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cis-2,5-Disubstituted Tetrahydrofurans from Pyranosides: A Novel Example of Remote Stereocontrol by the Aglycone

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Abstract: A stereoselective methodology, based on neighboring group participation by the acetal ring oxygen, is described for the preparation of highly functionalizable cis-2,5-disubstituted tetrahydrofurans from C6 alkenyl branched pyranosides.

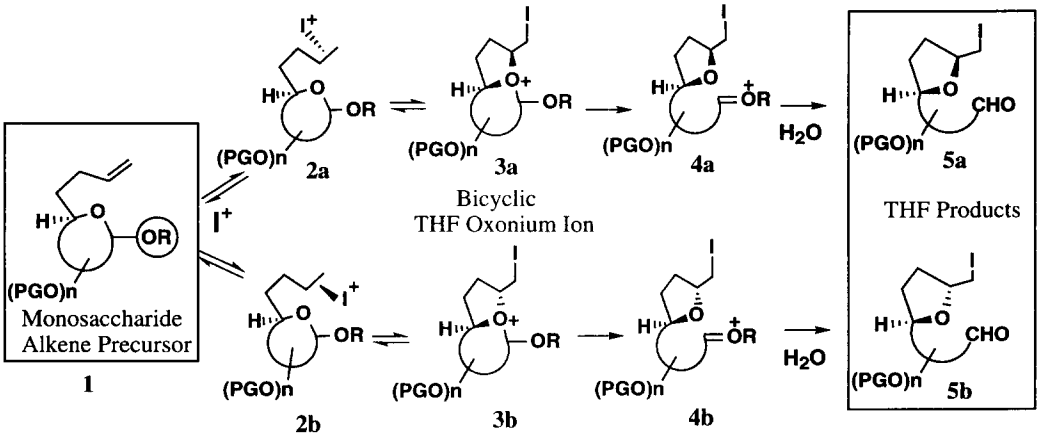
We have recently described the halonium ion mediated transformation of monosaccharide alkenes **1** into tetrahydrofurans (THF's) **5**.[1] The reaction presumably proceeds via initial formation of an onium ion or charge transfer complex **2**, thence the bicyclic THF-oxonium intermediate **3**, fragmentation of which leads to **4**, the progenitor of the product **5**. The bicyclic nature of intermediate **3** should allow for the communication of chirality from the monosaccharide template to the newly formed stereogenic center in the THF product.[2] In view of the rich literature for the synthetic modification of saccharide templates, the identification of structural features in the saccharide which correlate with high THF stereoselectivity would constitute a novel, versatile approach to 2,5 disubstituted THF's containing stereochemically complex branches (Scheme 1).

From a mechanistic standpoint, modification of the steric and electronic properties of the aglycone in a saccharide of fixed ring substitution appeared to be a reasonable starting point towards this goal. Thus, variation in electronegativity might be expected to alter the relative rate of fragmentation of the THF-oxonium ion compared to its reversal to the halonium ion, thereby favoring an increase in the thermodynamic product. On the other hand, changes in aglycone size might have a more pronounced effect on the relative rates of cyclization to the diastereomeric THF-oxonium ions.[3] Moreover, the use of the aglycone as the stereodetermining element would be a practical synthetic device, since it may easily be introduced or interchanged on the saccharide template.

In order to evaluate these ideas, simple C6 allyllated 2,3 dideoxy glucopyranosides, potential chirons for acetogenin synthesis, were investigated.[4] Substrates **6-9** were prepared in yields of ~80%, via the reaction of five equivalents of allylmagnesium bromide and the respective 4-O-benzyl-2,3-dideoxy-6-O-tosyl-glucopyranoside in TMEDA/ether.[5] The trityl derivative **10** was obtained from the t-butyl glycoside **9** in 82% yield via acetal hydrolysis followed by the silver triflate mediated tritylation of the resulting lactol in dichloromethane. This procedure yielded an inseparable 1:1 mixture of α/β anomers, which was used for the iodocyclization reaction. The cyclization reactions were carried out in wet dichloromethane with iodonium dicollidine perchlorate (IDCP) as the promoter.[6] The reactions proceeded extremely rapidly, were complete

within 10 min., and generally afforded yields of 75-85%. The stereochemistry of the THF products was assigned by comparison of the methylene resonances in the THF ring of the cis and trans isomers.[7] (Table 1)

