was stirred at room temperature for 6 h. The reaction mixture was neutralized with sodium carbonate powder, diluted with water (50 mL), and extracted with ether (3 × 50 mL). The combined ether extracts were washed with brine (30 mL) and dried over anhydrous sodium sulfate. The solvent was removed at reduced pressure. Flash chromatography of the residue (1:4:15 (v/v) *i*-PrOH–ethyl acetate–hexanes) afforded the diol **26**: 150 mg (65%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.01 [s, 9 H, $C(CH_3)_3$], 1.54 (m, 2 H, CH_2CH_2CH=CH), 1.80 (m, 2 H, CH_2CH_2CH=CH), 2.16 (m, 4 H, $MeOOCCH_2$, CH_2CHOSi), 3.62 (s, 3 H, OCH_3), 3.54–3.82 (m, 4 H, $SiOCHCH(OH)CH_2OH$), 4.26 (, 2 H, CH=CH), 7.40 (m, 6 H, *m,p*-Ar-H), 7.68 (m, 4 H, OArH).

Methyl 8(*S*)-[(*tert*-Butyldiphenylsilyl)oxy]-9-oxo-5(*Z*)-nonenoate (27) and Methyl 8(*S*)-[(*tert*-Butyldiphenylsilyl)oxy]-11-oxo-5(*Z*),9(*E*)-undecadienoate (28). To a solution of sodium periodate (492 mg, 3 equiv) in 30% aqueous acetone (3 mL) at room temperature was added a solution of the diol **26** (360 mg, 0.766 mmol) in THF (3 mL) over 2 min. The resulting mixture was stirred at room temperature for 15 min and then filtered through Celite, washing with water (50 mL) and ether (100 mL). The filtrate was partitioned, and the aqueous phase was extracted with ether (2 × 50 mL). The combined ether extracts were washed with brine (50 mL) and dried over anhydrous magnesium sulfate. Removal of solvent at reduced pressure afforded the crude aldehyde **27** [338 mg (100%)] which was mixed with (formylmethylene)triphenylphosphorane (1.1 equiv, 256 mg) in dry benzene (4 mL). The mixture was heated at 80 °C for 9 h and then filtered through a pad of silica gel, washing with ether (50 mL). Removal of the solvent in vacuo and chromatography of the residue (9% ethyl acetate in petroleum ether, Kieselgel 60 HF_{254} from BDH) afforded the desired α,β-unsaturated aldehyde **28**: 260 mg (73% yield based on the diol **26**); $[\alpha]^{22}_D$ +15.3° (*c* 2.9, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.09 [s, 3 H, $C(CH_3)_3$], 1.60 (m, 2 H, $MeOOCCH_2CH_2$), 1.82 (br t, 2 H, CH_2CH=CH), 2.20 (m, 4 H, $MeOOCCH_2$, CH_2CHOSi), 3.65 (s, 3 H, OCH_3), 4.46 (m, 1 H, CHCOSi), 5.33 (m, 2 H, CH_2CH=CHCH$_2$), 6.20 (dd, 1 H, J = 14 Hz, J' = 6.8 Hz, CH=CHCHO), 6.70 (dd, 1 H, J = 14 Hz, J' = 6.0 Hz, CH=CHCHO), 7.39 (m, 6 H, *m,p*-Ar-H), 7.62 (m, 4 H, OArH), 9.46 (d, 1 H, J = 6.8 Hz, CHO); MS [*m/e* (70 eV, %)] 464 ($M^{\bullet+}$, 0.9), 407 ($M^{\bullet+}$ – $C(CH_3)_3$, 100], 323 [$M^{\bullet+}$ – $MeOOC(CH_2)_3CH$=$CHCH_2$, 41.9].

Methyl 8(*S*)-[(*tert*-Butyldiphenylsilyl)oxy]-5(*Z*),9(*E*),11(*Z*),14(*Z*)-eicosatetraenoate (29). (a) To a solution of *n*-pentyl bromide (391 mg, 2.586 mmol) in THF (7 mL) at −78 °C was added *tert*-butyllithium (1.7 M, 3.04 mL, 5.172 mmol). The resulting mixture was stirred at −78 °C for 30 min. The reaction mixture was warmed to −50 °C and copper(I) bromide–dimethyl sulfide (311 mg, 1.509 mmol) was added. After the mixture was stirred 1 h, acetylene (58 mL) was bubbled into the solution. Stirring continued for 30 min. Then vinyltriphenylphosphonium bromide (477 mg, 1.293 mmol) was added followed by HMPA (0.7 mL) and stirring continued at −50 °C overnight (~18 h).

To a solution of the α,β-unsaturated aldehyde **28** (200 mg, 0.431 mmol) in THF (1 mL) at −50 °C was added dropwise the above ylide solution, and the resulting mixture was allowed to warm to −20 °C during 1.5 h and then to 0 °C during 1 h. The mixture was diluted with 10% aqueous ammonium chloride (10 mL) and ether (20 mL) and filtered through Celite, washing with ether (100 mL). The combined filtrate was washed with 10% aqueous ammonium chloride (50 mL). The aqueous phase was extracted with ether (100 mL). The combined ethereal phase was washed with brine (20 mL) and dried over anhydrous magnesium sulfate. The solvent was removed at reduced pressure. Flash chromatography of the residue (3% ethyl acetate in petroleum ether) gave the desired product [130 mg (53%)], which was contaminated with incorporation of two acetylene units.

