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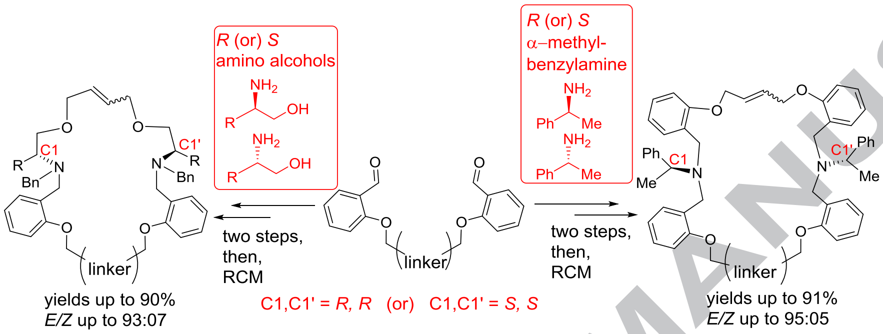
Naveen and Srinivasarao Arulananda Babu*

22-36 atom-membered optically active aza-oxo polyether macrocycles *via* the RCM reaction



RCM-based macrocyclization is the key step

relatively high yields

simple reaction conditions

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An Entry into New Classes of Optically Active Aza-Oxo Polyether Macrocycles *via* the Ring Closing Metathesis-Based Macrocyclization

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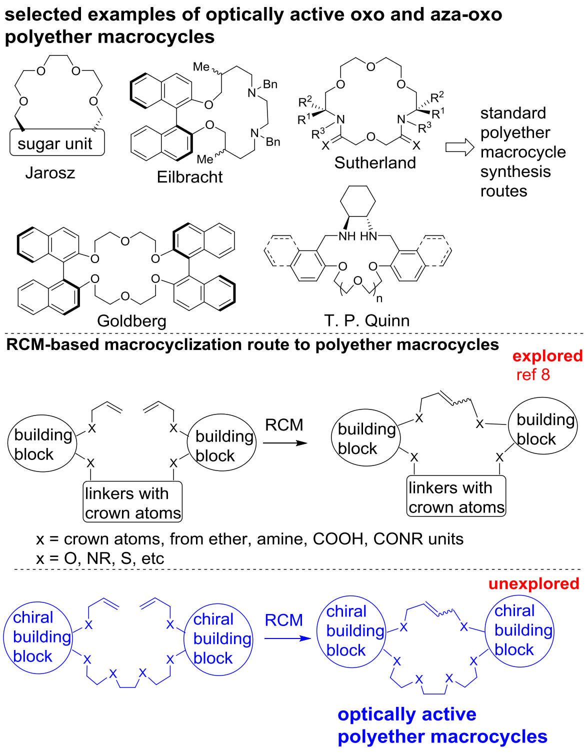
ABSTRACT

We report the application of ring closing metathesis-based macrocyclization route for synthesizing 22-36 membered optically active aza-oxo crowns/polyether macrocycles. While the RCM-based synthesis of polyether macrocycles was well explored in the literature, the synthesis of optically active polyether macrocycles was not explored *via* the RCM reaction. Accordingly, the present method reveals an efficient assembling of a library of new classes of optically active aza-oxo polyether macrocycles from optically active RCM precursors, which were assembled from easily available linkers, chiral α-methylbenzylamine and amino alcohol building blocks under simple reaction conditions.

The chemistry of crown ethers/polyether macrocycles has been one of the important subjects of intense research.[1] Polyether macrocycles have found numerous applications in various research fields and industry.[1,2] Apart from their popular chemical applications including separation, detection, molecular recognition, catalysis and biological activities; polyether macrocycles have been utilized to understand certain molecular processes and to obtain insights on molecular structure and conformational behaviors of macrocyclic systems.[1,2] Due to their immense importance across branches of chemical science, numerous oxo, aza, aza-oxo crown ethers/polyether macrocycles similar to the archetypal 18-crown-6 system were synthesized. Especially, the synthesis of periphery modified and large ring-based oxo and aza-oxo polyether macrocycles has received substantial attention due to their interesting properties.[1-5]

Alongside the classical polyether macrocycles, the synthesis of optically active oxo, aza, aza-oxo crown ethers/polyether macrocycles have received substantial attention[1,4,5] and these macrocycles have found various significant applications in organic synthesis.[1,4,5] Various linkers/building blocks including enantiopure building blocks (e.g., amino acids, sugars, BINOL, amines and amino alcohols, etc) were employed for synthesizing the corresponding optically active polyether macrocycles.[1,4,5] In general, optically active macrocycles/polyether macrocycles were assembled by using the conventional macrocyclization approaches, such as, Williamson ether synthesis, peptide coupling, macrolactonization, macrolactamization and other standard macrocyclization methods (Scheme 1).[6]



Scheme 1. Approaches toward optically active polyether macrocycles.

