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The Synthesis and Reactions of Some Novel Pyranoid 5,6-Glycals Derived From D-Fructose

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Abstract: In this paper, we describe a new synthetic pathway to ketopyranose 5,6-glycals. We also demonstrate the utility of these derivatives for preparing C(6)-functionalised ketopyranosides.
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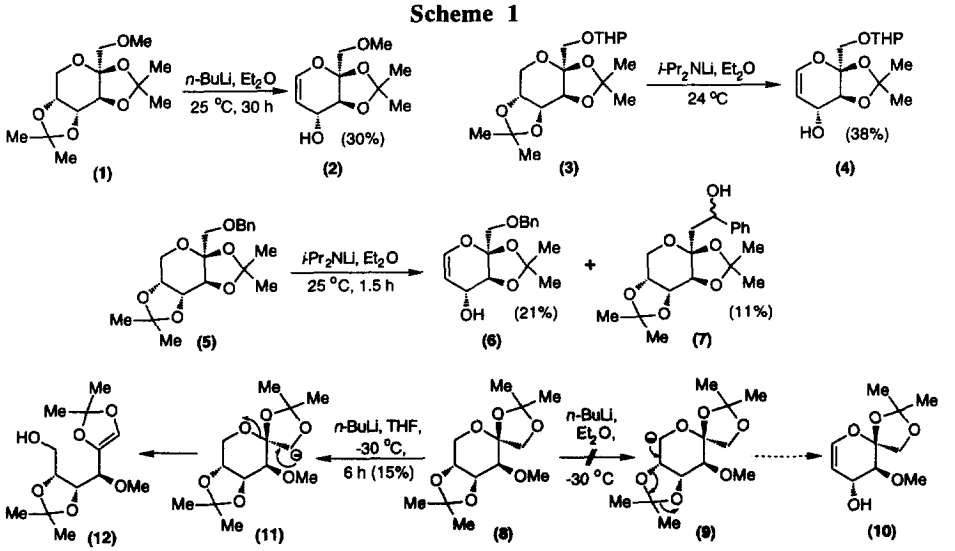
Compared with aldose-derived pyranoid glycals, for which a wealth of synthetic uses have been found,[1] the glycals of ketopyranoses[2] have remained largely unexploited, primarily due to the difficulties encountered in their synthesis. Particularly inaccessible are those glycals in which the enol ether unit spans the C(5) and C(6) positions of the ketopyranose ring. Interest in this class was sparked in the late 1970s when Klemer *et al.*[3a] demonstrated that 2,3:4,5-di-*O*-isopropylidene-1-*O*-methyl-β-D-fructopyranose **1** could be converted into 5-deoxy-2,3-*O*-isopropylidene-1-*O*-methyl-β-D-*threo*-hexulo-5-enopyranose **2** in 30% yield by the action of *n*-butyllithium in ether (Scheme 1). Klemer also found that a similar elimination could be induced in **3** with LDA,[3b] but observed a competing Wittig rearrangement when this reaction was attempted on **5**.[3a] Problems were also met when efforts were made to extend this reaction to **8**. Instead of obtaining glycal **10** via **9**, deprotonation occurred exclusively at C(1) to give anion **11** which then underwent ring-opening to give enol ether **12**.[3c]

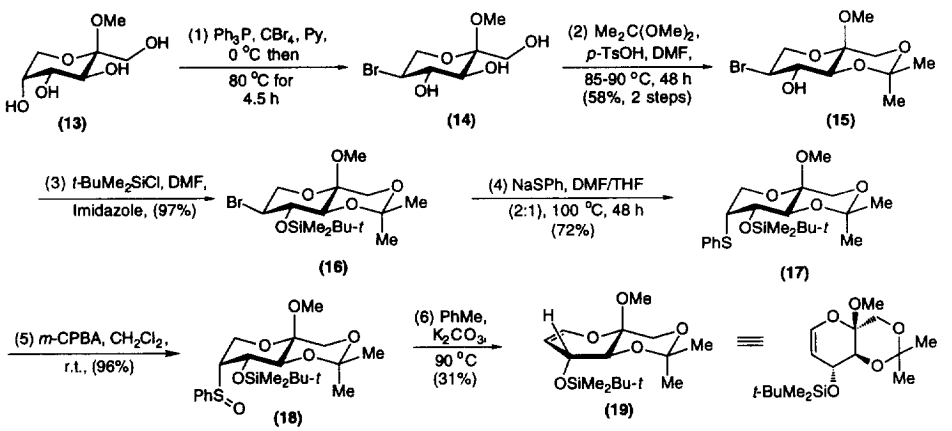
Scheme 1



In view of the low yields and rather restricted scope of the aforementioned methodology, and our desire to utilise such chiral synthons for an enantiospecific synthesis of bryostatin 1,[4] we decided to develop some new routes to differentially protected ketopyranoid 5,6-glycals, and discuss our results in this full paper.[5]

One of the first targets we selected for study was glycal **19**, since this molecule could potentially serve as a valuable precursor of C(5)- and C(6)-modified fructopyranosides. Our initial route to **19** started from methyl β-D-fructopyranoside **13**,[6] and is shown in Scheme 2. Compound **13** was selectively brominated at C(5), with inversion of configuration, by treatment with triphenylphosphine and carbon tetrabromide in pyridine at 80 °C for 4.5 h. After effecting a partial purification of the crude reaction mixture, methyl 5-bromo-5-deoxy-α-L-sorbopyranoside **14** was obtained, contaminated with approximately 10% of another unidentified product having an identical R_f value on t.l.c. Since we were unable to remove this by-product by multiple flash

