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Ortho-Condensed Oxane/Polyoxygenated Macrorings by Ruthenium-Catalyzed Ring Closing Metathesis

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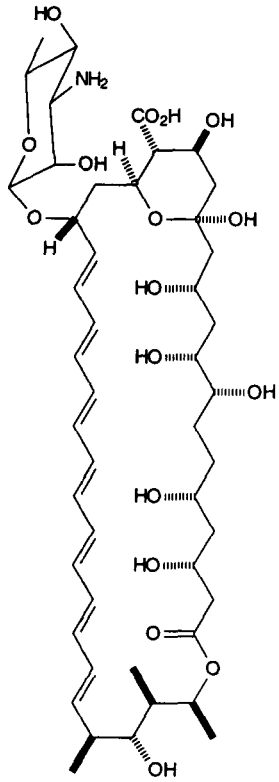
Abstract: A highly efficient and flexible route to *trans*-fused oxane/macrocyclic polyethers is outlined, which is based on the formation of 15-, 18-, and 21-membered oxacycles by ring-closing metathesis (RCM) as the key step. © 1997 Elsevier Science Ltd.

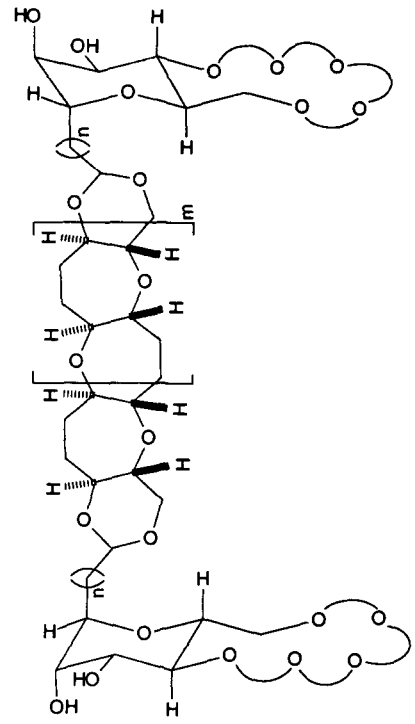
The transport of ions and molecules *in vivo* is a precisely regulated biological process that is accomplished almost exclusively with the aid of proteins believed to have multiple transmembrane spans.[1] Although many of the structural features of natural cation-conducting channels have been inferred from biophysical and molecular biological studies,[1,2] much of the molecular-scale details has been reached from natural ionophores such as gramicidin[3] or amphotericin[4] which show characteristics of channel behaviour.

We have recently begun a synthetic program[5] which is aimed at preparing functional equivalents of amphotericin-B (AmpB, **1**). Consideration of the AmpB molecule suggested[6] that the minimum structural elements that would be necessary in order to create functional equivalents would consists of (a) a long and rigid hydrophobic segment linked to a flexible hydrophilic fragment extended across its face, and (b) a pendant polar head group, i.e., analogs of the polyene/polyol, and carboxyl/mycosamine components of AmpB, respectively. In our model, **2**, the essential elements of the design included sugar containing macrocyclic polyether groups spaced at a (macrocycles face-to-face) distance > 30 Å (which corresponds to the thickness of the lipid bilayer) that function as entry portals for cations.[7] A *trans*-fused oxepanyl system[8] used as a spacer of the macrorings would be fairly stiff to provide structural control at the time that would incorporate both the polar and non-polar functionality required for a channel. Our choice of a *trans*-fused oxepanyl fragment as a "compacted" analogue of the polyene/polyol units of AmpB, was also based on the belief that it would be well-suited for future studies that focus both on membrane selectivity and activity.[9]

We have recently described[10] a general methodology for the synthesis of *trans*-fused oxepanyl systems. We now report an efficient strategy for the preparation of *ortho*-condensed oxane/polyoxygenated macrorings by ring-closing metathesis of their corresponding dienes.[11] The synthesis of dienes **3-5** is shown in Scheme 1.

