1,2-*O*-Isopropylidenefuranose Templates for the Synthesis of Complex Cyclic Ethers via Neighboring Group Participation by the Acetal Ring Oxygen

Weifang Shan, Phyllis Wilson, Wei Liang, and David R. Mootoo*

Department of Chemistry, Hunter College, 695 Park Avenue, New York, New York 10021

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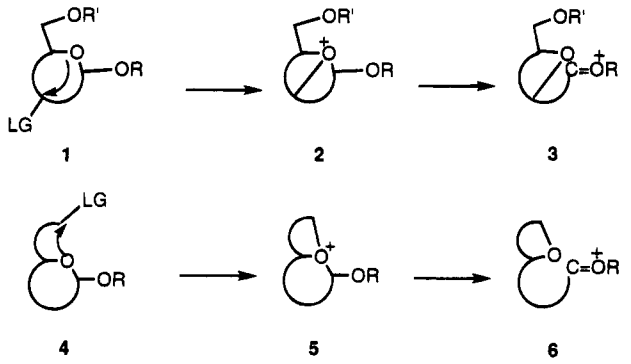
Novel strategies are described for the direct transformation of C5-allylated-1,2-O-isopropylidenefuranoses into complex cyclic ethers. Reaction of these substrates with iodonium ion under aqueous conditions resulted in the facile formation of 2,5-disubstituted tetrahydrofurans (THF's) containing highly substituted branches, in good to high yields, albeit with modest cis stereoselectivity. A similar result was obtained for the one case of the analogous tetrahydropyran (THP) system that was examined. These reactions presumably proceed via neighboring group participation by the acetal ring oxygen on an iodonium ion–alkene charge transfer complex to give a cyclic oxonium ion, thence a cyclic ether–oxocarbenium ion which undergoes intermolecular capture by water. Under anhydrous conditions, substrates which contained a 3-*O*-(2′-methyl-2′-buten-4′-yl) substituent led to high yields of adjacently connected THF–THP or THP–THP structures. These products are explainable in terms of a two-step process in which a cyclic ether–oxocarbenium ion, resulting from the initial participation reaction, undergoes nucleophilic capture by the activated alkene. A notable feature of this reaction was that only a single THP isomer was obtained in the second ring forming reaction, presumably a consequence of the cyclic nature of the oxocarbenium ion derived from the 1,2-*O*-isopropylidene acetal residue.

Introduction

Carbohydrate precursors are commonly used in the preparation of highly oxygenated cyclic ether compounds.[1] A central aspect of these procedures is the manipulation of the anomeric center and problems in this area usually lower synthetic efficiency.[2] Strategy based on neighboring group participation by the ring oxygen at a remote electrophilic site offers an expeditious way of transforming monosaccharides into cyclic ethers, since both acetal cleavage and ether formation may be accomplished in the same reaction. Two variations of this idea are conceivable, depending on whether the electrophilic center is positioned on the ring (i.e. **1**) or on a carbon branch (i.e. **4**). Conformational factors permitting, formation of the bicyclic oxonium ions **2** or **5**, followed by preferential cleavage of the internal C–O acetal bond would lead to highly substituted cyclic ether–oxocarbenium ion structures **3** and **6** (Scheme 1).

Isolated examples of ring oxygen participation reactions in which the leaving group is located on the ring have been reported.[3] However, methodology in this area has remained relatively undeveloped, primarily due to the harsh solvolysis conditions required to effect these reactions, or the regioselectivity of fragmentation of the bicyclic oxonium ion species. Halonium ion-mediated cleavage of alkenyl acetals opens up new possibilities because of the mildness of the reaction conditions.[4] One variation of this strategy corresponding to the situation described in **4**, employs a monosaccharide **7** which is allylated at its primary alcohol terminus.[5] Treatment of

Scheme 1



7 with halonium ion, results in the formation of the charge transfer complex **8** (or halonium ion). Neighboring group participation by the ring oxygen leads to the oxonium ion **9**, which fragments to the oxocarbenium **10**. Capture of **10** by a nucleophile gives rise to a cyclic ether **11** which contains highly functionalizable branches (Scheme 2).

1,2-*O*-Isopropylidenexylofuranose templates **12** were chosen for the evaluation of this plan since they are easily obtained and experimentally simple procedures for elaboration of the C3, C4 and C5 positions with high stereocontrol are well known.[6,7] Capture of the oxocarbenium

[⊗] Abstract published in *Advance ACS Abstracts,* November 15, 1994.

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(2) (a) Mootoo, D. R.; Fraser-Reid, B. *Carbohydr. Res.* **1988**, *74*, 99. (b) Askin, D.; Angst, C.; Danishefsky, S. *J. Org. Chem*, **1987**, *52*, 622.

(3) Capon, B. *Chem. Rev.* **1969**, *69*, 407.

(4) (a) Mootoo, D.; Fraser-Reid, B. *J. Chem. Soc. Chem. Commun.* **1986**, 1570. Mootoo, D. R.; Date, V. Fraser-Reid, B. *J. Chem. Soc. Chem. Commun.* **1987**, 1462. (b) Mootoo, D. R.; Date, V.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 2662.

(5) For preliminary accounts of this work: (a) Elvey, S.; Mootoo, D. R. *J. Am. Chem. Soc.* **1992**, *114*, 9685. (b) Wilson, P.; Shan, W.; Mootoo, D. R, *J. Carbohydr. Chem.* **1994**, *13*, 133.

(6) For recent examples: (a) Tulshian, D.; Doll, R. J.; Stansberry, M. F.; McPhail, A. T. *J. Org. Chem*, **1991**, *56*, 6819. (b) Tadano, K.; Murata, T.; Kumagai, T.; Isshiki, Y.; Ogawa, S. *J. Carbohydr. Chem.* **1993**, *12*, 1187. (c) Danishefsky, S. J.; DeNinno, M. P.; Phillips, G. B.; Zelle, R. E.; Lartey, P. A. *Tetrahedron* **1986**, *42*, 2809.

(7) For examples of the use of 1,2-*O*-isopropylidenefuranoses of other configurations: Witty, D. R.; Fleet, G. W. J.; Vogt, K.; Wilson, F. X.; Wang, Y.; Storer, R.; Myers, P. L.; Wallis, C. J. *Tetrahedron Lett.* **1990**, *31*, 4787.

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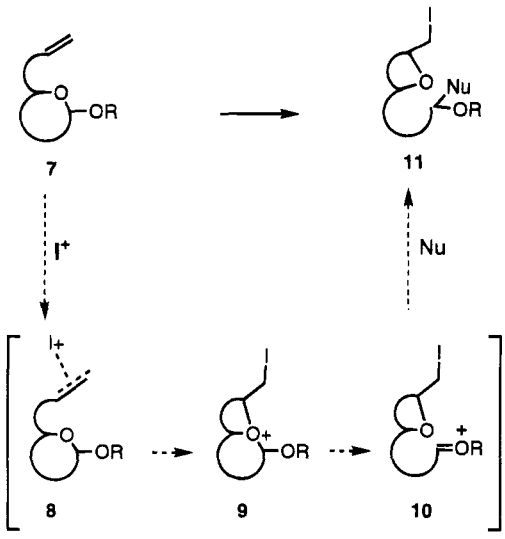
Scheme 2



ion **14** by water leads to synthetically versatile oxygenated cyclic ethers of the type **15**, which are structurally related to several interesting marine natural products.[8] One extension of this methodology relates to the capture of the oxocarbenium ion by a C-nucleophile tethered to one of the ring oxygen substituents. This will result in the tandem formation of two cyclic ethers. 1,2-*O*-isopropylidene precursors are especially appropriate for application of this idea since the C3-OH in these cases is readily distinguished from the other alcohols and therefore provides a convenient point of attachment to a nucleophilic site. In this case the product will be an adjacently linked bis-ether structure.[9] Furthermore, the conformational rigidity of the [3.3.0] system **13** and the cyclic nature of the oxocarbenium ion intermediate **14** could be important for conferring remote stereochemical control at the "off-template" stereogenic centers generated in both ether forming steps[6c,10] (Scheme 3).

Results

Initial Cyclic Ether Formation. One of the early concerns was that the conformational rigidity of the cis fused [5.5.0] bicyclic system would impose severe trajectory constraints on THF-oxonium ion formation and therefore decrease the propensity of neighboring group participation. In this case the intermolecular capture of **8** could predominate, leading to halohydrin type derivatives of the starting alkene. This problem might be exacerbated in the case of systems having C5 substituents due to unfavorable transannular interactions in the newly formed ether or with substituents on the sugar ring. In order to examine this problem the substrates **18**, **20**, and **22** were prepared. These compounds were obtained via benzylation or silylation of the previously prepared alcohol derivatives **17**,[11] **19**, and **21**[6c] (Scheme 4).