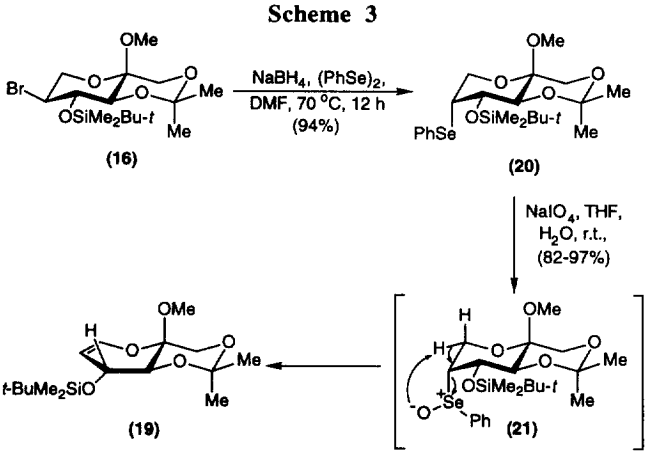
Scheme 2



chromatography, we elected to use it directly for the next step, which involved acetalation with dimethoxypropane and a catalytic quantity of *p*-toluenesulfonic acid in DMF at 85-90 °C. This regioselectively blocked the C(1) and C(3) hydroxyl groups of **14** with an *O*-isopropylidene group to deliver **15** as a crystalline solid, in 58% overall yield from **13**. The 400 MHz ^{1}H NMR spectrum of **15** in $CDCl_3$ confirmed the presence of two isopropylidene methyl groups, and displayed resonances at δ 4.11 (double doublet) and 3.57 (doublet) that were attributable to H-4 and H-3 respectively; a single hydroxyl resonance could also be seen at δ 2.60. The values of the coupling constants, $J_{3,4}$ (9.3 Hz) and $J_{4,5}$ (9.0 Hz) indicated that the *sorbo* configuration was present in **15**. Evidence that a dioxane acetal had been created, rather than a dioxolane, was provided by the ^{13}C NMR chemical shifts of the isopropylidene acetal carbon (δ_c 100.6 ppm) and its two methyl groups (δ_c 28.9 and 18.7 ppm), which were in agreement with the values typically found for 1,3-dioxane acetals by Buchanan *et al.*[7] A correct carbon and hydrogen microanalysis for **15** further validated its identity as did its high resolution mass spectrum which contained an $[M+Na]^+$ ion at *m/e* 319.0164. Silylation of **15** proceeded readily with *t*-butyldimethylsilyl chloride and imidazole in DMF at room temperature to provide bromide **16** in 97% yield. The structure of **16** was confirmed by its 400 MHz ^{1}H NMR spectrum in $CDCl_3$ which showed resonances at δ 0.07 and 0.13 due to the methyl groups of the newly-introduced silyl group. In addition there was a signal at δ 0.87 due to the silyl *t*-butyl substituent. The strong OH stretching absorption at 3439 cm^{-1}, previously present in the IR spectrum of **15**, was now absent in IR spectrum of **16**. The high resolution FAB

mass spectrum of **16** also contained an intense peak at *m/e* 433.1034 corresponding to an $(M+Na)^+$ ion. When bromide **16** was treated with sodium thiophenoxide in 2:1 DMF/THF at 100 °C it underwent a clean nucleophilic displacement to give phenylsulfide **17** in 72% yield. Phenylsulfide **17** was converted to a 1.6:1 mixture of diastereomeric phenylsulfoxides **18** in 96% yield when oxidised with *m*-CPBA in CH_2Cl_2. However, the thermally-induced *syn* elimination of **18** only proceeded slowly in toluene at 90 °C; use of higher temperatures brought about extensive decomposition. This reaction also proved very capricious, it generally affording **19** in low and variable yields (31% on a good run). In view of this unreliability, we decided to prepare phenylselenide **20**, oxidise it to selenoxide **21**, and then attempt *syn* elimination (Scheme 3).[8] Normally, *syn*-elimination reactions of phenylselenoxides proceed at much lower temperatures than those of the corresponding phenylsulfoxides, due to the longer, and hence weaker, C-Se bond which ruptures much more readily. Accordingly, we displaced bromide **16** with sodium phenylselenide in DMF at 70 °C to obtain **20** as a crystalline solid in 94% yield. The 400 MHz ^1H NMR spectrum of **20** in $CDCl_3$ was almost completely first-order. It contained a doublet at δ 4.03 and and a double-doublet at δ 4.23 that were mutually coupled; these were assigned to H-3 and H-4 respectively. The H-5 resonance appeared at higher field (δ 3.76) as a multiplet. The *fructo* configuration of **20** was deduced from the large $J_{3,4}$ splitting (9.4 Hz) and the smaller value seen for $J_{4,5}$ (5.2 Hz). Fortunately, the selenoxide elimination tactic proved very successful. The oxidation step was best performed with sodium periodate in aqueous THF at room temperature (Scheme 3); it led to **19** in up to 91% overall yield from **16**. Use of 30% aqueous H_2O_2 in THF as the oxidant gave unsatisfactory results. The regioselectivity of elimination in **21** derived from its D-*fructo* configuration, and the structural rigidity imparted by the *trans*-decalin ring system. This guaranteed that only the equatorial H-6 could be abstracted in the *syn*-elimination process. The positional integrity of the double bond in **19** was confirmed by its large $J_{3,4}$ coupling (8.1 Hz). Additional evidence for success was provided by the IR spectrum of **19** which contained a medium intensity C=C absorption at 1645 cm^{-1} indicative of an enol ether. Finally, the high resolution FAB mass spectrum of **19** exhibited an intense $(M+Na)^+$ peak at *m/e* 353.1752.

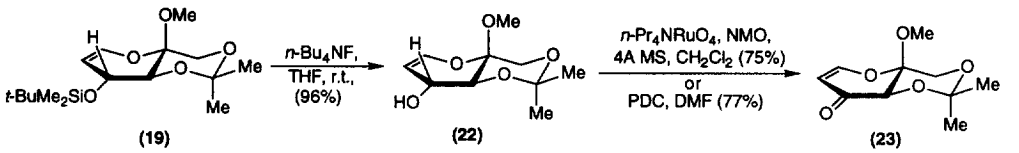
Scheme 3



In light of the ready accessibilty of glycal **19**, our next goal was to manipulate it into other synthetically useful ketopyranose 5,6-glycals such as enone **23** (Scheme 4). It was obtained from **19** by *O*-desilylation with tetra-*n*-butylammonium fluoride in THF and oxidation with tetra-*n*-propyl perruthenate in CH_2Cl_2 (75%),[9] or