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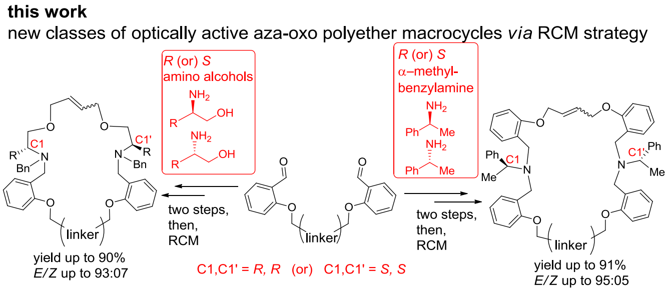
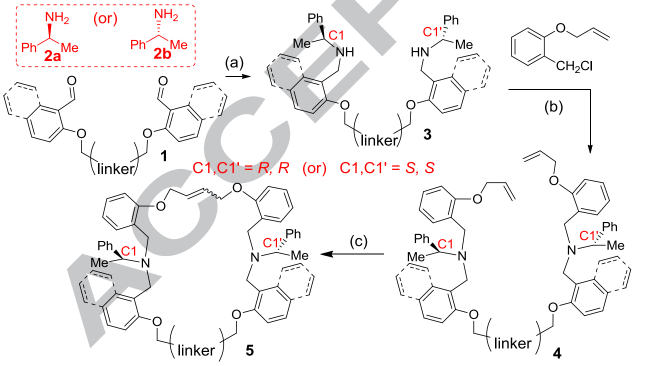
Ring closing metathesis (RCM) reaction is an extensively used strategy for the synthesis of natural products and small, medium and large-sized cyclic olefins.[7] Notably, various periphery modified oxo and aza-oxo polyether macrocycles and a variety of mechanically interlocked macrocyclic compounds (e.g., catenanes and rotaxanes, etc) were synthesized *via* the RCM-based macrocyclization.[8] Recently, we have reported the RCM-based macrocyclization route to polyether macrocycles starting from simple starting materials.[8f,g] When compared some of the conventional macrocyclization methods, the RCM-based macrocyclization method was found to be relatively efficient to afford high yields of polyether macrocyclic olefins.[8]



Scheme 2. Topic of this work.

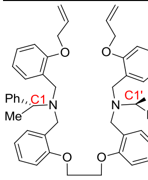
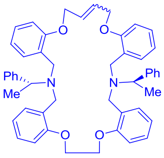
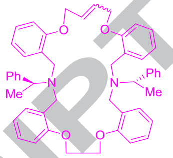
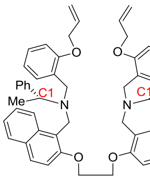
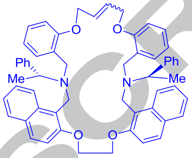
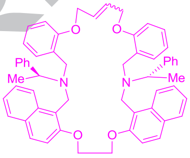
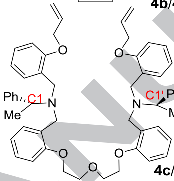
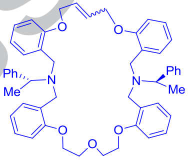
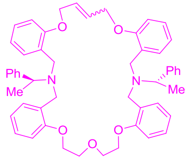
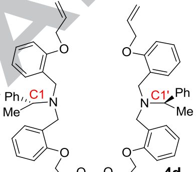
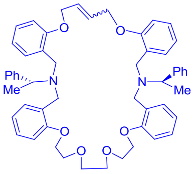
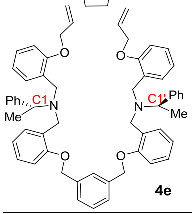
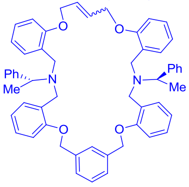
While the RCM technique was extensively used for synthesizing numerous racemic and optically active small, medium and large-sized cyclic olefins and natural products;[7] however, to the best of our knowledge, the RCM technique has not been explored for synthesizing optically active polyether macrocycles (Scheme 1).[1,4,5,7,8] Hence, given the efficiency and usefulness of the RCM strategy in organic synthesis,[7,8] we envisioned to utilize the RCM-based macrocyclization technique for assembling optically active aza-oxo polyether macrocycles and accordingly, herein, we report our preliminary works in this direction. This protocol has led to an efficient assembling of a library of new classes of optically active aza-oxo polyether macrocycles from optically active RCM precursors, which were prepared from various linkers, chiral α-methylbenzylamine and amino alcohol building blocks under simple reaction conditions (Scheme 2).



