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STEREOSELECTIVE GLYCOSIDATION REACTIONS OF ACTIVATED GLYCALS WITH A C1-OXYGENATED ALLYLSILANE: SYNTHESIS OF A CIS-PYRANO[2,3-b]PYRAN

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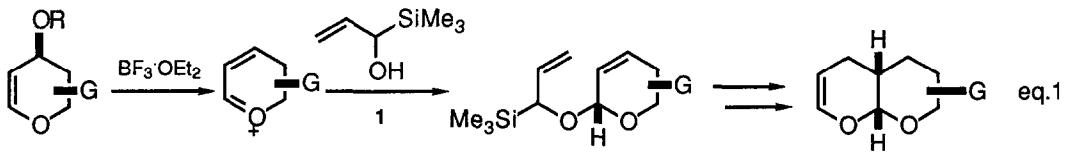
Abstract. A highly stereoselective synthesis of a cis-pyrano[2,3-b]pyran has been developed utilizing a BF_3·OEt_2 catalyzed glycosidation reaction of activated glycals with 1-hydroxy-2-propenyltrimethylsilane (**1**). The reaction resulted in incorporation of a 1-trimethylsilyl-2-propenyloxy-1-yl function. A subsequent fluoride ion promoted internal conjugate addition reaction was used for the construction of the cis-pyranopyran.

Asymmetric transformations of carbohydrate derivatives involving the use of organometallic nucleophiles have attracted considerable synthetic interest due primarily to the high levels of stereocontrol that may be obtained. In connection with our interest in the development of the synthetic utility of C1-oxygenated allylsilanes as bifunctional nucleophiles we recently reported a fluoride ion mediated conjugate addition reaction of 1-acyloxy-2-propenyltrimethylsilane to α, β-unsaturated ketones which resulted in the introduction of a 1-acyloxy-2-propenyl function.[1] These results suggested that in the presence of fluoride ion, the acylated C1-oxygenated allylsilane functions as an α -alkoxy stabilized allylic anion. Our interest in developing new synthetic strategies for the synthesis of polyoxygenated natural products led us to investigate efficient stereoselective routes to intermediates containing fused pyran ring systems. In pursuing these objectives we had envisioned 1-hydroxy-2-propenyltrimethylsilane (**1**) functioning as a heteronucleophile and effectively participating in Lewis acid catalyzed O-glycosidation reactions with activated glycals. The experimental success of the glycosidation reaction with **1**, relied on the nucleophilic character of the oxygen being greater than the propensity for the allylic silane to function as a carbon nucleophile. Thus, if **1** were to function as a suitable oxygen nucleophile, the process would lead to the anomeric functionalization of the pyran ring with incorporation of a 1-trimethylsilyl-2-propenyloxy-1-yl function. The oxygenated allylic silane appended to the pyran ring through a glycosidic linkage may function as a carbon nucleophile in a subsequent cyclization for the construction of a pyrano[2,3-b]pyran system (Equation 1).

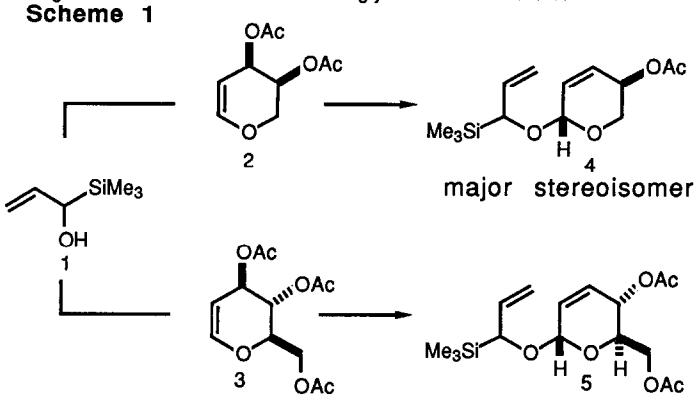


The purpose of this Letter is to disclose the development and application of such a strategy to the stereoselective synthesis of a cis-pyrano[2,3-b]pyran derived from D-glucose. The approach demonstrates the synthetic utility of a C1-oxygenated allylsilane as a carbon nucleophile[2] in an internal conjugate addition for the assembledge of a cis fused pyranopyran.