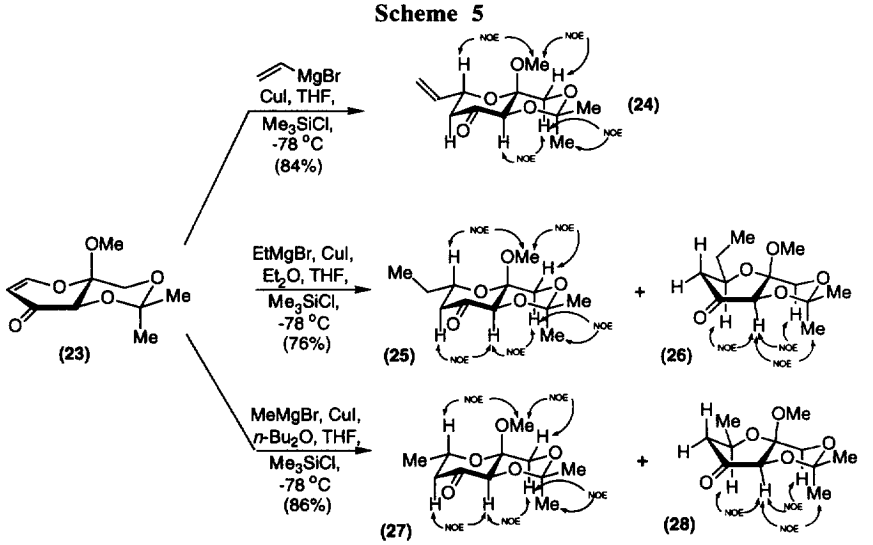
with PDC in DMF (77%).[10] The 400 MHz ^{1}H NMR spectrum of **23** in $CDCl_3$ firmly established its structure, it showing only eight signals. The two enol ether protons appeared as low-field doublets ($J_{5,6}$= 6.2 Hz) at δ 6.99 and 5.43, and H-3 gave rise to the expected singlet at δ 4.76. The C(1) protons resonated as doublets at δ 4.10 and 3.91, while the methoxy and methyl groups appeared as singlets at δ 3.35, 1.53 and 1.52 respectively. The IR spectrum of **23** was also highly informative, it containing two intense absorptions at 1696 and 1598 cm^{-1}, ascribable to the C=O and C=C stretching vibrations of a vinylogous lactone.

Scheme 4



In an effort to demonstrate the synthetic utility of enone **23**, we examined its reactivity towards a range organocuprate reagents (Scheme 5). A single 1,4-addition product **24** was formed in 84% yield when **23**

Scheme 5



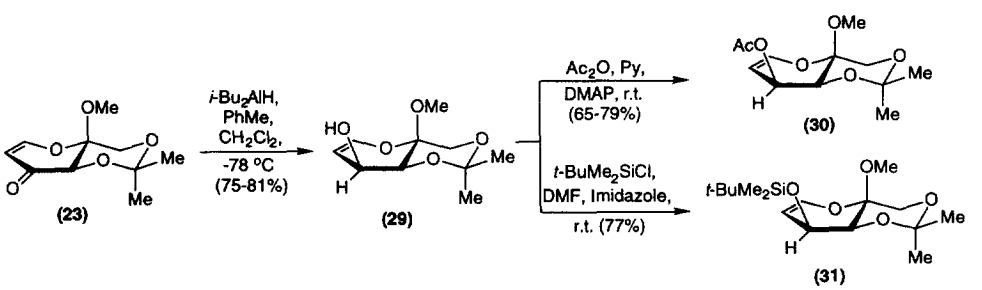
was reacted with vinylmagnesium bromide and 1 equiv. of cuprous iodide in THF in the presence of 5 equiv. of trimethylsilyl chloride at -78 °C for 1 h.[11] 400 MHz ^{1}H NMR NOESY spectroscopy in $CDCl_3$ helped define the configuration of the newly-established stereocentre in **24**. The presence of a significant cross peak between the H-6 multiplet at δ 4.50 and the methoxy resonance at δ 3.31 established that the methyl glycoside and H-6 were *syn*-related and that H-6 was therefore axial. Other strong NOE cross peaks seen in the spectrum of **24** were between the H-3 singlet at δ 4.51 and the H-1_{ax} doublet at δ 3.80, and between the methoxy resonance and the H-1_{eq} doublet at δ 4.02. Finally, the large $J_{5,6}$ splitting (10.5 Hz) between H-5_{ax} (δ 2.49) and H-6 further confirmed that the vinyl group at C(6) was equatorial.

An analogous reaction between the vinylogous lactone **23** and ethylmagnesium bromide, copper (I) iodide, and trimethylsilyl chloride in THF and ether at -78 °C proved considerably less stereoselective, it affording a 2.8:1 mixture of 1,4-adducts **25** and **26** in 76% combined yield. Unfortunately, both of these products had the same R_f value on t.l.c and could not be separated by flash chromatography. As previously, 400 MHz ^{1}H NMR NOESY spectroscopy in $CDCl_3$ allowed the configuration of the major isomer to be assigned as (*6S*). For compound **25** a significant cross-peak between the H-6 multiplet at δ 3.93 and the methoxy resonance at δ 3.26 secured their *syn*-relationship, as did the large value for $J_{5ax,6}$ (10.8 Hz). A cross-peak could not be detected between H-6 and the OMe in compound **26**. A NOE correlation was also apparent between H-6 (δ 4.24) and H-3 (δ 4.58) in **26** which was absent for compound **25**. This indicated that H-3 and H-6 were both residing on the underside of the pyran ring as drawn in **26**.

When methylmagnesium bromide, cuprous iodide, and trimethylsilyl chloride were reacted with **23** in THF and *n*-Bu_2O at -78 °C, an inseparable 5:1 mixture of 1,4-addition products **27** and **28** was isolated in 86% yield, the major isomer again having the (*6S*)-configuration. As previously, the observation of a significant NOE cross peak between the H-6 multiplet at δ 4.18 and the methoxy resonance at δ 3.28 in the 400 MHz ^{1}H NMR NOESY spectrum of **27** permitted this stereochemical assignment to be made. It was confirmed by the NOE cross peak between H-3 (δ 4.46) and H-5_{ax} (δ 2.35) and the large value for $J_{5ax,6}$ (10.6 Hz)

The reasonable to excellent stereoselectivity observed in these conjugate additions can be rationalised if one examines a Drieding molecular model of **23**. This shows that the C(2)-methoxy group can seriously impede *syn*-attack of a bulky nucleophile upon the vinylogous lactone system. The high facial-bias displayed by the vinyl cuprate reagent in its addition to **23** is presumably the consequence of its high steric bulk; the lower stereoselectivity observed for the ethylcuprate reagent, as compared with the methylcuprate, could be a consequence of it forming a less bulky aggregate in the reaction solvent employed.

