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# Double Stereodifferentiation in the Lewis Acid Promoted C-Glycosidation of Activated Glycals with Chiral (*E*)-Crotylsilanes§

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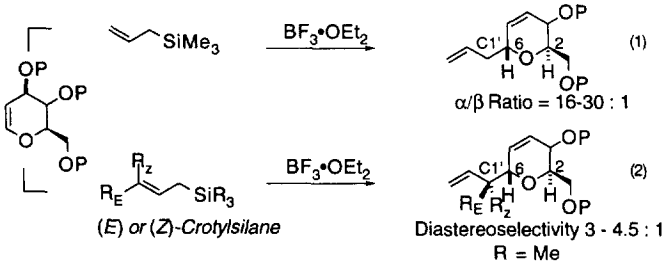
**Abstract:** Lewis acid promoted C-glycosidation reactions of activated glycals with chiral (*E*)-crotylsilanes were found to be highly regio- and diastereoselective. The reactions of chiral silane reagents proceed with the formation of a new C-C bond at C6 of the pyran ring with concomitant migration of C5-C6 double bond to the C5-C4 position of the pyran ring. The reactions are highly diastereoface selective as the crotylsilane (carbon nucleophile) approaches the derived oxonium ion *anti* to the C2 substituent. The stereochemical relationship between the methyl bearing stereogenic center at the C1' position and the C6 position of the pyran is defined by the chirality of the silane reagent as the configuration of the C-Si bond determines the stereochemistry of the C1'-methyl group. Our experiments have shown that the pair wise combination of the glycals with the chiral silane reagents give high levels of selectivity resulting from the existence of strong stereochemical control elements within each reaction component. The topological bias is principally controlled by stereoelectronic effects of the pyran oxonium ion and by the facial bias of the silane reagent. Levels of diastereoselectivity ranged from 10 to 30 : 1 (α/β ratio) in the presence of $BF_3$•$OEt_2$ which was found to be with TMSOTf the most effective Lewis acids to promote the reactions. Consistent with the behavior of these silane reagents and an *anti*-$S_E'$ mechanism, of the four possible diastereomers only the two isomers derived from the C1' stereochemical relationship are detectable.


**Introduction.** The utility of activated glycals for the stereoselective introduction of nucleophiles at the anomeric position of the pyran ring system has been well documented with heteroatom and carbon nucleophiles. In particular, recent applications have been directed towards the construction of complex carbohydrate and polypropionate-based natural products.[1] In this context, the application of glycals to the stereoselective synthesis of C-glycosides has played a key role in establishing an axial disposed allyl group at the C6 position of the pyran ring (eq. 1). This Lewis acid promoted reaction known as the "carbon Ferrier" process[2] was subsequently extended to include reactions of various glycals with *cis* and *trans*-crotylsilanes. Those reactions afforded methyl allylated glycosides with moderate to good levels of diastereoselectivity and were key reactions in the total synthesis of a variety of complex natural products.[3] The stereochemical relationship between the methyl bearing stereogenic center at the C1' position and the C6 position of the pyran is determined by the configuration of the crotyl moiety (eq. 2). For instance, the reaction of an activated glycal with (*E*)-crotylsilane affords an α-C-glycoside with the *syn* stereochemical relationship between the $R_E$ and the H6 hydrogen while the (*Z*)-isomer affords the *anti* relationship between $R_Z$ and the H6 hydrogen.

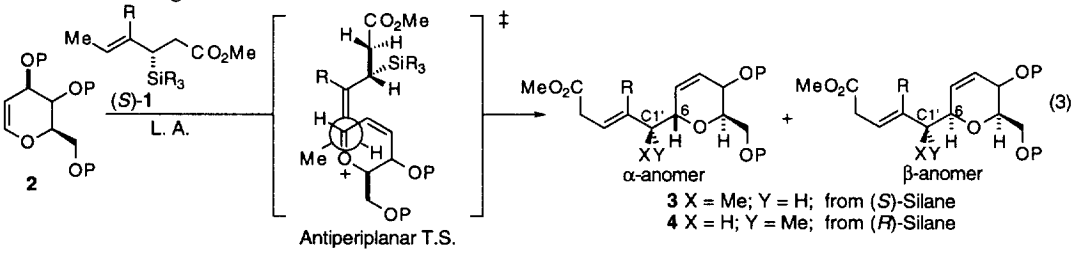



Research conducted in our laboratories has established the utility of functionalized (*E*)-crotylsilanes as reagents for highly diastereo- and enantioselective condensation reactions with C-X π-systems.[4,5] These studies

§ *This paper is dedicated to Professor Samuel Danishefsky for his contributions to organic chemistry.*

have culminated in the development of efficient methods for the asymmetric synthesis of functionalized homoallylic ethers and alcohols. Complementary efforts concerning the development of asymmetric [3+2]-annulations have provided routes to tetrahydrofurans, cyclopentanes, $\Delta^2$-isoxazolines and silyl-substituted pyrrolidines.[6] Within the context of acyclic stereocontrol, these silane reagents proved to be quite reciprocal to the existing chiral metal enolate[7] and allylboronate methodologies.[8] In contemplating the further development of our chiral silane reagents and given the problem that only moderate levels of selectivity in the C-glycosidation reactions have been achieved with achiral crotylsilane reagents, the use of chiral (*E*)-crotylsilane reagents as carbon nucleophiles seemed appealing. The synergism between the chirality of the silane reagent and the glycal should provide enhanced diastereoselection in the addition process. Furthermore, the side chain of the adduct could easily be transformed into a wide range of synthetically useful intermediates not readily accessable using simple unfunctionalized crotyl metal reagents.

