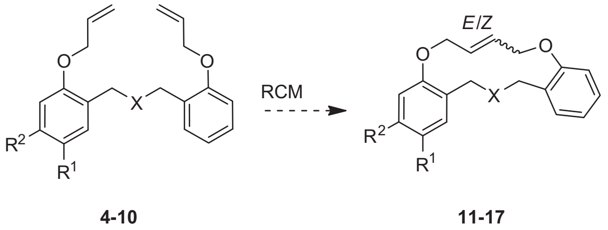
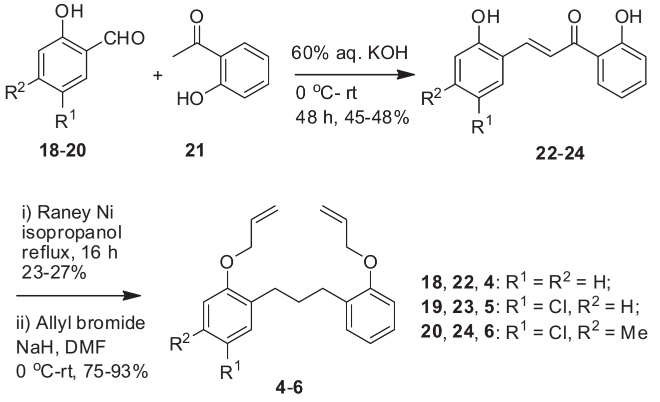


Scheme 1. Synthesis of 13-membered ring structures via RCM reaction.

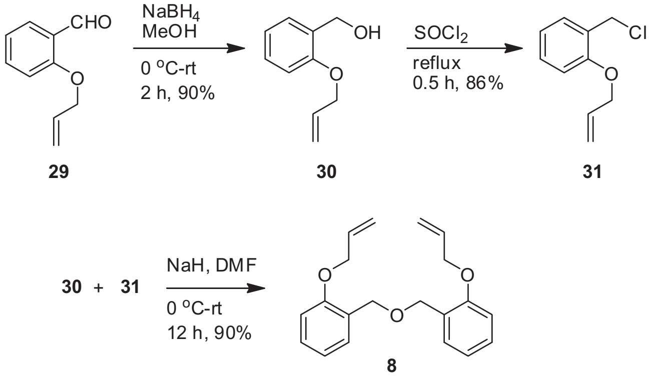


Scheme 2. Synthesis of bis-allyl ether precursors **4–6** for RCM reaction.

with allyl bromide and sodium hydride furnished bis-allyl ethers **4–6**.

The oxime[9] **25** derived from 2-hydroxybenzaldehyde **18** was treated with HCOONH$_4$/Pd–C to provide the secondary amine **26** (Scheme 3).[10] Attempted bis-allylation of **27** furnished undesired N-allylated product **27**. Therefore, the secondary amine was converted into *N*-formyl derivative **28** with ethyl formate.[11] Further reaction of phenolic hydroxy groups with allyl bromide furnished bis-allyl ether **7**.

The allyl protected 2-hydroxybenzaldehyde **29** was reduced with NaBH$_4$ in methanol to provide benzyl alcohol **30** (Scheme 4). This product was treated with thionyl chloride to furnish benzyl chloride **31**. The Williamson reaction between the benzylic alcohol **30** and benzylic chloride **31** in the presence of sodium hydride in DMF furnished **8.**[12]



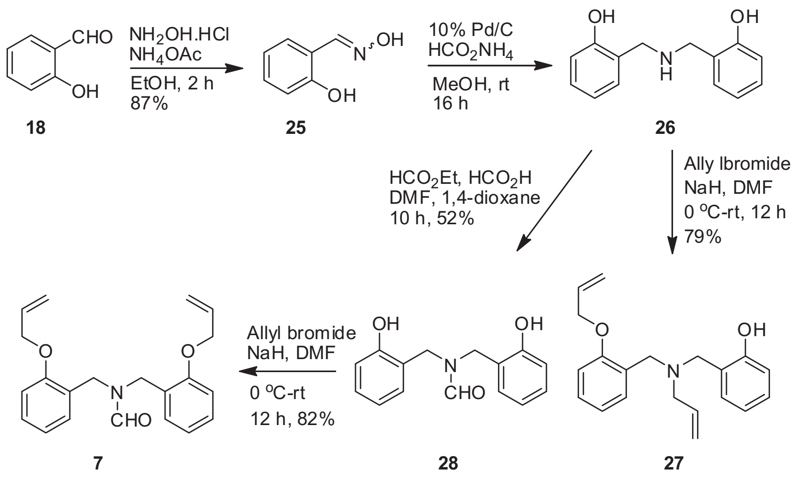
Scheme 4. Synthesis of bis-allyl ether precursor **8**.

The synthesis of sulfur incorporated bis-allyl thio ether **9** was achieved by the reaction of benzyl chloride **31** with Na$_2$S under basic conditions (Scheme 5). Further oxidation of **9** with oxone resulted in sulfone **10**.