Scheme 6



Our next objective was to obtain glycal **30** by inverting the stereochemistry of alcohol **22** through a Mitsunobu reaction[12] with acetic acid, triphenylphosphine and diisopropyl azodicarboxylate in THF. Unfortunately, a complicated mixture of products arose that were difficult to separate and properly characterise. Given these difficulties, and our finding that cuprates prefer to attack **23** *anti* to its methoxy group, we reasoned that hydride reduction of the ketone might also proceed preferentially from that direction to give **29**. Accordingly, we examined the reduction of **23** with sodium borohydride, but found that the reaction was not clean. We resorted, therefore, to the more sterically-demanding hydride reducing agent DIBAL-H to accomplish this inversion (Scheme 6).[13] When performed in a mixture of CH_2Cl_2 and toluene at -78 °C, DIBAL-H

reduction afforded alcohol **29** as the sole 1,2-reduction product in 75-81% yield. Conducting the reaction at room temperature led to an erosion of stereoselectivity, with a 9:1 mixture of **29** and **22** now arising. Evidence for successful reduction was provided by the IR spectrum of **29** which no longer contained a C=O absorption at 1696 cm^{-1}; it did, however, show a medium intensity OH absorption at 3542 cm^{-1} and a strong enol ether C=C stretching band at 1642 cm^{-1}. The *syn*-relationship between H(3) and H(4) was affirmed by the small value for $J_{3,4}$ (4.8 Hz). Combustion microanalytical data further corroborated the identity of **29**, it indicating an empirical formula of $C_{10}H_{16}O_5$. Allylic alcohol **29** readily underwent acetylation with acetic anhydride and pyridine, but prolonged reaction times (e.g. 12 h) had to be avoided, otherwise, the formation of by-products started to become an issue. The 400 MHz ^1H NMR spectrum of **30** in $CDCl_3$ showed the anticipated *O*-acetyl singlet at δ 2.11. The IR spectrum of **30** retained the expected enol ether C=C stretching band at 1642 cm^{-1} and, in addition, showed a strong absorption at 1732 cm^{-1} due to the newly-installed ester C=O group. Alcohol **29** also readily underwent *O*-silylation (77% yield) with *t*-butyldimethylsilyl chloride and imidazole in DMF at room temperature. Molecular models of glycal **31** indicate that electrophilic attack will probably proceed *anti* to the OTBS and methyl glycoside units, due to *syn*-approach being sterically-disfavoured.

In closing, facile methodology for the preparation ketopyranoside 5,6-glycals has been developed. We expect such intermediates to prove valuable for the preparation of ketosides modified at C(5) and C(6), and for the synthesis of novel oligosaccharides in which there is a ketose residue linked by two *O*-glycosidic bonds.

EXPERIMENTAL

Materials and Methods. THF, pyridine, CH_2Cl_2 and trimethylsilyl chloride were all freshly distilled from CaH_2 under N_2 and transferred via syringe. Purified copper (I) iodide was purchased from Aldrich and used without further purification. Precoated silica gel plates (250 mM) with a fluorescent indicator (Merck Kieselgel 60 F_{254}) were used for analytical thin layer chromatography. Flash column chromatography was carried out with Sorbsil C60 40/60A (230-400 mesh) silica gel. ^1H and ^{13}C NMR spectra were recorded on a Varian AX-400 (400 MHz) spectrometer. Chemical shifts that are reported in $CDCl_3$ are quoted in δ-values relative to the signal at 7.24 ppm for residual $CHCl_3$. All infrared spectra were recorded on a Nicolet 205 FT IR spectrophotometer. Melting points were measured on a Reichert micro hot stage apparatus and are uncorrected. Microanalyses were performed by the Microanalytical Laboratory of University College London. High- and low-resolution mass spectra were measured by the ULIRS Mass Spectrometry Service Centre at the London School of Pharmacy on a VG 70-70 or VG-ZAB instrument with a Finnigan Incos II data system. Optical rotations were recorded on a Perkin-Elmer Model 141 polarimeter.

Methyl 5-bromo-5-deoxy-1,3-O-isopropylidene-α-L-sorbopyranoside **15**. To a 0 °C solution of methyl β-D-fructopyranoside **13** (10 g, 51.5 mmol) and triphenylphosphine (46 g, 175.4 mmol) in dry pyridine (275 mL) was added a solution of carbon tetrabromide (65 g, 196.0 mmol) in dry pyridine (38 mL) dropwise over 30 min. After the addition was complete, the ice-bath was removed and the reaction mixture heated at 80 °C for 4.5 h. It was then cooled to room temperature, diluted with MeOH (200 mL), and concentrated *in vacuo*. The residue was purified by SiO_2 flash chromatography eluting with CH_2Cl_2-MeOH (60:1) to remove excess triphenylphosphine oxide followed by CH_2Cl_2-MeOH (45:1) to give **14** (12.1 g) as an off-white foam. Although purified **14** appears to be chromatograpically homogenous according to t.l.c, careful 400 MHz ^1H NMR analysis reveals that this material is in fact contaminated by approximately 10% of a presently unidentified

component. (The partially purified **14** used directly for the next step had the following physical properties: $[\alpha]_D$ -70.6 ° (*c* 1, CH_2Cl_2); IR (neat film) 3398 (s br), 2944 (m), 1456 (w), 1375 (w), 1266 (w), 1168 (m), 1091 (s), 1059 (s), 1035 (s), 910 (w), 869 (w), 784 (w), 755 (m) cm^{-1}; 100 MHz ^{13}C NMR spectral data for **14** ($CDCl_3$) δ 99.7, 74.8, 74.5, 63.4, 62.4, 49.0, 48.8 ppm; HRMS (FAB, MNOBA matrix) for $C_7H_{14}O_5BrNa$ $(M+H+Na)^+$ Calcd: 279.9922; Found: 279.9928).

The above partially-purified methyl 5-bromo-5-deoxy-α-L-sorbopyranoside **14** (12.1 g) was treated with 2,2-dimethoxypropane (126 mL, 1.03 mol), *p*-toluenesulfonic acid monohydrate (740 mg, 3.89 mmol) and DMF (7 mL) at room temperature. It was then heated at 85-90 °C for 48 h. After cooling to room temperature, the reaction mixture was neutralised with solid $NaHCO_3$. The resulting mixture was filtered and concentrated *in vacuo*. Purification of the residue by SiO_2 flash chromatography using hexanes-EtOAc (8:1) afforded pure **15** (8.9 g, 58% from **13**) as white crystals: m.p. 78.5-81 °C; $[\alpha]_D$ -26 ° (*c* 1, CH_2Cl_2); IR (KBr) 3439 (s), 2996 (m), 2946 (w), 1464 (w), 1372 (m), 1298 (m), 1276 (m), 1195 (s), 1139 (s), 1101 (s), 1029 (s), 995 (m), 946 (m), 903 (w), 850 (s), 795 (m), 739 (m), 520 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.11 (dd, *J* = 9.2, 9.0 Hz, 1 H), 3.93 (d, *J* = 12.4 Hz, 1 H), 3.90-3.78 (complex m, 3 H), 3.57 (d, *J* = 9.3 Hz, 1 H), 3.54 (d, *J* = 12.1 Hz, 1 H), 3.30 (s, 3 H), 2.60 (s, 1 H), 1.49 (s, 3 H), 1.47 (s, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 100.6, 93.3, 75.7, 70.7, 63.7, 60.6, 49.4, 48.2, 28.9, 18.7 ppm; HRMS (FAB, MNOBA matrix) for $C_{10}H_{17}O_5BrNa$ $(M+Na)^+$ Calcd: 319.0158; Found: 319.0164; Anal. calcd for $C_{10}H_{17}O_5Br$: C, 40.42; H, 5.77. Found: C, 40.28; H, 5.50.