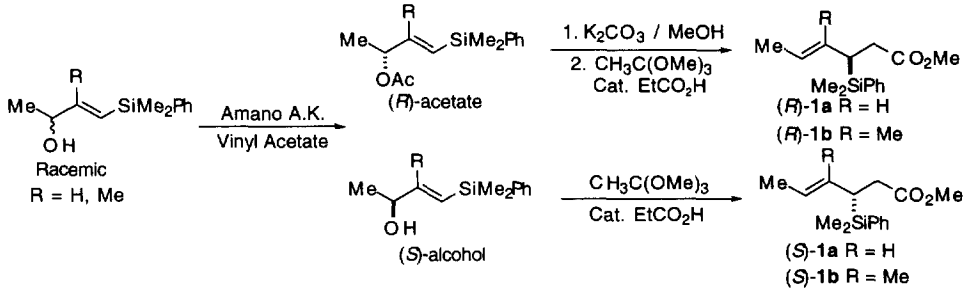
The objectives of the present study are the synthesis and continued development of silane reagents, possessing C-centered chirality, and of the strategies for the execution of double stereodifferentiating reactions with activated glycals. Here we summarized the synthesis of the chiral silane reagents where the ortho-ester Claisen rearrangement was used for the elaboration of the enantiomerically pure vinylsilane into the chiral crotylsilane reagent. The ensuing Lewis acid promoted C-glycosidation reaction of activated glycals with chiral (*E*)-crotylsilanes has been studied and was found to be highly regio- and diastereoselective. The reactions of chiral silane reagents proceed with the formation of a new C-C bond at C6 of the pyran ring with concomitant migration of the C6-C5 double bond to the C5-C4 position of the pyran ring. In contrast to the achiral crotylsilane reagents, the reactions of the chiral varients exhibit high diastereoface selectivity as the crotylsilane (carbon nucleophile) approaches the derived oxonium ion *anti* to the C2 substituent. This process is illustrated with (*S*)-**1** in Equation 3 with the formation of the α-isomer as the major stereoisomer. In this study, the stereochemical course of the C-glycosidations is consistent with the results of our earlier experiments concerning the Lewis acid promoted additions to aldehydes and acetals. Accordingly, the stereochemical relationship between the methyl bearing stereogenic center at the C1' position and the anomeric center of the pyran is defined by the chirality of the silane reagent as the configuration of the C-Si bond determines the stereochemistry of the C1'-methyl group. This result is completely consistent with an *anti*-$S_E'$ mode of addition of the oxonium ion with the silane reagent.[6]




**Synthesis of the Chiral Crotylsilanes.** The synthesis of the silane reagents, summarized in scheme 1, was initiated with an enzymatic resolution (*Pseudomonas* lipase)[9] of the racemic (*E*)-vinylsilanes which afforded the pure (*S, E*)-vinylsilane alcohol and the (*R, E*)-vinyl acetate in high enantiomeric purity after separation on $SiO_2$. A $LiAlH_4$ reduction or base catalyzed hydrolysis ($K_2CO_3$, MeOH) of the (*R*)-acetate provided the desired (*R, E*)-alcohol. The corresponding β-substituted (*R, E*)- and (*S, E*)-crotylsilanes were produced in high yield by

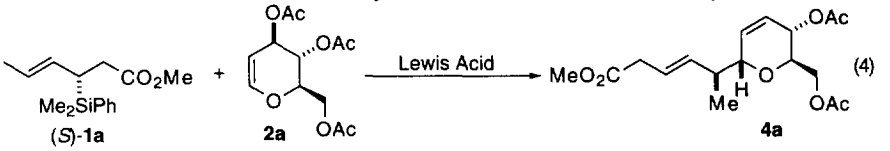
an ortho-ester-Claisen rearrangement on the individual secondary allylic alcohols. As anticipated, the sigmatropic rearrangement was highly stereospecific (ee's > 96%) and highly stereoselective with respect to the configuration of the *trans*-double bond, which was exclusively produced.[10,11,12]

**Scheme 1**




**Stereoselective C-Glycosidation Reactions.** In an effort to optimize the reaction conditions of the addition of crotylsilanes to the activated glycals, five different Lewis acids were surveyed employing tri-*O*-acetyl-D-glucal, and the results of those experiments are summarized in Table I and Equation 4. Based on previous results obtained in our laboratories while investigating the addition of silane reagents to iminium and oxonium ions[13] as well as documented addition reactions of achiral allylsilanes to activated glycals[14], $BF_3{\bullet}OEt_2$ was shown to be an effective Lewis acid for these reaction types. Generally, high levels of diasteroselectivity were exhibited (> 20:1) and the selectivity was shown to be independant of the type of Lewis acid. Importantly, nearly complete facial bias is observed in these double stereodifferentiating reactions; of the four possible diastereomers only the two isomers derived from the C1' stereochemical relationship are detectable.