(b) To a solution of α,β-unsaturated aldehyde **28** (100 mg, 0.216 mmol) in THF (5 mL), at −78 °C, was slowly added a red solution of the ylide **20** generated by treatment of (*Z*)-non-3-en-1-yltriphenylphosphonium iodide (596 mg, 1.160 mmol) with *n*-BuLi (1.6 M, 0.725 mL) in THF (8 mL) at 0 °C for 30 min, until red color existed. The resulting mixture was stirred for 15 min, and a few drops of water were added. The mixture was diluted with chloroform (100 mL) and washed with brine (30 mL) once. The organic phase was dried over anhydrous sodium sulfate, and solvent was removed under diminished pressure. Flash chromatography of the residue (3% EtOAc in hexanes) gave the desired Wittig adduct: 106 mg (86%); MS [*m/e* (70 eV, %)] 572 ($M^{\bullet+}$, 0.1)e, 515 [$M^{\bullet+}$ – $C(CH_3)_3$, 10.9], 431 [$M^{\bullet+}$ – $MeOOC(CH_2)_3CH$=$CHCH_2$, 100], 409 [$M^{\bullet+}$ – CH=CHCH=$CHCH_2CH$=$CH(CH_2)_4CH_3$, 1.2].

Methyl 8(*S*)-Hydroxy-5(*Z*),9(*E*),11(*E*),14(*Z*)-eicosatetraenoate (30). The mixture of the silyl ether **29** (130 mg, 0.227 mmol) and tetra-*n*-butylammonium fluoride dried from its trihydride (143 mg, 0.455 mmol) in THF (5 mL) was heated at 40–45 °C for 5 h. After workup as usual and flash chromatography (5% *i*-PrOH in hexanes), a yellow oil [69 mg (91%)] was obtained. Further purification by HPLC (Porasil, 0.2% *i*-PrOH in hexanes) gave the pure 8(*S*)-HETE methyl ester **30**: 40 mg (53%); $[\alpha]^{22}_D$ −4.75° (*c* 0.4, $CHCl_3$); UV (hexane) λ_{max} 235 nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, 3 H, C_{20}-H), 1.32 (m, 6 H, $C_{17,18,19}$-H), 1.56 (br s, 1 H, OH), 1.73 (pentet, 2 H, C_3-H), 2.11 (sextet, 4 H, $C_{2,16}$-H), 2.35 (t, 4 H, $C_{4,7}$-H), 2.95 (t, 2 H, C_{13}-H), 3.71 (s, 3 H, OCH_3), 4.23 (q, 1 H, C_8-H), 5.16–5.59 (m, 5 H, $C_{4,5,12,14,15}$-H), 5.72 (dd, 1 H, $J_{9,8}$ = 7.3 Hz, $J_{9,10}$ = 14.5 Hz, C_9-H), 6.00 (br t, 1 H, $J_{11,10}$ = 11.1 Hz, $J_{11,12}$ = 9.7 Hz, C_{11}-H), 6.56 (dd, 1 H, $J_{10,9}$ = 14.5 Hz, $J_{10,11}$ = 11.1 Hz, C_{10}-H); MS [*m/e* (70 eV, %)] (trimethylsilyl ether) 406 ($M^{\bullet+}$, 0.02), 391 ($M^{\bullet+}$ – CH_3, 0.3), 316 ($M^{\bullet+}$ – Me_3SiOH, 0.3), 265 [$M^{\bullet+}$ – $MeO_2C(CH_2)_3CH$=$CHCH_2$, 100], 243 [$M^{\bullet+}$ – CH=CHCH=$CHCH_2CH$=$CH(CH_2)_4CH_3$, 5.2]; HRMS (*m/z* for $C_{21}H_{32}O_4$ (M^+ – H_2O), calcd 316.240, found 316.244.

Methyl 3-Formyl-2,3-*O*-isopropylidene-D-erythrofuranoside (D-Apiose Aldal) and Derivatives

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A practical synthesis of the known 3-formyl-2,3-*O*-isopropylidene-D-erythrofuranose (D-apiose aldal, **2d**) is described. Several selectively protected derivatives and their transformations which allow preferential manipulation of the diastereotopic hydroxymethylene groups of apiose are reported.

A projected convergent synthesis of tetrodotoxin[1] required a suitably modified and protected form of the branched-chain sugar, D-apiose[2] (**1**). The key compound in this study is dialdehyde **2** in which the *pro-R* CH_2OH

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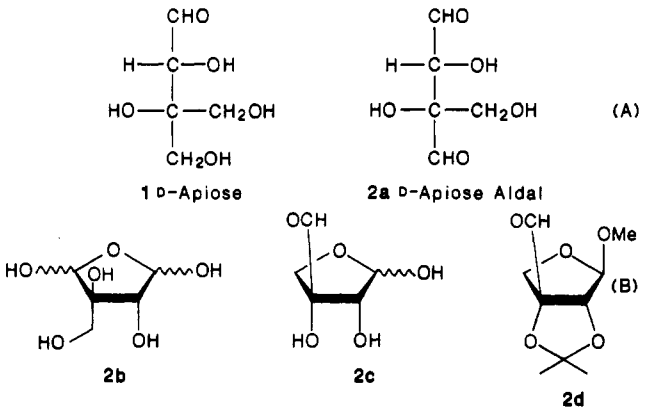
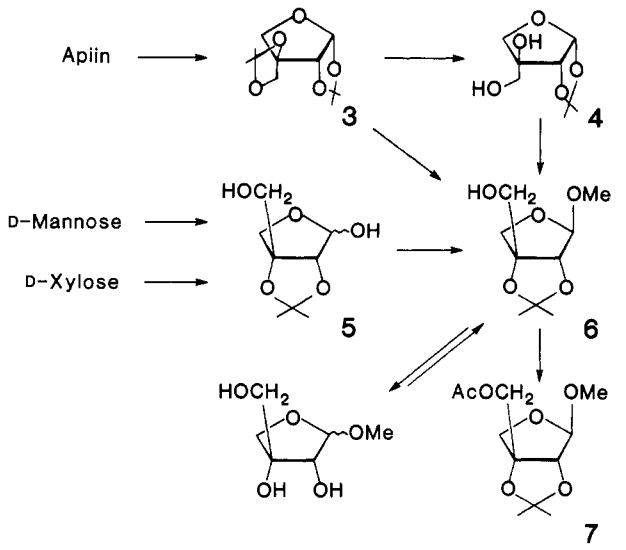


