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SYNTHESIS OF 6-HYDROXYCEMBRANE PRECURSORS BY CONFORMATIONALLY CONTROLLED DIASTEREOSELECTIVE [2,3] WITTIG RING CONTRACTION

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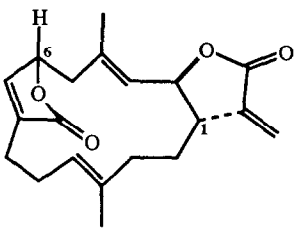
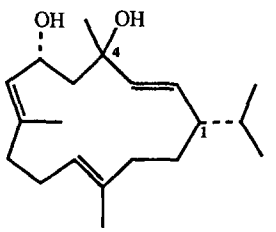
Summary: [2,3] Wittig ring contraction of the alkoxy substituted 17-membered allylic propargylic ethers **8** and **10** gives the trans/syn products **11** and **12** as the major diastereoisomers.

We recently described a new approach to cembrane natural products whereby [2,3] Wittig rearrangement of a 17-membered allylic propargylic ether is employed to construct the 14-membered cembranoid carbocycle.[1] A key feature of this approach is its potential for diastereoselective introduction of the C-1 isopropenyl and C-2 hydroxyl substituents characteristic of several members of the cembrane family.[2] In addition, promising levels of absolute stereochemical control have been achieved through use of a chiral amide base to initiate the rearrangement.[3]

The present study was prompted by an interest in applying the [2,3] Wittig methodology to C-6 oxygenated cembranoids such as ovatodiolide, a biologically active constituent of the Indochinese plant *Anisomeles ovata*,[4] and the epimeric α- and β-CBTs, plant growth inhibitors isolated from tobacco leaves.[5] Interestingly, these latter two natural products, also found in tobacco smoke condensate, have recently been shown to inhibit tumor promotion at a level comparable to retinoic acid.[6]

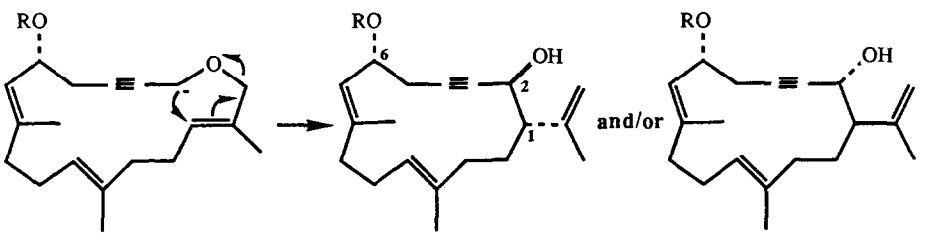


ovatodiolide, α H-6
isoovatodiolide, β H-6



β-CBT, β C-4 OH
α-CBT, α C-4 OH

Our approach utilizes the alkoxy substituent of macrocyclic ether I as a remote stereochemical directing group in the [2,3] Wittig ring contraction (Figure 1).[7]

