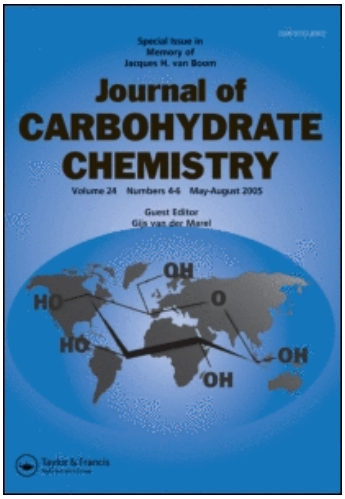

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A C3a-Hydroxylated Furanose Synthon for Sesquiterpene Lactones

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A C3a-HYDROXYLATED FURANOSE SYNTHON FOR SESQUITERPENE LACTONES

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ABSTRACT

A procedure for the stereocontrolled elaboration of a pendant oxirane at C3 of a 1,2-*O*-isopropylidenated glycofuranose has been developed. Cleavage of the oxirane with a functionalized carbon nucleophile give a C3a-hydroxylated product which is an attractive synthon for sesquiterpene lactones.

INTRODUCTION

The use of 1,2-*O*-isopropylidenated glycofuranoses as synthons for α-methylene lactones (Scheme I) has been a topic of interest in our laboratory for several years.[1] Initially we were attracted by the observation that in the readily prepared C3-branched derivatives such as **3**, the absolute configurations at C3 and C4 are coincident with the chiralities at the corresponding sites in a large number of naturally occurring terpenoids symbolized by **1**. Further inspection of these natural products showed that a contiguous C3'-OH is frequently an additional chiral center which can have either the *R* or *S* configuration, with the ring size n being 6[2], 7[3], or 10.[4] It was therefore of

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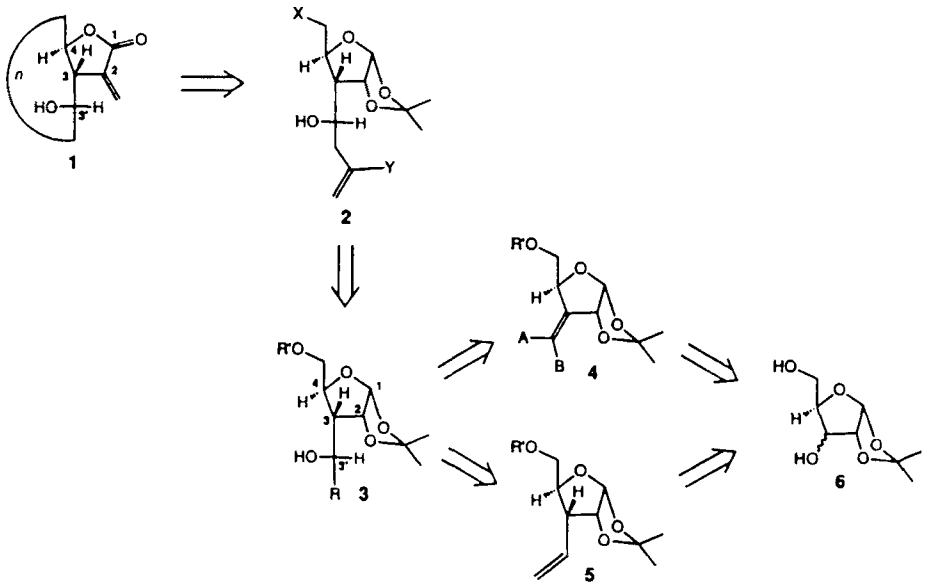


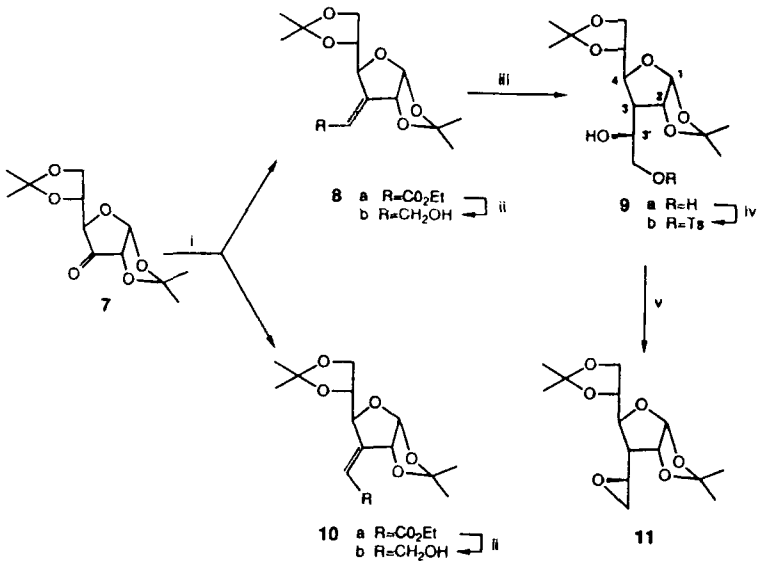
Scheme I

interest to make provisions in our synthetic plans for this additional chiral center. Simultaneously, consideration would have to be given to strategies for preparation of rings of various sizes. An alkene such as **2** offered the possibility of a wide variety of ring-forming reactions. In this manuscript we describe experiments designed to obtain such a C3 functionalized furanose.

RESULTS AND DISCUSSION

Control of stereochemistry at the off-template site[5] of **3** was an obvious problem and hence we decided to address this issue at the outset. It is now well precedented that with C3 trigonal substrates such as **4**, reagent approach from the β-face is heavily favored on steric grounds.[6] Since hydroboration involves *syn* addition,[7] the configurations at C3 and C3' would be established simultaneously, the latter configuration being entirely dependent on the geometry of the olefinic precursor. Alternatively, diastereofacial selectivity in the reactions of the vinyl derivative **5** could provide an alternative route to the synthon **3**.