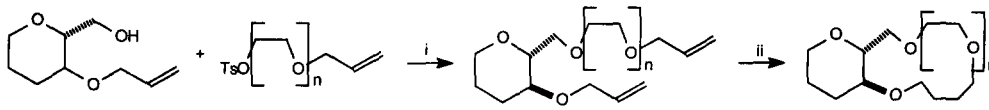


1



2

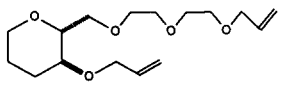
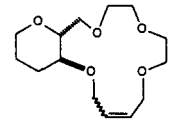
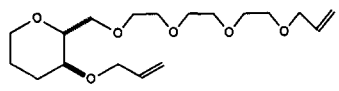
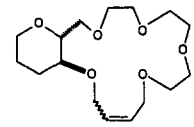
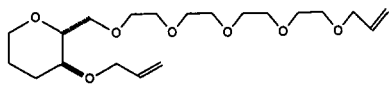
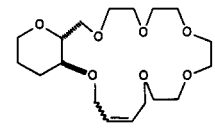
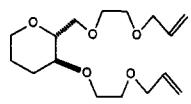
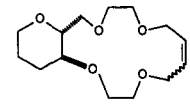
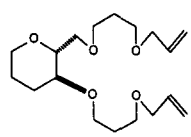
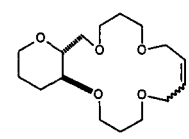
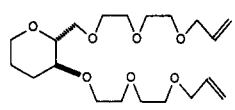
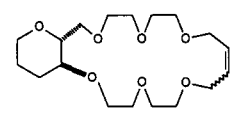
Scheme 1[a]



[a] Reagents: (i) *t*-BuOK, THF, 25°C. (ii) [$(PCy_3)_2$ RuCHPh] Cl_2, CH_2Cl_2, 25°C; H_2, Pd(C), MeOH.

Treatment of *trans*-3-allyloxy-2-hydroxymethyltetrahydropyran[12] with *t*-BuOK (1.2 equiv) and either allyl di-, tri-, tetraethylene glycol toluene-*p*-sulphonate in THF at 25°C gave, respectively, dienes **3**, **4** or **5** in >80% yields after column chromatography. Initial metathesis reactions were carried out with the 15-membered ring precursor diene **3**. Reaction of **3** in CH_2Cl_2 (0.005 M) with 10 mol % of [bis (tricyclohexylphosphine) benzylidene] ruthenium dichloride,[13] at room temperature for 3 h, provided 85% of the macrocycle **9**; see Table 1. Cyclization of diene **4** under similar conditions resulted in the formation of the 18-membered **10** in 92% yield. Diene **5** cyclized to the 21-membered polyether ring **11** in 88% yield. The reaction of **5** is essentially completed in 3 h.

Table 1[a]

Entry	Diene	Product	Yield[b]
1	 **3**	 **9**	85% (10:3)
2	 **4**	 **10**	92% (8.5:1)
3	 **5**	 **11**	88% (13:1)
4	 **6**	 **12**	65% (4:1)
5	 **7**	 **13**	76% (7:1)
6	 **8**	 **14**	72% (12:1)

[a] Reaction conditions: 0.005M, CH_2Cl_2, R.T., 10 mol % $[(PCy_3)_2RuCHPh]Cl_2$, 3-4 h.
[b] Isolated yield and, in parentheses, E:Z ratio.

To investigate the influence of the rigidifying of *trans*-2,3-substituted oxane units on the ring closure, the more flexible bis-allyl podands **6-8** were prepared by appropriate di-alkylations of *trans*-2-hydroxymethyl-3-hydroxytetrahydropyran (~50% yields) and subjected to the RCM reaction conditions. Macrocycles **12-14** were, respectively, formed albeit in lower yields (65-76%). The transition-state structure required for the intramolecular reaction seems then to be independent of the length of the connecting chains.[14]

In summary, a highly flexible and versatile method for the construction of macrocyclic polyethers and related systems is described.

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