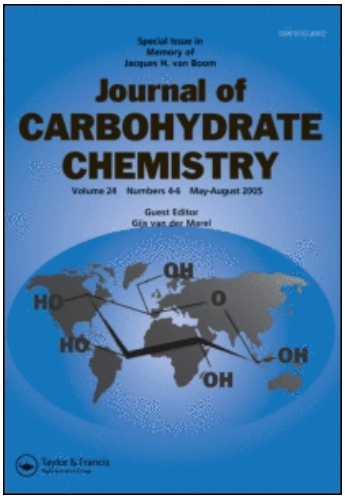

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A Novel Strategy for the Preparation of Substituted Tetrahydrofurans Based on Neighboring Group Participation by the Ring Oxygen of Monosaccharides

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COMMUNICATION

A NOVEL STRATEGY FOR THE PREPARATION OF SUBSTITUTED TETRAHYDROFURANS BASED ON NEIGHBORING GROUP PARTICIPATION BY THE RING OXYGEN OF MONOSACCHARIDES

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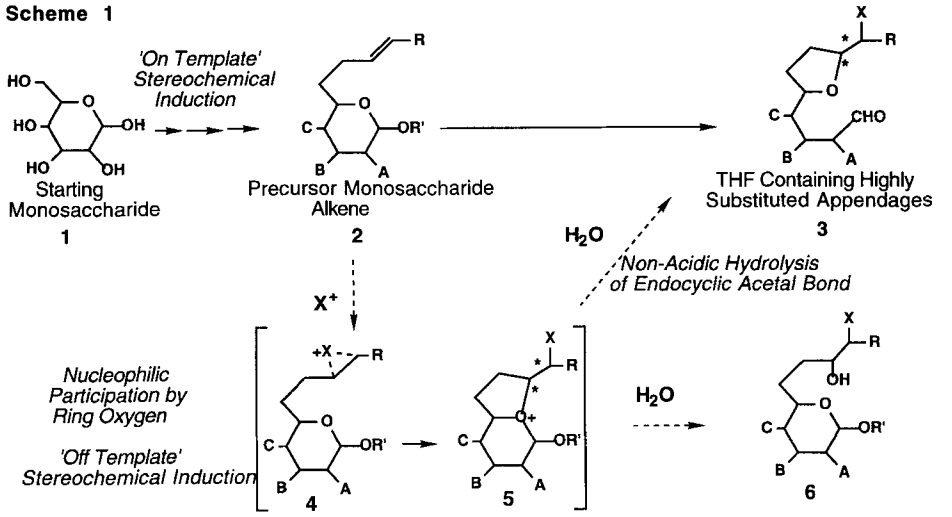
Simple monosaccharides, due to their ready availability and richly functionalized nature, have often proven practical in the preparation of complex natural products.[1] Important elements of these strategies usually entail the stereoselective introduction of substituents on the carbohydrate template, and the timely elaboration of the cyclic acetal, which represents a masked hydroxyaldehyde, into acyclic structures. Regarding stereoselectivity, several methodologies are available for the introduction of stereogenic centers at 'on template' positions but 'off template' stereoselectivity is a more formidable proposition and has not been as extensively explored.[2] The conversion of cyclic monosaccharides to acyclic forms is usually achieved via acid mediated acetal bond cleavage procedures to give the derived hydroxyaldehyde, invariably more stable as the hemiacetal, the dithioacetal,[3] or an acyclic dithioacetal or ether.[4] However, the highly acidic conditions usually required for these reactions, often presents functional group compatability problems. Additional complications occasionally arise because of the unusual stability of the hemiacetal or the cyclic monothioacetal, which limits further elaboration.[5]