We have examined a variety of Lewis acids[3] likely to promote the glycosidation reactions of **1** with di-O-acetyl-L-arabinal (**2**)[4a], and tri-O-acetyl-D-glucal (**3**).[4b] Best results were obtained under conditions similar to those known to be effective for O-glycosidations and C-glycosidations of glucopyranosides[5] and activated glycals.[6] A solution of 1-

hydroxy-2-propenyltrimethylsilane (1) with L-arabinal **2** or D-glucal **3**, 0.1-0.2 **M** in freshly distilled acetonitrile was treated with $BF_3{\cdot}OEt_2$ (0.2 to 1.0 equiv) to afford the pseudo glycosides **4** and **5** as mixtures of α and β epimers, each existing as a mixture of diastereomers. The yields for this process range from of 40 to 63 %, with varying amounts (10 to 15 %) of protodesilylated product (Scheme 1 and Table).[7,8] In both cases, the reactions were regiospecific resulting in the stereoselective[9] incorporation of a 1-trimethylsilyl-2-propenyloxy-1-yl function at the C1-position of the pyran ring with the concommitant migration of the double bond to the 2,3-position. No products arising from C3-addition of **1** with the glycals were detected.[10]

Scheme 1

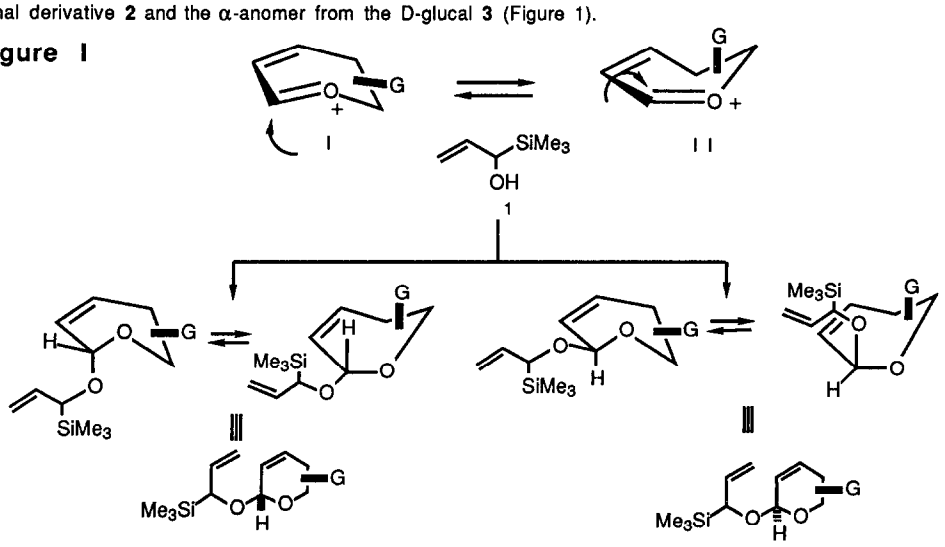


Table

equiv $BF_3{\cdot}OEt_2$	time h / temp °C		ratio[9] α/β	yield %
1.0	2.0	-30	1:8	45
0.2	3.0	23	1:4	50
1.0	3.0	-30	15:1	60
0.3	2.0	23	12:1	63
0.3	0.25	60	5:1	40

