Acetal Templates for the Synthesis of *trans*-2,5-Disubstituted Tetrahydrofurans

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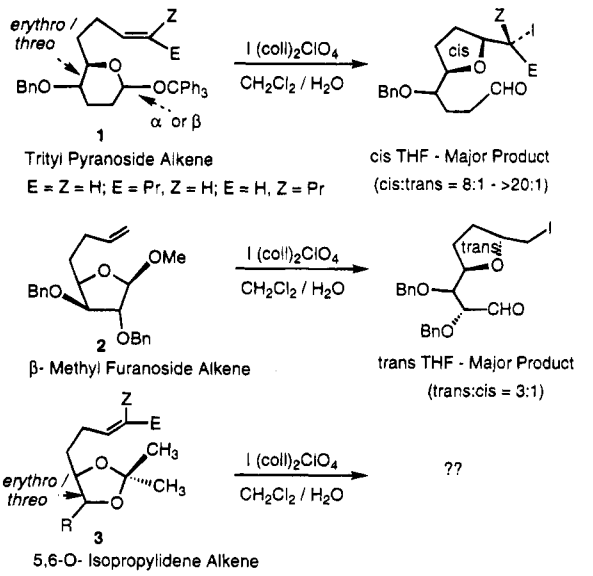
trans-2,5-Disubstituted tetrahydrofurans (THF's) are widely occurring subunits in several classes of natural products.[1] Among these are the rapidly expanding group of THF- and bis-THF-containing acetogenins, which have attracted attention because of their potent antitumor properties.[2] These compounds contain *cis*- or *trans*-2,5-disubstituted THF's which may be contiguous or adjacently connected to a flanking carbinol center. In view of the variety of different stereochemical motifs, highly versatile synthetic strategies are desirable.[3] Methodologies based on the halocyclization of 5-hydroxyalkenes are attractive since it has been shown that either *cis* or *trans* THF formation may be favored by varying the nature of the alcohol protecting group.[4] Furthermore, the alkenic nature of these substrates allows for their assembly in a convergent fashion, and this would be especially important for the synthesis of highly substituted systems.

We have previously shown that the halocyclization of hydroxyalkenes which are embedded in trityl pyranoside templates (e.g., **1**) leads to *cis*-2,5-disubstituted THF's with high stereoselectivity.[5] In this case, the internal acetal serves as a convenient hydroxy aldehyde protecting group. During the course of these studies, it was also observed that the cyclization of the structurally related β-methyl furanoside **2** resulted in a preference, albeit modest, for the *trans*-2,5-disubstituted THF.[6] In pursuing this idea of using conformationally restricted acetal alkenes as templates for stereoselective halocyclizations, we speculated that isopropylidene derivatives of 5,6-dihydroxyalkenes of the type **3** should be *trans* selective, because of the similarity of their topography to the β-furanoside framework. In order to test this hypothesis, the halocyclization reactions of isopropylidene derivatives of 5,6-dihydroxyalkenes of varying stereochemistry and alkene substitution were investigated. The results of this study are described herein (Scheme 1).

The preparation of the terminal alkene substrates started with the addition of 4-butenylmagnesium bromide to 2-hydroxyhexanal, obtained via the selective TEMPO oxidation of commercially available hexane-1,2-diol.[7] This led to an inseparable mixture of dihydroxyalkenes **4**:**5** (*threo*:*erythro* = ~3:2) which was converted to a mixture of isopropylidene alkenes **6**:**7**, also inseparable by chromatography. As events unfolded, it turned out that the halocyclization reaction was instrumental

Scheme 1



in the obtention of pure samples of **6** and **7**. Treatment of the mixture of **6** and **7** with iodonium dicollidine perchlorate (IDCP) in wet dichloromethane led to the formation of a mixture of two of the four possible THF's.[8] Chromatographic separation gave the THF's **8** and **9**, which were both subsequently determined to be the *trans* isomers. Zinc-mediated reductive elimination of pure **8** and **9** gave the *threo* and *erythro* diol alkenes **4** and **5**, respectively. Acetonation of **4** and **5** led to separated samples of isopropylidene alkenes *threo*-**6**, and *erythro*-**7**, respectively. Thus, it follows that the iodocyclization of **6** and **7** gave only the *trans* THF products. This was confirmed by repeating the iodocyclization on individual samples of **6** and **7** (Scheme 2).

For comparison, iodocyclization of the separated *threo* or *erythro* dihydroxyalkenes **4** and **5** led to an approximately 3:2 mixture of the *trans*:*cis* THF's in each case. The configuration of the THF products was assigned by observation of an NOE between the carbinol protons in the *cis* THF's and by comparison of the ^{13}CNMR spectra for the *cis* and *trans* isomers.[5,9] The configuration of *threo* and *erythro* isopropylidene precursors was assigned by comparing the chemical shifts of the methyl groups of the acetonide.[10]

The iodocyclization of isopropylidine *Z* and *E* alkenes, *threo*-(*Z*)-**10**, *erythro*-(*Z*)-**11**, *threo*-(*E*)-**14**, and *erythro*-(*E*)-**15**, were next examined. The *Z* derivatives were prepared by the Wittig olefination on the aldehydes derived from ozonolysis of the respective terminal alkenes **6** and **7**. The *E* substrates were obtained by application of the Vedejs alkene isomerization procedure on the corresponding *Z* compounds.[11] The reaction of each isopropylidene alkene **10**, **11**, **14**, or **15** led to a single trans THF product **12**, **13**, **16**, or **17**, respectively, in a yield of greater than 90%. As was observed for the terminal alkenes, the cyclization of the corresponding dihydroxyalkenes gave approximately equal proportions of the *cis* and *trans* isomers. THF stereochemistry was assigned as described for the simpler systems (Table 1).