Treatment of **18**, **20**, and **22** with iodonium dicollidine perchlorate (IDCP)[12] in wet CH_2Cl_2 resulted in each case, in disappearance of the starting compounds within 5 min. The NMR data of the crude reaction products showed no evidence for the H1 signal that is characteristic of the 1,2-*O*-isopropylidenated furanose and was consistent with the formation of the THF-isopropylidenated hemiacetal type structure **23**. Due to the instability of these compounds, the crude reaction product was subjected to reduction using sodium borohydride, leading to cis/trans mixtures of the iodo-THF diols **24c/t**, **25c/t**, and **26c/t** in good to moderate yields from the respective alkenes. Notably, there was no evidence for iodohydrin formation or for the isomeric tetrahydropyranyl products.[13]

Modest preference was observed for formation of the cis-THF in all cases. The stereochemistry of **24c/t** was assigned by deiodination to **29c/t**, which was subjected to a straightforward degradation sequence to give the known *cis*/*trans*-5-methyltetrahydrofuran-2-methanol isomers.[14] As was the case for related 2,5-disubstituted THF-iodide structures previously prepared in this laboratory, the ^{13}C NMR resonances of the methylene carbons in the THF ring of the cis-THF occurred upfield, compared to those of the trans isomer (**24c**: 27.53 and 30.73 vs **24t**: 28.56 and 32.01 ppm).[5] The cis/trans assignment in the oxygenated THF's, **25c/t** and **26c/t**, was facilitated by transformation of the individual cis/trans mixture of products to a common deoxygenated derivative **34c/t**, thence to the identical, dehalogenated mixture **29c/t** that was obtained in the deoxy series. This was carried out via a straightforward six-step sequence on **25c/t** and **26c/t** , involving deoxygenation of their respective xanthates, **31c/t** and **33c/t**[15] (Scheme 5).

In order to gain preliminary insight into the facility of neighboring group participation in related THP substrates, the homologous alkene **27** was prepared via a three-step hydroboration–oxidation–methylenation sequence on **18.** As for the THF precursor, treatment of **27**, under the standard cyclization conditions in wet CH_2Cl_2, led within 10 min to exclusive formation of the cyclic ether product **28** in 80% yield, as a 3.5:1 mixture of isomers (Scheme 4).

Tandem Ether Formation. The bis-alkenes **35** and **38** were chosen as test substrates for the tandem methodology. **35** was prepared by alkylation of **17** with isoprenyl bromide. The alkene **38** was obtained from **35** via the three-step homologation sequence described for the preparation of **27**. Treatment of **35** with IDCP under anhydrous conditions, at high dilution (0.01 M), led within 10 min to a 3.5:1 mixture of cis:trans THF, ring A isomers, **36c/t** in 90% yield. Application of the identical reaction conditions to the homologous alkene **38**, led within 45 min to a 3.5:1 cis/trans mixture of cis/trans THP, ring A isomers **39c/t**, in 89% yield. That the mixtures obtained in both reactions originated in ring A was confirmed by conversion of the cyclization products **36c/t** and **39c/t**, under zinc-mediated reductive elimina-

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(9) For examples of naturally occuring adjacently linked polyethers: *Polyether Antibiotics: Naturally Occurring Acid Ionophores*; Westley, J. W., Ed.; Marcel Dekker: New York, 1983; Vols. 1 and 2.

(10) For other studies on "off-template" diastereoselection: (a) Brimacombe, J. S.; Hanna, R.; Kabir, A. K. M. S.; Bennet, F.; Taylor, I. D. *J. Chem. Soc., Perkin Trans. 1* **1986**, 815. (b) Isobe, M.; Ichikawa, Y.; Funabashi, Y.; Mio, S.; Goto, T. *Tetrahedron* **1986**, *42*, 2863. (c) Jarosz, S., Fraser-Reid, B. *Tetrahedron Lett.* **1989**, *30*, 2359.

(11) Mootoo, D.; Wilson, P.; Jammalamadaka, V. *J. Carbohydr. Chem.* **1994**, *13*, 841.

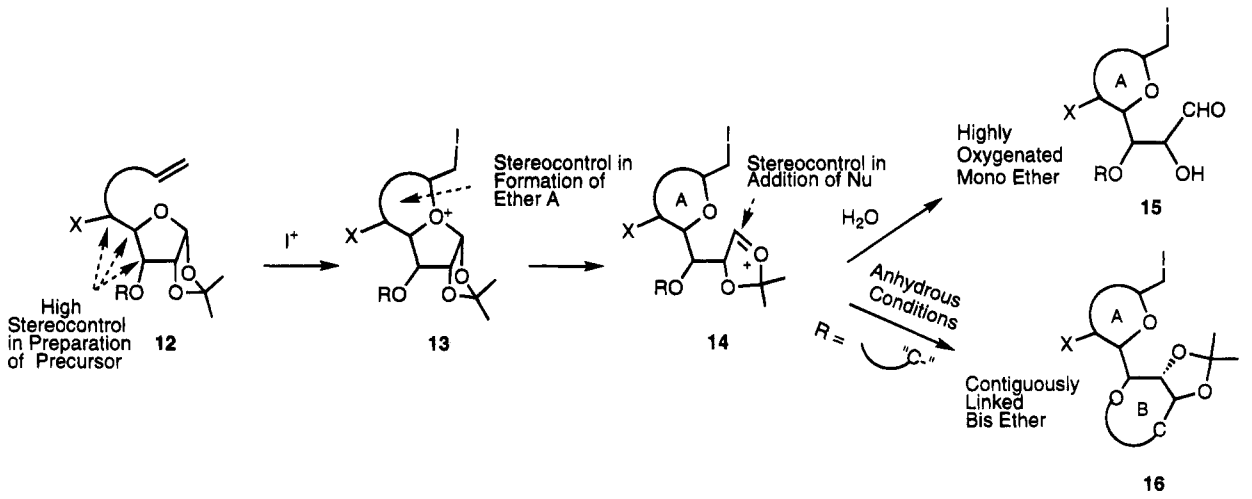
(12) Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2190.

(13) Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963. Bartlett, P. A.; Ting, P. C. *J. Org. Chem.* **1986**, *51*, 2230.

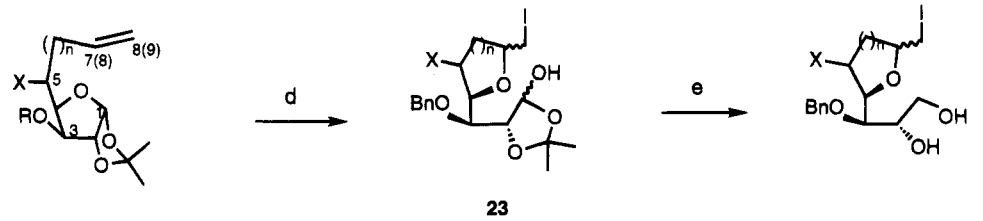
(14) Brown, H. C.; Lynch, G. T. *J. Org. Chem.* **1981**, *46*, 938. For comparison, a sample of *cis*/*trans*-5-methyltetrahydrofuran-2-methanol was prepared in two steps from commercially available 5-hexene-1,2-diol via iodoetherfication with NIS in dichloromethane to give the THF-iodide, which was subjected to n-Bu_3SnH reduction.

(15) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc. Perkin Trans. 1* **1975**, 1574.

Scheme 3



Scheme 4



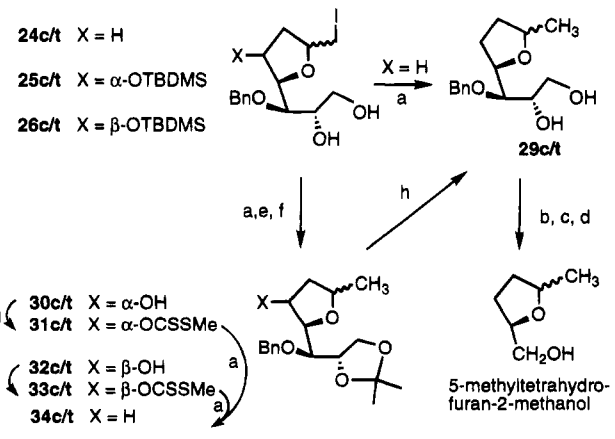
a 17 R = H, X = H
18 R = Bn, X = H
19 R = Bn, X = α-OH
20 R = Bn, X = α-OTBDMS
21 R = Bn, X = β-OH
22 R = Bn, X = β-OTBDMS
27 R = Bn, X = H
n = 1
n = 2

n = 1: **24c/t** X = H; 83%, c/t = 3.5/1; **25c/t** X = α-OTBDMS; 77%, c/t = 3/1; **26c/t** X = β-OTBDMS; 92%, c/t = 1.3/1

n = 2: **28c/t** X = H; 72%, c/t = 3.5/1

[a] (a) NaH, BnBr, nBu_4NI, DMF; (b) TBDMSCl, imidazole, DMF, 50 °C; (c) (i) 9-BBN, THF, and then Na_2O_2; (ii) Swern's oxidation; (iii) $Ph3P{=}CH_2$, THF; (d) $I(collidine)_2ClO_4$, $CH_2Cl_2-H_2O$; (e) $NaBH_4$, EtOH.