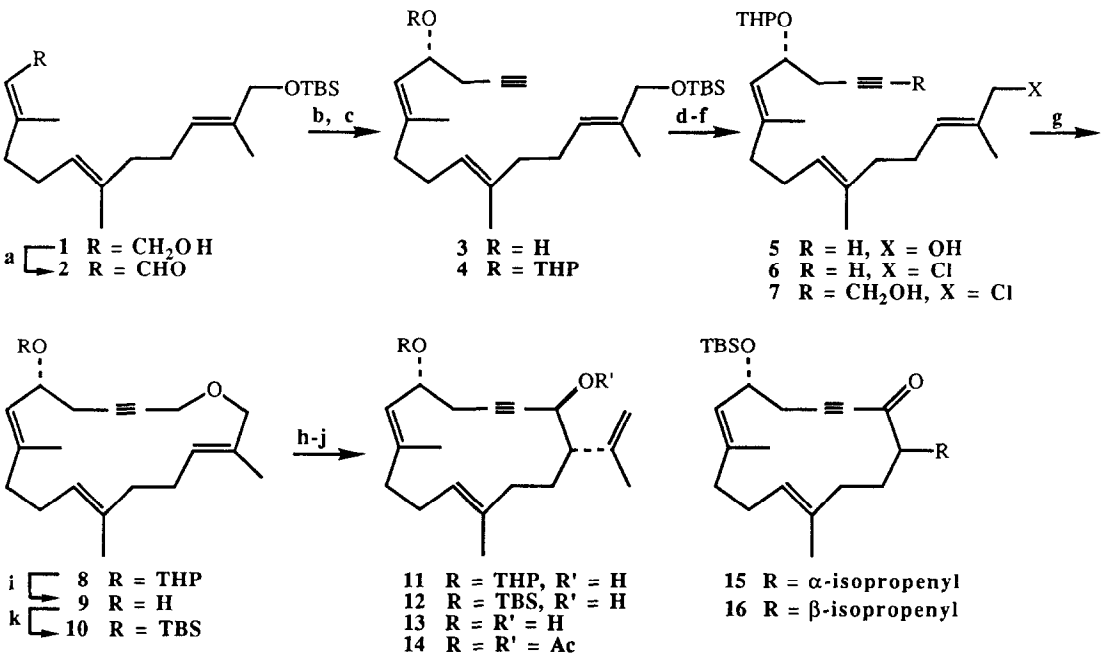


I II (trans/syn) III (trans/anti)

Figure 1. Synthetic plan for 6-hydroxycembranes employing remote diastereocontrol.

The starting point for this investigation was the alcohol **1**, derived from *trans,trans*-farnesyl acetate by selective allylic oxidation, alcohol protection with TBSCl and acetate cleavage.[1] Swern oxidation[9] to aldehyde **2** followed by addition of propargylmagnesium bromide afforded the alcohol **3**. The derived tetrahydropyranyl ether **4** was desilylated and the alcohol **5** was converted to the allylic chloride **6** by the Collington-Myers procedure.[9] Treatment of the lithiated acetylide with paraformaldehyde gave the chloro alcohol **7**. This cyclized to ether **8** upon addition of 1 equivalent of ethylmagnesium bromide at 0°C followed by heating at reflux.

The THP ether **8** could be cleaved to the alcohol **9** with PPTS in methanol. Ether **8**, alcohol **9** and the derived TBS derivative **10** readily underwent [2,3] Wittig rearrangement with *n*-butyllithium in a mixture of THF, pentane and TMEDA at -78°C. The resulting mixture of products after conversion to the diacetate **14** (and diastereoisomers) via the diol **13** (and diastereoisomers) was analyzed by capillary gas chromatography. The major diacetate **14** from rearrangement of the THP and TBS protected ethers **8** and **10** crystallized thus permitting its identification as the trans/syn isomer through single crystal x-ray structure analysis.[10]



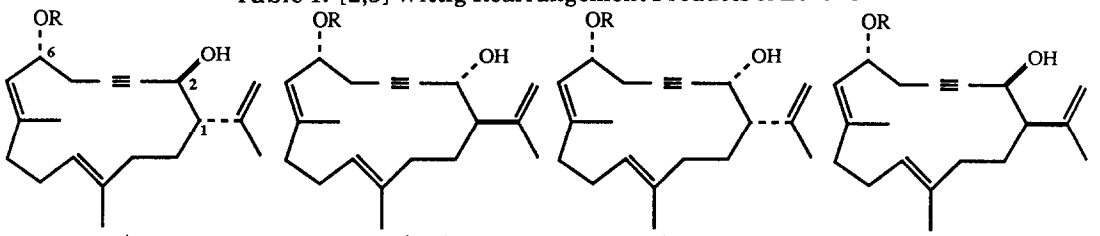
(a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C; 92%: (b) $BrMgCH_2C{\equiv}CH$, Et_2O, -20°C; 96%: (c) DHP, PPTS, CH_2Cl_2; 96%: (d) TBAF, THF, 0°C; 98%: (e) LiCl, DMF, MsCl, 2,6-lutidine, 0°C; 84%: (f) *n*-BuLi, THF, $(CH_2O)_n$, -78°C to 15°C; 83%: (g) EtMgBr, THF-HMPA, 0.01 *M*, 0°C to reflux; 84%: (h) *n*-BuLi, TMEDA, THF, pentane, -78°C (see Table 1): (i) PPTS, MeOH; 85%: (j) Ac_2O, C_5H_5N: (k) TBSCl, DMF, Im.

