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An entry into new classes of optically active aza-oxo polyether macrocycles *via* the ring closing metathesis-based macrocyclization

Naveen, Srinivasarao Arulananda Babu *

Department of Chemical Sciences, Indian Institute of Science Education and Research (IISER) Mohali, Knowledge City, Sector 81, SAS Nagar, Mohali, Manauli P.O., Punjab 140306, India

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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]

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]

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

* Corresponding author.
E-mail address: sababu@iisermohali.ac.in (S.A. Babu).

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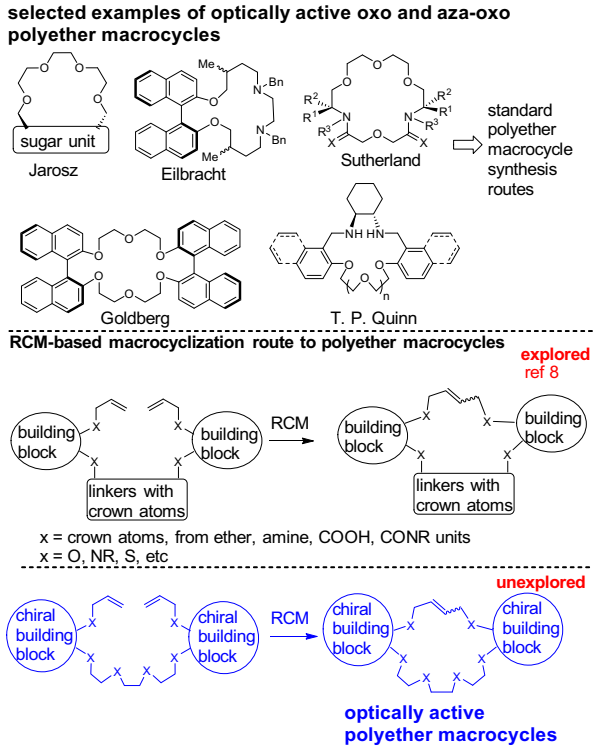
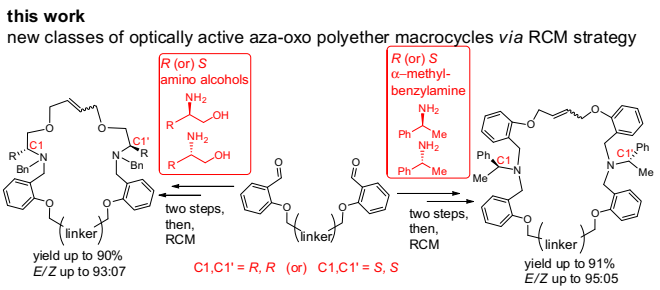


Scheme 1. Approaches toward optically active polyether macrocycles

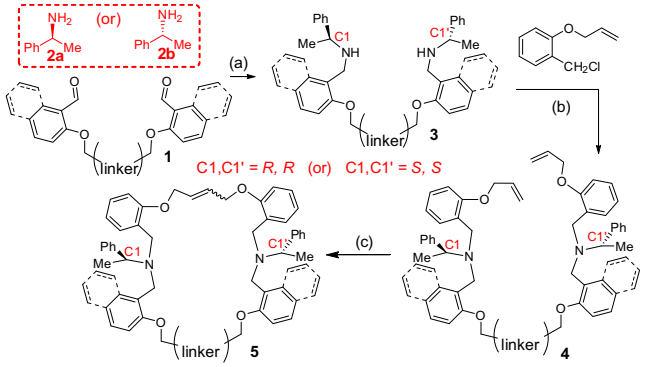
aza-oxo polyether macrocycles from optically active RCM precursors, which were prepared from various linkers, chiral α-methylbenzylamine and amino alcohol building blocks under simple reaction conditions (Scheme 2).

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).

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

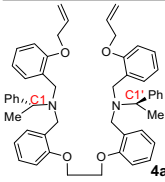
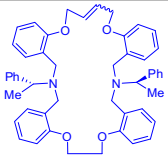
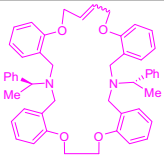
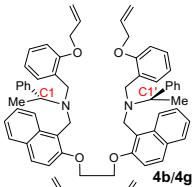
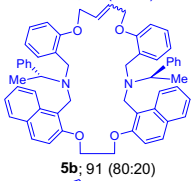
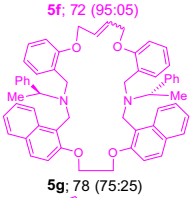
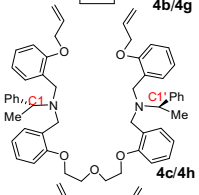
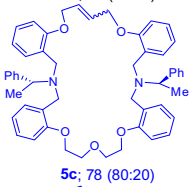
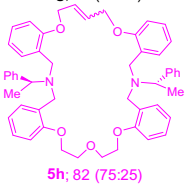
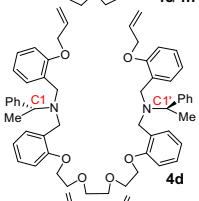
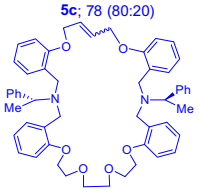
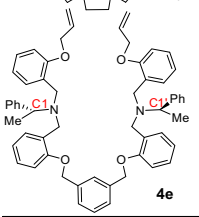
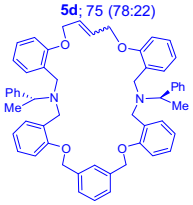


Scheme 2. Topic of this work



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

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)	—

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