Scheme 5



[a] (a) Bu_3SnH, AIBN, PhH, 80 °C; (b) 10% Pd/C, MeOH–HCOOH; (c) $NaIO_4$, $THF-H_2O$; (d) $NaBH_4$, MeOH; (e) Bu_4NF, THF; (f) $Me_2C(OMe)_2$, CH_2Cl_2, camphorsulfonic acid; (g) NaH, imidazole, THF, CS_2, and then MeI; (h) MeOH, HCl.

tion reaction conditions, to the derived hydroxyalkenes which were converted to a single, peracetylated THP diastereomer **37** or **40** in each case (Scheme 6).

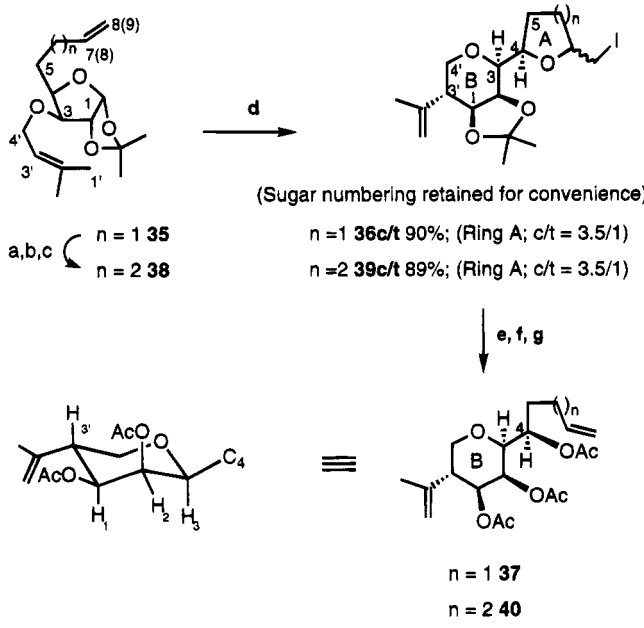
The THF configurations in **36c** and **36t** were assigned as for the mono THF **24c/t**, by comparison of the methylene carbons in the THF ring, (**36c:** 26.92 and 31.05 vs **36t:** 28.60 and 32.58 ppm). The major isomer in **39c/t** was assigned as the cis-THP in ring A based on the observation of a NOE effect between H-4 and H-8. The stereochemistry in ring B in both **36** and **39** was determined by analysis of the ^1H NMR coupling constants for **37** and **40**. This data indicated a chairlike conformation in which the C3 substituent is in an equatorial position, and the substituents attached to the contiguous C3′, C1, and C2 positions are equatorial, equatorial, axial, respectively, (for **37**: $J_{1,3'} = 11.5$, $J_{1,2} = 3.8$, $J_{2,3} < 0.5$ Hz; for **40**: $J_{1,3'} = 11.5$, $J_{1,2} = 3.2$, $J_{2,3} = 1.0$ Hz).

Discussion

Mechanistically, the reactions of the acetal alkenes involved in this study may be compared with the intramolecular haloetherification of alkoxyalkene derivatives,[13,16–18] Accordingly, electrophilic attack by the halonium ion leads initially to formation of a freely

(16) Reitz, A. B.; Nortey, S. O.; Maryanoff, B. E.; Liotta, D.; Monahan , R., III. *J. Org. Chem.* **1987**, *52*, 4191.
(17) Chamberlin, A. R.; Mulholland, R. L., Jr.; Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 672.
(18) Labelle, M.; Morton, H. E.; Guindon, Y.; Springer, J. P. *J. Am. Chem. Soc.* **1988**, *110*, 4533. Labelle, M.; Guindon, Y. *J. Am. Chem. Soc.* **1989**, *111*, 2204.

Scheme 6



[a] (a) 9-BBN, THF, and then Na_2O_2; (b) Swern's oxidation; (c) Ph_3PdCH_2; (d) $I(collidine)_2ClO_4$, CH_2Cl_2; (e) Zn, EtOH, reflux; (f) MeOH, HCl; (d) Ac_2O, DMAP, EtOAc.

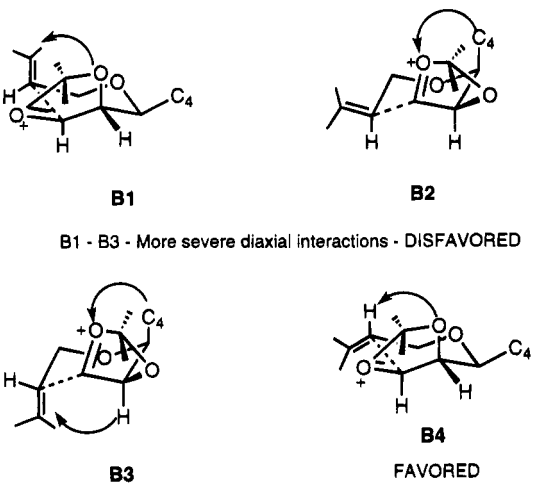
reversible charge transfer complex which undergoes rapid capture by the ring oxygen to give the bicyclic THF-oxonium ion, before progression to a three centered halonium ion can occur. All steps leading up to **10** are usually regarded as being reversible, although the extent of reversibility in the oxygen participation step has been debated. The subsequent fragmentation step is generally assumed to be irreversible. Thus, exclusive formation of THF type products over halohydrin arises from facile neighboring group participation and acetal bond cleavage steps. The low concentration of water in CH_2Cl_2 accentuates the relative rates of these two steps compared to the external capture of **8** or **9** by water.[19] This situation holds even in the case of the sterically more crowded allyl substrates **20** and **22** and the homoallyl THP precursor **27**, where the respective participation steps are expected to proceed more slowly than for the simple allyl substrate **18** (Scheme 2).

The preference, albeit modest, for the cis THF was somewhat surprising. The stereoselectivity of related haloetherification reactions has usually been rationalized in terms of the kinetic distribution of the initially formed charge transfer complexes, their relative rates of cyclization to the diastereomeric THF-oxonium ions and the extent to which the latter can equilibrate before fragmentation to the respective THF-oxocarbenium ions. If as generally believed, formation of the charge transfer complex is freely reversible, THF stereoselectivity will be determined solely in the cyclization step. Since the intermediate THF oxonium ion is expected to adopt a flattened cis fused [3.3.0] hydrindane type geometry, preference for the trans isomer was expected.[20] The

(19) Not suprisingly when the reaction of **20** was carried out in wet acetonitrile, an increasing proportion (compared to THF) of all four possible iodohydrin products was obtained as the concentration of water was increased.

(20) This is expected even allowing for a somewhat flattened geometry of the oxonium ion compared to 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 123).

Scheme 7



unexpected cis bias might be related to a relatively early transition state. In this case the relative energies of the diastereomeric transition states might be influenced more by torsional factors within the acyclic chain of the THF ring that is being formed, rather than by the structure of the fully formed bicyclic THF-oxonium ion intermediate.[18] Any further speculation regarding transition state geometry at this stage will be purely conjectural, in view of the low diastereoselectivity and limited number of examples examined.

On the other hand, the high stereoselectivity in formation of the THP ring (ring B) in the tandem reaction appears to be consistent with a relatively simple model based on conformational analysis of six-membered rings.[21] Thus a transition state in which the forming ring adopts a chair like geometry, and the direction of attack on the cyclic oxocarbenium ion is that which leads to a cis fused [4.3.0.] system, as opposed to the more strained trans fused structure, is reasonable. Four possible conformers **B1**–**B4** may be written which fulfill these requirements. Of these **B4** should be clearly favored due to severe 1,3 diaxial interactions in the others, thereby accounting for the high stereoselectivity. The size of the ring formed in the initial halocyclization reaction should have little effect on the geometry of the transition state involved in the second cyclization, thus accounting for the identical stereselectivity in formation of ring B in **36** and **39**.

In summary, a novel methodology for the direct transformation of monosaccharide alkenes into cyclic ether structures has been developed. The strategy is based on neighboring group participation by the ring oxygen and involves regiospecific endocyclic C–O bond cleavage to give the open chain aldehydium ion. The latter may be captured by water to give a monocyclic ether or by an internal carbon nucleophile tethered to one of the ring alcohols to give a bis cyclic ether. The approach is complementary to the more obvious one of converting monosaccharides to cyclic ethers via the cyclic oxocarbenium intermediate and opens up alternative ways of identifying hidden carbohydrate symmetry in complex targets. The mild, nonacidic reactions conditions are compatible with a number of alcohol protecting groups, and this presents an obvious advantage when dealing with highly oxygenated systems. The use of 1,2-O-isopropylidenefuranose building blocks facilitates the

(21) Winstead, R. C.; Simpson, T. H.; Lock, G. A.; Schiavelli, M. D.; Thompson, D. W. *J. Org. Chem.* **1986**, *51*, 275.

operation of novel mechanisms for transfer of chirality from the carbohydrate ring to "off template" positions, thereby illustrating the potential for preparation of compounds bearing multiple stereogenic centers. The application of these principles to natural product synthesis is currently in progress and will be reported in due course.