**Table I**: Effect of Lewis Acid on the C-Glycosidation Reaction of Tri-*O*-Acetyl-D-Glucal




| entry | Lewis Acid [equiv] [a] | de[b] | 4a Yield, % |
|---|---|---|---|
| 1 | $BF_3{\bullet}OEt_2$ [2.0] | 20 : 1 | 80 |
| 2 | $TiCl_4$ [2.0] | 17 : 1 | 50 |
| 3 | TMSOTf [0.25] | 12 : 1 | 62 |
| 4 | TMSOTf [0.5] | 15 : 1 | 92 |
| 5 | $AlCl_3$ [1.2] | — | Traces |
| 6 | $MgBr_2{\bullet}OEt_2$ [2.0] | — | NR |

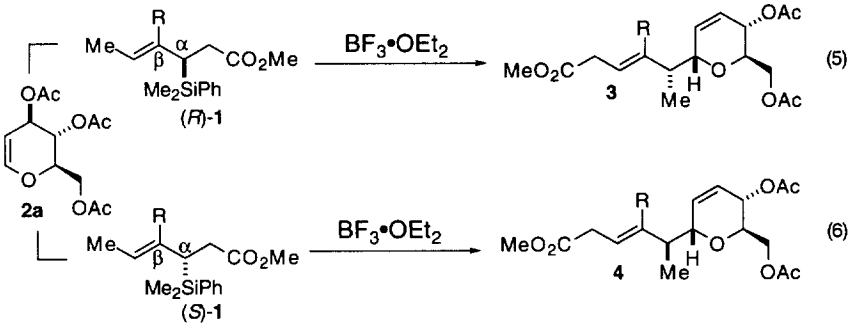
[a] All reactions were run in $CH_3CN$ (0.15 M) in substrate at -30°C for 2 hours before being diluted with saturated $NaHCO_3$. [b] Ratios of diastereomers (C1' Me-C6) were determined by $^1H$ NMR on the crude reaction mixture.

As shown in Table I, entries 2 and 3, when promoting the reaction with $TiCl_4$ or catalytic amount of TMSOTf (0.25 equiv) high levels of selectivity were still achieved but only moderate yields of the desired C-

glycosidation product were obtained. As shown in entry 4, increasing the amount of TMSOTf to 0.5 equivalent resulted in more efficient conversion as well as higher levels of diastereoselection. Entries 5 and 6 show that within the same reaction period, the use of $AlCl_3$ resulted in poor yield (< 10%) while the $MgBr_2 \cdot OEt_2$ promoted reaction showed no product formation under the described reaction conditions. The optimized conditions for the Lewis acid catalyzed C-glycosidation reactions were determined to be 2.0 equivalents of $BF_3 \cdot OEt_2$ at -30° C in acetonitrile (0.15 **M**) for 1.5 to 2 hours.

After optimization of the reaction described above, the use of unsubstituted (*R*)- and (*S*)-crotylsilanes **1a** lead to the obtention of the desired product in high yields with high regio- and diastereoselectivities (Table II). Addition of (*S*)-**1a** to the glucal derivative yielded 80% of the desired product with a de > 20 : 1. As expected, the addition of (*R*)-**1a** to **2a** was highly selective (de = 13:1) as well as high yielding (85%) (Equations 5, 6 and entries 1, 2). Concerning the development of our silane reagents and their addition to tri-*O*-acetyl-D-glucal, we have broadened the scope of this process with related β-methyl silane reagents. Their trisubstituted olefin synthon equivalencies have peviously been established.[15] The use of β-methyl substituted crotylsilane reagents resulted in the obtention of more moderate yields than for their corresponding unsubstituted silanes, however the stereoselectivity increased. The glycosidation of (*S*)-**1b** with **2a** yielded 71% of the compound **3b** with a de >30:1 while the condensation of (*R*)-**1b** with **2a** gave 70% of the desired product with a de of 23:1. Those successful experiments motivated us to pursue those addition reactions to the commercially available tri-*O*-acetyl-D-galactal.

**Table II**: C-Glycosidation of Tri-*O*-Acetyl-D-Glucal **2a**.

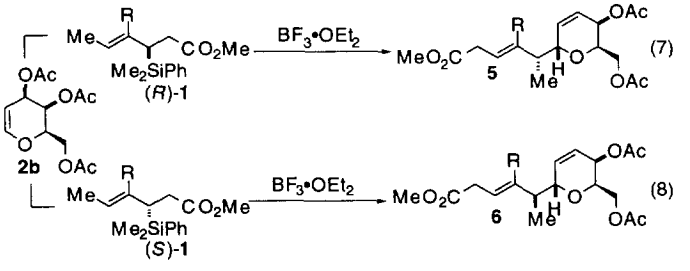



| entry[a] | Silane | R | de[b] | Major Product | Yield[c], % |
|---|---|---|---|---|---|
| 1 | (*R*)-**1a** | H | 13 : 1 | **3a** | 85 |
| 2 | (*S*)-**1a** | H | 20 : 1 | **4a** | 80 |
| 3 | (*R*)-**1b** | Me | 23 : 1 | **3b** | 71 |
| 4 | (*S*)-**1b** | Me | > 30 : 1 | **4b** | 70 |

[a] All reactions were run in $CH_3CN$ (0.15 **M**) in substrate at -30° C for 2 hours before being diluted with saturated $NaHCO_3$. [b] Ratios for for diastereomers were determined by $^1H$ NMR on the crude reaction mixture. [c] Yield of purified diastereomer after chromatography on $SiO_2$.

The reactivity of the tri-*O*-acetyl-D-galactal was similar to that of D-glucal, however lower levels of facial selectivity were observed. Those experiments are summarized in Equations 7, 8 and Table III. Addition of (*S*)-**1a** to the galactal **2b** afforded the desired C-glycoside in 81% with a de = 12.5:1. The glycosidation using silane (*R*)-**1a** was quantitative with a similar diastereoselectivity, de = 12:1. As observed in the case of D-glucal **2a**, the yields of the addition of methyl substituted crotylsilane (*S*)-**1b** and (*R*)-**1b** reagents were more moderate than the corresponding unsubstituted silane however the selectivity remained constant for all silane reagents. For those cases, C-glycosides **5b** and **6b** were obtained in yields of 72% with a de of 11:1 and 75 % with a de 10:1 respectively.