Scheme 3.[9] Generalized scheme comprising assembling of RCM precursors **4** from linkers and chiral α-methylbenzylamines.

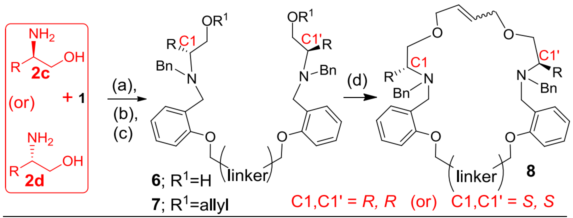
To execute the synthesis of optically active aza-oxo polyether macrocycles; at first we assembled various suitable optically active RCM precursors from different linkers and *R* or *S* α-methylbenzylamines (Scheme 3). Initially, various bis aldehydes **1** (generalized structure) were prepared from the corresponding *o*-hydroxyl benzaldehydes and different linkers by using the standard synthetic procedures. Next, the treatment of *R* and *S* α-methylbenzylamines (**2**) with **1** followed by the addition of $NaBH_4$ afforded the corresponding optically active bis amines **3**. Then, the *N*-benzylation of **3** with 1-(allyloxy)-2-(chloromethyl)benzene afforded the corresponding optically active RCM precursor **4** encompassing various aliphatic, polyether and aromatic ring-based linkers (Scheme 3).

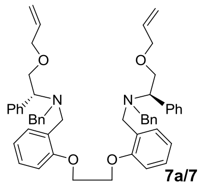
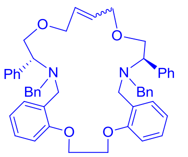
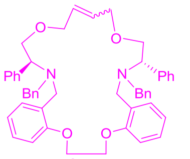
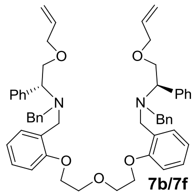
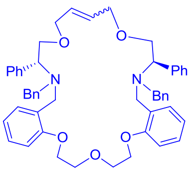
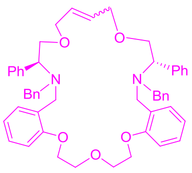
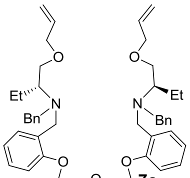
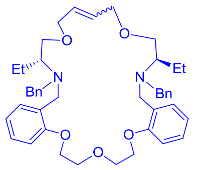
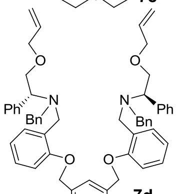
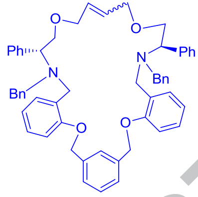
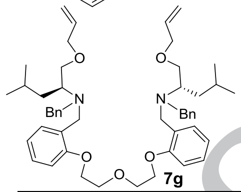
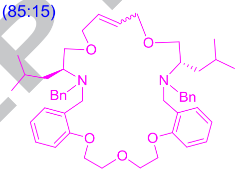
Table 1.[10] Synthesis of optically active aza-oxo polyether macrocycles **5a-h** *via* the RCM-based macrocyclization of **4a-h**.

substrate **4a–e**: C1,C1' = *R, R* **4f-h**: C1,C1' = *S, S*	macrocycle **5a–e** from **4a–e**: yield (%, *E/Z*)	macrocycle **5f-h** from **4f-h**: yield (%, *E/Z*)
 **4a/4f**	 **5a**; 80 (90:10)	 **5f**; 72 (95:05)
 **4b/4g**	 **5b**; 91 (80:20)	 **5g**; 78 (75:25)
 **4c/4h**	 **5c**; 78 (80:20)	 **5h**; 82 (75:25)
 **4d**	 **5d**; 75 (78:22)	—
 **4e**	 **5e**; 82 (87:13)	—