Scheme 1



Initial attention was focused on aglycones with similar size but different electronegativity. However, even though the relative reactivity of the substrates decreased with increasing aglycone electronegativity (R = CH_2CH_3 vs. CH_2CF_3), THF stereoselectivity remained unchanged (1.5:1 cis :trans). Variation of the size of the aglycone was more promising. An increasing preference for the cis THF was observed with the size of the aglycone. Notably, the most sterically demanding trityl aglycone afforded a single cis-THF in 81 % yield. Treatment of the isolated cis or trans product under the identical reaction conditions did not result in isomerization of the THF.

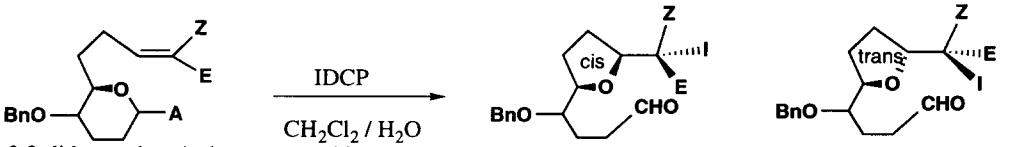
t-Butyl and trityl pyranosides of Z and E disubstituted alkenes were next investigated. The t-butyl-Z -alkene **15** was obtained in greater than 95% stereoselectivity from the Wittig reaction of butylidenetriphenylphosphorane and the aldehyde derived from ozonolysis of **9**. Isomerization of **15** via the Vedejs protocol gave the E isomer **16**.[8] The trityl glycosides were obtained from the corresponding t-butyl derivatives as previously described. As for the terminal alkene substrates, poor selectivity was observed for the t-butyl substrates. However, the trityl derivatives **17** and **18** were again highly cis selective.

In order to study the generality of these results, in other saccharide templates, the corresponding series of t-butyl (**11**, **17** and **23**) and trityl (**12**, **18** and **24**) 2,3-dideoxygalacto pyranosides also potential acetogenin precursors were evaluated.[9] Again the superior directing effect of the trityl glycoside was evident. As for the dideoxygluco series, high yields of THF products **14** (87%), **20** (91%) and **26** (79%) were obtained with almost exclusive formation of the cis isomer. Interestingly, the t-butyl glycoside of the E-alkene **23**, also shows high cis selectivity.

Two broad generalizations emerge from this study: (i) cis selectivity increases with aglycone size, but only becomes appreciable in the case of the very bulky trityl group, and (ii) Z alkenes are inherently less cis selective

than the E isomers. These results seem to fit the early transition state model which has been described by Guindon for the related haloetherification of 5-alkoxyalkenes.[3c]

Table 1 : Aglycone Structure vs. THF Stereoselectivity



2,3-dideoxygluco/galactopyranosides — cis/trans THF Products

SUGAR SUBSTITUTION	ALKENE SUBSTITUTION					
	Terminal (E=Z=H)		Z (Z= Pr; E=H)		E (Z= H; E=Pr)	
	Alkene Precursor	THF Product (c:t)-Yield%[a]	Alkene Precursor	THF Product (c:t)-Yield%[a]	Alkene Precursor	THF Product (c:t)-Yield%[a]
A = α-OCH_2CH_3; α-OBn	**6**	**13** (1.5:1)				
A = α-OCH_2CF_3; α-OBn	**7**	**13** (1.5:1)				
A = α-OCH_3; α-OBn	**8**	**13** (1:1)				
A = α-$OC(CH_2)_3$; α-OBn	**9**	**13** (3.5:1)	**15**	**19** (1:1.5)	**21**	**25** (3.5:1)
A = α/β-$OCPh_3$; α-OBn	**10**	**13** (c only)-80	**16**	**19** (8:1)-81	**22**	**25** (20:1)-78
A = α-$OC(CH_2)_3$; β-OBn	**11**	**14** (3.5:1)	**17**	**20** (1:1)	**23**	**26** (8:1)
A = α/β-$OCPh_3$; β-OBn	**12**	**14** (10:1)-87	**18**	**20** (c only)-91	**24**	**26** (c only)-79