**Table III**: C-Glycosidation of Tri-*O*-Acetyl-D-Galactal **2b**




| entry[a] | Silane | R | de[b] | Major Product | Yield [c], % |
|---|---|---|---|---|---|
| 1 | (*R*)-**1a** | H | 12 : 1 | **5a** | 99 |
| 2 | (*S*)-**1a** | H | 12.5 : 1 | **6a** | 81 |
| 3 | (*R*)-**1b** | Me | 11 : 1 | **5b** | 72 |
| 4 | (*S*)-**1b** | Me | 10 : 1 | **6b** | 75 |

[a] All reactions were run in $CH_3CN$ (0.15 **M**) in substrate at -30°C for 2 hours before being diluted with saturated $NaHCO_3$. [b] Ratios for diastereomers were determined by $^1H$ NMR on the crude reaction mixture. [c] Yield of purified diastereomer after chromatography on $SiO_2$.

**Stereochemistry Assignment of the C-glycosides.** The stereochemical assignment of the diastereomeric C-glycosides **3** through **6** were assigned by analogy with the bicyclic ethers **9** and **10** derived from **3a** and **4a** respectively. Their individual syntheses are described below in scheme 2. This required a selective oxidative cleavage of the *trans*-disubstituted double bond. This transformation was carried out in the presence of the glycal-olefin by a two step process, employing a dihydroxylation with $OsO_4$ (7 mol%) and NMO (2.5 equiv) in a 4:1 acetone:water mixture, the reaction was acidified to acidic pH using 3N $H_2SO_4$. Without further purification the diol was oxidatively cleaved with $Pb(OAc)_4$ (1.3 equiv) in benzene to afford aldehyde **7** which was then selectively reduced with $BH_3•Me_2S$ (1.6 equiv) to afford the primary alcohol **8**. A NBS promoted bromo-etherification afforded the bicyclic 5,6-*cis*-fused system **9** in 68% yield (four step sequence).

The stereochemistry assignment of the derived C-glycoside was accomplished by difference NOE experiments on diastereomeric bicyclic ethers **9** and **10** derived respectively from **3a** and **4a**. Difference NOE and COSY experiments on bicyclic ethers **9** and **10** revealed that the two diastereomers differed only at C1'. The important homonuclear couplings and difference NOE measurements are summarized in Table IV. In the case of compound **10**, no enhancement of H5 was observed upon irradiation of the 3'-methyl group. However, in compound **9**, a 5% NOE was measured for H5 via irradiation of the 3'-methyl group. Those experiments determined that the stereochemical relationship between the methyl bearing stereogenic center at the C1' position and the anomeric center of the pyran is defined by the chirality of the silane reagent as the configuration of the C-Si bond determines the stereochemistry of the C1'-methyl group.[6] The identical reaction sequence was performed on **4a** to obtain **10** in 70% overall yield.

**Scheme 2**

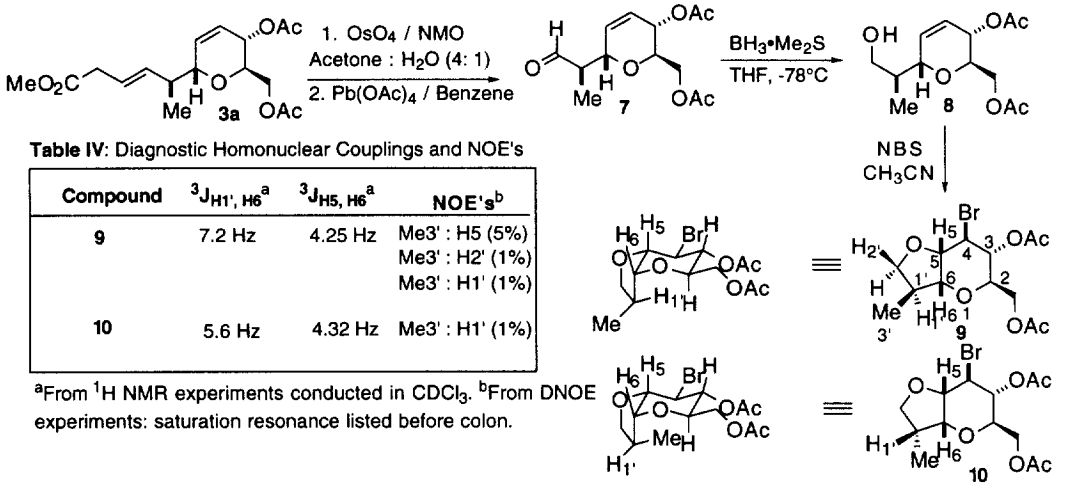



**Table IV:** Diagnostic Homonuclear Couplings and NOE's

| Compound | $^3J_{H1', H6}$[a] | $^3J_{H5, H6}$[a] | NOE's[b] |
|---|---|---|---|
| **9** | 7.2 Hz | 4.25 Hz | Me3' : H5 (5%)<br>Me3' : H2' (1%)<br>Me3' : H1' (1%) |
| **10** | 5.6 Hz | 4.32 Hz | Me3' : H1' (1%) |

[a]From $^1$H NMR experiments conducted in $CDCl_3$. [b]From DNOE experiments: saturation resonance listed before colon.

**Summary**. Lewis acid promoted C-glycosidation reactions of activated glycals with chiral (*E*)-crotylsilanes were found to be highly regio- and diastereoselective, high yielding, and should be applicable to a wide range of activated glycal substrates. These experiments have shown that the stereochemical relationship between the methyl bearing stereogenic center at the C1' position and the C6 position of the pyran is defined by the chirality of the silane reagent. In other words, the configuration of the C-Si bond determines the absolute stereochemistry of the C1'-methyl group. Our experiments have also shown that the pair wise combination of the glycals with the chiral silane reagents give high levels of selectivity resulting from the existence of strong sterechemical control elements within each reaction component. We anticipate that with the enhanced selectivity exhibited by the chiral silane reagents would prove useful in the context of natural product synthesis.