Next, we attempted the macrocyclization of the assembled optically active RCM precursors **4a-h** (Table 1). In this regard, at first we carried out the RCM-based macrocyclization of the RCM precursors **4a-e** which were prepared from (*R*)-α-methylbenzylamine. Accordingly, the reaction of the RCM precursor **4a** (derived from *o*-hydroxyl benzaldehyde) in the presence of 5 mol% of the Grubbs's 1st generation catalyst gave the optically active aza-oxo polyether macrocyclic olefin **5a** in 80% yield (*E/Z* = 90:10, Table 1). Similarly, the RCM reaction of the precursor **4b** (derived from 2-hydroxy-1-naphthalaldehyde) afforded the optically active aza-oxo polyether macrocyclic olefin **5b** in 91% yield (*E/Z* = 80:20, Table 1). Furthermore, the RCM precursors **4c-e** which were derived from the corresponding oxygen- and aromatic ring-based linkers were subjected to the RCM reaction in the presence of the Grubbs's 1st generation catalyst. These reactions gave the optically active aza-oxo polyether macrocyclic olefins **5c-e** in 75-82% yields, respectively (*E/Z* ratio up to 87:13, Table 1). Subsequently, we performed the RCM reaction of the starting materials **4f-h**, which were prepared from (*S*)-α-methylbenzylamine. Accordingly, the RCM-based macrocyclization of **4f-h** in the presence of the Grubbs's 1st generation catalyst afforded the optically active aza-oxo polyether macrocyclic olefins **5f-h** in 72-82% yields, respectively (*E/Z* ratio up to 95:05, Table 1).

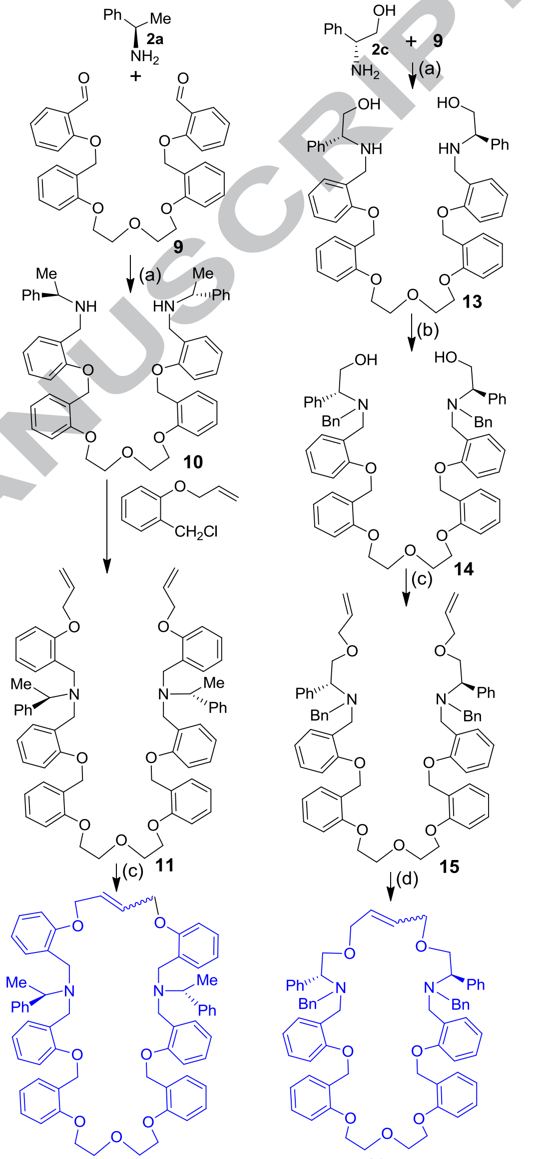
Table 2.[11] Assembling of RCM precursors **7a-g** from α-amino alcohols and synthesis of optically active aza-oxo polyether macrocycles **8a-g** *via* the RCM-based macrocyclization.