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Scheme 2

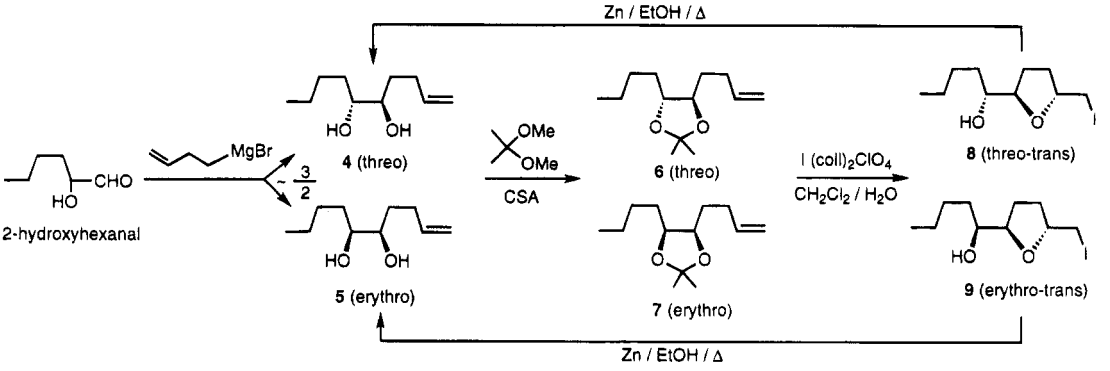


Table 1

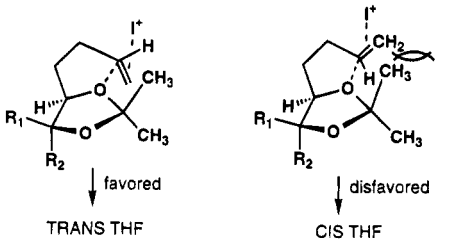
Alkene Precursor	THF Product - % Yield*
6 (threo)	8 (threo-trans) - 88
7 (erythro)	9 (erythro-trans) - 93
10 (threo-Z)	12 (threo-trans-threo) - 91
11 (erythro-Z)	13 (erythro-trans-threo) - 95
14 (threo-E)	16 (threo-trans-erythro) - 92
15 (erythro-E)	17 (erythro-trans-erythro) - 91

*Yield refers to isolated, purified material

The high stereoselectivity observed in the reactions of these isopropylidene alkene systems appears to be consistent with the formation of a THF-oxonium ion intermediate which has a cis fused [5.5.0]oxahydrindan type geometry. The THF-oxonium ion which leads to the *cis* THF product would be disfavored because of steric crowding (due to interactions between the C5 iodoalkyl substitutent of the eventual THF and the methyl group of the acetonide) in the concave region of the transition state.[12] The higher selectivity observed for these isopropylidene systems compared to the methyl β-furanoside prototype on which this idea was spawned might be a consequence of the increased spatial demands of the CH_3 group compared to that of the OCH_3 substituent[13] (Scheme 3).

Although moderate to high *trans* selectivity has been noted in the mercuriocyclization of related 5-hydroxy-

Scheme 3



alkenes,[14] the stereoselectivity of the halonium ion mediated process is usually modest and highly substrate dependent.[4] The high *trans* preference observed in this study is complementary to the *cis* selectivity which has been observed for the halocyclization of 2,6-dichlorobenzyl ethers of 5-hydroxyalkenes and, in our earlier investigation, on trityl pyranosides.[4,5] The isopropylidene methodology may be also compared with the metal-promoted, oxidative cyclizations of related 5,6-dihydroxyalkenes and 5-hydroxyalkenes which lead to *cis* and *trans* THF's, respectively, but it stands out because of the mildness of the reaction conditions and the high yields of the THF product.[15,16] The easy availabilty of D- or L-isopropylidenealkene precursors,[17] the extremely high stereoselectivity in substrates of different stereochemistry and alkene substitution, and the inherent advantage in terms of alcohol protecting group chemistry combine to make this a practical and versatile methodology for the preparation of complex *trans* 2,5-disubstituted THF's. Application of these results to the synthesis of the THF-containing acetogenins and to complex polyethers is currently in progress and will be reported in due course.

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Supporting Information Available: Representative procedures for the preparation of alkene precursors and the iodoetherification reaction as well as ^1H and ^{13}CNMR for compounds **4**−**17** are provided (32 pages).

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(12) This transition state geometry is expected even though a pyramidal oxonium ion might be somewhat flattened compared to a tetrahedral carbon. The methyl group in the methyl THF cation has been calculated to lie out of the C2−O−C5 plane by only 8.5° (ref 4). The analysis should be the same whether a halonium ion or charge transfer complex is the species which undergoes nucleophilic attack. For simplicity, the latter is depicted here.

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