Methyl 5-bromo-5-deoxy-4-O-tert-butyldimethylsilyl-1,3-O-isopropylidene-α-L-sorbopyranoside **16**. To a stirred solution of alcohol **15** (13.6 g, 45.77 mmol) and imidazole (4.7 g, 69.04 mmol) in dry *N,N*-dimethylformamide (38 mL) was added *tert*-butyldimethylsilyl chloride (10.3 g, 68.33 mmol) in one portion. After 18 h at room temperature the reaction mixture was poured into saturated aq. $NaHCO_3$ (200 mL) and extracted with Et_2O (3 x 200 mL). The combined ethereal extracts were washed with H_2O (1 x 200 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the residue by SiO_2 flash chromatography using hexanes-EtOAc (25:1) as eluent furnished 18.2 g (97%) of **16** as an oil: $[\alpha]_D$ -12.5 ° (*c* 0.8, CH_2Cl_2); IR (neat film) 2992 (m), 2947 (m), 2934 (m), 2888 (m), 2857 (m), 1473 (m), 1463 (m), 1373 (m), 1290 (m), 1259 (m), 1195 (s), 1147 (s), 1107 (s), 1087 (m), 1044 (s), 1005 (w), 946 (m), 911 (m), 852 (s), 838 (s), 780 (s), 736 (w), 669 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.01 (m, 1 H), 3.89 (d, *J* = 12.4 Hz, 1 H), 3.79 (m, 3 H), 3.49 (d, *J* = 12.4 Hz, 1 H), 3.47 (d, *J* = 9.1 Hz, 1 H), 3.27 (s, 3 H), 1.44 (s, 3 H), 1.42 (s, 3 H), 0.87 (s, 9 H), 0.13 (s, 3 H), 0.07 (s, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 100.0, 93.6, 76.3, 72.1, 64.0, 60.7, 51.0, 48.0, 28.9, 25.9, 18.6, 18.4, -4.0, -4.5 ppm; HRMS (FAB, MNOBA matrix) for $C_{16}H_{31}O_5SiBrNa$ $(M+Na)^+$ Calcd: 433.1023; Found: 433.1034.

Methyl 5-selenophenyl-5-deoxy-4-O-tert-butyldimethylsilyl-1,3-O-isopropylidene-β-D-fructopyranoside **20**. To a solution of diphenyl diselenide (28.68 g, 91.88 mmol) in dry *N,N*-dimethylformamide (110 mL) was added cautiously sodium borohydride (6.95 g, 183.7 mmol) in small portions whilst maintaining a N_2 atmosphere. The reaction mixture was stirred at room temperature for 5 min whereupon bromide **16** (18.9 g, 45.94 mmol) in dry *N,N*-dimethylformamide (20 mL) was added in one portion. The reaction mixture was heated at 70 °C for 12 h, after which, t.l.c. indicated the formation of a single slower-moving product. The reaction mixture was cooled, diluted with Et_2O (500 mL), neutralized with saturated aq. NH_4Cl, and extracted

with Et_2O (3 x 200 mL). The combined ethereal extracts were washed with H_2O (1 x 100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the residue by SiO_2 flash chromatography with neat hexanes removed excess diphenyl diselenide; eluting with hexanes-EtOAc (12:1) provided **20** (21.1 g, 94%) as white crystals: m.p. 56-57 °C; $[\alpha]_D$ +155.0 ° (*c* 1, CH_2Cl_2); IR (KBr) 2991 (m), 2950 (m), 2928 (m), 2893 (m), 2856 (m), 1476 (m), 1371 (m), 1284 (m), 1253 (m), 1205 (m), 1194 (m), 1149 (s), 1109 (s), 1055 (s), 952 (m), 925 (m), 860 (s), 838 (s), 780 (s), 741 (m), 693 (m), 671 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60-7.22 (complex m, 5 H), 4.23 (dd, *J* = 5.2, 9.4 Hz, 1 H), 4.03 (d, *J* = 9.4 Hz, 1 H), 3.92 (dd, *J* = 2.6, 12.7 Hz, 1 H), 3.87 (d, *J* = 12.2 Hz, 1 H), 3.76 (m, 1 H), 3.61 (d, *J* = 12.3 Hz, 1 H), 3.49 (dd, *J* = 1.6, 12.7 Hz, 1 H), 3.22 (s, 3 H), 1.49 (s, 3 H), 1.42 (s, 3 H), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.06 (s, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 129.0, 127.8, 100.2, 94.1, 73.9, 67.5, 61.8, 61.0, 50.2, 47.8, 29.1, 25.7, 19.0, 18.3, -4.3, -4.8 ppm; HRMS (FAB, MNOBA matrix) for $C_{22}H_{36}O_5SiSeNa$ $(M+Na)^+$ Calcd: 511.1395; Found: 511.1390; Anal. Calcd for $C_{22}H_{36}O_5SiSe$: C, 54.19; H, 7.44. Found: C, 53.82; H, 7.62.