substrate **7a-d**: C1,C1' = *R, R* **7e-g**: C1,C1' = *S, S*	macrocycle **8a-d** from **7a-d**: yield (%, *E/Z*)	macrocycle **8e-g** from **7e-g**: yield (%, *E/Z*)
 **7a/7e**	 **8a**; 90 (93:07)	 **8e**; 72 (82:18)
 **7b/7f**	 **8b**; 80 (80:20)	 **8f**; 74 (78:22)
 **7c**	 **8c**; 85 (81:19)	—
 **7d**	 **8d**; 82 (85:15)	—
 **7g**	—	 **8g**; 88 (80:20)

Having done the synthesis of optically active aza-oxo polyether macrocycles from **4a-h**, which were prepared from *R* and *S* α-methylbenzylamines; then, we wished to increase the generality of this method by using *R* and *S* amino alcohols as chiral building blocks. Accordingly, the reductive amination of bis aldehydes **1** with *R* and *S* α-amino alcohols followed by the *N*-benzylation gave the bis alcohols **6**, which were subsequently subjected to the *O*-allylation to afford the optically active RCM precursors **7a-g** encompassing various aliphatic, polyether and aromatic linkers (Table 2, see the supplementary material).

After assembling the RCM precursors **7a-g**, we then attempted the macrocyclization of these substrates. At first, we carried out the RCM-based macrocyclization of **7a**,**b**,**d**, which were prepared from (*R*)-2-amino-2-phenylethanol and different linkers. Accordingly, the RCM reactions of **7a**,**b**,**d** in the presence of the Grubbs's 1st generation catalyst afforded the optically active aza-oxo polyether macrocyclic olefins **8a**,**b**,**d** in 80-90% yields, respectively (*E/Z* ratio up to 93:07, Table 2). Similarly, the RCM reaction of **7c** which was prepared from (*R*)-2-aminobutan-1-ol afforded the optically active aza-oxo polyether macrocyclic olefin **8c** in 85% yield (*E/Z* = 81:19, Table 2). Having done the synthesis of aza-oxo polyether macrocycles **8a-d** based on the (*R*)-α-amino alcohols; subsequently, we carried out the RCM reactions of **7e-g** which were prepared from (*S*)-*α*-amino alcohols and different linkers. Accordingly, the macrocyclization of **7e-g** in the presence of the Grubbs's 1st generation catalyst afforded the optically active aza-oxo polyether macrocyclic olefins **8e-g** in 72-88% yields, respectively (*E/Z* ratio up to 82:18, Table 2).



12; 71 (76:24)

16; 75 (75:25)

Scheme 4. Synthesis of optically active aza-oxo polyether macrocycles **12**[9] and **16**[11].

Successively, we were further interested to elaborate the generality of this method by synthesizing large cavity-based, optically active polyether macrocycles **12** and **16**. Accordingly, the bis aldehyde **9** was synthesized using the standard synthetic procedures.[8f] Next, the reductive amination of (*R*)-α-methylbenzylamine (**2a**) with **9** gave the optically active bis amine **10**. Further, the *N*-benzylation of **10** with 1-(allyloxy)-2-(chloromethyl)benzene gave the RCM precursor **11** (Scheme 4). Then, we attempted the Grubbs's 1st generation catalyst-catalyzed macrocyclization of **11**, which successfully afforded the optically active aza-oxo polyether macrocycle **12** in 71% yield (*E/Z* = 76:24, Scheme 4). Finally, we were interested to prepare an amino alcohol building block-based optically active polyether macrocycle similar to **12**. In this regard, at first we prepared the RCM precursor **15** from (*R*)-2-amino-2-phenylethanol (**2c**) and **9** involving the reductive amination, *N*-benzylation and *O*-allylation steps as shown in Scheme 4. Then, we attempted the Grubbs's 1st generation catalyst-catalyzed macrocyclization of **15**, which successfully afforded the optically active aza-oxo polyether macrocycle **16** in 75% yield (*E/Z* = 75:25, Scheme 4).

In summary, we have disclosed the application of ring closing metathesis-based macrocyclization route for an efficient assembling of a library of new classes of optically active aza-oxo polyether macrocycles in very good yields under simple macrocyclization reaction conditions. Further works are in progress to explore the synthetic utility of optically active aza-oxo polyether macrocycles obtained in this work.