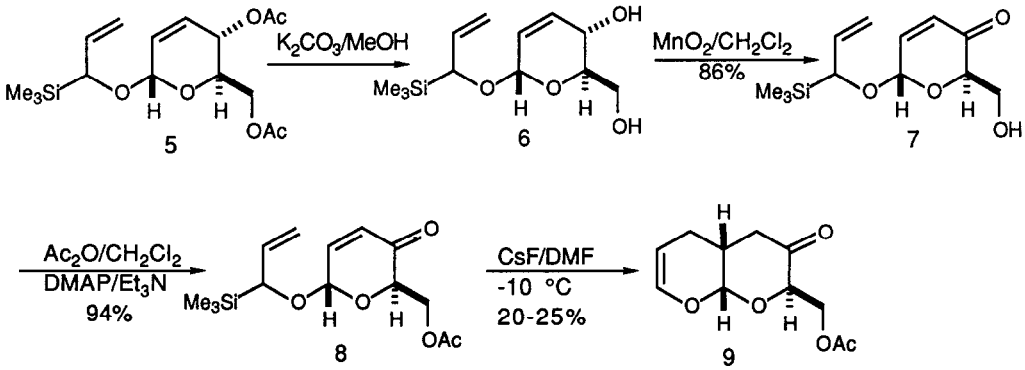
The regiochemical outcome of the glycosidations indicates that the reactions proceed in an S_N2' fashion with the leaving group in an anti orientation with respect to the incoming oxygen nucleophile. We postulate the reactions preferentially occur from conformer I, generated from glycals **2** and **3** in the presence of $BF_3{\cdot}OEt_2$, with the oxygen nucleophile entering with a stereoelectronically preferred axial orientation leading predominantly to the β-anomer from the L-arabinal derivative **2** and the α-anomer from the D-glucal **3** (Figure 1).

Figure I



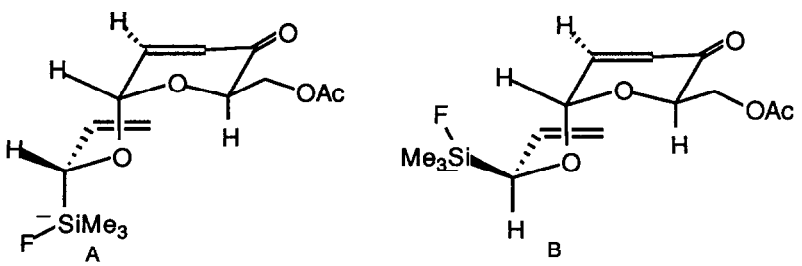
The preparation of the cis-pyrano[2,3-b]pyran **9** is detailed in Scheme 2. The pyranopyran derived from tri-O-acetyl-D-glucal **3** was synthesized in four steps starting from the diastereomeric glycoside **5**. Reaction of **5** with potassium carbonate (MeOH-THF; 1:1) gave the diol **6**. This was followed by a selective oxidation of the secondary allylic alcohol with excess MnO_2 to give the pyranone system **7.** This compound was acylated under standard conditions to produce the primary acetate **8.** Upon treatment with cesium fluoride (3.0 equiv) in DMF, **8** underwent an internal conjugate addition to afford the cis pyranopyran **9.** [8,11,12]

Scheme 2



In conclusion, the $BF_3{\cdot}OEt_2$ catalyzed glycosidation reaction of glycals **2** and **3** with 1-hydroxy-2-propenyltrimethylsilane (**1**) resulted in the stereoselective incorporation of a 1-trimethylsilyl-2-propenyloxy-1-yl function. A cesium fluoride catalyzed internal conjugate addition reaction of the allylsilane glycoside **8** resulted in the formation of a cis-pyrano[2,3-b]pyran. Although the chemical yield of the cyclization step needs to be improved to make the reaction synthetically useful, this approach demonstrates the utility of **1** as a useful bifunctional nucleophile and broadens our knowledge of asymmetric transformations with allylic silanes. Since the α-glycoside **8** is epimeric at the C1 position of the allylic silane, we surmize that only diastereomer A, having the C-Si sigma bond coplanar with the p-orbitals of the adjacent olefin, is most likely to participate in a successful internal conjugate addition (Figure II). In addition, the electronegative oxygen atom on the allylic silane may be attenuating the nucleophilic character of the C3-carbon by stabilizing the adjacent hypervalent silicon species and preventing cyclization. Furthermore, the sensitive nature of the enol-acetal functionality present in the pyranopyran **9** may also be responsible for the diminished chemical yields. Efforts to further improve the yield of the cyclization by using a homochiral varient of **1**, combined with applications of this methodology to the synthesis of polyoxygenated natural products are currently under investigation.