**General Experimental Section.** $^1$H NMR spectra were recorded on a Varian Unity (400 MHz) spectrometer at ambident temperature. Data are reported as follows: chemical shift in ppm from internal standard tetramethysilane on the d scale, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), integration, and coupling constant (Hz). $^{13}$C NMR were recorded on a Jeol Varian (67.5 Hz),

spectrometers at ambient temperature. Chemical shifts are reported in ppm from tetramethylsilane on the δ scale, with the solvent resonance employed as the internal standard (deuterochloroform at 77.0 ppm). All $^{13}C$ spectra were recorded with complete proton decoupling. Difference NOE (DNOE) were recorded with 1024 accumulated transients each. The irradiation delay was set to 8s. No special precautions were taken in sample preparation prior to recording the DNOE spectra (no degassing, etc). Optical rotations were recorded on a AUTOPOL III digital polarimeter at 589 nm or other λ, and are reported as $[\alpha]^{D}_{25}$ (concentration in grams/100 mL solvent). High resolution mass spectra were obtained on MAT-90 spectrometer.

Analytical thin layer chromatography was performed on Whatman 0.25 mm silica gel 60-F plates. Flash chromatography was preformed as previously described.[16] When specified as "anhydrous", solvents were distilled and / or stored over 4 Å sieves prior to use. Tetrahydrofuran (THF) was distilled from sodium metal / benzophenone ketyl. Dichloromethane ($CH_2Cl_2$) was distilled from calcium hydride. Acetonitrile was purchased from Aldrich in a "sure sealed" bottle and used as purchased. *N*-bromosuccinimide (NBS) was recrystalized from water and lead tetracacetate ($Pb(OAc)_4$) was purchased from Sigma and was used without purification. Unless otherwise noted, non aqueous reactions were carried out in oven dried glassware under a nitrogen atmosphere.

**General Procedure for the C-Glycosidation Reaction Illustrated with Tri-O-Acetyl-D-Glucal 2a and (*S*)-Silane 1a. [2*R*-{2α,3β,6β (1*S*, 2*E*)]]-3-(Acetyloxy)-3,6-dihydro-6-(4-carbomethoxy-1-methyl-2-butenyl)-2*H*-pyran-2-methanol acetate (3a).** In a dry 50 mL round bottom flask was dissolved tri-*O*-acetyl-D-glucal (500 mg, 1.88 mmol) and the silane reagent (*S*)-**1a** (476 mg, 1.80 mmol) in $CH_3CN$ (3.6 mL). The solution was cooled to -30° C and $BF_3{\bullet}OEt_2$ (0.223 mL, 2 equiv) was added via microsyringe. The reaction mixture was stirred at -30° C for two hours before being diluted with saturated solution of $NaHCO_3$ (10 mL). The resulting solution was then extracted with $CHCl_3$ (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The resulting clear yellow oil was flushed through a short plug of $SiO_2$, eluting with 20-30% EtOAc:Hexanes, to yield **3a** (534.0 mg, 1.5 mmol, 80%) as a colorless oil. $^1H$ NMR ($CDCl_3$) δ: 5.93 (dd, 1H, J = 1.2 Hz, J = 1.2 Hz); 5.74 (dd, 1H, J = 2.0 Hz, J = 2.0 Hz); 5.56 (m, 1H); 5.41 (m, 1H); 5.05 (m, 1H); 4.13 (m, 2H); 3.88 (m, 2H); 3.63 (s, 3H); 3.00 (d, 2H, J = 7.2 Hz); 2.47 (m, 1H); 2.03 (s, 3H); 2.02 (s, 3H); 1.05 (d, 3H, J = 6.8 Hz). $^{13}C$ NMR ($CDCl_3$) δ: 172.1; 170.7; 170.4; 135.7; 132.1; 123.7; 122.9; 75.0; 70.0; 64.9; 62.8; 51.7; 40.8; 37.8; 20.9; 16.8. IR (neat) $cm^{-1}$: 33459; 2960; 2127; 1700; 1437; 1374; 1241; 1048; 971; 908. CIMS+$NH_4$ ($NH_3$ gas): 358, 281, 221, 213, 153, 111. CIHRMS+$NH_4$ calculated for $C_{17}H_{24}O_7$+$NH_4$= 358.1865; found 358.1879. $[\alpha]^{D}_{25}$: +25.7° ($CH_2Cl_2$, *c* 1.55).

**[2*R*-{2α,3β,6β(1*R*,2*E*)]]-3-(Acetyloxy)-3,6-dihydro-6-(4-carbomethoxy-1-methyl-2-butenyl)-2*H*-pyran-2-methanol acetate (4a).** $^1H$ NMR ($CDCl_3$) δ: 6.56 (m, 1H); 6.45 (m, 1H); 6.19 (m, 2H); 5.67 (m, 1H); 4.84 (m, 1H); 4.66 (m, 2H); 4.27 (s, 3H); 3.67 (d, 3H, J = 4.8 Hz); 3.13 (m, 1H); 2.68 (s, 3H); 2.67 (s, 3H); 1.65 (d, 3H, J = 6.4 Hz). $^{13}C$ NMR ($CDCl_3$) δ: 172.2; 170.8; 170.5; 135.8; 131.9; 123.9; 122.3; 74.7; 70.6; 64.8; 62.5; 51.7; 40.1; 37.8; 21.0; 20.8; 15.7. IR (neat) $cm^{-1}$: 3854; 3744; 3447; 2360; 1734; 1718; 1700; 1696; 1684; 1653; 1559; 1539; 1521; 1507; 1457; 1437; 1227. CIMS+$NH_4$ ($NH_3$ gas): 358, 281,

246, 229, 187, 169, 126, 109. CIHRMS+$NH_4$ calculated for $C_{17}H_{24}O_7$+$NH_4$= 358.1865; found 358.1884. $[\alpha]^D_{25}$: +40.0° ($CH_2Cl_2$, *c* 0.94).