Acknowledgments

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References and notes

1. For selected reviews/articles, see: (a) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 2495. (b) Lehn, J.-M. *Supramolecular Chemistry: Concepts and Perspectives*, VCH: New York, 1995. (c) Cragg, P. J.; Vahora, R. *Crown and Lariat Ethers.* In *Supramolecular Chemistry: From Molecules to Nanomaterials*; Gale, P. A.; Steed, J., Eds.; John Wiley & Sons, Ltd: Chichester, **2012**; pp 733-752. (d) Gokel, G. W.; Leevy, W. M.; Weber, M. E. *Chem. Rev.* **2004**, *104*, 2723. (e) Habata, Y.; Akabori, S.; Bradshaw, J. S.; Izatt, R. M. *Ind. Eng. Chem. Res.* **2000**, *39*, 3465. (f) Krakowiak, K. E.; Bradshaw, J. S.; Zamecka-Krakowiak, D. J. *Chem. Rev.* **1989**, *89*, 929. (g) Erk, C. *Ind. Eng. Chem. Res.* **2000**, *39*, 3582.
2. For selected reviews, see: (a) Kralj, M.; Tušek-Božić, L.; Frkanec, L. *ChemMedChem* **2008**, *3*, 1478. (b) Huszthy, P.; Tünde Tóth, T. *Per. Pol. Chem. Eng.* **2007**, *51*, 45. (c) Gokel, G. W.; Leevy, W. M.; Weber, M. E. *Model Systems for Biological Processes*, in *Macrocyclic Chemistry,Gloe, K. Ed.;* Springer: Netherlands, **2005**; pp 253-265. (d) Hiraoka, M. *Crown Ethers and Analogous Compounds,* Elsevier, Amsterdam, **1992**. (e) Alexandratos, S. D.; Stine, C. L. *React. Funct. Polym*. **2004**, *60*, 3.
3. For selected reviews/articles, see: (a) Wenzel, M.; Gloe, K.; Gloe, K.; Bernhard, G.; Clegg, J. K.; Ji, X-K.; Lindoy, L. F. *New J. Chem.* **2008**, *32*, 132. (b) Chou, T.-C.; Chen, S.-Y.; Chen, Y.-H. *Tetrahedron* **2003**, *59*, 9939. (c) Ebrahimi, S.; Moghanian, H. *Heterocycl. Commun.* **2012**, *18*, 29. (d) Maitra, U.; Bag, B. G. *J. Org. Chem.* **1994**, *59*, 6114. (e) Su, C.-C.; Lu, L.H. *J. Mol. Struct.* **2004**, *702*, 23. (f) Buchanan, G. W.; Laister, R. C.; Yap, G. P. A. *J. Mol. Struct.* **2000**, *523*, 261. (g) Kotha, S.; Waghule, G. T. *J. Org. Chem.* **2012**, *77*, 6314. (h) Agnihotri, P.; Suresh, E.; Ganguly, B.; Paul, P.; Ghosh, P. K. *Polyhedron* **2005**, *24*, 1023. (i) Naveen, Babu, S. A.; Kaur, G.; Aslam, N. A.; Karanam, M. *RSC Adv*. **2013**, *4*, 18904. (j) For Glaser-Eglinton-Hay reaction-based synthesis of optically active aza-oxo-thia polyether macrocycles, see: Naveen; Babu, S. A. DOI: 10.1055/s-0036-1588329; Art ID: st-2016-d0472-l.
4. For selected reviews, see: (a) Hyun, M.H. 8.13 *Chromatographic Separations and Analysis: Chiral Crown Ether-Based Chiral Stationary Phases.* In *Comprehensive Chirality*, Elsevier, Amsterdam, **2012**, Pages 263-285. (b) Shirakawa, S.; Maruoka, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 4312. (c) Kakhki, R. M. *J. Incl. Phenom. Macrocycl. Chem.* **2013**, *75*, 11. (d) Bako, P.; Keglevich, G.; Rapi, Z.; Toke, L. *Curr. Org. Chem.* **2012**, *16*, 297. (e) Wenzel, T. J. *Top. Curr. Chem.* **2013**, *341*, 1. (f) Granda, J. M.; Jurczak, J. *Curr. Org. Chem.* **2014**, *18*, 1886.