Our first experiments began with the diastereomeric α,β-unsaturated esters **8a** and **10a** (Scheme II) whose preparation from the 3-ulose **7** has been described by



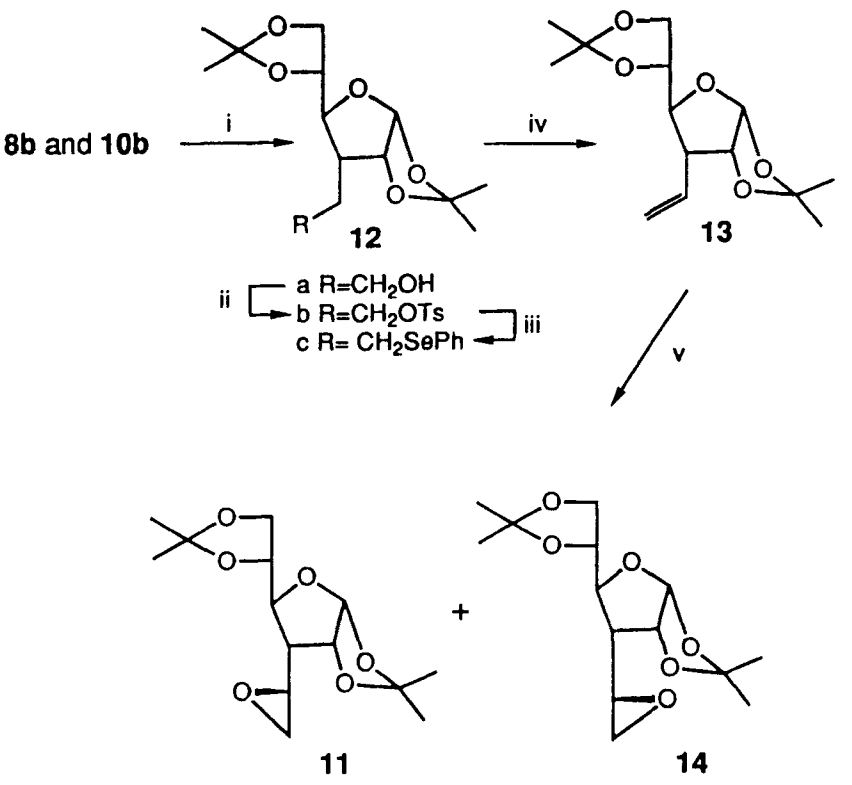
(i) Ph_3PCO_2Et (ii) DIBAL (iii) BH_3-THF (iv) TsCl / DMAP / Et_3N (v) NaH

Scheme II

Tronchet and Gentile.[8] The esters were reduced to the corresponding allylic alcohols **8b** and **10b** respectively, whose structures have been verified by Tadano and coworkers.[9]

Hydroboration of compound **8b** gave a single product **9a** whose configuration at C3 was readily assigned as shown in view of the coupling constants $J_{2,3}$ = 4.2 Hz; $J_{3,4}$ = 9.9 Hz. The configuration shown for C3' was assumed to be *R* on the basis of the mechanism of hydroboration.[7] The diol **9a** was selectively sulfonated, and treatment of the resulting **9b** with sodium hydride afforded an oxirane, presumed to be **11** in 80% yield.

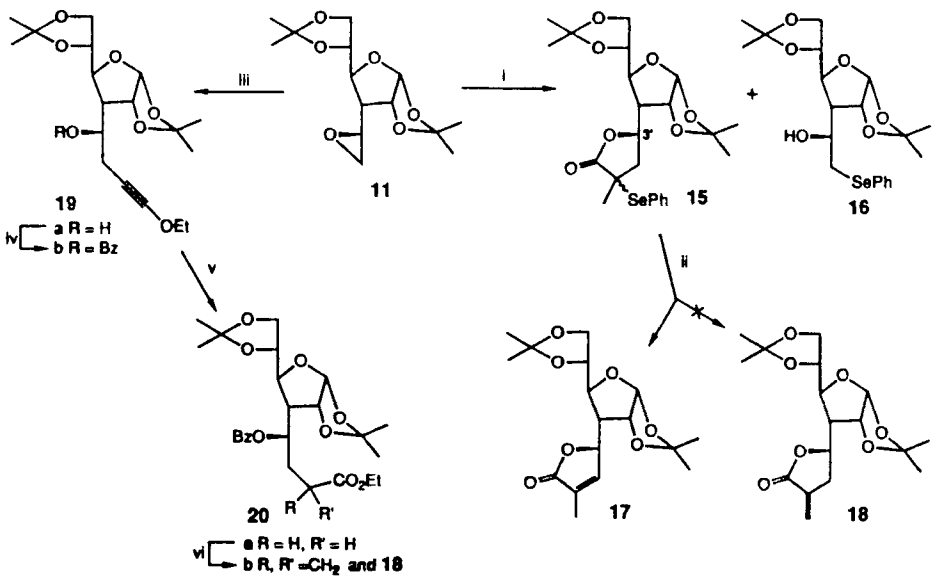
The forgoing route established the identity of the epoxide **11**. This approach, however, was compromise by the fact that ester **8a** was the minor geometric isomer from the Wittig reaction of **7**. An approach that would make use of both geometric isomers was appealing. The C3 vinyl derivative **13** (Scheme III), seemed an attractive target on the assumption that stereoselective epoxidation to obtain **11** could be effected. Accordingly, the mixture of allylic alcohols **8b** and **10b** was hydrogenated to give the previously reported[6] alcohol **12a** and some of the corresponding aldehyde.



Scheme III

Attempts to effect β-elimination by base treatment of the derived sulfonate **12b** proved to be unrewarding and hence we turned our attention to selenoxide elimination.[10] The selenide was prepared by treatment of **12b** with sodium phenylselenide, and oxidation of the product **12c** afforded the alkene **13** in virtually quantitative yield. Epoxidation of the latter with *m*-chloroperoxybenzoic acid gave the previously described epoxide **11** as well as its diastereomer **14** in a 3:1 ratio. The isomers were readily separated by column chromatography.