group of apiose is oxidized to an aldehyde function as shown in **2a**. Dialdehyde **2** is unreported in its open-chain form **2a** or its ring forms **2b** or **2c**, but the protected derivative methyl 3-formyl-2,3-*O*-isopropylidene-D-erythrofuranoside (**2d**) is known.[3,4] This paper reports a practical synthesis of **2d** along with some of its transformations and a series of selectively protected derivatives which are based on ring structure **2c** rather than **2b**.

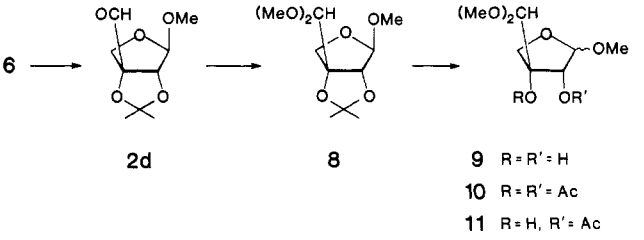
The key intermediate for the synthesis of **2d** is compound **6**, methyl 2,3-*O*-isopropylidene-D-*erythro*-apiofuranoside whose synthesis can be achieved in several ways as diagrammed in Scheme I. The flavanoid apioglucoside, apiin,[2] upon treatment with acetone and methanolic hydrogen chloride gives 1,2:3,5-di-*O*-isopropylidene-D-*threo*-apiofuranoside[5] (**3**). Selective hydrolysis of **3** gives 1,2-*O*-isospropylidene derivative **4** (70% yield), which upon treatment with dry methanolic hydrogen chloride undergoes rearrangement[3,5] to give **6** (84% yield) in which the ring and side-chain CH_2O groups are interchanged. We have found that direct treatment of the diisopropylidene derivative **3** with anhydrous methanolic hydrogen chloride gives the rearranged product **6** (81%). Thus **6** appears to be a thermodynamic sink for the system **3** ⇄ **4** ⇄ **6** under these conditions. This one-step synthesis, from the available, but expensive **3**, is the method of choice for a small amount of **6**.

Compound **5** is readily prepared from D-xylose[6] in four steps (36–38% yield) or from D-mannose[7] in five steps (50% yield). Initially we experienced difficulties in increasing the scale of this latter preparation,[7] and it was for this reason that the former procedure was developed.[6] However, more recently we were able to realize good yields of **5** by minor modifications of the method of Ho[7] starting with 50–100 g of D-mannose (cf. Experimental Section). Although **6** is produced directly by rearrangement of either **2** or **3** upon treatment with methanolic hydrogen chloride, the conversion of **5** to **6** is unreported. Treatment of **5** in methanol with trimethyl orthoformate and pyridinium *p*-toluenesulfonate (24 h, reflux) gave **6** in 75% yield. Although treatment of **5** with anhydrous methanolic hydrogen chloride (7 h, 25 °C) gave **6** (95% crude yield), it was accompanied by impurities which were difficult to remove. One of these impurities was methyl D-*erythro*-apiofuranoside, whose structure was confirmed by conversion to **6** upon treatment with dry acetone and strong acid resin catalyst.

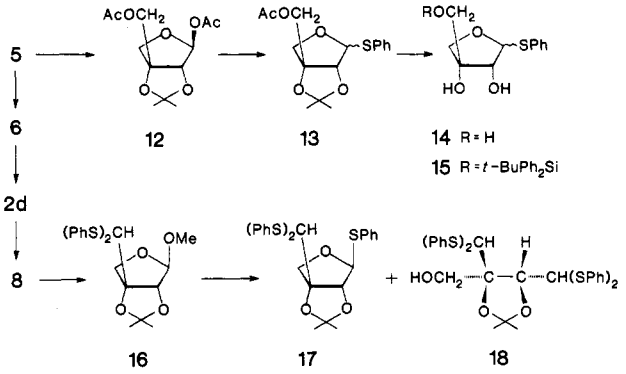
Scheme I



Scheme II



Scheme III



The Pfitzner–Moffatt oxidation of **6** to aldehyde **2d** (Scheme II) has been reported,[3] but the reaction is slow, and we have been unable to obtain good, consistent yields of pure **2d** by this mehtod, especially when dealing with more than a few grams of substrate.[1] The use of Collins reagent[9] as reported by Horton and co-workers[4] was superior. However, we found that the modification of Garegg and Samuelson[10] (CrO_3–pyridine–Ac_2O) gave the most consistent yields (better than 70%) in larger scale preparations. It was convenient to immediately protect the free aldehyde of this aldal[11] by conversion to the dimethyl acetal, **8**.