5. For selected reviews/articles, see: (a) Bodwin, J. J.; Cutland, A. D.; Malkani, R. G.; Pecoraro, V. L. *Coord. Chem. Rev.* **2001**, *216-217*, 489. (b) North, M. *Crown Ethers, Taddol, Nobin and Metal (salen) Complexes as Chiral Phase-Transfer Catalysts for Asymmetric Synthesis.* In *Asymmetric Phase Transfer Catalysis*, Maruoka, K. Ed.; Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, **2008**, Chapter 8. (c) Bradshaw, J S. *J. Incl. Phenom. Macrocycl. Chem.* **1997**, *29*, 221. (d) Hyun, M. H. *Chirality* **2015**, *27*, 576. (e) Landis, C. R.; Sawyer, R. A.; Somsook, E. *Organometallics* **2000**, *19*, 994. (f) Yang, X.-f.; Ning, R.; Xie, L.-j.; Cui, Y.; Zhang, Y.-l.; Zheng, L.-y. *Bull. Chem. Soc. Jpn.* **2013**, *86*, 987. (g) Deniz, P.; Turgut, Y.; Togrul, M.; Hosgoren, H. *Tetrahedron* **2011**, *67*, 6227. (h) Chadwick, D. J.; Cliffe, I. A.; Sutherland, I. O. *J.C.S. Chem. Comm.* **1981**, 992. (i) Gao, J.; Martell, A. E. *Org. Biomol. Chem.* **2003**, *1*, 2801. (j) Joly, J.-P.; Shroder, G. *Tetrahedron Lett.* **1997**, *38*, 8197. (k) Demirel, N.; Bulut, Y. *Tetrahedron: Asymmetry* **2003**, *14*, 2633. (l) Jarosz, S.; Lewandowski, B. *Carbohydr. Res.* **2008**, *343*, 965. (m) Goldberg, I. *J. Am. Chem. Soc.* **1977**, *99*, 6049. (n) Angelovski, G.; Eilbracht, P. *Tetrahedron* **2003**, *59*, 8265.
6. (a) Shu, C.; Zeng, X.; Hao, M.-H.; Wei, X.; Yee, N. K.; Busacca, C. A.; Han, Z.; Farina V.; Senanayake, C. H. *Org. Lett.* **2008**, *10*, 1303. (b) White C. J.; Yudin, A. K. *Nature Chem.* **2011**, *3*, 509. (c) Fürstner A.; Langemann, K. *Synthesis* **1997**, 792. (d) Gradillas A.; Perez-Castells, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6086.
7. For selected reviews/articles, see: (a) Grubbs, R. H.; Trnka, T. M. *Ruthenium-Catalyzed Olefin Metathesis, in Ruthenium in Organic Synthesis*; Murahashi, S.-I., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, FRG, **2004**; pp 153-177. (b) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117. (c) Fürstner, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3012. (d) Kotha, S.; Lahiri, K. *Synlett* **2007**, 2767. (e) Chen, C.-y. *Top. Organomet. Chem.* **2012**, *42*, 135.
8. For RCM-based synthesis of polyether macrocycles, see: (a) Vignon, S. A.; Jarrosson, T.; Iijima, T.; Tseng, H.-R.; Sanders, J. K. M.; Stoddart, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 9884. (b) Coumans, R. G. E.; Elemans, J. A. A. W.; Thordarson, P.; Nolte, R. J. M.; Rowan, A. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 650. (c) Li, S.; Liu, M.; Zheng, B.; Zhu, K.; Wang, F.; Li, N.; Zhao, X.- L.; Huang, F.*Org. Lett.* **2009**, *11*, 3350. (d) Kilbinger, A. F. M.; Cantrill, S. J.; Waltman, A. W.; Day, M. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 3281. (e) Sambrook, M. R.; Beer, P. D.; Wisner, J. A.; Paul, R. L.; Cowley, A. R. *J. Am. Chem. Soc.* **2004**, *126*, 15364. (f) Naveen; Babu, S. A. *Tetrahedron* **2015**, *71*, 7758 and references cited therein. (g) Naveen; Parella, R.; Babu, S. A. *Tetrahedron Lett.* **2013**, *54*, 2255. (h) König, B.; Horn, C. *Synlett* **1996**, 1013 (i) Umemiya, T.; Takeuchi, D.; Osakada, K. *J. Organomet. Chem.* **2006**, *691*, 5260. (j) Ibrahim, Y. A. *J. Mol. Catal. A: Chem.* **2006**, *254*, 43. (k) Malhas, R. N.; Ibrahim, Y. A. *Synthesis* **2006**, 3261. (l) Rao, H. S. P.; Rafi, S.; Kumar, P. R. Guravaiah, C.; Muthanna, N. *Tetrahedron Lett.* **2012**, *53*, 6877. (m) Maynard, H. D.; Grubbs, R. H. *Macromolecules* **1999**, *32*, 6917. (n) Ibrahim, Y. A.; Behbehani, H.; Ibrahim, M. R.; Abrar, N. M. *Tetrahedron* **2003**, *59*, 7273. (o) Iwamoto, H.; Itoh, K.; Nagamiya, H.; Fukazawa, Y.; *Tetrahedron Lett.* **2003**, *44*, 5773. (p) Behbehani, H.; Ibrahim, M. R.; Ibrahim, Y. A. *Tetrahedron Lett.* **2002**, *43*, 6421.