Methyl 5-deoxy-4-O-tert-butyldimethylsilyl-1,3-O-isopropylidene-β-D-threo-hexulo-5-enopyranoside **19**. To a stirred solution of phenylselenide **20** (21.1 g, 43.28 mmol) in THF (190 mL) was added a solution of sodium periodate (18.5 g, 86.49 mmol) dissolved in H_2O (190 mL). The reactants were stirred at room temperature for 18 h after which time a white suspension had formed. The mixture was diluted with Et_2O (500 mL) and quenched with a saturated solution of aqueous $NaHCO_3$. The organic layer was separated, and the aqueous phase extracted with Et_2O (3 x 400 mL). The combined organic extracts were washed with H_2O (2 x 200 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the residue by SiO_2 flash chromatography with neat CH_2Cl_2 or alternatively with (40:1 to 30:1 gradient) hexanes-EtOAc as eluent furnished glycal **19** (13.8 g, 97 %) as a colourless oil: $[\alpha]_D$ -131.1 ° (*c* 1, CH_2Cl_2); IR (neat film) 2993 (w), 2953 (m), 2930 (m), 2898 (m), 2857 (m), 1645 (m), 1473 (w), 1463 (w), 1382 (m), 1369 (m), 1295 (w), 1259 (m), 1229 (m), 1208 (m), 1191 (m), 1142 (s), 1112 (s), 1057 (s), 1041 (s), 1017 (m), 940 (m), 885 (s), 838 (m), 779 (m), 666 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.03 (dd, *J* = 1.7, 6.3 Hz, 1 H), 4.73 (dd, *J* = 2.0, 6.3 Hz, 1 H), 4.38 (ddd, *J* = 1.7, 2.0, 8.1 Hz, 1 H), 3.95 (d, *J* = 12.5 Hz, 1 H), 3.87 (d, *J* = 8.1 Hz, 1 H), 3.62 (d, *J* = 12.5 Hz, 1 H), 3.29 (s, 3 H), 1.46 (s, 3 H), 1.43 (s, 3 H), 0.85 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 107.4, 99.9, 93.9, 74.6, 64.9, 60.1, 49.0, 28.9, 25.8, 18.7, 18.3, -4.4, -4.7 ppm; HRMS (FAB, MNOBA matrix) for $C_{16}H_{30}O_5SiNa$ $(M+Na)^+$ Calcd: 353.1760; Found: 353.1752.

Methyl 5-deoxy-1,3-O-isopropylidene-β-D-threo-hexulo-5-enopyranoside **22.** To a solution of glycal **19** (4.73 g, 14.31 mmol) in dry THF (26 mL) under N_2 was added tetra-*n*-butylammonium fluoride (Aldrich, 1.0 M solution in THF) (22.9 mL, 22.9 mmol) rapidly in one portion. The reactants were stirred at room temperature for 21 h and the solvent removed *in vacuo*. The residue was purified by SiO_2 flash chromatography using hexanes-EtOAc (4:1) as eluent. Allylic alcohol **22** (2.77 g, 90%) was obtained as a colourless oil: $[\alpha]_D$ -126.6 ° (*c* 1, CH_2Cl_2); IR (neat film) 3460 (m br), 2994 (m), 2942 (w), 2899 (w), 1645 (s), 1464 (w), 1384 (m), 1371 (m), 1264 (m), 1230 (s), 1208 (s), 1191 (s), 1137 (s), 1107 (s), 1035 (s), 937 (m), 870 (s), 791 (m), 754 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.08 (dd, *J* = 1.9, 6.3 Hz, 1 H), 4.87 (dd, *J* = 1.9, 6.3 Hz, 1 H), 4.42 (br d, *J* = 8.4 Hz, 1 H), 3.98 (d, *J* = 12.6 Hz, 1 H), 3.87 (d, *J* = 8.4 Hz, 1 H), 3.65 (d, *J* = 12.6 Hz, 1 H), 3.30 (s, 3 H), 2.30 (br s, 1 H), 1.50 (s, 3 H), 1.46 (s, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ

139.5, 105.6, 100.3, 93.5, 74.8, 64.0, 60.0, 49.1, 28.9, 18.7 ppm; HRMS (FAB, MNOBA matrix) for $C_{10}H_{16}O_5Na$ $(M+Na)^+$ Calcd: 239.0896; Found: 239.0895.

Enone **23**. To a solution of allylic alcohol **22** (3.28 g, 15.17 mmol) in dry *N,N*-dimethylformamide (53.0 mL) was added pyridinium dichromate (22.83 g, 60.68 mmol) in one portion. The mixture was stirred at room temperature for 21 h and then diluted with Et_2O (300 mL) and saturated aq. $NaHCO_3$ (200 mL). The organic layer was separated, and the aqueous layer extracted with Et_2O (8 x 100 mL). The combined organic extracts were washed with brine (1 x 100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by SiO_2 flash chromatography with hexanes-EtOAc (3:1). This afforded enone **23** (2.49 g, 77%) as white crystals: m.p. 85-88.5 °C; $[\alpha]_D$ -137.7 ° (*c* 1, CH_2Cl_2); IR (KBr) 3001 (m), 2947 (w), 1696 (s), 1598 (s), 1464 (w), 1404 (m), 1389 (m), 1297 (m), 1262 (s), 1202 (m), 1121 (s), 1061 (m), 1022 (m), 998 (m), 975 (m), 910 (m), 865 (m), 773 (m), 609 (w), 562 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, *J* = 6.2 Hz, 1 H), 5.43 (d, *J* = 6.2 Hz, 1 H), 4.76 (s, 1 H), 4.10 (d, *J* = 12.6 Hz, 1 H), 3.91 (d, *J* = 12.6 Hz, 1 H), 3.35 (s, 3 H), 1.53 (s, 3 H), 1.52 (s, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.4, 155.7, 107.1, 101.0, 99.2, 74.3, 59.7, 50.2, 28.5, 18.2 ppm; HRMS (FAB, MNOBA matrix) for $C_{10}H_{14}O_5Na$ $(M+Na)^+$ Calcd: 237.0739. Found: 237.0734; Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 55.61; H, 6.48.