Experimental Section

General. TLC was performed on aluminum sheets precoated with silica gel 60 (HF-254, E. Merck) to a thickness of 0.25 mm. Flash column chromatography was performed using Kieselgel 60 (230–400 mesh, E. Merck) and employed a stepwise solvent polarity gradient, correlated with TLC mobility. ^1H and ^{13}C NMR spectra were recorded on a GE QE 300 instrument at 300 and 75.5 MHz, respectively, in $CDCl_3$ solutions, with $CHCl_3$ as internal standard. Chemical shifts are reported in parts per million Optical rotations were determined on a Rudolph Research AUTOPOL III automatic polarimeter. Melting points are reported uncorrected.

5,6,7,8-Tetradeoxy-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-oct-7-enofuranose (18). NaH (78 mg, 1.95 mmol, 60% suspension in mineral oil) and n-Bu_4NI (27 mg, 0.07 mmol) was added to a solution of **17**[11] (150 mg, 0.7 mmol) in anhydrous DMF (3 mL) at 0 °C. The suspension was stirred at this temperature for 15 min, at which time benzyl bromide (0.17 mL, 1.4 mmol) was added. The reaction was warmed to rt and stirred for an additional 1 h. MeOH (0.1 mL) was then added and stirring continued for 15 min The reaction mixture was poured into water (25 mL) and extracted with ether (4 × 15 mL). The organic phase was washed with brine (25 mL), dried (Na_2SO_4), filtered, and evaporated in vacuo to give a brown syrup. Flash column chromatography afforded **18** (195 mg, 92%): clear oil; R_f 0.65 (20% EtOAc/PE); $[\alpha]^{25}_D$ −50.9° (*c* 3.0, $CHCl_3$); ^1H NMR 1.32, 1.49 (both s, 3H ea), 1.65–2.20 (m, 4H), 3.77 (d, J = 3.02 Hz, 1H), 4.15 (m, 1H), 4.59 (ABq, $\Delta\delta$ = 0.23 ppm, J = 12.0 Hz, 2H), 4.62 (d, J = 3.95 Hz, 1H), 4.99 (m, 1H), 5.81 (m, 1H), 5.91 (d, J = 3.92 Hz, 1H), 7.34 (m, 5H). Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.01; H, 7.96. Found: C, 71.11; H, 7.97.

6,7,8,-Trideoxy-3-*O*-benzyl-5-*O*-(*tert*-butyldimethylsilyl)-1,2-*O*-isopropylidene-α-D-*gluco*-oct-7-enofuranose (20). TBDMSCl (460 mg, 3.0 mmol) and imidazole (230 mg, 3.38 mmol) were added to a solution of alcohol **19**[6c] (480 mg, 1.58 mmol) in dry DMF (5 mL). The temperature was raised to 50 °C and the reaction mixture stirred at this temperature for 2 h. The reaction mixture was poured into water (100 mL) and extracted with ether (4 × 50 mL). The organic phase was washed with brine (50 mL), dried (Na_2SO_4), filtered, and evaporated in vacuo. Flash chromatography of the crude product gave **20** (502 mg, 73%): clear oil; R_f 0.80 (10% EtOAc/PE); $[\alpha]^{25}_D$ −29.09° (*c* 1.3, $CHCl_3$); ^1H NMR 0.04, 0.11, (both s, 3H ea), 0.93 (s, 9H), 1.37, 1.54 (both s, 3H ea), 2.49 (m, 2H), 4.05 (d, J = 2.7 Hz, 1H), 4.12 (dd, J = 2.7, 8.0 Hz, 1H), 4.25 (m, 1H), 4.66 (m, 3H), 5.18 (m, 2H), 5.91 (d, J = 3.6 Hz, 1H), 5.98 (m, 1H), 7.37 (m, 5H). Anal. Calcd for $C_{24}H_{38}O_5Si$: C, 66.32; H, 8.81. Found: C, 66.49; H, 8.76.

6,7,8,-Trideoxy-3-*O*-benzyl-5-*O*-(*tert*-butyldimethylsilyl)-1,2-*O*-isopropylidene-α-L-*ido*-oct-7-enofuranose (22). Alcohol **21**[6c] (1.63 g, 5.10 mmol) was treated under the conditions described for the preparation of **20**, using dry DMF (10 mL), TBDMSCl (1.54 g, 10.2 mmol), and imidazole (0.76 g, 11.2 mmol). Flash chromatography of the crude product gave **22** (2.53 g, 90%): clear oil; R_f 0.85 (10% EtOAc/PE); $[\alpha]^{25}_D$ −5.7° (*c* 1.0, $CHCl_3$); ^1H NMR: 0.12, 0.16 (both s, 3H ea), 0.93 (s, 9H), 1.38, 1.54 (both s, 3H ea), 2.20 (m, 2H), 3.90 (d, J = 2.7 Hz, 1H), 4.05 (m, 2H), 4.60 (ABq, $\Delta\delta$ = 0.22 ppm, J = 12.0 Hz, 2H), 4.65 (d, J = 3.6 Hz, 1H), 5.01 (m, 2H), 5.94 (m, 1H), 5.99 (d, J = 3.6 Hz), 7.39 (m, 5H). Anal. Calcd for $C_{24}H_{38}O_5Si$: C, 66.32; H, 8.81. Found: C, 66.45; H, 8.73.

5,6,7,8,9-Pentadeoxy-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-non-8-enofuranose (27). 9-BBN (6.90 mL, 0.5 M solution in THF, 3.45 mmol) was added at 0°C to a solution of **18** (705 mg, 2.32 mmol) in anhydrous THF (12 mL), under an argon atmosphere. The reaction was warmed to rt and stirred at this temperature for an additional 8 h. The solution was then cooled to 0 °C, a mixture of 30% H_2O_2 (2 mL) and 3 N NaOH (2 mL) carefully added, and stirring was continued for an additional 0.5 h. The resulting suspension was diluted with water (100 mL) and extracted with ether (4 × 50 mL). The organic phase was washed with brine (50 mL), dried (Na_2SO_4), filtered, and evaporated in vacuo to give a pale brown syrup. Flash column chromatography afforded the primary alcohol derivative (612 mg, 72%): R_f 0.20 (30% EtOAc/PE); ^1H NMR: 1.32, 1.48 (both s, 3H ea), 1.40–1.90 (m, 6H), 3.66 (t, J = 6.0 Hz, 1H), 3.78 (d, J = 3.0 Hz, 1H), 4.12 (m, 1H), 4.48 (d, J = 12.0 Hz, 1H), 4.62 (d, J = 3.9 Hz, 1H), 4.71 (d, J = 12.0 Hz, 1H), 5.91 (d, J = 3.9 Hz, 1H), 7.35 (m, 5H).

DMSO (0.73 mL, 10.2 mmol) was added dropwise to a solution of oxalyl chloride (0.74 mL, 8.5 mmol) in dry CH_2Cl_2 (20 mL) at −78 °C, under an atmosphere of argon. After stirring for 20 min at this temperature, a sample of the alcohol that was obtained in the previous step (550 mg, 1.70 mmol) in dry CH_2Cl_2 (10 mL) was slowly introduced via syringe. The reaction was maintained at −78 °C for 25 min at which time Et_3N (2.35 mL, 17.0 mmol) was slowly added, the mixture warmed to 0 °C, and then diluted with water (50 mL). The resulting suspension was extracted with ether (3 × 50 mL) and the organic phase washed with brine (50 mL), dried (Na_2SO_4), filtered, and evaporated in vacuo to give a yellow syrup. Flash column chromatography afforded the derived aldehyde (405 mg, 74%): R_f 0.50 (30% EtOAc/PE); ^1H NMR 1.34, 1.48 (both s, 3H ea), 1.42–1.85 (m, 4H), 2.50 (m, 2H), 3.80 (d, J = 3.6 Hz, 1H), 4.15 (m, 1H), 4.27 (d, J = 11 Hz, 1H), 4.62 (d, J = 4.2 Hz, 1H), 4.74 (d, J = 11 Hz, 1H), 5.92 (d, J = 4.0 Hz, 1H), 7.20–7.50 (m, 5H), 9.74 (br s, 1H).