**[2*R*-{2α,3β,6β (1*S*, 2*E*)]]-3-(Acetyloxy)-3,6-dihydro-6-(4-carbomethoxy-1,2-dimethyl-2-butenyl)-2*H*-pyran-2-methanol acetate (3b).** $^1H$ NMR ($CDCl_3$) δ: 5.88 (m, 1H); 5.85 (m, 1H); 5.42 (m, 1H); 5.09 (m, 1H); 4.16 (m, 2H); 4.04 (dd, 1H, J = 2.4 Hz, J = 2.4 Hz); 3.87 (m, 1H); 3.65 (s, 3H); 3.03 (d, 2H, J = 7.2 Hz); 2.46 (m, 1H); 2.07 (s, 3H); 2.06 (s, 3H); 1.58 (d, 3H, J = 1.2 Hz); 1.12 (d, 3H, J = 6.8 Hz). $^{13}$CNMR ($CDCl_3$) δ: 170.6; 170.5; 140.4; 133.6; 122.4; 117.3; 76.6; 74.4; 68.2; 63.6; 62.4; 51.7; 45.3; 33.3; 20.9; 20.7; 15.8; 12.6. IR (neat) $cm^{-1}$: 3854; 3745; 3447; 1734; 1700; 1684; 1653; 1559; 1539; 1507; 1457; 1437; 1374; 1231; 1046. CIMS+$NH_4$ ($NH_3$ gas): 372, 295, 235, 217, 153, 141. CIHRMS+$NH_4$ calculated for $C_{18}H_{26}O_7$+$NH_4$ = 372.2022; found 372.2010. $[\alpha]^D_{25}$: +35.6° ($CH_2Cl_2$, *c* 0.46).

**[2*R*-{2α,3β,6β (1*R*, 2*E*)]]-3-(Acetyloxy)-3,6-dihydro-6-(4-carbomethoxy-1,2-dimethyl-2-butenyl)-2*H*-pyran-2-methanol acetate (4b).** $^1H$ NMR ($CDCl_3$) δ: 6.00 (m, 1H); 5.79 (m, 1H); 5.39 (m, 1H); 5.12 (m, 1H); 4.22 (m, 1H); 4.07 (m, 1H); 4.01 (m, 1H); 3.89 (m, 1H); 3.66 (s, 3H); 3.06 (d, 2H, J = 6.4 Hz); 2.56 (m, 1H); 2.05 (s, 3H); 2.04 (s, 3H); 1.62 (d, 3H, J = 1.6 Hz); 1.02 (d, 3H, J = 7.2 Hz). $^{13}$C NMR ($CDCl_3$) δ:172.6, 170.8, 170.4, 140.2, 131.9, 124.0, 117.3, 73.6, 69.7, 64.8, 62.7, 51.7, 45.9, 33.2, 21.0, 20.8, 15.5, 13.0. IR $cm^{-1}$: 3854; 3744; 3448; 2104; 1734; 1700; 1684; 1653; 1559; 1539; 1507; 1457; 1437; 1374; 1226. [.CIHRMS+$NH_4$ calculated for $C_{18}H_{26}O_7$ +$NH_4$ = 372.2022; found 372.1988. $[\alpha]^D_{25}$: +18.9° ($CH_2Cl_2$, *c* 0.38).

**[2*R*-{2α,3α,6β (1*S*, 2*E*)]]-3-(Acetyloxy)-3,6-dihydro-6-(4-carbomethoxy-1-methyl-2-butenyl)-2*H*-pyran-2-methanol acetate (5a).** $^1H$ NMR ($CDCl_3$) δ: 5.99 (m, 2H); 5.56 (m, 2H); 5.07 (d, 1H, J = 3.2 Hz); 4.13 (m, 2H); 4.06 (m, 1H); 3.92 (d, 1H, J = 9.2 Hz); 3.64 (s, 3H); 3.03 (dd, 2H, J = 3.2 Hz, J = 5.6 Hz); 2.48 (m, 1H); 2.03 (s, 6H); 1.04 (d, 3H, J = 7.6 Hz).$^{13}$C NMR ($CDCl_3$) δ: 172.1; 170.7; 170.5; 135.5; 133.9; 128.3; 122.1; 68.6; 63.8; 63.1; 51.8; 40.3; 37.7; 20.9; 20.8; 17.1; 15.2.IR (neat) $cm^{-1}$: 3405; 2098; 1647; 1437; 1371; 1229; 1092; 1047. CIHRMS+$NH_4$ calculated for $C_{17}H_{24}O_7$+$NH_4$= 358.1865; found 358.1902. $[\alpha]^D_{25}$: -213.4° ($CH_2Cl_2$, *c* 0.93).