Ketone **24**. To a -78 °C suspension of copper (I) iodide (178 mg, 0.935 mmol) in dry THF (0.5 mL) under N_2 was added vinylmagnesium bromide (Aldrich, 1.0 M solution in THF) (1.9 mL, 1.9 mmol) over 1 min. Trimethylsilyl chloride (0.6 mL, 4.73 mmol) was then added dropwise over 1 min. Enone **23** (200 mg, 0.934 mmol) in dry THF (2 mL) was added to this mixture dropwise over 5 min. After 1 h at -78 °C, the reaction was quenched by dropwise addition of Et_3N (2.6 mL, 18.65 mmol). Solid $NaHCO_3$ (1.0 g) was then added in one portion and the resulting suspension diluted with Et_2O (50 mL) and saturated aq. $NaHCO_3$ (50 mL). The organic layer was removed and the aqueous layer extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with H_2O (2 x 50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by SiO_2 flash chromatography with hexanes-EtOAc (4:1). Ketone **24** (189 mg, 84%) was obtained as white crystals: m.p. 137-139 °C; $[\alpha]_D$ -42.1 ° (*c* 1, CH_2Cl_2); IR (KBr) 3009 (m), 2988 (m), 2950 (m), 2900 (m), 2838 (w), 1740 (s), 1457 (w), 1441 (w), 1428 (w), 1397 (m), 1387 (m), 1370 (m), 1338 (m), 1304 (m), 1283 (m), 1262 (s), 1195 (s), 1116 (s), 1063 (s), 1050 (s), 1034 (s), 1000 (m), 944 (s), 888 (m), 857 (s), 780 (w), 757 (w), 698 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.86 (m, 1 H), 5.30 (d, *J* = 17.2 Hz, 1 H), 5.21 (d, *J* = 10.4 Hz, 1 H), 4.51 (s, 1 H), 4.50 (m, 1 H), 4.02 (d, *J* = 12.6 Hz, 1 H), 3.80 (d, *J* = 12.6 Hz, 1 H), 3.31 (s, 3 H), 2.55 (dd, *J* = 4.1, 14.5 Hz, 1 H), 2.49 (ddd, *J* = 1.2, 10.5, 14.5 Hz, 1 H), 1.52 (s, 3 H), 1.49 (s, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 136.0, 117.1, 100.5, 96.3, 77.9, 72.4, 60.3, 48.6, 46.1, 28.7, 18.4 ppm; HRMS (FAB, MNOBA matrix) for $C_{12}H_{19}O_5$ $(M+H)^+$ Calcd: 243.1232; Found: 243.1230; Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.19; H, 7.54.

Ketones **25** *and* **26**. To a cooled suspension of copper (I) iodide (178 mg, 0.935 mmol) in dry THF (0.5 mL) at -78 °C under N_2 was added ethylmagnesium bromide (Aldrich, 3.0 M solution in Et_2O) (0.6 mL, 1.8 mmol) and trimethylsilyl chloride (0.6 mL, 4.73 mmol) dropwise over 1 min. Enone **23** (200 mg, 0.934 mmol) in dry THF (2.0 mL) was added to this mixture dropwise over 5 min. After 1 h at -78 °C, the reactants were quenched by dropwise addition of Et_3N (2.6 mL, 18.65 mmol) and solid $NaHCO_3$ (1.0 g) in one portion. The mixture

was diluted with Et_2O (50 mL) and saturated aq. $NaHCO_3$ (50 mL). The organic layer was separated, and the aqueous phase extracted with Et_2O (4 x 100 mL). The combined extracts were washed with H_2O (2 x 50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by SiO_2 flash chromatography with hexanes-EtOAc (5:1) to obtain **25** and **26** (174 mg, 76%, 2.8:1 mixture) as a white solid; $[\alpha]_D$ (of mixture) -86.0 ° (*c* 1, CH_2Cl_2); IR (KBr) (mixture) 2975 (m), 2944 (m), 2892 (m), 2824 (w), 1740 (s), 1461 (m), 1386 (m), 1370 (m), 1285 (m), 1263 (m), 1193 (s), 1154 (m), 1118 (s), 1075 (s), 1060 (s), 1050 (s), 1006 (w), 965 (w), 944 (w), 882 (w), 858 (m), 780 (w), 753 (w), 521 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (for major isomer **25**) δ 4.45 (d, 1 H), 3.96 (d, *J* = 12.6 Hz, 1 H), 3.93 (complex m, 1 H), 3.73 (d, *J* = 12.6 Hz, 1 H), 3.26 (s, 3 H), 2.46 (dd, *J* = 3.3, 14.5 Hz, 1 H), 2.33 (dd, *J* = 10.8, 14.5 Hz, 1 H), 1.62 (m, 2 H), 1.49 (s, 3 H), 1.47 (s, 3 H), 0.94 (t, *J* = 7.3 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) (for major isomer **25**) δ 199.3, 100.4, 95.9, 78.0, 73.0, 60.3, 48.2, 46.2, 29.3, 28.6, 18.3, 9.6 ppm; HRMS (FAB, MNOBA matrix) for $C_{12}H_{21}O_5$ $(M+H)^+$ Calcd: 245.1389; Found: 245.1385; Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.77; H, 8.19.

Ketones **27** *and* **28**. To a -78 °C suspension of copper (I) iodide (178 mg, 0.935 mmol) in dry THF (0.5 mL) under N_2 was added methylmagnesium bromide (Aldrich, 1.0 M solution in *n*-Bu_2O) (1.9 mL, 1.9 mmol) over 1 min followed by trimethylsilyl chloride (0.6 mL, 4.73 mmol) also over 1 min. Enone **23** (200 mg, 0.934 mmol) in dry THF (2 mL) was then added over 5 min. After 1 h, the reaction mixture was quenched by dropwise addition of Et_3N (2.6 mL, 18.65 mmol) followed by solid $NaHCO_3$ (1.0 g) in one portion. The reaction mixture was diluted with Et_2O (50 mL) and saturated aq. $NaHCO_3$ (50 mL). The organic layer was separated, and the aqueous layer extracted with Et_2O (4 x 100 mL). The combined ethereal extracts were washed with H_2O (3 x 50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the residue was carried out by SiO_2 flash chromatography with hexanes-EtOAc (5:1) as eluent. The resulting ketones (185 mg, 86%) were obtained as a white solid that was a 5:1 mixture of **27** and **28**; $[\alpha]_D$ (of mixture) -42.3 ° (*c* 1, CH_2Cl_2); IR (KBr) 2981 (m), 2940 (m), 2901 (m), 1744 (s), 1440 (w), 1390 (m), 1382 (m), 1281 (m), 1260 (m), 1196 (s), 1119 (s), 1061 (s), 1046 (s), 949 (w), 924 (m), 856 (m), 780 (w), 753 (w), 527 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (resonances for **27** only) δ 4.46 (d, *J* = 1.5 Hz, 1 H), 4.18 (complex m, 1 H), 3.98 (d, *J* = 12.6 Hz, 1 H), 3.75 (d, *J* = 12.6 Hz, 1 H), 3.28 (s, 3 H), 2.49 (dd, *J* = 3.4, 14.4 Hz, 1 H), 2.35 (ddd, *J* = 1.4, 10.6, 14.4 Hz, 1 H), 1.51 (s, 3 H), 1.48 (s, 3 H), 1.29 (d, *J* = 6.3 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) (for **27** only) δ 199.1, 100.5, 96.0, 77.8, 68.1, 60.3, 48.4, 48.1, 28.7, 21.3, 18.4 ppm; HRMS (FAB, MNOBA matrix) for $C_{11}H_{19}O_5$ $(M+H)^+$ Calcd: 231.1232; Found: 231.1230; Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.20; H, 7.79.