Treatment of **2d** with methanolic hydrogen chloride at 25 °C (48 h) gave a 65:35 mixture of acetal **8** (β-anomer) and unreacted starting material. When this reaction was carried out at reflux, a 30:70 mixture of the methyl α- and

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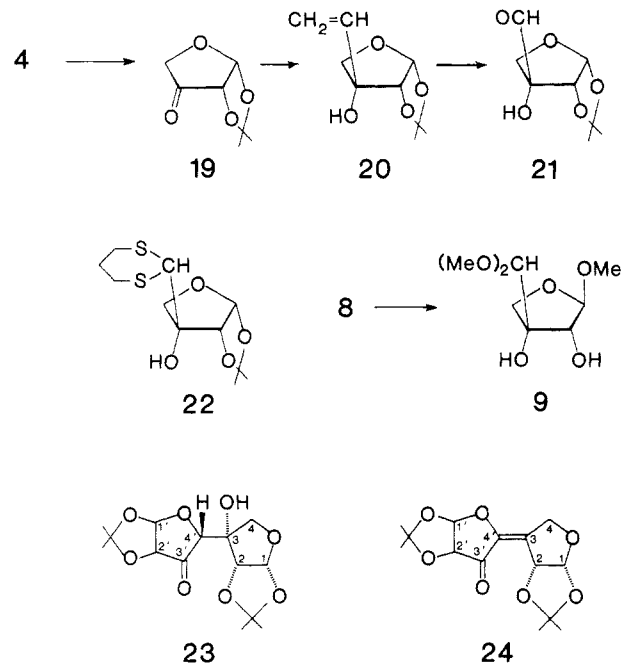
Scheme IV



β-glycoside diols **9** were formed. The α- and β-anomers of **9** were identified by the coupling constants of the C-1, C-2 protons (α-**9**, J_{1-2} = 4.9 Hz; β-**9**, J_{1-2} = 2.8 Hz) and by the conversion of the minor isomer (α-**9**) back to α-**8** (J_{1-2} = 5 Hz) and the major isomer (β-**9**) back to β-**8** ($J_{1-2} \cong 0$ Hz). Treatment of aldal **2d** first with aqueous hydrochloric acid in THF followed by retreatment with anhydrous methanolic hydrogen chloride gave α-**9** and β-**9**. No product based on structure **2b** was detected. The major anomer β-**9** was converted into the di- and monoacetates, **10** and **11**, which retained the β-anomeric configuration.

Phenyl thioglycosides (Scheme III) offer an alternate method for protecting the anomeric group of apiose in place of the methyl glycoside as in **6** or the aldal as in **8**. Such derivatives can be deprotected by methods other than acid hydrolysis. Treatment of diacetate **12** with trimethylsilyl phenyl sulfide in the presence of trimethylsilyl triflate[12,13] gave **13**. This reaction was unsuccessful when attempted on the methyl glycoside **7** instead of the acetate. Product **13** was hydrolyzed to remove both the acetate and isopropylidene protecting groups to give **14**. The primary alcohol function of **14** was preferentially reprotected with the *tert*-butyldiphenylsilyl group[14] to give **15**. Alternatively, **8** was treated with trimethylsilyl phenyl sulfide (0 °C → 20 °C) to give **16** (87%). This structure was confirmed by conversion of **16** back to aldehyde **2d** upon removal of the thiophenyl groups (NBS, CH_3CN, lutidine[13]). Treatment of **16** with these same reagents at 70 °C for 18 h gave two products both of which retained the isopropylidene group. The first, an oil, contained three thiophenyl groups; its NMR was in accord with phenylthio, glycoside **17**. The second, a white solid, contained four phenylthio groups; its NMR was compatible with the acyclic structure **18**.

Another approach to a protected apiose aldal is shown in Scheme IV. 1,2-*O*-Isopropylidene-D-*glycero*-tetrose-3-ulose (**19**) prepared by oxidation of **4**,[5,14-17] was converted into the C-3 vinyl derivative[17] **20** (CH_2=CHMgBr, 65% yield) that on ozonolysis gave aldal **21** (18% yield). In the previous report of this sequence,[18] aldal **21** was not isolated but was directly reduced to 1,2-*O*-isopropylidene-D-*erythro*-apiofuranose (C-3 epimer of **4**). Aldal **21** was also obtained from dithiane **22** (vide infra) whose structure was confirmed by treatment with anhydrous methanolic hydrogen chloride to give diol **9** that had been made previously from **8**.

Crystalline dithiane **22** was prepared (71% yield) by treatment of ulose **19** with 2-lithio-1,3-dithiane[18] in dilute THF solution. This dithiane was converted to aldal **21** (BF_3·Et_2O·HgO)[20] but in poor yield (15%). The low yield in making **21** by either of these methods renders this approach to protected apiose aldal derivatives unattractive.

An initial reaction of ulose **19** with 2-lithio-1,3-dithane in concentrated solution under the conditions reported by Paulsen and co-workers[20] gave, instead of the dithane derivative **22**, a crystalline dimer (70% yield) whose NMR was compatible with the self-aldol condensation structure **23**. Mechanistic considerations predict the stereochemistry at 3 and 4′ positions as shown; those at the 1,2,1′,2′ positions should be unchanged from the starting material. An aldol dimer was reported[12] for the enantiomer of ulose **19**. The NMR and melting point of **23** and this dimer were the same. The optical rotation was the same with opposite sign. We observed that **19** on storage at room temperature was slowly converted into an α,β-unsaturated system, presumably with structure **24**.