With gram quantities of **11** thereby available by the route shown in Scheme III, we addressed the task of installing functional groups that could be used to obtain the carbocyclic ring of **1**. A wide variety of carbon nucleophiles including



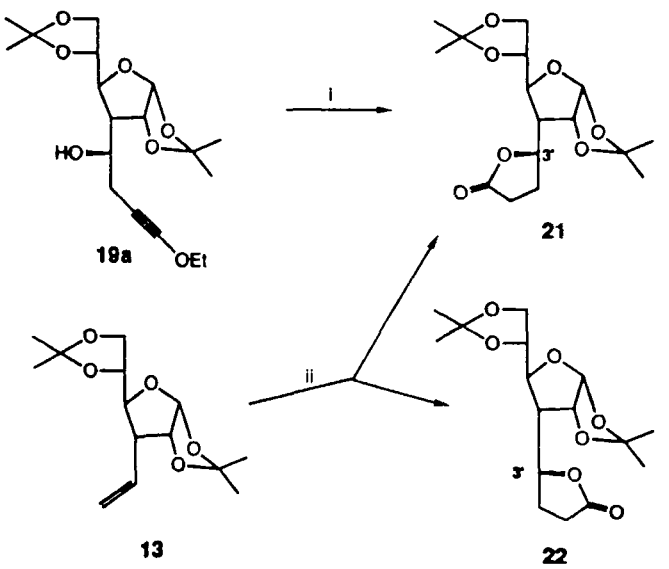
(i) LDA / $CH_3CH(SePh)CO_2H$ (ii) m-CPBA / Et_3N (iii) $Et_2AlCCOEt$ (iv) BzCl / pyridine (v) $HgSO_4$ / H_2SO_4, $NaBH_4$ work-up (vi) LDA / $H_2C{=}O$; MsCl / pyridine; pyridine / heat

Scheme IV

$LiCH_2CO_2Et$,[11] $NaCH(CO_2Et)_2$[12], $LiCH_2COOLi$[13], $LiCH(SPh)CO_2Li$[14] and $LiOCH_2C(=CH_2)Li$[15] either failed to react with **11** or gave intractable mixtures. Some success was had, however, with the dianion of 2-phenylselenopropionic acid[16] whereby lactone **15** was obtained as a mixture of epimers (Scheme IV). However, the route was compromised by the formation of appreciable amounts of the selenoalcohol **16**. Selenoxide elimination of **15** gave the endocyclic product **17**[17] with none of the desired exocyclic isomer **18** (which is consonant with synthon **2**) (Scheme IV).

A more efficient procedure for opening the epoxide **11** was finally found. Thus treatment with diethyl(ethoxyethynyl)alane[18] resulted in smooth ring-opening to give compound **19a** in 70% yield. Benzoylation to **19b** followed by oxymercuration then afforded the saturated diester **20a**, and standard processing[19] was then applied to obtain the α-methylenated ester **20b** and some of the corresponding lactone **18**. Alternatively, if the C3'-OH of **19a** was not protected, oxymercuration led directly to lactone **21** (Scheme V).

A direct route from the vinyl derivative **13** to **21** *via* free radical induced lactonization was conceivable. Indeed treatment of **13** with iodoacetic acid in the



Scheme V

presence of 2,2'-azo-bis-2-methylpropanenitrile and tri-*n*-butyltinhydride[20] gave lactone **21** along with an equal amount of the isomer **22** in 64% overall yield (Scheme V). The mixture and modest yield compromised this approach.

EXPERIMENTAL

General Procedures. Melting points were determined in capillary tubes and are uncorrected. Elemental analyses were performed by M-H-W Laboratories, PO Box 15149, Phoenix, Arizona. High resolution mass spectra were run by the Midwest Center for Mass Spectrometry, University of Nebraska, Lincoln, NE, 68588. Proton magnetic resonance spectra (1H NMR) were recorded on a Varian XL 300 spectrometer using deuterochloroform as the solvent. Chemical shifts are reported in parts per million (δ) downfield from internal tetramethylsilane. Coupling constants were calculated from peak listings. The numbering pattern used for assignment of protons follows standard carbohydrate numbering up to C6, then continues away from the ring along the C3 side-chain.

The progress of all reactions was monitored by thin-layer chromatography (TLC) using aluminum sheets coated with silica gel 60 to a thickness of 0.25 mm (HF-254, E. Merck). The following solvent systems were used as eluants: (A) ethyl acetate-petroleum ether (35-60 °C), 10:90; (B) 20:80; (C) 30:70; (D) 40:60: (E) 50:50; (F) 60:40. Chromatograms were visualized by dipping in a solution of ceric ammonium molybdate and heating or observed under ultraviolet light. Flash column chromatography was performed using Kiesel gel 60 (230-400 mesh, E. Merck) Optical rotations $[\alpha]_D^T$ were determined at the sodium D line (589 nm) at room temperature using a Perkin-Elmer 241 polarimeter. Concentrations were between 0.500 and 1.50 g/100 mL made up in spectroscopic grade chloroform. Infra-red spectra (IR) were recorded on a Perkin-Elmer 297 instrument using sodium chloride cells and methylene chloride as a solvent. The absorption bands (cm^{-1}) were calibrated against the 1601 cm^{-1} band of polystyrene. Only absorptions relevant to structural proof are reported.

3-Deoxy-3-*C*-(1'*R*,2'-dihydroxyethyl)-1,2:5,6-*O*-isopropylidene-α-D-allofuranose (9a). The allylic alcohol **8b** (189 mg, 0.661 mmol) was dissolved in dry tetrahydrofuran (1 mL) and cooled to 0 °C under argon. A solution of borane tetrahydrofuran complex (2.8 mL of a 1.0 M solution in tetrahydrofuran) was added dropwise. The solution was warmed to room temperature and stirred for 6 h, then cooled to 0 °C and quenched with 2.1 mL each of a 3.0 M aqueous sodium hydroxide solution and a 30% hydrogen peroxide solution. The mixture was allowed to stir 4 h before addition of saturated sodium thiosulfate solution (2 mL). Tetrahydrofuran was removed *in vacuo*, the aqueous layer saturated with sodium chloride and extracted with ether. The solvent was dried over sodium sulfate and concentrated *in vacuo*. The residue was chromatographed (solvent D) to give a clear syrup **9a** (74 mg, 37%) : TLC R_f = 0.14 (F); $[\alpha]_D^{25}$ = +39.8°; IR (CH_2Cl_2) 3500 (OH) cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 1.35, 1.38, 1.48, 1.58 (4s, 12, CMe_2), 2.19 (qn, 1, $J_{2,3} = J_{3,7}$ = 4.2 Hz, $J_{3,4}$ = 9.9 Hz, H3), 2.35 (dd, 1, $J_{8,OH}$ = 5.1 Hz, $J_{8',OH}$ = 8.1 Hz, C8-OH), 3.33 (d, 1, $J_{7,OH}$ = 9.9 Hz, C7-OH), 3.79 (m, 2, H8), 4.10 (m, 4, H5, 2H6, H7), 4.25 (dd, 1, $J_{4,5}$ = 7.2 Hz, H4), 4.88 (t, 1, H2), 5.79 (d, 1, $J_{1,2}$ = 4.2 Hz, H1).