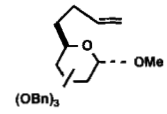
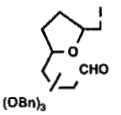
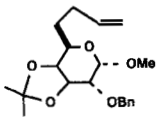
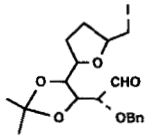
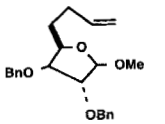
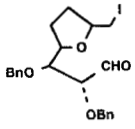
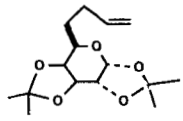
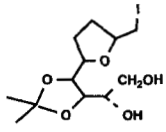
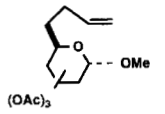
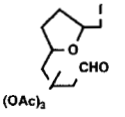
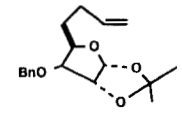
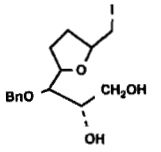
Against this backdrop, pentenyl acetals have recently been shown to undergo acetal bond cleavage under non acidic conditions, with concomitant tetrahydrofuran (THF) formation.[6] In this manuscript, we report that this chemistry provides the basis of a novel



strategy for the preparation of THF rings with highly substituted appendages[7] in a single step, from monosaccharide alkene precursors. The methodology is illustrated by the preparation of a substituted alkene precursor **2** from a starting monosaccharide **1**, and the subsequent conversion of **2** to the halo-THF-aldehyde **3** (Scheme 1). Attractive aspects of this approach relate to (i) availability of alkene precursors via straightforward procedures, (ii) non-acid promoted acetal bond cleavage, which occurs regiospecifically to liberate the free aldehyde and (iii) stereocontrol at 'off template' positions. The mildness and specificity of acetal cleavage derives from the chemospecificity of the reaction of 4-alken-1-yl acetals with halonium ions, and enhances the role of the cyclic acetal as a protecting group.[6] Regarding stereoselectivity, the monosaccharide ring not only serves the traditional role as a template for functionalization at ring positions, but in addition, because of the cyclic nature of the transition state leading to formation of the presumed oxonium ion intermediate **5**, the chirality of the sugar could be communicated to remote "off template" sites.

In order to assess the scope and limitations of this plan, the iodocyclization of several monosaccharide alkenes derived from widely used saccharide building blocks[1,8] were examined with respect to the facility and the stereoselectivity of the central transformation (i.e. **2** --> **3**). The key steps in the synthesis of these model compounds were the preparation of the primary iodide derivative[9] from the appropriate monosaccharide polyol or isopropylidinated monosaccharide alcohol,[10-13] and the application of the Keck allyl radical coupling procedure to the iodide.[14] The cyclization reactions on the alkene substrates were carried out in wet dichloromethane with iodonium dicollidine perchlorate (IDCP) as the halonium ion source.[15] Structures of the cyclization products were confirmed by conversion to the dimethyl acetal or primary alcohol derivative. (Table 1)

Table 1 : Reactions of Saccharide Alkenes with IDCP / H_2O / CH_2Cl_2

Alkene	THF %[a].(cis:trans)[b]	Iodohydrin%[a]	Alkene	THF %[a].(cis:trans)[b]	Iodohydrin%[a]
CONFORMATIONALLY MOBILE SYSTEMS			**CONFORMATIONALLY RESTRAINED SYSTEMS**		
Less electronegative ring substituents					
					
7 *Gluco*[10]	**10** 76 (4 : 5)	--	**23**[12]	**24** 84 (5 : 4)	--
8 *Manno*	**11** 72 (5 : 2)	--			
9 *Galacto*	**12** 65 (5 : 3)	--			
					
13 α-OMe[11]	**15** 80 (1 : 2)	--	**25**[13]	**26**[d] 75 (1 : 5)	--
14 β-OMe	**16** 92 (1 : 3)	--			
More electronegative ring substituents					
					
17 *Gluco*[10]	**20** 32[c]	34[c]	**27**[11]	**28**[d] 70 (7 : 2)	--
18 *Manno*	**21** 37[c]	12[c]			
19 *Galacto*	**22** 28[c]	12[c]			

a Yields are for chromatographically isolated products unless stated otherwise.

b Diastereomer ratios were determined from ^1H and ^{13}C NMR spectra.

c Yields were calculated from H NMR data for isolated THF/Iodohydrin mixtures and are based on recovered starting material. Exact diastereomer ratio was not possible, but estimated to be similar to that obtained for the tri-*O*-benzyl derivative.