A solution of methyltriphenylphosphorane in THF was prepared by addition of n-BuLi (4.4 mL, 1.6 M solution in hexanes, 7.04 mmol) to a suspension of methyl triphenylphosphonium bromide (2.62 g, 7.34 mmol) in dry THF (20 mL) under an argon atmosphere. The resulting bright yellow solution was stirred at rt for 20 min and then cooled to −78 °C. A solution of the aldehyde (402 mg, 0.97 mmol) which was obtained in the previous step, in anhydrous toluene (10 mL), was slowly introduced via syringe over a period of 10 min and the temperature warmed to rt. The reaction mixture was diluted with ether (100 mL) and the suspension filtered through a bed of Celite. The filtrate was evaporated in vacuo and the residual oil purified by flash chromatography to give **27** (322 mg, 80%): clear oil; R_f 0.60 (20% EtOAc/PE); ^1H NMR 1.32, 1.48 (both s, 3H ea), 1.30, 1.50 (both m, 1H ea buried under s at 1.32 and 1.48), 1.60–1.86 (m, 2H), 2.08 (m, 2H), 3.78 (d, J = 3.0 Hz, 1H), 4.14 (m, 1H), 4.48 (ABq, $\Delta\delta$ = 0.25 ppm, J = 12.0 Hz, 2H), 4.62 (d, J = 3.6 Hz, 1H), 4.88–5.08 (m, 2H), 5.78 (m, 1H), 5.91 (d, J = 3.6 Hz, 1H), 7.2–7.5 (m, 5H). Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.56; H, 8.59.

5,6,7,8,-Tetradeoxy-3-*O*-(2′-methyl-2′-buten-4′-yl)-1,2-*O*-isopropylidene-α-D-*xylo*-oct-7-enofuranose (35). Alcohol **17** (210 mg, 0.98 mmol) was treated under the standard O-alkylation procedure described for the preparation of **18**, using NaH (120 mg , 60% suspension in mineral oil, 2.78 mmol), 1-bromo-2-methyl-2-butene (0.34 mL, 3.0 mmol), and n-Bu_4NI (30 mg, 0.08 mmol) in dry DMF (2 mL). Flash chromatography of the crude product gave **33** (0.23 g, 83%): clear oil; R_f 0.65 (20% EtOAc/PE); ^1H NMR 1.25, 1.44 (both s, 3H ea), 1.64, 1.66 (both s, 3H ea), 1.68 (m, 2H), 2.10 (m, 2H), 3.62 (d, J = 3.0 Hz, 1H), 3.96 (dd, J = 8.8, 13.2 Hz, 1H), 4.14 (m, 2H), 4.56 (d,, J = 3,6 Hz, 1H), 4.96 (dd, J = 1.2, 13.2 Hz, 1H), 5.04 (dd, J = 1.2, 17.6 Hz, 1H), 5.16 (br t, J = 8.8 Hz, 1H), 5.83 (m, 1H), 5.90 (d, J = 3.6 Hz, 1H). Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.05; H, 9.28. Found: C, 68.18; H, 9.12.

5,6,7,8,9-Pentadeoxy-3-*O*-(2′-methyl-2′-buten-4′-yl)-1,2-*O*-isopropylidene-α-D-*xylo*-non-8-enofuranose (38). 9-BBN (4.1 mL, 0.5M solution in THF, 2.1 mmol) was added at 0 °C to a solution of **34** (482 mg, 1.7 mmol) in anhydrous THF (20 mL), under an argon atmosphere. The reaction was maintained at this temperature for 1.5 h and then warmed to rt and stirred at for an additional 4 h. The solution was then cooled to 0 °C, a mixture of 30% H_2O_2 (2 mL) and 3 N NaOH

(2 mL) carefully added, and stirring continued for an additional 0.5 h. The resulting suspension was processed as described in the preparation of **27**. Flash column chromatography afforded the primary alcohol (370 mg, 72%): R_f 0.15 (20% EtOAc/PE); ^{1}H NMR 1.28, 1.46 (both s, 3H ea), 1.65, 1.76 (both s, 3H ea), 1.30–1.80 (m, 6H), 3.62 (t, J = 7.2 Hz, 2H), 3.68 (d, J = 3.0 Hz, 1H), 3.94 (dd, J = 10.5, 14.0 Hz, 1H), 4.08 (m, 1H), 4.54 (d, J = 3.6 Hz, 1H), 5.28 (br t, J = 10.5 Hz, 1H), 5.85 (d, J = 3.6 Hz, 1H).

The Swern procedure described in the preparation of **27** was applied to a sample of the primary alcohol (350 mg, 1.2 mmol) obtained in the previous step. Flash column chromatography of the crude reaction mixture afforded the aldehyde (290 mg, 84%): R_f 0.30 (20% EtOAc/PE); ^{1}H NMR 1.16, 1.26 (both s, 3H ea), 1.64, 1.77 (both s, 3H ea), 1.73 (m, 4H), 2.49 (m, 2H), 3.66 (d, J = 2.4 Hz, 1H), 3.94 (dd, J = 11.0, 13.2 Hz, 1H), 4.10 (m, 2H), 4.55 (d, J = 3.8 Hz, 1H), 5.28 (br t, J = 8.4 Hz, 1H), 5.86 (d, J = 3.8 Hz, 1H), 9.75 (br s, 1H).

The Wittig procedure described in the preparation of **27** was applied to the aldehyde (290 mg, 0.97 mmol) which was obtained in the previous step. Flash column chromatography of the crude reaction mixture afforded **38** (250 mg, 85%): clear oil; R_f 0.65 (20% EtOAc/PE); $[\alpha]^{25}_D$ −46° (c 0.7, $CHCl_3$); ^{1}H NMR 1.31, 1.48 (both s, 3H ea), 1.5 (m, 2H), 1.67, 1.74 (both s, 3H ea), 1.70 (m, 2H), 2.09 (q, J = 6.9 Hz, 1H), 3.68 (d, J = 3.0 Hz, 1H), 3.96 (dd, J = 7.2, 12.4 Hz, 1H), 4.10 (m, 2H), 4.55 (d, J = 3.6 Hz, 1H), 4.94 (m, 1H), 5.04 (m, 1H), 5.30 (m, 1H), 5.82 (m, 1H), 5.87 (d, J = 3.6 Hz, 1H). Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.05; H, 9.28. Found: C, 71.56; H, 8.59.

Preparation of THF 24c/t. I(coll)$_2$ClO$_4$[12] (180 mg, 0.39 mmol) was added to a solution of **18** (100 mg, 0.33 mmol) in a mixture of CH_2Cl_2 (3 mL) and water (0.3 mL). After 10 min, the reaction mixture was poured into 10% aqueous $Na_2S_2O_3$ (20 mL) and extracted with ether (3 × 15 mL). The organic phase was washed with brine (20 mL), dried (Na_2SO_4), filtered, and evaporated in vacuo to give a crude sample of **23** (X = H) as a brown syrup; ^{1}H NMR 1.36, 1.46, 1.51, 1.56 (all s, 6H), 1.90 (m, 4H), 3.20 (m, 2H), 3.48, 3.73 (both m, 1H), 4.17 (m, 3H), 4.80 (m, 2H), 5.56, 5.60, 5.62, 5.64 (all d, J = 2.4 Hz ea), 7.30 (m, 5H).

The crude product from above was triturated with EtOAc and filtered through a short column of silica gel, and the filtrate was concentrated in vacuo. The residue was dissolved in MeOH (5 mL) and treated with $NaBH_4$ (20 mg, 0.54 mmol) at rt for 30 min. The reaction mixture was cooled to 0 °C and carefully neutralized by the addition of a 5% solution of hydrochloric acid in MeOH. The solvent was removed in vacuo, the residue triturated with ethyl acetate, and the resulting suspension filtered through a bed of Celite. Removal of the volatiles in vacuo, followed by flash chromatography of the residual syrup, gave as an inseparable mixture of THF isomers, **24c/t** (110 mg, 83%, resp ratio = 3.5:1 as determined from the di-*O*-acetate derivative): clear gum; R_f 0.25 (50% EtOAc/PE); ^{1}H NMR 1.85, 2.15 (both m, 2H ea) 2.94 (br s, 2 × OH), 3.30 (m, 2H), 3.46 (m, 1H), 3.62 (m, 1H), 3.82 (m, 2H), 4.18 (m, 1H), 4.38 (m, 1H), 4.80 (m, 2H), 7.42 (m, 5H); ^{13}C NMR 10.14, 10.25, 27.53, 28.56, 30.73, 32.01, 62.95, 63.11, 71.14 , 71.32, 73.81, 78.58, 78.69, 79.68, 80.45, 80.68, 127.51, 127.90, 127.95, 137.88.

For characterization purposes, **24c/t** was converted to the di-*O*-acetate derivative via the following procedure. Acetic anhydride (0.1 mL, 1.1 mmol) and DMAP (10 mg, 0.08 mmol) were added to a solution of **24c/t** (80 mg, 0.26 mmol) in EtOAc (5 mL). After stirring at rt for 30 min, MeOH (0.1 mL) was added to the reaction mixture and the solvent removed in vacuo. The resultant syrup was purified by flash chromatography to give as an inseparable mixture, **24c/t**-di-*O*-acetate (81 mg, 83%): clear oil; R_f 0.60 (50% EtOAc/PE); ^{1}H NMR: 1.60–2.20 (m, 4H), 1.99, 2.00, 2.03 and 2.06 (all s, 6H), 3.20 (m, 2H), 3.51 (m, 1H), 4.06–4.30, 4.55 (m, dd resp , J = 3.6, 12 Hz, 4H), 4.75 (m, 2H), 5.14, 5.27 (both m, resp ratio = 1:3.5, 1H), 7.32 (m, 5H). Anal. (mixture) Calcd for $C_{19}H_{25}IO_6$: C, 47.90; H, 5.30; I, 26.64. Found: C, 47.69; H, 5.40; I, 26.56.