Anal. Calcd for $C_{14}H_{24}O_7$: C, 55.25; H, 7.95. Found: C, 55.27; H, 7.92.

3-Deoxy-3-*C*-(1'*R*,2'-dihydroxyethyl)-1,2:5,6-di-*O*-isopropylidene-2'-*O*-*p*-toluenesulfonyl-α-D-allofuranose (9b). The diol **9a** (37 mg, 0.12 mmol) was dissolved in dry methylene chloride (1 mL). Triethylamine (0.10 mL, 0.719 mmol) was added to this solution, followed by *p*-toluenesulfonyl chloride (25 mg, 0.130

mmol) and a catalytic amount of 4-dimethylaminopyridine. The mixture was allowed to stir 1 h, then quenched with methanol at 0 °C. The solvents were removed *in vacuo* and the residue was chromatographed (solvent B) to yield a colorless syrup **9b** (36 mg, 65%): TLC R_f= 0.52 (F); $[\alpha]_D^{25}$ = +25.6° IR (CH_2Cl_2) 3500 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32, 1.36, 1.43, 1.54, (4s, 12, CMe_2), 2.19 (ddd, 1, $J_{2,3}$ = 4.5 Hz, $J_{3,4}$ = 9.9 Hz, $J_{3,7}$ = 3.3 Hz, H3), 2.48 (s, 3, tosyl-Me), 3.46 (d, 1, $J_{7,OH}$ = 9.9 Hz, C7-OH), 3.98 (dd, 1, $J_{7,8}$ = 4.5 Hz, $J_{8,8'}$ = 8.0 Hz, H8), 4.08 (m, 1, H5), 4.11 (dd, 1, $J_{7,8'}$ = 6.6, H8'), 4.24 (m, 4, H4, 2H6, H7), 4.81 (t, 1, H2) 5.76 (d, 1, $J_{1,2}$ = 4.0, H1), 7.40 (d, 2, tosyl), 7.85 (d, 2, tosyl).

Anal. Calcd for $C_{21}H_{30}O_9S$: C, 55.01; H, 6.59. Found: C, 55.19; H, 6.99.

3-Deoxy-3-*C*-(1'*R*,2'-epoxyethyl)-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (11) The alcohol **9b** (20 mg, 0.044 mmol) was dissolved in dry tetrahydrofuran (2 mL) and treated with an excess of sodium hydride at room temperature. The reaction was quenched with methanol after a few minutes, diluted with saturated sodium chloride solution, and extracted with ether. The solution was dried over sodium sulfate and concentrated *in vacuo*. The residue was chromatographed (solvent C) to yield a colorless syrup **11** (10 mg, 80%): TLC R_f = 0.24 (C); $[\alpha]_D^{25}$ = +51.9°; ^1H NMR (300 MHz, $CDCl_3$) δ 1.33, 1.37, 1.42, 1.58 (4s, 12, CMe_2), 1.64 (m, 1, H3), 2.70 (dd, 1, $J_{7,8}$ = 2.0 Hz, $J_{8,8'}$ = 4.7 Hz, H8), 2.90 (dd, 1, $J_{7,8'}$ = 4.1 Hz, H8'), 3.19 (ddd, 1, $J_{3,7}$ = 9.3 Hz, H7), 3.95 (m, 1, H5), 4.07 (m, 3, H4, H6, H6'), 4.84 (dd, 1, $J_{2,3}$ = 3.9 Hz, H2), 5.82 (d, 1, $J_{1,2}$ = 4.5 Hz, H1).

Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.71; H, 7.75. Found: C, 58.82; H, 7.64.

3-Deoxy-3-*C*-(2'-hydroxyethyl)-1,2:5,6-*O*-isopropylidene-α-D-allofuranose (12a). A mixture of allylic alcohols **8b** and **10b** (1.39 mg, 4.86 mmol) was dissolved in dry ethanol (10 mL) to which was added 10% palladium on carbon (70 mg, 0.066 mmol). The mixture was allowed to stir under hydrogen at 1 atm. for 5 h, after which the catalyst was removed by filtration through a bed of celite. The reaction was monitored by TLC using a 5:10:85 mixture of methanol-ether-methylene chloride, so that product and starting material could be easily distinguished. The filtered solution was concentrated *in vacuo* and chromatographed (solvent C) to yield a colorless syrup **12a** (956 mg, 68%): TLC R_f = 0.08 (C); $[\alpha]_D^{25}$ = +54.3°; IR (CH_2Cl_2) 3500 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.34, 1.36, 1.45, 1.53 (4s, 12, CMe_2), 2.00 (dm, 4, H3, 2H7, C8-OH), 3.81 (m, 3, H4, 2H8), 3.96 (dd, 1, $J_{5,6}$ = 4.5 Hz, $J_{6,6'}$ = 7.6 Hz, H6), 4.04 (m, 1, H5), 4.13 (dd, 1, $J_{5,6'}$ = 6.0 Hz, H6'), 4.74 (t, 1, $J_{2,3}$ = 3.9 Hz, H2), 5.80 (d, 1, $J_{1,2}$ = 3.9 Hz, H1).

Anal. Calcd for $C_{14}H_{24}O_6$: C, 58.32; H, 8.39. Found: C, 58.32; H, 8.24.