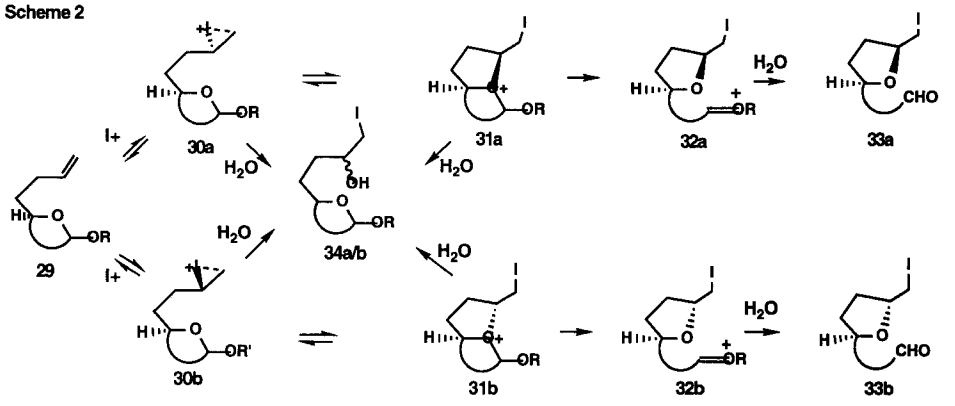
d Product was characterized as the diol obtained after reduction of the crude reaction product with $NaBH_4$

Facility of the Neighboring Group Participation Reaction: One of the early concerns was the competing formation of the undesired iodohydrin derivative **6** (X = I), which could arise from intermolecular nucleophilic attack on intermediates such as **4** or **5**. In particular, it was considered that changes with respect to the configuration and electronic properties of ring substituents, and ring flexibility, might lead to high proportions of the iodohydrin product by reducing the facility of the participation reaction and, or the acetal bond cleavage steps. The iodocyclization reaction was therefore investigated for conformationally mobile substrates with less, or more electronegative substituents as represented by benzyloxy or acetoxy groups, and also for conformationally restrained systems.

In the case of the conformationally mobile systems with *O*-benzyl substituents, the THF product was obtained exclusively within 0.5 h in high yields, for both pyranosides **7-9**, and furanosides **13** and **14**. When these reactions were performed in aqueous acetonitrile, increased levels of the iodohydrin product resulted as the concentration of water was increased. The reactions of the acetylated pyranosides **17-19** proceeded more slowly, resulting in unreacted alkene after similar reaction times as for the *O*-benzyl systems, and also gave appreciable amounts of the iodohydrin product. On the other hand, the conformationally restrained systems were as reactive as the more mobile cases with less electronegative groups. For these reactions, good to high yields of THF products were obtained, with no evidence for iodohydrin formation, even in the case of the highly strained 1,2-*O*-isopropylidene furanose **27**. In none of the above reactions was the tetrahydropyran compound formally resulting from 6-endo attack on the alkene, detected.

THF Stereoselectivity: The configuration of the new stereogenic center in **10-12**, was assigned by degradation[16] of the initial THF product to the known 5-methyltetrahydrofuran-2-methanol isomers.[17] In each case, the three methylene carbons in the *cis* iodotetrahydrofuran residue had upfield carbon resonances compared to those in the corresponding *trans* diastereomer. Subsequently the *cis/trans* ratios for the remaining THF products were assigned by correlation with the ^{13}CNMR data for the compounds **10-12**. The stereoselectivity varied considerably for the different substrates. Generally the more conformationally rigid systems were more selective, but no clear correlation between saccharide structure and stereochemistry emerged.