Experimental Section

Uncorrected melting points were determined in capillary on a "Meltemp" aluminum block. Infrared (IR) spectra were determined on a Perkin-Elmer 237 B grating instrument in CCl_4 solvent; major signals were recorded in cm^{-1}. All nuclear magnetic resonance (NMR) measurements were proton spectra determined in $CDCl_3$ solvent on a Nicolet 100 MHz instrument in the FT mode, (or 300 MHz Nicolet instrument where noted) and recorded in parts per million (ppm, δ) downfield from internal tetramethylsilane (Me_4Si) unless otherwise noted. Coupling constants (J) are in hertz (Hz), and splitting pattern abbreviations are s, singlet; d, doublet; t, triplet, q, quartet; m, unresolved multiplet; br, broad; and dd, doublet of doublets. Optical rotations were taken on a Rudolph Autopol III, which reads to 0.001°, with permanent-window cells, 10 cm, thermostated at 20.0 °C. Reactions were followed routinely by using silica gel GF thin-layer chromatography (TLC) plates (250 μm, Analtech). Preparative TLC separations were accomplished on silica gel GF plates (1000 μm, Analtech). TLC plates were visualized either by spraying with 10% H_2SO_4 followed by heating to 150 °C or by dipping into a 7% solution of phosphomolybdic acid in ethanol followed by heating to 150 °C. Column chromatography refers to flash chromatography as described by Still, Kahn, and Mitra[22] and was performed on silica gel G (0.032–0.063 mm, ICN Nutritional Biochemicals).

Methyl 2,3-*O*-Isopropylidene-β-D-*erythro*-apiofuranoside (β-6). From 1,2:3,5-diisopropylidene-α-D-*threo*-apiofuranoside[5] (3). Diisopropylidene compound **3** (500 mg, Pfanstiehl Laboratories) in anhydrous CH_3OH·HCl (35 mL, 0.1 N) was stirred at 25 °C for 15 h, under N_2. The solution was concentrated, and the residue codistilled with benzene to give **6** as a chromatographically homogeneous oil (400 mg, 91%) whose NMR was identical with that of the product made according to the literature.[4]

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The same transformation was effected by stirring **3** (19.85 g) in methanol (800 mL) with dry Dowex 50W-X8 resin (H^+ form, 8.9 g) at 53 °C for 15 h. Removal of the resin and solvent (0.1 torr, 25 °C) gave a syrup (14.33 g, 81%). A sample was purified by bulb-to-bulb distillation. The NMR was identified with that obtained starting from mannose (vide infra).

2,3-*O*-Isopropylidene-D-*erythro*-apiofuranose (5) from Mannose by the Method of Ho.[7] 2,3:5,6-Di-*O*-isopropylidene-D-mannofuranose[8] (80 g, mp 125–126 °C), formaldehyde (175 mL, 37% solution), potassium carbonate (30 g), and methanol (350 mL) were refluxed with stirring under argon for 48 h. The reaction mixture was processed as described[7] and the initial crude syrup, dissolved in $CHCl_3$, was dried (Drierite), the $CHCl_3$ removed, and the residue dissolved in an equal volume of ethyl acetate and chromatographed on silica gel (60 g, 0.032–0.063 mm, deactivated with 10% water, eluted with 1:1 $CHCl_3$/EtOAc). The residue from evaporation of the eluate (88 g) was crystallized from 9:1 hexane/ether (200 mL) at 5–10 °C to give a white powder (56.6 g, 62%, mp 103–104 °C; no literature melting point[7] reported). Two modifications which allowed scaling up this preparation successfully were (1) the amount of excess formaldehyde was reduced from about 18 to 4 molar equiv, which greatly reduced the amount of formaldehyde polymer that was formed; (2) a crystalline product seemed to be necessary for good yields in the subsequent steps; (3) the methanol solution was about 3 times as concentrated.

The above diisopropylidene formaldehyde adduct (50.0 g, mp 103–104 °C) was selectively hydrolyzed, reduced ($NaBH_4$), and oxidized ($NaIO_4$) as described[7] with the precaution that the excess $NaBH_4$ was completely destroyed by slow neutralization at 0 °C with 40 mL of 10% HCl (instead of HOAc). Stirring was continued until the pH stabilized at 7 before the oxidation. The yield of **5** was 29.1 g, 80%, mp 69 °C. It was identical with that made from D-xylose[6] and from the hydrolysis of the methyl glycoside of **6** made from **3**.

Methyl 2,3-*O*-Isopropylidene-β-D-*erythro*-apiofuranoside (6). The above isopropylideneapiose **5** (2.5 g) was refluxed (24 h) with methanol (125 mL, distilled from magnesium methylate), trimethyl orthoformate (15 mL), and pyridinium *p*-toluenesulfonate (100 mg) under argon. The methanol was removed under vacuum and the residue dissolved in ether (300 mL). The ether solution was washed with water (6 mL) and saturated NaCl (6 mL), dried ($MgSO_4$), and concentrated to give **6** (2.08 g, 75%) as a syrup. This was purified for analysis by chromatography (silica gel, 50 g, 0.032–0.063 mm deactivated with 10% H_2O, eluted with 3:7 ethyl acetate/hexane): NMR ($CDCl_3$) δ 4.95 ppm (s, 1 H, H-1), 4.29 (s, 1 H, H-2), 3.97, 3.80 (q, 2 H, 4a–4b, J_{4a-4b} = 10.2), 3.75 (d, 2 H, H-5, J_{5-5OH} = 6.1), 3.32 (s, 3 H, OCH_3), 2.58 (t, 1 H, OH-5, J_{5-5OH} = 6.1), 1.51, 1.44 ppm (2 s, 6 H, $C(CH_3)_2$). Anal. Calcd for $C_9H_{16}O_5$: C, 52.93; H, 7.90. Found: C, 53.21; H, 7.87.