Preparation of THF 25c/t. Furanoside alkene **20** (260 mg, 0.60 mmol) was subjected to the standard iodocyclization-reduction procedure described for the reaction of **18**. Flash chromatography of the crude product obtained after the reduction step, afforded as an inseparable mixture **25c/t** (0.25 g, 80%, resp ratio 3:1 as determined from the di-*O*-acetate derivative), clear gum; R_f 0.45 (50% EtOAc/PE); ^{1}H NMR: 0.30, 0.37 (both s, 6H), 2.28, 2.50 (both s, 9H), 1.73, 1.85, 2.22 (all m, 2H), 2.86 (m, 2 × OH), 3.20 (m, 2H), 3.48 (m, 2H), 3.79 (m, 2H), 4,15 (m, 3H), 4.53 (m , 2H), 7.30 (m, 5H); ^{13}C NMR −4.20, −4.12, −3.92, 9.36, 10.80, 18.49, 26.42, 41.20, 42.71, 63.16, 71.41, 74.26, 75.02, 75.58, 78.75, 79.12, 80.28, 86.80, 88.01, 128.62, 128.80, 128.86, 129.13, 138.50. Anal. Calcd (mixture) $C_{21}H_{35}IO_5Si$: C, 48.27; H, 6.75. Found: C, 48.68; H, 6.85.

For characterization purposes, **25c/t** was converted to the di-*O*-acetate derivative according to the procedure described for the acetylation of **24c/t**. For **25c/t**-di-*O*-acetate: R_f 0.55 (20% EtOAc/PE); ^{1}H NMR: 0.72, 0.73 (both s, 6H), 1.66, 1,83, 2.17 (all m, 2H), 1.94, 1.95 (both s, 6H), 3.14 (m, 2H), 3.50 (dd, J = 2.1, 6.0 Hz, 1H), 3.86 (m, 1H), 4.96, 4.03 (both m, resp ratio = 3:1, 1H), 4.18 (m, 2H), 4.45 (m, 2H), 4.69, 4,70 (overlapping d, J = 11.7 Hz ea, 1H), 5.28 (m, 1H), 7.22 (m, 5H).

Preparation of THF 26c/t. Furanoside alkene **22** (260 mg, 0.60 mmol) was subjected to the standard iodocyclization–reduction procedure described for the reaction **18**. Flash chromatography of the crude product obtained after the reduction step afforded **26c/t** (280 mg, 92%, resp ratio = 1.3:1); clear gum. Samples of the pure components were obtained after repeated chromatography. For **26c**: R_f 0.40 (50% EtOAc/PE); ^{1}H NMR 0.13, 0.18 (both s, 3H ea), 0.95 (s, 9H), 2.01 (ddd, J = 4.2, 4.7, 13.3 Hz, 1H), 2.32 (ddd, J = 5.7, 7.9, 13.4 Hz, 1H), 2.60 (m, 2 × OH), 3.38 (m, 2H), 3.54 (m, 1H), 3.73 (m, 2H), 3.80 (dd, J = 2.0, 6.5 Hz, 1H), 4.26 (dd, J = 4.5, 6.5 Hz, 1H), 4.33 (m, 1H), 4.53 (br q, J = 4.2 Hz, 1H), 4.83 (ABq, $\Delta\delta$ = 0.23 ppm, J = 11.1 Hz, 2H), 7.40 (m, 5H). For **26t**: R_f 0.43 (50% EtOAc/PE); ^{1}H NMR 0.14, 0.18 (both s, 3H ea), 0.95 (s, 9H), 1.86 (ddd, J = 5.7, 8.2, 13.4 Hz, 1H), 2.25 (ddd, J = 2.0, 8.2, 13.3 Hz, 1H), 2.50, 2.64 (both m, 2 × OH), 3.34 (m, 2H), 3.57 (m, 1H), 3.75 (m, 3H), 4.40 (m, 2H), 4.60 (m, 1H), 4.33 (m, 1H), 4.53 (br q, J = 4.2 Hz, 1H), 4.80 (ABq, $\Delta\delta$ = 0.27 ppm, J = 11.1 Hz, 2H), 7.40 (m, 5H). Anal. (mixture) Calcd for $C_{21}H_{35}IO_5Si$: C, 48.27; H, 6.75. Found: C, 48.82; H, 6.91.

Preparation of THP 28c/t. Furanoside alkene **27** (250 mg, 0.83 mmol) was subjected to the standard iodocyclization–reduction procedure described for the reaction of **18**. Flash chromatography of the crude product obtained after the reduction step afforded mixture **28c/t** (250 mg, 77%, resp ratio = 3.5:1): R_f 0.30 (50% EtOAc/PE); ^{1}H NMR 1.10–1.90 (m, 6H), 2.60 (m, OH), 2.92 (m, OH), 3.18 (m, 2H), 3.42 (m, 2H), 3.70 (m, 3H), 3.88, 4.14 (both m, resp ratio = 3.5:1, 1H), 4.65 (m, 1H), 4.81, 4.90 (both d, resp ratio: 1:3.5, J = 12.0 Hz ea 1H), 7.36 (m, 5H). Anal. (mixture) Calcd for $C_{16}H_{23}IO_4$: C, 47.30; H, 5.71; I, 31.24. Found: C, 47.53; H, 6.02; I, 31.39.

For characterization purposes, **28c/t** was converted to the di-*O*-acetate derivative via the procedure described for the acetylation of **24c/t**. For **28c/t**-di-*O*-acetate: R_f 0.50 (20% EtOAc/PE); ^{1}H NMR 1.08–1.86 (m, 6H), 1.91. 1.92, 1.98 (all s, 6H), 3.10 (m, 2H), 3.27 (m, 2H), 3.48, 3.67 (both m, 2H), 4.20 (m, 2H), 4.70 (m, 2H), 5.27 (m, 1H), 7.28 (m, 5H); ^{13}CNMR 6.65, 9.11, 18.11, 20.80, 21.01, 23.11, 26.51, 27.69, 31.16, 63.41, 70.50, 71.13, 71.29, 73.98, 74.62, 74.76, 76.98, 78.76, 79.18, 127.78, 127.84, 128.35, 138.21, 170.25, 170.57.

Preparation of THF 29c/t. AIBN (20 mg, 0.12 mmol) and Bu_3SnH (0.6 mL, 2.1 mmol) were added to a solution of **24c/t** (690 mg, 1.76 mmol) in benzene (5 mL). The reaction mixture was heated at reflux for 2 h. Evaporation of the solvent afforded a residual oil which was purified by flash chromatography to give **29c/t** (322 mg, 68%): R_f 0.00 (50% EtOAc/PE); ^{1}H NMR 1.22, 1.25 (both d, J = 6.0 Hz ea, resp ratio: 1:2.5, 3H), 1.50, 1.80, 2.00 (all m, 4H), 2.85 (m, 2 × OH), 3.42, 3.58 (both m, 2H), 3.58 (m, 2H), 4.06, 4.20, 4.34 (all m, 2H), 4.76 (m, 2H), 7.36 (m, 5H); ^{13}C NMR (selected resonances) 22.35, 29.07, 29.84, 33.74, 34.99. Anal. (mixture) Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.49; H, 8.42.

Degradation of 29c/t to *cis*/*trans*-5-Methyltetrahydrofuran-2-methanol. 10% Pd/C (1.0 g) was added to a solution of **29c/t** (322 mg, 1.20 mmol) in a mixture of formic acid (1 mL) and MeOH (10 mL) under argon. The reaction mixture

was stirred at rt for 4 h, and then filtered through a bed of Celite. The filtrate was evaporated and the crude residue purified by flash chromatography to give the triol derivative (205 mg, 97%): clear gum; R_f 0.15 (80% EtOAc/PE);^{1}H NMR 1.19, 1.24 (overlapping d, J = 6.0 Hz ea, 3H), 1.48 (m, 1H), 1.94 (m, 3H), 3.42 (m, 4H), 3.72 (m, 3H), 4.06 (m, 2H); ^{13}C NMR 21.63, 28.31, 28.94 , 33.42, 34.41, 64.78, 64.92, 73.24, 73.48, 73.54, 73.70, 76.91, 76.94, 80.63, 81.31. Anal. Calcd for $C_8H_{16}O_4$: C, 54.54; H, 9.15. Found: C, 54.22; H, 9.61.