The identity of the cis/syn product was surmised as follows: A 64:11:24:1 mixture of TBS protected rearrangement products **12** (and diastereoisomers) upon Swern oxidation[8] afforded an 88:12 mixture of

ketones **15** and **16**. Accordingly, the 24% component of the foregoing alcohol mixture must be epimeric at C-2 with the 64% component. The 11% and the 1% components are likewise related, but with anti OTBS and isopropenyl substituents. Assignment of trans stereochemistry to the major anti product is based on the preferred envelope transition state geometry for (*E*)-allylic ether rearrangements.[11]

Both the THP and the TBS protected ethers **8** and **10** show high levels of remote diastereocontrol (Table 1) in favor of the syn isomers. The trans/cis ratios are comparable to those found for the parent macrocyclic ether.[1] The hydroxy substituted ether, on the other hand, rearranges with negligible stereoselectivity.

Table 1. [2,3] Wittig Rearrangement Products of Ether **8**



R	Yield[a]	t/s	t/a[b]	c/s	c/a[b]	trans/cis	syn/anti
THP	90%	81	7	6	6	88:12	87:13
TBS	94%	74	8	14	4	82:18	88:12
H	71%	20	29	39	12	49:51	59:41

[a] *n*-BuLi added slowly to the allylic propargylic ether in pentane-THF-TMEDA at -78°C. [b] The assignments are tentative.

The remote directing effect is thought to arise from conformational preferences of the macrocyclic ring engendered by the alkoxy substituent as illustrated in Figure 2. Models indicate that for large OR groupings the extended-boat/envelope arrangement Ia is preferred to the extended-chair/envelope arrangement Ib, thereby favoring the formation of diastereoisomer II.[12]

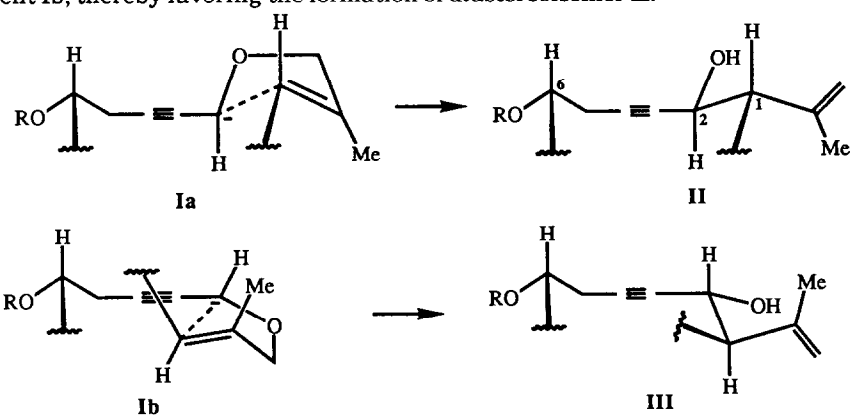


Figure 2. Conformationally controlled diastereoselective [2,3] Wittig ring contraction.

The foregoing results demonstrate that remote substituents can exert significant stereochemical control over [2,3] Wittig ring contractions. Although the present study was carried out on racemic ethers, the findings are clearly applicable to homochiral synthesis. Additional studies along these lines are in progress.

Abbreviations: DHP = 2,3-dihydropyran; DMF = Me_2NCHO; DMSO = Me_2SO; HMPA = $(Me_2N)_3PO$; Im = imidazole; MsCl = $MeSO_2Cl$; PPTS = pyridinium *p*-toluenesulfonate; TBAF = Bu_4NF; TBS = *t*-BuSiMe_2; THF = tetrahydrofuran; THP = tetrahydropyranyl; TMEDA = $Me_2NCH_2CH_2NMe_2$.

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References and Notes

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12. The cis/trans diastereoselectivity arises from conformational preferences in the five-membered envelope transition state of the [2,3] rearrangement.[11] Though related, the syn/anti selectivity is a more subtle issue. As our working hypothesis, we presume the OR grouping prefers an equatorial-like orientation to minimize 1,3-interactions with the gamma vinyl CH_3. The transition state is assumed to possess propargylic as opposed to allenic character in the absence of evidence to the contrary.[11] Given these assumptions, the macrocyclic cavity of **1a** adopts a nearly circular arrangement whereas that of **1b** appears elliptical according to Darling models. The latter arrangement would expectedly possess higher energy owing to transannular interactions. Additional experimental testing of this concept and a more rigorous MM2 analysis of likely transition states is in progress and will be the subject of a future report.

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