3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-vinyl-α-D-allofuranose (13). The alcohol **12a** (10.7 g, 37.2 mmol) was dissolved in dry pyridine (40 mL) to which was added *p*-toluenesulfonyl chloride (10.6 g, 55.7 mmol). After stirring 4 h at room temperature, the reaction was diluted with water and extracted with methylene chloride. The solution was dried over sodium sulfate, concentrated *in vacuo* and the residue azeotroped with toluene to give crude **12b** (15.8 g) as an orange syrup. This material was dissolved in dry tetrahydrofuran (50 mL) and the solution added dropwise to a phenylselenide solution prepared by dissolving diphenyl selenide (5.6g, 17.9 mmol) in absolute ethanol (400 mL) at 0 °C and treating it with small portions of sodium borohydride until the yellow color disappeared and left a white cloudy mixture. More sodium borohydride was added to maintain the white colour. After stirring 5 h at 0 °C, the reaction was quenched with saturated sodium carbonate solution and filtered through a bed of celite. The organic solvents were removed *in vacuo* and the aqueous solution extracted with ether, which was then dried over sodium sulfate, and concentrated to give crude **12c** (15.2g) as a yellow syrup. This syrup was dissolved in dry methylene chloride, (300 mL), cooled to 0 °C, and treated with *m*-chloroperoxybenzoic acid (11.5 g, 53.4 mmol). After 15 min, triethylamine (35 mL, 0.26 moles) was added and mixture refluxed for 4 h. The dark reaction mixture was then diluted with water, and extracted with methylene chloride. The solution was dried over magnesium sulfate, concentrated *in vacuo* and the residue chromatographed (solvent B) to yield **13** (8.5 g, 85%) as a colorless syrup: TLC R_f = 0.49 (C); $[\alpha]_D^{25}$ = +95.7°; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33, 1.37, 1.46, 1.57 (4s, 12, CMe_2), 2.65 (dt, 1, $J_{2,3}$ = 4.5 Hz, $J_{3,4}$ = 10.4 Hz, $J_{3,7}$ = 10.8 Hz, H3), 3.92 (dd, 1, $J_{5,6}$ = 7.4 Hz, $J_{6,6'}$ = 8.5 Hz, H6), 4.02 (dd, 1, $J_{5,6'}$ = 7.5 Hz, H6'), 4.14 (dd, 1, $J_{4,5}$ = 3.9 Hz, H4), 4.29 (dt, 1, H5), 4.66 (t, 1, H2), 5.28 (m, 2, $J_{7,8}$ = 11.0 Hz, $J_{7,8'}$ = 18.0 Hz, H8, H8'), 5.85 (d, 1, $J_{1,2}$ = 4.0 Hz, H1), 5.92 (m, 1, H7).

Anal. Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 62.02; H, 8.04.

Compound (11) and 3-Deoxy-3-*C*-(1'*S*,2'-epoxyethyl)-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (14). The alkene **13** (261 mg, 0.967 mmol) was dissolved in dry methylene chloride (20 mL) and treated with *m*-chloroperoxybenzoic acid (965 mg, 4.49 mmol) and sodium acetate (367 mg, 4.49 mmol). After 40 h at room temperature saturated sodium bicarbonate was added and the mixture extracted with methylene chloride. The organic layer was washed with saturated sodium thiosulfate solution and saturated sodium chloride solution,

dried over magnesium sulfate,and concentrated *in vacuo*. The products were separated by chromatography (solvent A) to yield a colorless syrup **11** (198 mg, 72%) and a white crystalline solid **14** (72 mg, 26%). The physical properties of **11** are recorded above and those of **14** are as follows: mp 64-66 °C; TLC R_f = 0.14 (C); $[\alpha]_D^{25}$ = +60.3°; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34, 1.40, 1.47, 1.56, (4s, 12, CMe_2), 1.64 (m, 1, H3), 2.69 (dd, 1, $J_{7,8}$ = 6.0 Hz, $J_{8,8'}$ = 4.2 Hz, H8), 2.88 (t, 1, $J_{7,8'}$ =4.2, H8'), 3.11 (ddd, 1, $J_{3,7}$ = 3.0 Hz, H7), 3.98 (dd, 1, $J_{5,6}$ = 6.6 Hz, $J_{6,6'}$ = 8.1 Hz, H6), 4.04 (dd, 1, $J_{5,6'}$ = 6.0 Hz, H6'), 4.32 (m, 2, H4, H5), 4.70 (dd, 1, $J_{2,3}$ = 4.8 Hz, H2), 5.83 (d, 1, $J_{1,2}$ = 4.5 Hz, H1).

Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.71; H, 7.75. Found: C, 58.73; H, 7.72.

3-Deoxy-3-*C*-(1'*S*-hydroxy-3'-methyl-3'-phenylselenyl-4-γ-butyrolactone)-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranoses (15) and 3-Deoxy-3-*C*-(1'*R*-hydroxy-2'-phenylselenoethyl)-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (16). A solution of lithium diisopropylamide (1.2 mmol) was prepared under argon at 0 °C in dry tetrahydrofuran (2 mL). After 15 min, a solution of 2-phenylselenopropionic acid (118 mg, 0.515 mmol) in dry tetrahydrofuran (2 mL) was added dropwise. The mixture was warmed to 40 °C for 0.5 h, then cooled to 0 °C. The epoxide **11** (70 mg, 0.25 mmol) was dissolved in tetrahydrofuran (3 mL, and added dropwise to the mixture, after which it was immediately warmed to 60 °C and stirred for 5 h. Reaction progress was monitored by TLC (10:10:80 methanol-ether-petroleum ether). The reaction was quenched with saturated ammonium chloride solution at 0 °C. The aqueous layer was extracted with ethyl acetate, dried over sodium sulfate, and concentrated *in vacuo*. The residue were purified by chromatography (solvent A) to give the less polar epimer of **15** (26 mg, 25%) and **16** (30 mg, 25%) as a mixture of a white crystalline solid and a colorless syrup and the more polar epimer of **15** (43 mg, 35%) as a colorless syrup. Compound **16** could be separated by further reaction. The physical properties of the less polar epimer of **15** are as follows: mp 112-114 °C; TLC R_f = 0.28 (C); $[\alpha]_D^{25}$ = +53.3°; IR (CH_2Cl_2) 1760 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33, 1.37, 1.39, 1.52 (4s, 12, CMe_2), 1.67 (s, 3, Me), 1.92 (ddd, 1, $J_{3,4}$ = 8.4 Hz, $J_{3,7}$ = 5.0 Hz, H3), 2.51 (dd, 1, $J_{7,8}$ = 7.8 Hz, $J_{8,8'}$ = 14.4 Hz, H8), 2.68 (dd, 1, $J_{7,8'}$ = 6.0 Hz, H8'), 3.86 (m, 3, H4, 2H6), 4.09 (m, 1, H5), 4.76 (m, 2, H2, H7), 5.69 (d, 1, $J_{1,2}$ = 3.3 Hz, H1), 7.40 (m, 3, SePh), 7.70 (d, 2, SePh).