A solution of $NaIO_4$ (50 mg, 2.3 mmol) in water (4 mL) was added at 0 °C to a solution of the triol obtained in the previous step (100 mg, 0.57 mmol) in THF (2 mL). The reaction was warmed to rt and stirred at this temperature for an additional 30 min. The reaction mixture was diluted with water (5 mL) and the resulting solution was extracted with ether (3 × 10 mL). The combined organic layer was washed with brine (10 mL), dried (Na_2SO_4), and filtered. The filtrate was concentrated at rt and 25 mmHg and the oily residue dissolved in ethanol (2mL). $NaBH_4$ (25 mg, 0.67 mmol) was added to the solution at 0 °C and the reaction mixture stirred at this temperature for 10 min. At that time a 5% solution of hydrochloric acid in MeOH was added dropwise to the reaction mixture until a pH of 7 was attained. The solution was concentrated at rt and 25 mmHg, $CHCl_3$ and anhydrous Na_2SO_4 were added to the oily residue, and the mixture was filtered. The filtrate was evaporated under the conditions described above. The ^{1}H and ^{13}C NMR spectra indicated that major components of the crude residue (43 mg, 65%) were *cis*- and *trans*-5-methyltetrahydrofuran-2-methanol[14] (resp ratio = 2:1): ^{1}H NMR 1.28, 1.30 (overlapping d, J = 6.0 Hz ea, 3H), 1.52 (m, 1H), 1.78 (m, 1H), 2.05 (m, 2H), 2.38 (br s, OH), 3.54 (br dd, 1H, J = 6.0, 12.0 Hz, 1H), 3.68, 3.76 (both d, J = 3.6, 12.0 Hz ea resp ratio = 1:2, 1H), 4.10 (m, 2H); ^{13}C NMR 20.78, 20.91, 27.17, 27.66, 32.93, 33.66, 64.88, 65.09, 75.10, 75.81, 79.02, 79.54; MS (EI) m/z (rel inten) 116 (0.3) [M$^+$], 101 (0.4), 98 (1.2), 85 (100), 67 (28), 57 (30).

Transformation of 25c/t to Acetonide 34c/t. A solution of **25c/t** (250 mg, 0.48 mmol), Bu_3SnH (0.3 mL, 1.1 mmol), and AIBN (25 mg, 0.15 mmol) in benzene (5 mL) was heated at reflux under an argon atmosphere for 4 h. The reaction mixture was then concentrated in vacuo. The residual oil was dissolved in THF (2 mL), to which was added n-Bu_4NF (1 mL of a 1 M solution in THF, 1.0 mmol). The reaction mixture was heated at 50 °C for 0.5 h and then concentrated in vacuo. Flash chromatography of the brown residue gave a hard gum (109 mg, 81%), R_f 0.20 (EtOAc), which was used directly in the next step.

The material obtained in the previous step was dissolved in dry CH_2Cl_2, and 2,2-dimethoxypropane (0.5 mL, 4.1 mmol) and camphorsulfonic acid (5 mg, 0.02 mmol) were added to the solution. The reaction mixture was stirred at rt for 10 min and then neutralized by the addition of a solution of NaOMe in MeOH. The solvent was removed in vacuo and the residue purified by flash chromatography to give the hydroxy acetonide derivative **30c/t** as a gum (86 mg, 68% from **25c/t**): R_f 0.55 (EtOAc); ^{1}H NMR 1.24, 1.27 (overlapping d, J = 7.0 Hz ea, 3H), 1.38, 1.44 (both s, 3H ea), 1.68, 1.87, 2.35 (all m, 2H), 2.17 (br s, OH), 3.55 (m, 1H), 3.75 (m, 2H), 4.04 (m, 1H), 4.18 (m, 1H), 4.35 (m, 2H), 4.70 (m, 1H), 4.86 (m, 1H), 7.36 (m, 5H).

A sample of **30c/t** (62 mg, 0.19 mmol mmol) was dissolved in anhydrous THF (5 mL). NaH (34 mg of 60% suspension in mineral oil, 0.85 mmol) and imidazole (5 mg, 0.07 mmol) were added to the solution at 0 °C. The reaction mixture was then heated at 50 °C for 30 min, at which time CS_2 (0.25 mL, 4.2 mmol) was added. After heating at reflux for an additional 30 min, MeI (0.5 mL, 8 mmol) was added and heating continued for 1 h. The reaction mixture was then diluted with water (20 mL) and the resulting suspension extracted with ether (3 × 15 mL). The ether extract was dried (Na_2SO_4), filtered, and evaporated in vacuo. Flash chromatography of the oily residue afforded **31c/t** (68 mg, 86%): clear oil; R_f 0.70 (20% EtOAc/petroleum ether); ^{1}H NMR 1.31, 1.34 (both d, J = 6.3 Hz, resp ratio = 1: 2.5, 3H), 1.44, 1.51 (both s, 3H ea), 1.82, 2.15 (m, dd resp J = 4.5, 13.5 Hz, 2H), 2.60 (s, 3H), 3.76 (m, 2H), 4.02, 4.18 (both m, 3H), 4.47 (m, 1H), 4.72, 4.75 (both d, resp ratio = 1:2.5, J = 12.0 Hz ea, 1H), 5.00, 5.11 (both d, resp ratio = 2.5:1, J = 12.0 Hz ea 1H), 5.84, 5.92 (br d, dt, J = 5.7 and 2.7, 7.2 Hz resp , resp ratio = 2.5:1, 1H), 7.40 (m, 5H); HRMS calcd for $C_{20}H_{28}O_5S_2-CH_3$ 397.1143, found 397.1168.

A solution of **31c/t** (60 mg, 0.15 mmol), AIBN (20 mg, 0.12 mmol), and Bu_3SnH (0.15 mL, 0.56 mmol) in degassed toluene (5 mL) was heated at reflux under an argon atmosphere for 1 h. The solvent was then removed in vacuo and the oily residue purified by flash chromatography to give **34c/t** (36 mg, 78%, resp ratio = 3:1): clear gum; R_f 0.20 (5% EtOAc/petroleum ether); ^{1}H NMR 1.24, 1.28 (both d, J = 6.3 Hz, resp ratio = 1:3, 3H), 1.43, 1.49 (both s, 3H ea), 1.50, 1.97 (both m, 4H), 3.40, 3.44 (overlapping dd, J = 2.0, 6.0 Hz ea, 1H), 3.80, 3.83 (overlapping t, J = 8.1 Hz ea 1H), 4.08 (m, 3H), 4.40 (m, 1H), 4.88 (m, 2H), 7.40 (m, 5H); HRMS calcd for $C_{18}H_{26}O_4$ 306.1831, found 306.1820.

Transformation of 34c/t to 29c/t. A solution of **34c/t** (30 mg, 0.10 mmol) in anhydrous methanolic HCl (2 mL, ~pH 2) was stirred at rt for 1 h. The solvent was then removed in vacuo and the crude residue filtered through a short column of silica gel. Evaporation of the filtrate yielded a mixture (25 mg, 94%) which contained the identical components as in **29c/t** (NMR, TLC) in a ratio of 3:1 as determined from the ^{1}H NMR; 1.24, 1.22 (both d, J = 6.0 Hz ea, resp ratio = 3:1, 3H).

Transformation of 26c/t to 34c/t. A sample of **26c/t** (170 mg, 0.33 mmol, 3:2 resp ratio) was subjected to the identical three-step sequence of reactions involving reduction of the iodide, deprotection of the silyl ether, and isopropylidenation of the resulting triol, as was described for **25c/t**. Flash chromatography of the crude product obtained after the isopropylidenation step afforded the 5-hydroxy derivative **32c/t** (63 mg, 59% from **26c/t**): clear gum; R_f 0.55 (EtOAc); ^{1}H NMR 1.25 (d, J = 6.0 Hz ea, 3H), 1.34, 1.35, 1.46 (all s, 6H), 1.62, 2.02, 2.35 (all m, 2H), 3.14, 3.48 (both d, J = 4.0, 5.0 Hz resp, ratio: 3:2, OH), 3.70, 3.95 (both m, 4H), 4.44 (m, 2H), 4.82 (m, 2H), 7.36 (m, 5H).

32c/t (63 mg, 0.19 mmol) was converted to the xanthate derivative following the procedure that was used for the preparation of **31c/t**. Flash chromatography of the crude reaction product yielded **33c/t**: (65 mg, 81%): oil; R_f 0.20 (5% EtOAc/petroleum ether); ^{1}H NMR 1.32, 1.39 (both d, J = 6.3 Hz, d at 1.39 buried under s at 1.38, 3H) 1.38, 1.48 (both s, 3H ea), 1.82, 1.95, 2.43 (all m, 2H), 2.60 (s, 3H), 3.71, 3.77 (both dd, J = 4.4, 6.3 and 3.9, 7.1 Hz resp ratio = 2:3, 1H), 3.96 (m, 2H), 4.18 (m, 2H), 4.48 (m, 1H), 4.79, 4.80 (overlapping d, J = 12.0 Hz ea, 1H), 4.95, 4,99 (both d, J = 12.0 Hz ea 1H), 6.05, 6.18 (both m, resp ratio = 3:2, 1H), 7.40 (m, 5H). Anal. (mixture) Calcd for $C_{20}H_{28}O_5S_2$: C, 58.22; H, 6.84; S, 15.55. Found: C, 58.11; H, 7.10; S, 15.63.