9. (a) EtOH, 80 °C, 12 h, then, $NaBH_4$, 80 °C, 12 h. (b) K_2CO_3, CH_3CN, 80 °C, 3 d. (c) Grubbs's catalyst I, DCM, reflux, 20 h.
10. (a) **Typical procedure for the synthesis of 5a.** A solution of **4a** (0.1 mmol) and Grubbs's catalyst (1st generation, 5 mol%) in anhydrous DCM (7 mL) was refluxed for 20 h. Then, the solvent was evaporated in *vacuo* and the residue was purified by neutral Al_2O_3 chromatography to afford **5a** (80%, 59 mg, *E/Z* = 90:10). **5a** (major isomer, *E*). Colorless solid; mp 158-160 °C; R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2971,1600, 1588, 1490, 1452 and 1236 cm^{-1}; $[\alpha]^{25}_D$ + 64.11 (c 0.13, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.83 (4 H, t, J = 6.1 Hz), 7.52 (4 H, d, J = 7.6 Hz), 7.29-7.17 (10 H , m), 7.07-7.02 (4 H, m), 6.86 (4 H, t, J = 8.4 Hz), 6.16 (2 H, s), 4.55 (4 H, br. s), 4.30-4.28 (4 H, m), 4.05 (2 H, q, J = 6.8 Hz,), 3.96 (4 H, dd, J_1 = 15.6 Hz, J_2 = 6.7 Hz), 3.59 (4 H, t, J = 17.9 Hz), 1.49 (6 H, d, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.7, 156.4, 144.5, 129.4, 129.3, 129.2, 129.1, 127.9, 127.6, 127.4, 127.1, 127.1, 126.3, 121.1, 120.9, 111.1, 111.0, 67.4, 67.0, 56.5, 47.3, 47.1, 12.5; HRMS (ESI): MH^+, found 745.4016. $C_{50}H_{53}N_2O_4$ requires 745.4005. (b) In concurrence with the reports by other groups on RCM-based synthesis of polyether macrocyclic olefins[8h-p] and based on our previous studies, see refs.[8f,g], the major isomers **5**, **8**, **12** and **16** were denoted to have the *E*-geometry. (c) Further, the optical rotation values reported for all the compounds correspond to the *E/Z* mixtures. (d) We have also carried out the RCM reactions of RCM precursors **7c** and **8e** using Grubb's 2nd generation catalyst. The *E/Z* ratio of the corresponding products **7c** and **8e** obtained using the Grubb's 2nd generation catalyst was comparable to the reactions carried out using Grubb's 1st generation catalyst (see the supplementary material for the corresponding crude NMRs of these reactions.

11. (a) EtOH, 80 °C, 12 h, then, $NaBH_4$, 80 °C, 12 h. (b) BnBr, K_2CO_3, CH_3CN, 80 °C, 3 d. (b) allyl bromide, NaH, THF, rt. (d) Grubbs's catalyst I, DCM, reflux, 24 h.

Supplementary Material

Supplementary data (procedures and copy of ^{1}H, ^{13}C NMR Charts of compounds) associated with this article can be found in the online version.

Highlights

- RCM-based macrocyclization and polyether macrocycle synthesis.
- Synthesis of 22-36 membered optically active aza-oxo polyether macrocyclic olefins.
- Optically active aza-oxo polyether macrocycle synthesis under relatively simple reaction conditions.
- Macrocyclization using easily available linkers, chiral α-methylbenzylamine and amino alcohol building blocks.