Allylic alcohol **29**. To enone **23** (2.49 g, 11.62 mmol) in dry CH_2Cl_2 (90 mL) at -78 °C was added diisobutylaluminum hydride (Aldrich, 1.5 M solution in PhMe) (7.8 mL, 11.7 mmol) dropwise over 15 min and the mixture warmed to room temperature. After 30 min, the reactants were recooled to -78 °C and a further portion of diisobutylaluminum hydride (1.5 M solution in PhMe) (3.9 mL, 5.85 mmol) was added dropwise over 5 min. The reaction mixture was warmed to room temperature and stirred for another 15 min and then diluted with EtOAc (250 mL) and a saturated aqueous solution of potassium sodium tartrate. The organic layer was separated, and the aqueous phase extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with H_2O (1 x 100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was

purified by SiO_2 flash chromatography with hexanes-EtOAc (3:1) as eluent. This afforded allylic alcohol **29** (2.02 g, 80%) as white crystals: m.p. 91-96.5 °C; $[\alpha]_D$ +31.8 ° (*c* 1, CH_2Cl_2); IR (KBr) 3542 (m), 2994 (m), 2942 (m), 2888 (m), 1642 (s), 1464 (m), 1423 (m), 1384 (s), 1264 (s), 1238 (s), 1215 (s), 1191 (s), 1175 (s), 1135 (s), 1106 (s), 1076 (s), 1044 (s), 1016 (s), 990 (s), 949 (s), 895 (s), 850 (m), 787 (m), 765 (s), 664 (w), 589 (s), 576 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.16 (dd, *J* = 0.6, 6.1 Hz, 1 H), 5.17 (dd, *J* = 5.9, 5.9 Hz, 1 H), 4.04 (d, *J* = 4.8 Hz, 1 H), 4.02 (d, *J* = 12.6 Hz, 1 H), 3.96 (m, 1 H), 3.68 (d, *J* = 12.6 Hz, 1 H), 3.44 (d, *J* = 11.0 Hz, 1 H), 3.33 (s, 3 H), 1.52 (s, 3 H), 1.51 (s, 3 H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$) δ 139.8, 106.1, 100.2, 94.1, 70.8, 61.2, 60.3, 49.2, 28.9, 18.6 ppm; HRMS (FAB, MNOBA matrix) for $C_{10}H_{16}O_5Na$ $(M+Na)^+$ Calcd: 239.0896; Found: 239.0890; Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.54; H, 7.46. Found: C, 55.47; H, 7.64.

O-Acetate **30**. To a stirred solution of allylic alcohol **29** (2.02 g, 9.34 mmol) in pyridine (38 mL) was added acetic anhydride (6.14 mL, 65.04 mmol) and 4-dimethylaminopyridine (DMAP) (1.1 g, 9.01 mmol). After 4 h at room temperature, the reaction mixture was diluted with CH_2Cl_2 (200 mL) and saturated aqueous $NaHCO_3$ (200 mL). The organic layer was separated and the aqueous fraction extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were washed with H_2O (3 x 50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the residue was achieved by SiO_2 flash chromatography with hexanes-EtOAc (5:1) as eluent. This afforded **30** (1.65 g, 65%) as white crystals: m.p. 111.5-112.5 °C; $[\alpha]_D$ +107.6 ° (*c* 0.75, CH_2Cl_2); IR (KBr) 2995 (m), 2940 (m), 1732 (s), 1642 (m), 1464 (w), 1368 (m), 1307 (w), 1261 (s), 1241 (s), 1207 (s), 1190 (m), 1143 (m), 1107 (s), 1067 (m), 1048 (s), 1006 (m), 944 (m), 903 (w), 862 (m), 767 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.28 (dd, *J* = 0.9, 6.2 Hz, 1 H), 5.27 (dd, *J* = 5.3, 5.1 Hz, 1 H), 5.09 (t, *J* = 5.7, 5.5 Hz, 1 H), 4.17 (d, *J* = 5.6 Hz, 1 H), 4.10 (d, *J* = 12.6 Hz, 1 H), 3.69 (d, *J* = 12.6 Hz, 1 H), 3.36 (s, 3 H), 2.11 (s, 3 H), 1.51 (s, 3 H), 1.48 (s, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 142.8, 101.0, 100.6, 92.2, 70.5, 61.0, 60.7, 49.5, 28.7, 21.4, 18.6 ppm; HRMS (FAB, MNOBA matrix) for $C_{12}H_{19}O_6$ $(M+H)^+$ Calcd: 259.1182; Found: 259.1185.

Glycal **31**. To a stirred solution of allylic alcohol **29** (127 mg, 0.587 mmol) and imidazole (40 mg, 0.587 mmol) in dry *N,N*-dimethylformamide (1.5 mL) was added *tert*-butyldimethylsilyl chloride (88.5 mg, 0.587 mmol) in one portion. After 17 h at room temperature the reaction was quenched with saturated aq. $NaHCO_3$ and extracted with Et_2O (3 x 100 mL). The combined ethereal extracts were washed with H_2O (1 x 100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by SiO_2 flash chromatography with hexanes-EtOAc (25:1) as eluent. This furnished glycal **31** (149 mg, 77%) as white crystals: m.p. 45-46 °C; $[\alpha]_D$ +10.0 ° (*c* 0.14, CH_2Cl_2); IR (KBr) 2992 (m), 2952 (s), 2930 (s), 2885 (s), 2856 (s), 1644 (s), 1463 (m), 1382 (m), 1367 (m), 1303 (m), 1261 (s), 1246 (s), 1192 (s), 1154 (s), 1114 (s), 1092 (s), 1056 (s), 1018 (s), 967 (m), 940 (m), 927 (m), 885 (m), 864 (m), 836 (s), 777 (s), 661 (m), 578 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.17 (d, *J* = 6.2 Hz, 1 H), 4.95 (dd, *J* = 5.9, 5.7 Hz, 1 H), 4.13 (dd, *J* = 5.0, 5.1 Hz, 1 H), 4.04 (d, *J* = 12.3 Hz, 1 H), 3.89 (d, *J* = 4.8 Hz, 1 H), 3.64 (d, *J* = 12.4 Hz, 1 H), 3.32 (s, 3 H), 1.48 (s, 3 H), 1.46 (s, 3 H), 0.88 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 3 H) ppm; HRMS (FAB, MNOBA matrix) for $C_{16}H_{30}O_5SiNa$ $(M+Na)^+$ Calcd: 353.1760; Found: 353.1764.

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