Scheme 2



The variation in THF/iodohydrin ratios observed for the different substrates, appear to be consistent with the mechanism shown in Scheme 2. Thus, the formation of the THF product proceeds via the initial formation of the iodonium species **30** (or a charge transfer complex), to the bicyclic oxonium ion **31**, which undergoes fragmentation to the

oxocarbenium ion **32**. Capture of the latter by water leads to the aldehyde **33**. A reversible mechanism for oxonium ion formation has been written in line with the mechanistically related halocyclization reactions of 5-alkoxyalkenes.[18,19] Accordingly, iodohydrin **34** may result by direct attack of water on the initial halonium species **30**, or on the oxonium ion **31**, and the rate of formation should depend on the concentration of nucleophile, whereas THF ring formation is expected to be independent of nucleophile concentration. Indeed, the lower THF/iodohydrin ratios observed at higher aqueous concentrations is consistent with this analysis. It also follows from this mechanism, that the proportion of iodohydrin should increase when the facility of **30** --> **32** is reduced. This should be the case when there is a decrease in the electrofugality of the ring oxygen or in the propensity for cleavage of the acetal bond to give the acyclic oxocarbenium ion. Both of these factors presumably operate in the case of the acetylated substrates, for which extensive iodohydrin formation was observed. That exclusive THF formation was obtained even in cases where the transition state for the formation of the bicyclic THF-oxonium ion was expected to be highly strained, suggests that the fragmentation step is the slow step in the transformation of **30** --> **32**.

The factors governing stereoselectivity are less clearly understood at this stage. Due to the remoteness of the reacting alkene from the asymmetric sugar residue, the stereoselectivity of initial halonium ion formation step (i.e. **29** --> **30**), is not expected to be high, or to be affected by structural changes in the sugar template. Therefore, it appears certain that the wide variation in the observed results cannot be rationalized solely on the basis of any stereochemical biases in this step. Instead the results seem to reflect an interplay of kinetic and thermodynamic factors relating to the formation, equilibration, and decomposition of the diastereomeric bicyclic THF-oxonium ion intermediates **31a/b**.[18,19] Elucidation of this picture requires consideration of: the reactive conformation of the starting sugar, the trajectory of approach of the initially formed halonium ion or charge transfer complex onto the ring oxygen, and oxonium ion geometry. The overall analysis is further clouded by configurational instability of diastereomeric oxonium ions. [19,20] It is reasonable that conformationally rigid systems should show higher stereoselectivity than the more flexible substrates. Studies relating to the stereochemical aspects and the application to natural products synthesis are currently in progress and will be reported in due course.

Physical Data for Cyclization Precursors and Products (Table 1, 7 - 28)

^{1}H 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. Elemental analyses were performed by Spang Analytical, Eagle Harbor, Michigan.

Precursors **7-9**; Anal. Calcd for C_{31} H_{36} O_5: C, 76.23; H, 7.38.
7; Found: C, 76.35; H, 7.41. **8**; Found: C, 76.29; H, 7.42. **9**; Found: C, 76.05; H, 7.47.

Cis/Trans THF-aldehyde mixture **10**: ^{1}HNMR : 1.74-2.06 (m, 4H), 3.20-3.27 (m, 2H), 3.85-4.22 (m, 5H), 4.58-4.91 (m, 6H), 7.30-7.42 (m, 15H), 9.82-9.83 (d, 1H).
Anal. (dimethyl acetal derivative) Calcd for C_{32} H_{39} O_6I: C, 59.44 ; H, 6.09; I, 19.63. Found: C, 59.52 ; H, 5.99; I, 19.60.

Cis/Trans THF-aldehyde mixture **11**: ^{1}HNMR : 1.52-2.05 (m, 4H), 3.29-3.31 (m, 2H), 3.80-4.16 (m, 5H), 4.67-4.75 (m, 6H), 7.30-7.37 (m, 15H), 9.70-9.74 (d, 1H).
Anal. (dimethyl acetal derivative) Calcd for C_{32} H_{39} O_6I: C, 59.44 ; H, 6.09; I, 19.63. Found: C, 59.56 ; H, 6.13; I, 19.71.