Methyl furanoside **6** (109 mg, not chromatographed) was acetylated with acetic anhydride (0.5 mL) and pyridine (0.64 mL) in CH_2Cl_2 (3 mL) to give a syrup which on chromatography gave a single major component, **7** (107 mg, 82%): NMR ($CDCl_3$) δ 4.96 ppm (s, 1 H, H-1), 4.36 (s, 1 H, H-2), 4.29 (ABq, 2 H, $\Delta\nu$ = 56 Hz, J_{AB} = 11.7), 3.91 (ABq, 2 H, $\Delta\nu$ = 48.2 Hz, J_{AB} = 9.7), 3.32 (s, 3 H, OCH_3), 2.11 (s, 3 H, Ac), 1.49, 1.42 (2 s, 6 H, $C(CH_3)_2$). Anal. Calcd for $C_{11}H_{18}O_6$: C, 53.65; H, 7.35. Found: C, 53.44; H, 7.06.

Methyl 3-Formyl-2,3-*O*-isopropylidene-β-D-erythrofuranoside (2d).[3,4] A solution of dried, powdered CrO_3 (17.7 g, 0.177 mol) in ahydrous pyridine (27.9 g, 0.35.3 mol), and CH_2Cl_2 (400 mL) was prepared by vigorous stirring for 1 h under N_2. A solution of carbinol **6** (6.0 g, 29 mmol) and acetic anhydride (2.77 mL, 30 mmol) in CH_2Cl_2 (100 mL) was slowly added with stirring to the CrO_3·2Py solution at 20–25 °C. After 20 min stirring, during which time a black sludge formed, anhydrous ethanol/ethyl acetate (30 mL, 1:2) was added and the mixture washed (saturated $NaHCO_3$), and the chromium salts were removed by passing through a silica gel column (10 × 15 cm) and eluting with ethyl acetate. The eluate was concentrated (to 0.1 torr) and the residue reevaporated with benzene to give aldehyde **2d** as a light brown syrup (4.45 g, 75%) which could be utilized in subsequent steps as such. A portion was chromatographed (silica gel, EtOAc/cyclohexane, 3:2) to give **2d**: mp 60–61 °C, $[\alpha]_D^{20}$ −218° (*c* 1, $CHCl_3$); lit. ca 18 °C,[3] 60–61 °C;[4] IR 1730 cm^{-1} (CHO); NMR ($CDCl_3$) δ 9.83 ppm (s, 1 H, H-5), 4.99 (s, 1 H, H-1), 4.52 (s, 1 H, H-2), 4.18, 3.97 (q, 2 H, H-4a, 4b, J_{4a-4b} = 10.1), 3.37 (s, 3 H, OCH_3), 1.56, 1.39 (2 d, 6 H, $C(CH_3)_2$).

Methyl 3-*C*-(Dimethoxymethyl)-2,3-*O*-isopropylidene-β-D-erythrofuranoside (8). Aldehyde **2d** (4.0 g) in methanol (30 mL dried over magnesium methylate) was stirred with Dowex 50W-X8 ion exchange resin (4 g, acid form) for 48 h under N_2. The solvent was removed from the filtered reaction mixture and the residue vacuum evaporated with benzene to give a chromatographically homogeneous syrup, **8**, (4.3 g, 88%): NMR ($CDCl_3$) δ 4.82 ppm (s, 1 H, H-1), 4.33 (d, 1 H, H-4a or 4b, J_{4a-4b} = 2.44), 4.31 (s, 1 H, H-5), 3.90 (d, 1 H, H-4b or -4a, J_{4a-4b} = 2.44), 3.88 (s, 1 H, H-2), 3.46, 3.44 (2 s, 6 H, $(OCH_3)_2$), 3.26 (s, 3 H, OCH_3), 1.40, 1.36 (2 s, 6 H, $C(CH_3)_2$). Anal. Calcd for $C_{11}H_{20}O_6$: C, 53.19; H, 8.12. Found: C, 53.35; H, 7.91.

Methyl 3-*C*-(Dimethoxymethyl)-α-(and β-)D-erythrofuranoside (Diols α-9 and β-9). A solution of **8** (4.3 g, β-anomer) in methanol (30 mL), in which dry Dowex 50W-X8 resin (H^+ form, 4.0 g) was suspended, was refluxed under N_2 for 7 h. As evidenced by TLC, the reaction was incomplete. The solution was filtered, the methanol removed (vacuum), and the residue boiled down with benzene, and the original treatment repeated. The syrup resulting after removal of resin and solvent was chromatographed (silica gel; EtOAc/Et_2O, 1:4) to give 2 fractions, diol α-**9** (0.5 g) and β-**9** (1.2 g): minor α-isomer NMR ($CDCl_3$) δ 4.82 ppm (d, 1 H, H-1, J_{1-2} = 4.9), 4.22 (s, 1 H, H-5), 4.08, 3.76 (d, 2 H, H 4a, 4b, J_{4a-4b}, $J_{4b,4a}$ = 9.9), ca 3.4 masked (H-1), 3.49, 3.46 (2 s, 6 H $(OCH_3)_2$), 3.39 (s, 3 H, OCH_3), 2.9 (b, 2 H, 2-OH); major β-isomer NMR ($CDCl_3$) δ 4.78 ppm (d, 1 H, H-1, J_{1-2} = 2.8), 4.25 (s, 1 H, H-5), 4.00, 3.76 (d, 2 H, H-4a, 4b, J_{4a-4b}, $J_{4b,4a}$ = 9.8), 3.97 (d, 1 H, H-2, J_{2-1} = 2.8), 3.47, 3.45 (2 s, 6 H, $(OCH_3)_2$), 3.33 (s, 3 H, OCH_3), 3.00, 2.67 (2s, 2H, 2-OH). Anal. Calcd for $C_8H_{16}O_6$, mixture of isomers before chromatographic separation: C, 46.15; H, 7.74. Found: C, 46.35; H, 7.78. The same mixture of diols α-**9** and β-**9** resulted from similar direct treatment of aldehyde **2d** with CH_3OH·HCl.