**[2*R*-{2α,3α,6β (1*R*, 2*E*)]]-3-(Acetyloxy)-3,6-dihydro-6-(4-carbomethoxy-1-methyl-2-butenyl)-2*H*-pyran-2-methanol acetate (6a).** $^1H$ NMR ($CDCl_3$) δ: 6.08 (m, 1H); 5.77 (m, 1H); 5.55 (m, 1 H); 5.40 (m, 1H); 5.02 (m, 1H); 4.18 (m, 2H); 4.09 (m, 1H); 3.92 (d, 1H, J = 9.2 Hz); 3.65 (s, 3H); 3.02 (d, 2H, J = 6.8 Hz); 2.47 (m, 1H); 2.04 (s, 6 H); 1.075 (d, 3H, J = 6.8 Hz). $^{13}$C NMR ($CDCl_3$) δ: 170.9; 170.5; 135.9; 133.1; 122.9; 122.2; 122.1; 75.9; 68.8; 63.9; 62.6; 51.7; 39.6; 37.9; 20.9; 20.8; 16.0. IR (neat) $cm^{-1}$: 3854; 3420; 2359; 2093; 1736; 1653; 1559; 1541; 1507; 1457; 1437; 1372; 1234; 1167; 1094; 1048; 978. CIHRMS+$NH_4$ calculated for $C_{17}H_{24}O_7$+$NH_4$= 358.1865; found 358.1880. $[\alpha]^D_{25}$: -151.7° ($CH_2Cl_2$, *c* 1.36).

**[2*R*-{2α,3α,6β(1*S*, 2*E*)]]-3-(Acetyloxy)-3,6-dihydro-6-(4-carbomethoxy-1,2-dimethyl-2-butenyl)-2*H*-pyran-2-methanol acetate (5b).** $^1$H NMR ($CDCl_3$) δ: 5.986 (m, 2H); 5.40 (m, 1H); 5.01 (m, 1H); 4.18 (m, 1H); 4.08 (m, 2H), 3.66 (s, 3H); 3.04 (d, 2H, J = 7.2 Hz); 2.46 (t, 1H, J = 3.2 Hz); 2.10 (m, 1H); 2.05 (s, 6H); 1.58 (s, 3H, ); 1.12 (d, 3H, J = 6.8 Hz). $^{13}$C NMR ($CDCl_3$) δ172.0; 170.4; 170.0; 139.4; 132.0; 123.2; 117.7; 74.1; 69.2; 64.7; 62.7; 51.4; 45.7; 32.9; 20.8; 20.5; 15.8; 13.3. CIHRMS+$NH_4$ calculated for $C_{18}H_{26}O_7$+$NH_4$ = 372.2022; found 372.2009. IR (neat) cm$^{-1}$: 3456; 2094; 1653; 1437; 1374; 1231; 1045; 835. $[\alpha]^D_{25}$: -157.9° ($CH_2Cl_2$, *c* 0.54).

**[2*R*-{2α,3α,6β(1*R*, 2*E*)]]-3-(Acetyloxy)-3,6-dihydro-6-(4-carbomethoxy-1,2-dimethyl-2-butenyl)-2*H*-pyran-2-methanol acetate (6b).** $^1$H NMR ($CDCl_3$) δ: 6.14 (m,1H); 5.97 (m, 1H); 5.39 (t, 1H, J = 7.2 Hz); 5.05 (d, 1H, J = 5.2 Hz); 4.09 (m, 4H); 3.65 (s, 3H); 3.07 (dd, 2H, J = 0.8 Hz, J = 2.4 Hz); 2.55 (m, 1H); 2.04 (s, 3H); 2.01 (s, 3H); 1.61 (s, 3H); 1.02 (d, 3H, J = 6.8 Hz). $^{13}$C NMR ($CDCl_3$) δ:170.6, 170.5, 140.3, 133.6, 122.5, 117.4, 76.5, 74.5, 68.2, 63.6, 64.4, 51.7, 45.3, 33.3, 20.9, 20.7, 154.9, 12.6. IR (neat) cm$^{-1}$: 3854; 3418; 2090; 1734; 1700; 1653; 1559; 1539; 1507; 1457; 1437; 1374; 1231; 1046. CIMS+$NH_4$ ($NH_3$ gas): 368, 351, 291, 211, 169, 151. CIHRMS+$NH_4$ calculated for $C_{18}H_{26}O_7$+$NH_4$ = 372.2022; found 372.2010. $[\alpha]^D_{25}$: -155.7° ($CH_2Cl_2$, *c* 0.53).

**Experimental Procedures for the Stereochemical Assignment of C-Glycosides 3a and 4a: Synthesis of Bicyclic-Bromo Ethers 9 and 10.** The stereochemistry of the C-glycosides was assigned by analogy through the measurement of the three-bond coupling constants and DNOE experiments on the diastereomeric bicyclic ethers **9** and **10**. These materials were prepared in three steps from the C-glycosides, (1) selective $OsO_4$ promoted dihydroxylation and oxidative cleavage of the *trans* -double bond, (2) reduction of the derived α-methyl aldehyde, (3) bromonium ion (NBS) induced etherification of the derived primary alcohol.

**Selective Oxidative Cleavage.** The olefin **3a / 4a** (50 mg, 0.1405 mmol) was dissolved in a 4:1 mixture of acetone to water (0.04 **M**). The solution was treated with NMO (41 mg, 0.3512 mmol) followed by addition of a 0.2 **M** solution of $OsO_4$ in toluene (5 mL, 0.010 mmol). The light yellow mixture was stirred for 2 hours at room temperature before being acidified to pH 2 with 3 **N** $H_2SO_4$. The solution was then diluted with EtOAc. The organic layer was separated, and the aqueous layer extracted with EtOAc (2 x 3 mL). The combined organic layers were washed with a saturated solution of $NaHCO_3$, followed by brine before being dried over $MgSO_4$ and concentrated under reduced pressure. The crude diol was used in the oxidation step without purification.