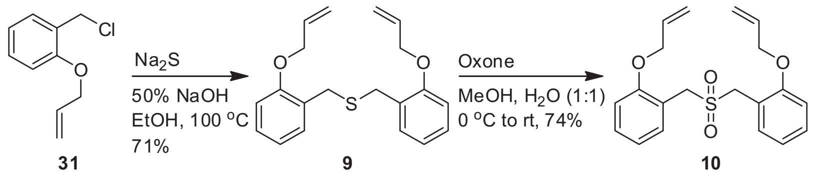
Besides characteristic peaks, the ^{1}H and ^{13}C NMR spectra of allyl ethers/allyl thioethers **4**, **7–10** revealed C$_2$-symmetric nature of the molecules.

The reaction of bis-allyl ether **4** (X = CH$_2$) with 10 mol % of Grubbs 1st generation ruthenium carbene complex in dry dichloromethane reflux for 14 h yielded (*E*)-**11** as a single geometrical isomer in 63% yield (Scheme 6, Table 1, entry 1).

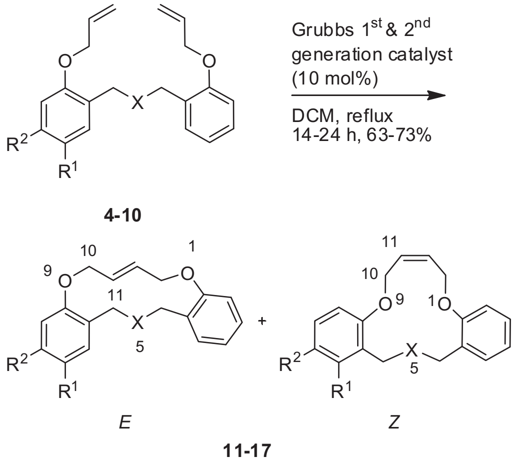
The cyclic olefin (*E*)-**11** was characterized on the basis of spectral (^{1}H, ^{13}C, DEPT NMR, and MS spectra) and analytical data. C$_2$-symmetric nature of (*E*)-**11** was evident from its ^{1}H NMR spectrum, which displayed characteristic singlets at δ 4.54 for C10 and C13 methylenes and at 6.05 ppm for C11 and C12 olefinic hydrogen atoms. The ^{13}C NMR spectrum showed 10 signals with diagnostic peaks located at δ 67.8 for C10 and C13 carbons and 111.7 ppm for the C11 and C12 olefinic carbons. Stereochemistry of the double bond was assigned *E* (*trans*) on the basis of ^{1}H and ^{13}C NMR spectral data. The data reported by Ibrahim and coworkers for crown formazans **32** (Fig. 2) were used to assign stereochemistry to the double bond in **11.**[13] In the ^{1}H NMR spectrum of **32** the OCH$_2$ hydrogens of the *E*-isomer appeared upfield at δ 4.60 ppm as singlet whereas for the *Z* isomer of **32** it appeared downfield at δ 4.77 ppm as doublet (*J* = 3.7 Hz). Similarly in the ^{13}C NMR spectrum, corresponding OCH$_2$ carbon in *E*-isomer appeared downfield



Scheme 3. Synthesis of bis-allyl ether precursor **7** for RCM reaction.



Scheme 5. Synthesis of bis-allyl thioether **9** and sulfone **10**.



4, 11: $R^1 = R^2 = H$, X = CH_2; **5, 12**: R^1 = Cl, R^2 = H, X = CH_2; **6, 13**: R^1 = Cl, R^2 = Me, X = CH_2; **7, 14**: $R_1 = R_2$ = H, X = NCHO; **8, 15**: $R_1 = R_2$ = H, X = O; **9, 16**: $R^1 = R^2$ = H, X = S; **10, 17**: $R^1 = R^2$ = H, X = SO_2

Scheme 6. The RCM reaction on bis-allyl ethers **4**–**10** leading to 13-membered ring formation.

at δ 70.8 ppm, whereas in *Z*-isomer it appeared upfield at δ 62.6 ppm. For the cyclic olefin (*E*)-**11** the OCH_2 hydrogens appeared at δ 4.54 ppm as singlet in the ^1H NMR spectrum and at δ 67.8 ppm for the corresponding carbon in the ^{13}C NMR spectrum indicating *E*-stereochemistry of the double bond.