Diol Diacetate 10. The major isomer from above (β-**9**, 45 mg) was refluxed with acetic anhydride (42 μL), and pyridine (35 μL) in $CHCl_3$ (3 mL) for 15 h. The product was chromatographed (silica gel, ethyl acetate) to give **10** (β-isomer 48 mg): IR 1755 and 1740 cm^{-1}; NMR ($CDCl_3$) δ 5.36 ppm (d, 1 H, H-1, J_{1-2} = 3.3), 5.25 (s, 1 H, H-5), 4.90 (d, 1 H, H-2, J_{2-1} = 3.3), 4.35, 3.99 (2 d, 2 H, H 4a, 4b, J_{4a-4b} = 10.4), 3.59 (s, 3 H, OCH_3), 3.38, 3.32 (2 s, 6 H, $(OCH_3)_2$), 2.02, 1.98 (2 s, 6 H 2 CH_3). Anal. Calcd for $C_{12}H_{20}O_8$: C, 49.31, H, 6.90. Found C, 49.50; H, 6.87.

Diol Monoacetate 11. A solution of the above diacetate (**10**, 45 mg) in methanol (6 mL) containing NaOH (0.3 mL, 46%) was stirred at 0 °C for 15 min and then neutralized with HOAc and worked up to give the monoacetate **11** (15 mg) as a syrup: NMR ($CDCl_3$) δ 5.13 ppm (d, 1 H, H-1, J_{1-2} = 3.1), 4.75 (s, 1 H, H-5), 4.58 (d, 1 H, H-2, J_{2-1} = 3.1), 4.26, 3.88 (2 d, 2 H, H-4a, 4b, J_{4a-4b} = 10.1), 3.53, 3.39 (2 s, 6 H, $(OCH_3)_2$), 3.31 (s, 3 H, OCH_3), 1.99 (s, 3 H, OAc); IR 1760 cm^{-1} (acetate).

Acetyl 3-*C*-(Acetoxymethyl)-2,3-*O*-isopropylidene-β-D-erythrofuranose (12). 2,3-*O*-Isopropylidene-D-*erythro*-apiofuranose (**5**, 7.9 g, crude product)[5] in $CHCl_3$ (100 mL) was treated with pyridine (20 mL) and acetic anhydride (15.6 mL) first at 0 °C and then at 25 °C (12 h). After appropriate extraction and washing, drying, and evaporating the solvent, this gave acetate **12** (10.0 g, 88%) as a thick oil. A sample was purified on silica gel (eluant: acetone/hexane, 15:85): IR (CCl_4) 1750, 1375 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 6.21 ppm (s, 1 H), 4.46 (s, 1 H), 4.39 (d, 1 H, *J* = 11.7), 4.25 (d, 1 H, *J* = 11.7), 4.11 (d, 1 H, *J* = 10.2), 3.97 (d, 1 H, *J* = 10.2), 2.12 (s, 3 H), 2.07 (s, 3 H), 1.50, 1.42 (2 s, 6 H). Anal. Calcd for $C_{12}H_{18}O_7$: C, 52.55; H, 6.60. Found: C, 52.48; H, 6.52.

Phenylthio 3-*C*-Acetoxymethyl-2,3-*O*-isopropylidene-α-(and β-)D-erythrofuranoside (α-13 and β-13). Diacetate **12** (501 mg) in CH_2Cl_2 (3 mL) was treated at 0 °C under argon with (phenylthio)trimethylsilane (1.75 mL, Petrach Systems Inc.) and trimethylsilyl triflate[12,13] (1.05 mL) for 2 h and then at 23 °C for 2.5 h. The mixture was worked up in the appropriate manner[13] to give crude product (1.01 g) which was chromatographed on silica gel (32 g deactivated with 15% H_2O; eluted with acetone/hexane, 1:9). The mixed α- and β-anomers (**13**, 403 mg, 68%) were not completely separated. A second fraction (63 mg, 12%) represented material which had undergone loss of one or more protecting

groups. Rechromatographing of the mixed anomers gave an approximately equal amount of α-**13** and β-**13** samples. **13** α-anomer: IR (CCl_4) 3075, 1750, 1375 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 7.54 ppm (m, 2 H), 7.30 (m, 3 H), 5.12 (d, 1 H, J = 3.8 Hz), 4.73 (d, 1 H, J = 3.8), 4.27 (ABq, 2 H, $\Delta\nu$ = 25.8 Hz, J_{AB} = 11.7), 4.13 (d, 1 H, J = 10.2), 3.66 (d, 1 H, J = 10.2), 2.11 (s, 3 H), 1.62 (s, 3 H), 1.46 (s, 3 H). Anal. Calcd for $C_{16}H_{20}SO_5$: C, 59.24; H, 6.21; S, 9.88. Found: C, 59.33, H, 6.20; S, 10.38. **13**, β-anomer: IR (CCl_4) 3075, 1750, 1375 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 7.48 ppm (m, 2 H), 7.30 (m, 3 H), 5.66 (s, 1 H), 4.56 (s, 1 H), 4.41 (d, 1 H, J = 11.7), 4.30 (d, 1 H, J = 11.7), 4.16 (d, 1 H, J = 10.5), 4.04 (d, 1 H, J = 10.5), 2.15 (s, 3 H), 1.41 (s, 3 H), 1.49 (s, 3 H). Anal. Calcd for $C_{16}H_{20}SO_5$: C, 59.24; H, 6.21; S, 9.88. Found: C, 59.33; H, 5.99; S, 10.62.