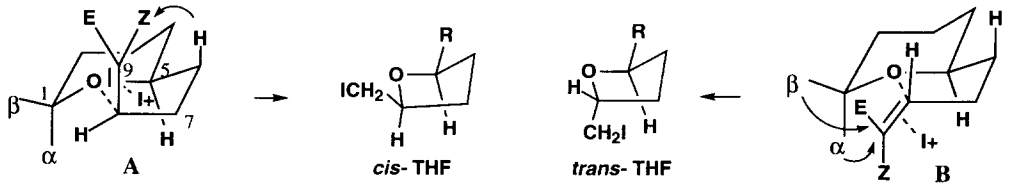
[a] Yields have been optimized only for the reactions of the trityl glycosides

Accordingly, a chair like reactive conformation involving the four carbon atoms of the eventual THF ring is favored, with a preferred 'up' (**A**), vs. 'down' (**B**), orientation of the π-alkene complex or iodonium ion, leading to the cis THF. Due to the distance of the reacting center to the substituents on the sugar ring, only a very bulky aglycone such as the trityl residue can induce any appreciable stereodirecting effect. The lower cis selectivity of the Z alkenes might be related to destabilizing $A^{(1,3)}$ interactions in **A**. That high selectivity was observed for both α and β glycosides, suggests that the C8-C9 bond in **B** lies within the dihedral angle containing the α and β anomeric substituents. However, it is not immediately clear why conformation **A** should be favored over **B** in the case of the β-glycoside since in both **A** and **B**, C9 is positioned in a gauche like conformation relative to the β–O_1 substituent. The answer to this question might lie in a more precise placement (than that indicated in **A** and **B**), of the C9 substituent in the β-$O_1C_1H_1$ dihedral angle in **A** or in the β-$O_1C_1O_5$ dihedral angle in **B**.

In conclusion this study represents a novel example of the use of the aglycone substituent to control stereochemistry at a remote off template center. Studies involving other pyranoside configurations and alkene

substitutions are currently in progress in order to get a closer understanding of the stereochemistry, and widen the applicability of this methodology.

Fig. 1



'olefin-up' favored
Z-alkenes- less selective

'olefin-down' disfavored

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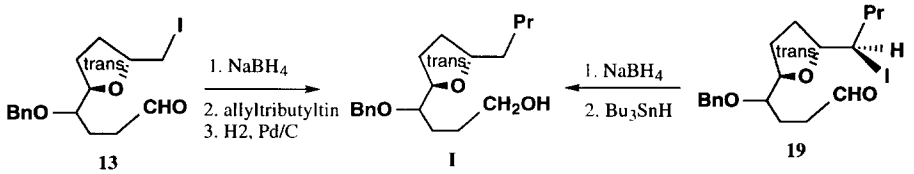
7. The primary iodide THF products **13** and **14** were assigned by ^{13}CNMR comparison with closely related 2,5 disubstituted THF's for which it was observed that the methylene resonances for the trans isomer occur consistently downfield relative to those of the cis isomer.[1] The stereochemistry in the more substituted THF **19t** was assigned by correlation with **13** via the common derivative **I**. The configurations of THF's **20c/t**, **25c/t** and **26c/t** were deduced by ^{13}CNMR comparisons with **19c/t**.



13 I 19

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9. The 2,3 dideoxygalactopyranoside alkenes were obtained as described for the dideoxygluco series starting from the corresponding 4-O-benzyl-6-O-tosyl pyranoside. The latter was prepared from the 6-O-tosyl-2,3-dideoxygluco pyranoside precursor over 3 steps which involved Mitsonobu inversion of the C4 alcohol with benzoate, hydrolysis of the derived ester and O-benzylation of the resulting alcohol.

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