Calcd mass for $C_{23}H_{30}O_7Se$: 498.1158. Found (HRMS): 49.1180.

The physical properties of the more polar epimer of **15** are as follows: TLC R_f = 0.19 (C); IR (CH_2Cl_2) 1760 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33,

1.40, 1.56, 1.67 (4s, 12, CMe_2), 2.13 (m, 1, H3), 2.28 (dd, 1, $J_{7,8}$ = 10.2 Hz, $J_{8,8}$ = 14.5 Hz, H8), 2.66 (dd, 1, $J_{7,8'}$ = 6.0 Hz, H8'), 3.95 (m, 3, H4, 2H6), 4.12 (m, 1, H5), 4.81 (m, 2, H2, H7), 5.76 (d, 1, $J_{1,2}$ = 4.5 Hz, H1), 7.36 (t, 2, SePh), 7.46 (t, 1, SePh), 7.68 (d, 2, SePh).

Anal. Calcd for $C_{23}H_{30}O_7Se$: C, 55.53; H, 6.08. Found: C, 55.66; H, 6.16.

The characteristics of compound **16** are as follows: TLC R_f = 0.28 (C); IR (CH_2Cl_2) 3500 (O-H) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.33, 1.39, 1.56 (3s, 12, CMe_2), 2.43 (qn, 1, $J_{2,3} = J_{3,7}$ = 4.5 Hz, $J_{3,4}$ = 10.0 Hz, H3), 3.21 (dd, 1, $J_{7,8}$ = 6.9 Hz, $J_{8,8'}$ = 12. 0 Hz, H8), 3.34 (dd, 1, $J_{7,8'}$ = 6.9 Hz, H8'), 3.44 (d, 1, $J_{7,OH}$ = 13.2 Hz, C7-OH), 3.98 (dd, 1, $J_{5,6}$ = 8.1 Hz, $J_{6,6'}$ = 11.1 Hz, H6), 4.13 (m, 2, H_5, $J_{5,6'}$ = 6.2 Hz, H5, H6'), 4.19 (m, 1, H7), 4.32 (dd, 1, $J_{4,5}$ = 5.4 Hz, H4), 4.75 (t, 1, H2), 5.76 (d, 1, $J_{1,2}$ = 4.0 Hz, H1), 7.28 (m, 3, SePh), 7.58 (m, 2, SePh)

Anal. Calcd for $C_{20}H_{28}O_6Se$: C, 54.18; H, 6.37. Found: C, 54.44; H, 6.57.

3-Deoxy-3-*C*-(1'*S*-hydroxy-3'-methyl-4'-γ-but-2'-enyrolactone)-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (17). The less polar epimer of lactone **15** γ (33 mg, 0.066 mmol) was dissolved in dry methylene chloride (4 mL) and treated with *m*-chloroperoxybenzoic acid (30 mg, 0.140 mmol) at 0 °C. After 15 min, triethylamine (0.20 mL, 1.4 mmol) was added and the reaction warmed to room temperature for 0.5 h. The mixture was diluted with water, extracted with methylene chloride, dried over sodium sulfate, and concentrated *in vacuo*. The residue was chromatographed (solvent A) to yield a white crystalline solid **17** (17 mg, 75%): mp 102-104 °C; TLC R_f = 0.18 (C); $[\alpha]_D^{25}$ = +1.5°; IR (CH_2Cl_2) 1760 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.36, 1.38, 1.43, 1.58 (4s, 12, CMe_2), 1.94 (s, 3, Me), 2.16 (ddd, 1, $J_{2,3}$ = 4.2 Hz, $J_{3,4}$ = 8.7 Hz, $J_{3,7}$ = 6.0 Hz, H3), 3.98 (m, 3, H4, 2H6), 4.13 (td, 1, H5), 4.83 (t, 1, H2), 5.26 (dt, 1, H7), 5.77 (d, 1, $J_{1,2}$ = 4.2 Hz, H1), H7 and H11 both show some allylic coupling.

Anal. Calcd for $C_{17}H_{24}O_7$: C, 59.99; H, 7.11. Found C, 59.75; H, 6.97.

Compound **17** was also synthesized from the more polar epimer of lactone **15** (27 mg, 0.054 mmol) as described above. Chromatography yielded a white crystalline solid which was identified by NMR as **17** (16 mg, 86%)

3-Deoxy-3-*C*-(4'-ethoxy-2'*S*-hydroxy-3'-butynyl)-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (19a). Freshly distilled ethyl ethynyl ether (1.37 g, 19.6 mmol) was dissolved in dry toluene (60 mL) and cooled to -78 °C under argon. *n*-Butyllithium (6.5 mL of a 2.3 M solution in hexane) was added dropwise and the reaction stirred for 0.5 h. Diethylaluminum chloride (7.5 mL of a 1.0 M solution in

hexane) was then added dropwise using a syringe, the solution warmed to 0 °C and stirred for 1.5 h. The epoxide **11** (336 mg, 1.17 mmol) was dissolved in dry toluene (5 mL) and added slowly to the reaction. The reaction was warmed to room temperature for 5-24 h and monitored by TLC (10:10:80 methanol-ether-petroleum ether) for the disappearance of starting material. The brown solution was quenched with celite and saturated ammonium chloride at 0 °C and filtered through a bed of celite. The solids were washed with ethyl acetate and the solvents removed *in vacuo*. The orange residue was chromatographed (solvent A) to yield a fairly stable colorless syrup **19a** (293 mg, 70%): TLC R_f = 0.23 (C); $[a]_D^{25}$ = +48.9°; IR (CH_2Cl_2) 3500 (OH) 2260 (CC) cm-1; 1H NMR (300 MHz, $CDCl_3$) δ 1.35 (m, 9, CMe_2, OCH_2CH_3), 1.48, 1.54 (2s, 6, CMe_2), 2.44 (m, 1, H3), 2.50 (dd, 1, $J_{7,8}$ = 9.3 Hz, $J_{8,8'}$ = 16.2 Hz, H8), 2.67 (dd, 1, $J_{7,8'}$ = 6.0 Hz, H8'), 3.24 (d, 1, $J_{7,OH}$ = 10.8 Hz, C7-OH), 4.06 (m, 5, 2H6, H7, OCH_2CH_3), 4.22 (dd, 1, $J_{4,5}$ = 5.2 Hz, $J_{5,6}$= 12.0 Hz, H5), 4.35 (dd, 1, $J_{3,4}$ = 9.9 Hz, H4), 4.95 (t, 1, $J_{2,3}$ = 4.0 Hz, H2), 5.80 (d, 1, $J_{1,2}$ = 4.0 Hz, H1).