Generality of the exclusive formation of *E*-isomeric cyclic olefin in the RCM reaction on **4** (X = CH_2) was ascertained by exposing dienes **5** (X = CH_2) and **6** (X = CH_2) to Grubbs 1st generation catalyst and in both the instances only *E*-isomeric cyclic olefins (*E*)-**12** and (*E*)-**13** were obtained (Scheme 6, Table 1, entries 2 and 3). There was no trace of *Z*-isomer. Exclusive arrival of *E*-isomer (*E*)-**11** in RCM reaction prompted us to study the influence of heteroatom on the stereochemistry of the alkene. Accordingly, the bis-allyl ethers **7**–**10** were subjected to RCM reaction and the results are gathered in Table 1. Cyclization of the bis-allyl ether **7** (X = NCHO) provided inseparable *E*/*Z* mixture of **14** in 70% yield in the ratio of 29:71 (Table 1, entry 4). Both ^1H and ^{13}C NMR spectra of **14** displayed two sets of signals for each isomer due to restricted rotation in the formamide moiety. RCM reaction of bis-allyl ether **8** (X = O) provided (*E*)-**15** exclusively (Table 1, entry 5). Next, the sulfur containing allyl ether **8** (X = S) was subjected to RCM reaction to realize the inseparable mixture of *E* and *Z* isomers of **16** in 72% yield in the ratio of 57:43 (Table 1, entry 6). Although there are a few reports that the sulfur atom present in dienes can poison the Grubbs 1st generation catalyst,[14] we did not encounter any difficulty. To establish the stereochemistry of the newly formed double bond in **16** we have independently synthesized the *Z*-isomer (*Z*)-**16** from (*Z*)-1,4-bis(2-(chloromethyl)phenoxy)but-2-ene **33**[15] by treating with Na_2S (Scheme 7). The ^1H and ^{13}C NMR spectral values of (*Z*)-**16** were used to identify this isomer in the mixture obtained from RCM reaction. Finally we subjected sulfone **10** (X = SO_2) to RCM reaction and it provided an inseparable *E* and *Z* isomer mixture of **17** in the ratio of 52:48 in 81% yield (Table 1, entry 7). Diagnostic ^{13}C NMR chemical shift values (δ) of allylic OCH_2 carbons for **11–17** are given in Table 1.

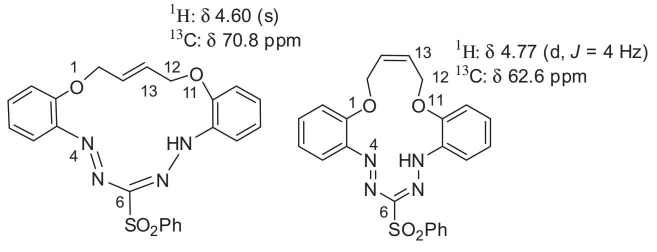
Even though the present work is preliminary to predict the precise influence of a remote heteroatom on the transition states involved in the RCM reaction, it is clear that remote heteroatoms do interact with ruthenium and influence transition state geometries. To evaluate kinetic versus thermodynamic control on the reaction, we repeated the RCM on **4** (X = CH_2), **8** (X = O), and **9** (X = S) with Grubbs 2nd generation catalyst, both at 40 °C (dichloromethane reflux) and at elevated temperature (65 °C in dry benzene). In all the cases there was no change in the ratio of *E*/*Z* isomers as compared to when we employed the Grubbs 1st generation catalyst (Table 1), which indicates the kinetic control in the reaction.[16] Finally we found that at dichloromethane reflux (40 °C) the RCM was at least two times slower with Grubbs 2nd generation catalyst compared to that of the Grubbs 1st generation catalyst.

In conclusion, we have prepared heteroatom (oxygen, nitrogen, and sulfur) substituted 13-membered rings with *E*/*Z*-olefinic double bonds from corresponding bis-allyl ethers by RCM reaction and delineated their stereochemistry on the basis of NMR chemical shifts. Stereochemistry of the olefinic double bond appears to be influenced by the presence of remote hetero-atom.

Table 1
Diagnostic ^{13}C NMR spectral values of allylic OCH_2 carbons in olefins **14–20** and *E*/*Z* ratio

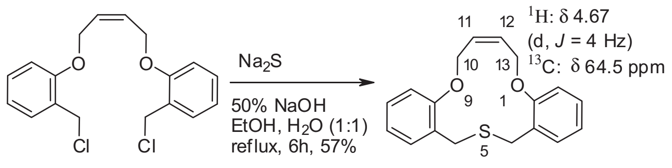
Entry	Substrate	Product	X	R_1	R_2	^{13}C NMR spectral values (in δ ppm) for allylic OCH_2 (C10 and C13) carbons of *E*/*Z*-isomers	Yield (%)	Ratio of *E*/*Z* isomers[a]
1	**4**	**11**	CH_2	H	H	69.0/–	63	100:0
2	**5**	**12**	CH_2	Cl	H	68.2/–	73	100:0
3	**6**	**13**	CH_2	Cl	Me	68.3/–	71	100:0
4	**7**	**14**	NCHO	H	H	70.8/61.9	70	29:71
5	**8**	**15**	O	H	H	67.7/–	69	100:0
6	**9**	**16**	S	H	H	71.4/64.6	72	57:43
7	**10**	**17**	SO_2	H	H	71.2/65.1	81	52:48

[a] Average of integration of at least two relevant signals in the ^{13}C NMR spectra of the crude products was used to elicit the ratio of *E*/*Z* isomeric olefins.



(*E*)-**32** (*Z*)-**32**

Figure 2. Structure and NMR spectral values (O*CH*$_2$C=) of *E* and *Z*-isomeric crown formazans prepared by Ibrahim and coworkers (Ref. 13).



33 (*Z*)-**16**

Scheme 7. Independent synthesis of 13-membered dioxa-thia macrocycle (*Z*)-**16** and diagnostic NMR spectral values.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.09.065.

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