Cis/Trans THF-aldehyde mixture **12**: ^{1}HNMR : 1.72-2.08 (m, 4H), 3.29-3.31 (m, 2H), 3.80-4.18 (m, 5H), 4.54-4.84 (m, 6H), 7.30-7.39 (m, 15H), 9.70-9.76 (d, 1H).
Anal. (dimethyl acetal derivative) Calcd for C_{32} H_{39} O_6I: C, 59.44 ; H, 6.09; I, 19.63. Found: C, 59.50 ; H, 6.06; I, 19.70.

Precursor **13**: ^{1}HNMR: 1.78 (m, 2H), 2.20 (m, 2H), 3.43 (s, 3H), 4.02 (t, J = 4.4 Hz, 1H), 4.21 (m, 2H), 4.50-4.77 (m, 4H), 4.86 (d, J = 4.3 Hz, 1H), 5.13 (m, 2H), 5.87 (m, 2H), 7.37 (m, 10H). ^{13}CNMR: 100.42 (C1α).

Precursor **14**: ^{1}HNMR: 1.85 (m, 2H), 2.17, 2.28 (both m, 2H ea), 3.46 (s, 3H), 3.98 (dd, J = 1.8, 5.6 Hz, 1H), 4.14 (m, 1H), 4.21 (m, 1H), 4.45-4.70 (m, 4H), 4.93 (d, J = 1.8 Hz, 1H), 5.15 (m, 2H), 5.88 (m, 2H), 7.37 (m, 10H). ^{13}CNMR: 104.92 (C1β).

Cis/Trans THF-aldehyde mixture **15** (**16**): ^{1}HNMR : 1.48-2.23 (m, 4H), 3.14-3.30 (m, 2H), 3.67 (m, 1H), 3.95, 4.10 (both m, 2H), 4.27, 4.46 (both m, 1H), 4.49-4.86 (m, 4H), 7.38 (m, 10H), 9.78 (bs, 1H). Selected ^{13}CNMR: 10.03, 10.58 ($\underline{C}H_2$I), 27.32, 27.90, 31.54, 32.58 ($\underline{C}H_2$-6, $\underline{C}H_2$-7), 201.72, 202.13 ($\underline{C}$HO).

Precursor **17**: ^{1}HNMR: 1.58-1.65 (m, 2H), 1.94, 2.00, 2.10 (all s, 3H each), 2.10 - 2.22 (m, 1H), 2.25 (m, 1H) 3.42 (s, 3H), 3.80 (dt, J = 4.6, 9.4 Hz, 1H), 4.84 - 4.98 (m, 3H), 5.00-5.13 (m, 2H), 5.46 (t, J = 9.6 Hz, 1H), 5.84 (m, 1H).
Anal. Calcd for C_{16} H_{24} O_8: C, 55.81; H, 7.03. Found: C, 55.92; H, 7.00.

Precursor **18**: ^{1}HNMR: 1.52-1.67 (m, 2H), 1.95, 2.00, 2.05 (all s, 3H each), 2.05 - 2.15 (m, 1H), 2.22 -2.35 (m, 1H), 3.38 (s, 3H), 3.75 (m, 1H), 4.63 (s, 1H), 4.95 - 5.15 (m, 3H), 5.20-5.34 (m, 2H), 5.80 (m, 1H).
Anal. Calcd for C_{16} H_{24} O_8: C, 55.81; H, 7.03. Found: C, 55.77; H, 6.98.

Precursor **19**: ^{1}HNMR: 1.53 - 1.62 (m, 2H), 1.97, 2.06, 2.15 (all s, 3H each), 2.10 - 2.22 (m, 2H), 3.38 (s, 3H), 3.95 (dd, J = 5.2, 10.7 Hz, 1H), 4.92 - 5.05 (m, 3H), 5.14 (dd, J = 4.6, 12.6 Hz, 1H), 5.32 (m, 2H), 5.69 (m, 1H).
Anal. Calcd for C_{16} H_{24} O_8: C, 55.81; H, 7.03. Found: C, 55.65; H, 6.74.