Anal. Calcd for $C_{18}H_{28}O_7$: C, 60.66; H, 7.92. Found: C, 60.75; H, 8.03.

3-Deoxy-3-*C*-(4'-ethoxy-2'*S*-benzyloxy-3'-butynyl)-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (19b). The alcohol **19a** (225 mg, 0.632 mmol) was dissolved in dry pyridine (1 mL) and cooled to 0 °C. Benzoyl chloride (0.10 mL, 0.86 mmol) was added and the mixture warmed slowly to room temperature. The mixture was quenched after an hour with methanol and the solvents removed *in vacuo*. The residue was chromatographed (solvent A) to yield a stable colorless syrup **19b** (250 mg, 86%): TLC R_f = 0.40 (C); $[\alpha]_D^{25}$ = +41.3°; IR (CH_2Cl_2) 2260 (CC) 1720 (C=O) cm^{-1}; 1H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 3, CMe_2), 1.35 (m, 9, CMe_2, OCH_2CH_3), 1.62 (s, 3, CMe_2), 2.56 (ddd, 1, $J_{2,3}$ = 4.0 Hz, $J_{3,4}$ = 10.5 Hz, $J_{3,7}$ = 6.3 Hz, H3), 2.74 (dd, 1, $J_{7,8}$ = 8.0 Hz, H8), 2.88 (dd, 1, $J_{7,8'}$ = 5.8 Hz, H8'), 3.91 (m, 1, OCH_2CH_3), 4.12 (m, 5, H4, H5, 2H6, OCH_2CH_3), 4.92 (t, 1, H2), 5.52 (dt, 1, H7), 5.81 (d, 1, $J_{1,2}$ = 3.6 Hz, H1), 7.44 (t, 2, OBz), 7.58 (t, 1, OBz), 8.10 (d, 2, OBz).

Anal. Calcd for $C_{25}H_{32}O_8$: C, 65.20; 7.00. Found: C, 65.12; H, 7.24.

3-Deoxy-3-*C*-(ethyl-1'*S*-benzyloxy-4'-butyrate)-1,2:5,6-di-*O*-isopropylidene-α-D-allo-furanose (20a). The acetylenic ether **19b** (61 mg, 1.3 mmol) was dissolved in tetrahydrofuran (8 mL) and cooled to -10 °C. A 5% mercuric sulfate solution in 10% sulfuric acid was added dropwise till all of the starting material was consumed by TLC. Small portions of sodium borohydride were then added

(vigorous bubbling) until TLC indicated the formation of a new product and complete disappearance of the baseline material formed in the previous step. The reaction was quenched with 10% hydrochloric acid, diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution followed by saturated sodium chloride solution. The mixture was dried over sodium sulfate, concentrated *in vacuo*, and chromatographed (solvent B) to yield a colorless syrup **20a** (53 mg, 83%): TLC R_f = 0.26 (C); $[\alpha]_D^{25}$= +21.7°; IR (CH_2Cl_2) 1720 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (t, 3, $OCH_2\underline{CH_3}$), 1.31, 1.34, 1.58 (3s, 12, CMe_2), 2.21 (qn, 1, $J_{2,3}$ = 3.9 Hz, $J_{3,7}$ = 4.4 Hz, H3), 2.31 (m, 2, $J_{8,8'}$ = 11.4 Hz), 2.46 (m, 2, 2H9), 3.91 (dd, 1, $J_{4,5}$ = 9.5 Hz, $J_{5,6}$ = 11.4 Hz, H5), 4.07 (m, 4, 2H6, $OC\underline{H_2}CH_3$), 4.18 (dd, 1, H4), 4.85 (t, 1, H2), 5.56 (qn, 1, $J_{7,8}$ = 4.2 Hz, H7), 5.36 (d, 1, $J_{1,2}$ = 3.6 Hz, H1), 7.43 (t, 2, OBz), 7.58 (t, 1, OBz), 8.08 (d, 2, OBz).

Anal. Calcd for $C_{25}H_{34}O_9$: C, 62.75; H, 7.16. Found: C, 62.60; H, 7.06.

3-Deoxy-3-*C*-(ethyl-1'*S*-benzyloxy-3'-methylene-4'-butyrate)-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (20b) and 3-Deoxy-3-*C*-(1'*S*-hydroxy-3'-methylene-4'-γ-butyrolactone)1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (18) The diester **20a** (64 mg, 0.13 mmol) was dissolved in dry tetrahydrofuran (2 mL) and added dropwise at -78 °C under argon to a previously prepared solution of lithium diisopropylamide (2 mL, 0.34 mmol) and stirred for 15 min. Gaseous formaldehyde was generated by heating dry *p*-formaldehyde (300 mg, 10.0 mmol) at 180 °C and carried into the reaction flask by a stream of argon. The reaction was agitated vigorously until all the *p*-formaldehyde had vaporized, and was then quenched with saturated ammonium chloride solution. The organic solvents were removed *in vacuo* and the aqueous mixture extracted with ethyl acetate. The solution was filtered through a bed of celite, dried over sodium sulfate, and concentrated *in vacuo* to yield a yellow syrup (74 mg). The crude residue was dissolved in dry pyridine (1 mL), cooled to 0 °C, and treated with excess methanesulfonyl chloride. The reaction was quenched after 15 min with a few drops of methanol and the mixture extracted with methylene chloride. The organic layer was dried over sodium sulfate, concentrated *in vacuo*, and azeotroped with toluene to yield of a yellow syrup (100 mg). This residue was dissolved in dry pyridine (2 mL) and refluxed for 1 h. The solvent was removed *in vacuo* and the residue azeotroped with toluene. The products were separated by chromatography (solvent A) to yield two colorless syrups **20b** (11 mg, 17%) and **18** (8 mg, 18%). Compound