33c/t (45 mg, 0.11 mmol) was subjected to the identical deoxygenation procedure as described for **31c/t**. Flash chromatography of the crude product afforded a mixture (27 mg, 82%) which contained the two identical components as for **34c/t** (NMR, TLC) in a ratio of 3:2, as determined from the ^{1}H NMR; 1.26, 1.23 (both d, J = 6.0 Hz ea, resp ratio: 3:2, 3H).

Preparation of THF–THP Bis-Ether 36c/t. $I(coll)_2ClO_4$ (160 mg, 0.34 mmol) was added to a solution of **35** (64 mg, 0.23 mmol) in dry CH_2Cl_2 (25 mL) containing freshly activated, powdered, 4 Å molecular sieves (250 mg). After stirring at room temperature for 10 min, the solution was filtered, diluted with ether (50 mL), and washed with 10% aqueous $Na_2S_2O_3$ (25 mL) and brine (25 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography of the resulting oil afforded **36c/t** (87 mg, 93%, resp ratio = 3.5:1) as a mixture of ring A diastereomers: oil; R_f 0.45, 0.40 resp (20% EtOAc/PE). Repeated chromatography gave samples of the pure components. For **36c**: ^{1}H NMR 1.22, 1.42, 1.66 (all s, 3H ea), 1.70 (m, 2H), 2.00 (m, 2H), 2.35 (ddd, J = 5.4, 8.8, 11.5 Hz, 1H), 3.13 (m, 2H), 3.25 (dd, J = 3.4, 14.4 Hz, 1H), 3.53 (dd, J = 2.2, 8.1 Hz, 1H), 3.82 (dd, J = 5.4, 11.7 Hz, 1H), 3.94 (m, 2H), 4.06 (m, 2H), 4.68, 4.82 (both br s, 1H ea); ^{13}C NMR 11.35, 21.85, 26.27, 26.92, 28.36, 31.05, 46.72, 68.31, 72.23, 76.36, 78.03, 79.70, 80.68, 109.11, 112.39, 142.85. For **36t**: ^{1}H NMR 1.22, 1.42, 1.66 (all s, 3H ea), 1.70 (m, 2H), 2.16

(m, 2H), 2.35 (m, 1H), 3.08 (m, 2H), 3.30 (dd, J = 3.5, 9.5 Hz, 1H), 3.44 (dd, J = 2.1, 8.2 Hz, 1H), 3.84 (dd, J = 4.1, 11.8 Hz, 1H), 3.90 (m, 1H), 4.08 (m, 2H), 4.38 (m, 1H), 4.68, 4.82 (both br s, 1H ea); ^{13}C NMR 10.50, 21.85, 26.27, 28.36, 28.60, 32.58, 46.72, 68.31, 71.95, 76.36, 78.62, 79.82, 79.96, 109.11, 112.39, 142.85. Anal (mixture). Calcd for $C_{16}H_{25}IO_4$: C, 47.07; H, 6.17; I, 31.08. Found: C, 47.11; H, 6.18; I, 30.91.

Preparation of THP–THP Bis-Ether 39c/t. **38** (105 mg, 0.36 mmol) in dry CH_2Cl_2 (35 mL) containing molecular sieves (350 mg) was treated with $I(coll)_2ClO_4$ (253 mg, 0.54 mmol) as described for **35**. The reaction was allowed to proceed for 45 min and then processed to give **39c/t** (133 mg, 89%, resp ratio = 3.5:1) as a mixture of ring A diastereomers: oil; R_f 0.45, 0.42 resp (20% EtOAc/PE); ^{1}H NMR (major isomer) 1.35 (m, 2H), 1.31, 1.52 (both s, 3H ea), 1.67 (m, 2H), 1.76 (s, 3H), 1.94 (m, 2H), 2.46 (m, 2H), 3.15 (m, 2H), 3.28 (dd, J = 4.6, 9.9 Hz, 1H), 3.40 (m, 1H), 3.57 (dd, J = 2.2, 8.1 Hz, 1H), 3.75 (ddd, J = 1.9, 9.9, 11.8 Hz, 1H; ~10% enhancement on irradiation of m at 3.40 ppm), 3.92 (dd, J = 4.4, 11.8 Hz, 1H), 4.02 (dd, J = 2.2, 5.0 Hz, 1H), 4.11 (dd, J = 5.0, 9.6 Hz, 1H), 4.77 (br s, 1H), 4.91 (t, J = 1.3 Hz, 1H); ^{13}C NMR **39c**: 9.5, 21.8, 22.7, 25.9, 26.2, 28.3, 30.8, 46.7, 68.3 71.5, 76.5, 76.6, 78.2, 79.2, 108.9, 112.2, 142.9. **39t** (selected resonances): 6.6, 17.7, 21.8, 25.5, 25.9, 27.1, 28.3, 46.7, 108.9, 112.2, 142.9. Anal. (mixture) Calcd for $C_{17}H_{27}IO_4$: C, 48.35; H, 6.45; I, 30.05. Found: C, 48.29; H, 6.57; I, 30.22.

Preparation of Tri-*O*-acetate 37. A sample of **36c/t** (182 mg, 0.45 mmol) in 95% EtOH (5 mL) and freshly activated zinc dust (400 mg) was heated at reflux for 1 h. The reaction mixture was then diluted with ether (100 mL) and filtered through Florisil, and the filtrate was evaporated in vacuo. The brown syrup so obtained was triturated with EtOAc, the suspension filtered through a short column of silica gel, and the filtrate evaporated in vacuo. The crude residue was dissolved in methanolic HCl (5 mL, pH ~ 2), and the reaction mixture was stirred at rt for 2 h, neutralized by the addition of solid $NaHCO_3$, and filtered. The filtrate was evaporated in vacuo, and the oily residue triturated with EtOAc. The suspension was filtered through a short column of silica gel and the filtrate evaporated in vacuo. The residue was dried under high vacuum and subjected to the general procedure described for the acetylation of **24c/t**. Flash chromatography of the crude product gave **37** (115 mg, 70% from **36c/t**): oil, R_f 0.30 (20% EtOAc/PE); ^{1}H NMR 1.55 (m, 2H), 1.62 (br s, 1H), 1.90, 2.02, 2.12 (all s, 3H ea), 1.96 (m, 2H), 2.78 (dt, J = 4.7, 11.5 Hz, 1H), 3.23 (t, J = 11.5 Hz, 1H), 3.43 (br d, J = 8.0 Hz, 1H), 3.94 (dd, J = 4.7, 11.5 Hz, 1H), 4.73, 4.83 (both br s, 1H ea), 4.91 (m, 1H), 4.99 (m, 2H), 5.03 (dt, J = 3.8, 8.0 Hz, 1H), 5.30 (br d, J = 3.8 Hz, 1H), 5.68 (m, 1H); ^{13}C NMR 20.46, 20.67, 20.83, 28.86, 29.01, 43.10, 66.72, 70.26, 71.37, 71.42, 78.54, 113.67, 115.44, 136.91, 140.24, 170.15, 170.21. Anal. Calcd for $C_{19}H_{28}O_7$: C: 61.95; H: 7.66. Found: C, 61.56; H, 7.68.

Preparation of Tri-*O*-acetate 40. A sample of **39c/t** (200 mg, 0.47 mmol) was subjected to a similar three-step sequence of reductive elimination, acetonide hydrolysis, and peracetylation as described for **36c/t**. Flash chromatography of the crude acetylation product gave **40** (131 mg, 72% from **39c/t**): oil; R_f 0.30 (20% EtOAc/PE); ^{1}H NMR 1.42 (m, 4H), 1.67 (br s, 1H), 1.95 (s, 3H), 2.02 (m, 2H), 2.07, 2.15 (both s, 3H ea), 2,83 (dt, J = 4.7, 11.5 Hz, 1H), 3.27 (t, J = 11.5 Hz, 1H), 3.46 (dd, J = 3.5, 8.1 Hz, 1H), 3.99 (dd, J = 4.8, 11.5 Hz, 1H), 4.79 (br s, 1H), 4.88 (t, J = 1.4 Hz, 1H), 4.94 (m, 1H), 5.04 (m, 3H), 5.34 (dd, J = 1.0, 3.2 Hz, 1H), 5.72 (m, 1H); ^{13}CNMR 20.47, 20.69, 20.83, 28.89, 28.95, 32.93, 43.13, 66.76, 70.27, 71.48, 71.77, 78.65, 113.67, 114.87, 137.80, 140.27, 170.09, 170.18, 170.30. Anal. Calcd for $C_{20}H_{30}O_7$: C: 62.81; H: 7.91. Found: C, 62.88; H, 7.99.

Supplementary Material Available: Copies of NMR spectra of **18**, **20**, **22-29**, **31**, and **33–40** (36 pages). This material is contained in libraries on microfiche, immediately follows this article in the micrfilm version of the journal, and can be ordered from the ACS; see any current masthead for ordering information.