Figure II



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References and Footnotes

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2. For earlier reports of homoenolate equivalents, see: (a). Corey, E.J.; Cane, D.E.; *J. Org. Chem.* **1970**, 35, 3405; (b). Corey, E.J.; Erickson, B.W.; Noryori, R. *J. Am. Chem. Soc.* **1971**, 93, 1724; (c) Hosomi, A.; Hashimoto, H.; Sakurai, H. *J. Org. Chem.* **1978**, 43, 2551; (d) Still,W. C.; Macdonald,T.L. *J. Am. Chem. Soc.* **1974**, 96, 5561; (e) Evans, D.A.; Andrews, G. C.; Buckwalter, B. *J. Am. Chem. Soc.* **1974**, 96, 5560.
3. Other Lewis acids that were examined include: $BF_3{\cdot}OEt_2$, $TiCl_4$, TMSOTf, TBSOTf at various temperatures, were less effective or failed to provide the desired product. Attempts to promote the glycosidation reaction with acid catalysts (PPTS or p-TsOH) were ineffective.
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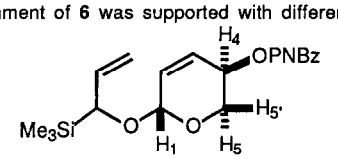
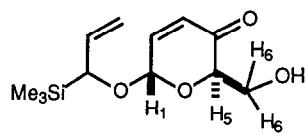
7. The protodesilylated products were confirmed by comparison with products obtained from the "Ferrier Reaction" of allyl alcohol with glycals **2** and **3** in the presence of $BF_3{\cdot}OEt_2$
8. All new compounds gave ^1H NMR (400 MHz), IR and MS data consistent with their assigned structures.
9. The α/β–ratios for the glycosidation products **4** and **5** were determined by integration of the anomeric carbon resonances using inverse gated decoupling experiments. The stereochemical assignments for the major diastereomers **4** and **5** could not be determined directly and thus were based on $^3J_{H1,H2}$ values for their respective derivatives, for **4**: para-nitrobenzoate derivative i and, for **5**: enone **6**. The stereochemical assignment of **6** was supported with difference NOE experiments.



i

$^3J_{H1,H2}$ = 3.0 Hz (β-anomer)
$^3J_{H1,H2}$ = 1.8 Hz (α-anomer)



6

$^3J_{H1,H2}$ = 3.2 Hz (α–anomer)

10. Unidentifiable, low Rf material was isolated from the reactions (<10%) however no products were detected spectroscopically which were derived from **1** functioning as a homoenolate equivalent.
11. Attempts to catalyze the cyclization with $BF_3{\cdot}OEt_2$, $TiCl_4$, TMSOTf, $MgBr_2{\cdot}OEt_2$ in a variety of solvents resulted in protodesilylation or recovered starting material. The use of $SbCl_5$ (CH_2Cl_2/ -78 °C) gave traces (< 5%) of product **8**. Compound **7** failed to react when treated with triphenylcarbenium hexachloroantimonate [$(Ph)_3CSbCl_5$] in CH_2Cl_2 from 0 to 25 °C . Conditions described for carbocyclizations employing nBu_4NF gave only desilylated products *cf.* Majetich, G., Desmond, R.W., Soria, J. *J. Org. Chem.* **1986**, 51, 1753.
12. Spectral data for compound **9** follows: ^1H NMR ($CDCl_3$, 93.94 KG, 400MHz) δ 6.38 (d,1H, J = 5.91Hz), 5.34 (d, 1H, J < 1.0Hz), 4.69 (m, 1H), 4.54 (m, 1H), 4.51 (m, 2H), 4.38 (dd, 1H, J = 4.60, 11.84Hz), 2.61 - 2.47 (m, 4H), 2.08 (s, 3H), 1.77 (dd, 1H, J = 5.25, 17.51Hz). ^{13}C (C_6D_6, 93.94 KG, 100 MHz) δ 20.31, 25.46, 32.84, 38.66, 62.88, 74.26, 94.33, 97.62, 141.97, 169.88, 203.33. IR ($CHCl_3$, λ max) 2910, 1730, 1640, 1440, 1365, 1230, 1150, 1025 cm^{-1}. FABMS (glycerol), m/z 227 $(M+H)^+$.

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