**Aldehyde formation**: The crude diol (229 mg, 0.59 mmol) was taken into a 0.03 **M** solution in benzene (20.0 mL) which was cooled to 0° C. Then $Pb(OAc)_4$ (340 mg, 0.767 mmol) was added in four portions over 10 minutes. The resulting mixture was stirred for an additional 1.0 h before being quenched with ethylene glycol (4.2 mL) and then diluted with pH 7 buffer (35.0 mL). The solution was then extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with a saturated solution of NaCl (2 x 10 mL) and dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude aldehyde **7** was used without purification in the following hydride reduction step. Spectra; data for aldehyde **7**: $^1$H NMR ($CDCl_3$) δ:

9.72 (s, 1H); 5.95 (m, 2H); 5.00 (m, 1H); 4.58 (dd, 1H, $J_1$ = 2Hz, $J_2$ = 5.6 Hz); 4.30 (m, 1H); 4.05 (m, 2H); 2.65 (m, 1H); 2.06 (m, 6H); 1.16 (d, 3H, J = 7.6 Hz). $^{13}C$ NMR ($CDCl_3$) δ: 202.7, 170.7, 170.4, 131.5, 124.0, 71.8, 69.9, 64.2, 62.0, 49.7, 20.9, 20.7, 8.9.

**Reduction to the alcohol**: A 0.25 **M** solution of the crude aldehyde (133 mg, 0.59 mmol) in THF (2.5 mL) was cooled to -78° C and treated with borane dimethylsulfide (94.0 μL, 1.6 equiv). The solution was stirred at -78° C for forty minutes and the excess borane reagent was destroyed by addition of reagent grade MeOH (without purification). The mixture was then concentrated under reduce pressure. Spectral data for the crude alcohol follows: $^1H$ NMR ($CDCl_3$) δ: 5.96-5.90 (m, 2H); 4.94-4.94.91 (m, 1H); 4.33-4.24 (m, 2H); 4.06-4.01 (m, 2H); 3.62-3.54 (m, 3H); 2.344 (broad, 1H); 2.05 (s, 3H); 2.03 (s, 3H); 1.97-1.93 (m, 1H); 0.914 (d, 3H, J = 7.2 Hz). $^{13}C$ NMR ($CDCl_3$) δ: 170.8; 170.5; 133.1; 122.9; 72.4; 72.2; 65.6; 64.5; 61.8; 39.1; 21.0; 20.8; 11.7. IR (neat) $cm^{-1}$: 3435; 2961; 1739; 1372; 1235; 1044.

**Formation of the *cis*-fused bicyclic ethers 9 and 10.** The alcohols (for **9**: 32 mg, 0.14 mmol; for **10**: 130 mg, 0.59 mmol) were dissolved in $CH_3CN$ (0.05 **M**). These solutions were treated with *N*-bromosuccinimide (NBS, for **9**: 30.0 mg 0.17 mmol; for **10**: 126 mg, 0.708 mmol). The individual solutions were stirred at room temperature for 20 hours. The reactions were then diluted with $CHCl_3$ (ca. 5 mL) before being transfered to a 30 mL separatory funnel. The respective reaction mixtures were washed with 1**M** KOH (1 x 4 mL), and water (1 x 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduce pressure. Purification on $SiO_2$ (30% EtOAc-Pet. ether eluant) afforeded the bicyclic ethers as colorles oils: (32 mg, 0.105 mmol, 75 % yield for **9**) and (144 mg, 0.47 mmol, 80 % yield for **10**). The spectral characteristic for the individual bicyclic ethers are given below.

Spectral charateristics for **9**: $^1H$ NMR ($CDCl_3$) δ: 5.01(dd, 1H, J = 6.8 Hz, J = 9.2 Hz); 4.48 (dd, 1H, J = 8.0 Hz, J = 12 Hz); 4.32 (dd, 1H, J = 4.4 Hz, J = 6.0 Hz); 4.24 (t, 1H, J = 4.8 Hz); 4.06 (m, 1H); 3.97 (d, 1H, J = 3.2 Hz); 3.94 (d, 1H, J = 1.2 Hz); 3.90 (m, 1H); 3.52 (dd, 1H, J = 8.0 Hz, J = 10.4 Hz); 2.32 (m, 1H, J = 5.6 Hz); 2.08 (s, 3H); 2.04 (s, 3H); 0.96 (d, 3H, J = 6.8 Hz). CIMS+$NH_4$ ($NH_3$ gas): 368, 351, 291, 211, 169, 151. CIHRMS+$NH_4$ calculated for $C_{13}H_{19}BrO_6$+$NH_4$= 368.0708; found 368.0693.

Spectral charateristics for **10**: $^1H$ NMR ($CDCl_3$) δ: 5.04 (dd, 1H, J = 7.6 Hz); 4.33 (dd, 1H, J = 6.0 Hz, J = 12 Hz); 4.25 (dd, 1H, J = 6Hz, J = 7.6 Hz); 4.14 (dd, 1H, J = 7.2 Hz, J = 9.2 Hz); 4.08 (d, 1H, J = 6.8 Hz); 4.05 (dd, 1H, J = 2.4 Hz, J = 5.6 Hz); 4.02 (d, 1H, J = 2.8 Hz); 3.84 (m, 1H); 3.45 (dd, 1H, J = 7.2 Hz, J = 9.2 Hz); 2.40 (m, J = 7.2 Hz); 2.08 (s, 3H); 2.07 (s, 3H); 1.05 (d, 3H, J = 6.8 Hz). CIMS+$NH_4$ ($NH_3$ gas): 368, 351, 291, 211, 169, 151. CIHRMS+$NH_4$ calculated for $C_{13}H_{19}BrO_6$+$NH_4$= 368.0708; found 368.0671.

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