20b has the following physical properties: TLC R_f = 0.40 (C); $[\alpha]_D^{25}$ = +9.1°; IR (CH_2Cl_2) 1720 cm-1; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (m, 15, $2CMe_2$, $OCH_2\underline{CH_3}$), 2.20 (qn, 1, $J_{2,3}$ = 3.9 Hz, $J_{3,4}$ = 9.9 Hz, $J_{3,7}$ = 4.0 Hz, H3), 2.84 (dd, 1, $J_{7,8}$ = 8.7 Hz, $J_{8,8'}$ = 14.1 Hz, H8), 3.05 (dd, 1, $J_{7,8'}$ = 4.5 Hz, H8'), 3.88 (m, 1, $O\underline{CH_2}CH_3$), 4.10 (m, 5, H4, H5, 2H6, $O\underline{CH_2}CH_3$), 4.85 (t, 1, $J_{1,2}$ = 3.9 Hz, H2), 5.63 (s, 1, H11), 5.72 (m, 2, H12, H7), 6.17 (s, 1, H11'), 7.38 (t, 2, OBz), 7.52 (t, 1, OBz), 8.03 (d, 2, OBz).

Anal. Calcd for $C_{26}H_{34}O_9$: C, 63.66; H, 6.99. Found: C, 63.74; H, 7.09.

The properties of compound **18** are: TLC R_f = 0.16 (C); $[\alpha]_D^{25}$ = +68.5°; IR (CH_2Cl_2) 1760 (C=O) cm-1; ^1H NMR (300 MHz, $CDCl_3$) δ 1.33, 1.37, 1.42, 1.54 (4s, 12, CMe_2), 2.19 (ddd, 1, $J_{2,3}$ = 3.6 Hz, $J_{3,4}$ = 9.3 Hz, H3), 3.00 (ddt, 1, $J_{7,8}$ = 6.6 Hz, $J_{8,8'}$ = 17.6 Hz, $J_{8,11}$ = 3.0 Hz, H8), 3.16 (ddt, 1, H8'), 4.07 (m, 4, H4, H5, 2H6), 4.86 (t, 1, H2) 4.95 (dd, 1, H7), 5.65 (t, 1, H11), 5.78 (d, 1, $J_{1,2}$ = 3.3 Hz, H1), 6.24 (t, 1, H11').

Anal. Calcd for $C_{17}H_{24}O_7$: C, 59.99; H, 7.11. Found: C, 60.04; H, 7.07.

3-Deoxy-3-*C*-(1'*S*-hydroxy-4'-γ-butyrolactone)-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (21) and **3-Deoxy-3-*C*-(1'*R*-hydroxy-4'-γ-butyrolactone)-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (22)**. The alkene **13** (350 mg, 1.30 mmol) was placed in a flask with freshly distilled tri-*n*-butyltin iodoacetate (1.5 g, 31 mmol) and a stir bar were added to the flask. The mixture was heated under a blanket of argon. When the reagent melted and the stir bar began to spin, small portions of 2,2'-azobis(2-methylpropanenitrile) were added through the open neck. After 1 h, the reaction was diluted with acetonitrile and washed with petroleum ether. The acetonitrile layer was concentrated *in vacuo* and the products separated by chromatography (solvent B) to yield a colorless syrup **21** (134 mg, 32%) and a white crystalline solid **22** (134 mg, 32%). Compound **21** has the following physical properties: TLC R_f = 0.12 (C); $[\alpha]_D^{25}$ = +73.6°; IR (CH_2Cl_2) 1775 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.34, 1.37, 1.44 (3s, 12, CMe_2), 2.22 (m, 2, H3, H8), 2.60 (m, 3, H8', 2H9), 4.08 (m, 4, H4, H5, 2H6), 4.86 (t, 1, $J_{2,3}$ = 4.0 Hz, H2), 4.95 (qn, 1, $J_{3,7}$ = 6.6 Hz, $J_{7,8}$ = 14.0 Hz, H7), 5.80 (d, 1, $J_{1,2}$ = 3.8 Hz, H1).

Anal. Calcd for $C_{16}H_{24}O_7$: C, 58.53; H, 7.37. Found: C, 58.35; H, 7.33.

Compound **22** has the following characteristics: mp 106-108 °C; TLC R_f = 0.08 (C); $[\alpha]_D^{25}$ = +49°; IR (CH_2Cl_2) 1770 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.33, 1.38, 1.46, 1.54 (4s, 12, CMe_2), 2.08 (m, 1, H3), 2.38 (m, 1, H8), 2.47 (m, 1, H8'), 2.59 (m, 2, 2H9), 3.94 (dd, 1, $J_{5,6}$ = 6.4 Hz, $J_{6,6'}$ = 8.6 Hz, H6),

4.06 (dd, 1, $J_{5,6'}$ = 6.8 Hz, H6'), 4.27 (dd, 1, $J_{4,5}$ = 10.8 Hz, H4), 4.34 (m, 1, H5), 4.76 (t, 1, $J_{2,3}$ = 3.6 Hz, H2), 4.80 (dd, 1, $J_{3,7}$ = 14.4 Hz, $J_{7,8}$ = 8.4 Hz, H7), 5.86 (d, 1, $J_{1,2}$ = 3.6 Hz, H1).

Anal. Calcd for $C_{16}H_{24}O_7$: C, 58.53; H, 7.37. Found: C, 58.66; H, 7.16.

Compound **21** was also made in the following manner: The alcohol **19a** (158 mg, 4.44 mmol) was dissolved in tetrahydrofuran (20 mL) and treated with 5% mercuric sulfate solution in 10% sulfuric acid. The resulting mercurial was decomposed with 10% sodium hydroxide solution (5 mL) at room temperature. The mixture was acidified to pH 5 with sulfuric acid after 2 h and extracted with ethyl acetate. The organic layer was washed successively with saturated sodium bicarbonate solution and saturated sodium chloride solution, then dried over magnesium sulfate and concentrated *in vacuo*. The residue was chromatographed (solvent C) to yield a colorless syrup **21** (61 mg, 42%).

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