THF/Iodohydrin mixture **20**: ^{1}HNMR : 9.58 (d, C$\underline{H}$O - THF), 3.20-3.25 (m, C$\underline{H}_2$I, THF and iodohydrin), 3.40 (s, C$\underline{H}_3$O, Iodohydrin).

THF/Iodohydrin mixture **21**: ^{1}HNMR : 9.55, 9.58 (both d, C$\underline{H}$O, THF), 3.20-3.25 (m, C$\underline{H}_2$I, THF and iodohydrin), 3.40 (s, C$\underline{H}_3$O, Iodohydrin).

THF/ Iodohydrin mixture **22**: ^{1}HNMR : 9.60 (d, C$\underline{H}$O, THF), 3.20-3.26 (m, C$\underline{H}_2$I, THF and iodohydrin), 3.40 (s, C$\underline{H}_3$O, Iodohydrin).

Precursor **23**: ^{1}HNMR: 1.38, 1.42 (both s, 3H ea), 1.78, 1.90, 2.20, 2.31 (all m, 1H ea), 3.39 (s, 3H), 3.54 (dd, J = 3.6, 8.0 Hz, 1H), 3.94 (m, 1H), 4.00 (dd, J = 2.4, 5.3 Hz, 1H), 4.35 (dd, J = 5.4, 7.9 Hz, 1H), 4.67 (d, J = 3.5 Hz, 1H), 4.20 (ABq, J = 12.7 Hz, $\Delta\delta$ = 0.1ppm, 2H), 5.07 (m, 2H), 5.88 (m, 1H), 7.35 (m, 5H).

Cis/Trans THF-aldehyde mixture **24**: ^{1}HNMR : 1.36, 1.45, 1,47 (all s, 6H), 1.80-2.20 (m, 4H), 3.08-3.32 (m, 2H), 3.85 - 4.50 (m, 6H), 4.60-4.90 (m, 2H), 7.38 (m, 10H), 9.73 (s, 1H). Selected ^{13}CNMR: 10.30, 10.80 ($\underline{C}H_2I$), 28.10, 29.10, 31.70, 32.60 ($\underline{C}H_2$-6, $\underline{C}H_2$-7), 201.65, 202.05 ($\underline{C}HO$)

Precursor **25**: Anal. Calcd for C_{15} H_{24} O_5: C, 63.38; H, 8.45. Found: C, 63.42; H, 8.52.

Cis/Trans THF mixture **26**: Anal. Calcd for C_{12} H_{22} O_6I: C, 38.61; H, 5.99; I: 33.99. Found: C, 38.49; H, 5.77; I: 34.00.

Precursor **27**: Anal. Calcd for C_{18} H_{24} O_4: C, 71.01; H, 7.96. Found: C, 71.11; H, 7.97.

Cis/Trans THF mixture **28-diacetate**: Anal. Calcd for C_{19} H_{25} O_4I: C, 47.90; H, 5.30; I: 26.64. Found: C, 47.69; H, 5.40; I: 26.56.

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10. **7-9** and **17-19** were prepared from the corresponding methyl-α-D-pyranosides; Aldrich Chemical Co.

11. **13** and **14** were obtained from **27** after methanolysis followed by O-benzylation. **27** was prepared from 1,2-*O*-isopropylidene-α-D-xylofuranose: Pfanstiehl Laboratories Inc.

12. **23** was prepared from methyl 3,4-*O*-isopropylidene-α-D-galactopyranose: A. Stoffyn and P. Stoffyn, *J. Org. Chem.*, **32**, 4001 (1967).

13. **25** was prepared from 1,2,3,4-di-*O*-isopropyliene-α-D-galactopyranoside: Pfanstiehl Laboratories, Inc.

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16. The iodo-THF-aldehyde product was converted to a mixture of 5-methyltetrahydrofuran-2-methanol via the following sequence: (i) CH_2Cl_2 - MeOH, $BF_3.OEt_2$ (ii) nBu_3SnH, PhH, reflux; (iii) Na/NH_3, ether, -33 °C; (iv) $NaIO_4$, $THF-H_2O$; (v) $NaBH_4$, EtOH.

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