Attempts to prepare the phenyl thioglycoside **13** from methyl acetylglycoside **7** instead of the diacetate **12** gave either no reaction, or under forcing conditions, products in poor yield which had lost the isopropylidene group.

Phenyl β-D-*erythro*-Thioapiofuranoside (β-14). Thioglycoside β-**13** (621 mg) in aqueous isopropyl alcohol (10 mL), 1:1) was heated (70 °C, under argon) with Dowex 50W-X8 resin (3 g, acid form). The mixture was worked up to give a residue which was chromatographed on silica gel (28 g, deactivated with 15% H_2O, eluted with CH_2Cl_2/EtOAc/CH_3OH, 70:29:1). The phenyl thioapioside β-**14** was obtained as a white solid (279 mg, 60%) which was recrystallized from ether–hexane: mp 45.5–46.0 °C, $[\alpha]^{20}_D$ −186° (*c* 10, CH_3OH); IR ($CHCl_3$) 3670–3100, 3020, 2940, 1550 cm^{-1}; NMR ($CDCl_3/D_2O$, 300 MHz) δ 7.51 ppm (m, 2 H), 7.30 (m, 3 H), 5.28 (d, 1 H, J = 5.7), 3.98 (d, 1 H, J = 5.7), 3.95 (ABq, 2 H, $\Delta\nu$ = 25.0 Hz, J = 10.3), 3.66 (ABq, 2 H, $\Delta\nu$ = 9.8 Hz, J_{AB} = 11.3). Anal. Calcd for $C_{11}H_{14}SO_4$: C, 54.53; H, 5.82; S, 13.23. Found: C, 54.44; H, 5.66; S, 13.37.

Phenyl 3-*C*-((*tert*-Butyldiphenylsilyl)oxy)methyl-β-D-thioerythrofuranoside (β-15). To a solution of triol β-**14** (241 mg) in dry DMF (8 mL) containing imidazole (150 mg) under argon, *tert*-butyldiphenylsilyl chloride[14] (0.28 mL) was added by syringe. After 3 h at 25 °C the mixture was processed[14] to give a syrup (510 mg) which was chromatographed on silica gel (20 g, eluted with acetone/hexane, 1:4) to give β-**15** (372 mg, 80%) as a foam on vacuum evaporation: IR (neat film) 3400 (br), 3080, 2860, 1590 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 7.63 ppm (m, 4 H), 7.45 (m, 8 H), 7.28 (m, 3 H), 5.28 (d, 1 H, J = 6.0), 4.01 (d, 1 H, J = 10.1), 3.93 (t, 1 H, J = 6.4), 3.89 (d, 1 H, J = 10.1), 3.70 (ABq, 2 H, $\Delta\nu$ = 12.4 Hz, J_{AB} = 10.4), 3.03 (s, 1 H, OH), 2.65 (d, 1 H, OH, J = 6.8), 1.07 (s, 9 H).

Phenylthiolation of Aldal 8. Aldal **8** (90 mg) was treated with (phenylthio)trimethylsilane[13] (TPTMS, 0.68 mL in CH_2Cl_2, 3 mL) and trimethylsilyl trifluoromethane sulfonate (TMSOTFS, 0.41 mL) for 2 h at 0° under argon. Appropriate workup[13] followed by column chromatography (60 mL silica gel deactivated with 5% acetone in hexane) gave a clear oil, **16** (127 mg, 87%) which was homogeneous by TLC: NMR ($CDCl_3$, 300 MHz) δ 7.4–7.2 ppm (m 10 H, Ar), 4.93 (s, 1 H), 4.60 (s, 1 H), 4.53 (s, 1 H), 4.09 (ABq, $\Delta\nu$ = 63.4 Hz, J_{AB} = 14.4), 3.30 (s, 3 H, OCH_3), 155, 153 (2 s, 6 H, $C(CH_3)_2$). Anal. Calcd for $C_{21}H_{24}O_4S_2$: C, 62.35; H, 5.98; S, 15.85. Found C, 62.05; H, 6.00; S, 14.77.

Using essentially the same procedure, the above diphenylthio derivative **16** (16.9 mg) was treated with TPTMS (0.04 mL) and TMSOTFS (0.04 mL) in 1,2-dichloroethane (3 mL) for 18 h at 70 °C to give the triphenylthioacetal **17** (6.3 mg, 27%): NMR ($CDCl_3$, 300 MHz) δ 7.4–7.2 (m, 15 H, ArH), 5.64 (s, 1 H), 4.79 (s, 1 H), 4.66 (s, 1 H), 4.29 (ABq, 2 H, $\Delta\nu$ = 33 Hz, J = 15), 1.55 (s, 6 H, $C(CH_3)_2$). The major product was a white solid (10.0 mg, 65%), mp dec, which from the NMR contained four phenyl groups and corresponded to the open ring form **18**: NMR ($CDCl_3$) δ 7.6–7.1 ppm (m 20 H, ArH), 5.06 (d, 1 H, J = 5), 4.98 (s, 1 H), 4.85 (d, 1 H, J = 5), 4.16 (q, 2 H, $\Delta\nu$ = 33 Hz, J = 12), 1.52, 1.49 (2 s, 6 H), $C(CH_3)_2$).

Methyl 3-*C*-(Dimethoxymethyl)-α-D-erythrofuranoside (9) from 1,2-*O*-Isopropylidene-3-*C*-vinyl-α-D-erythrofuranose (20) via Aldal 21. The reaction of vinyl-Grignard with ulose **19** (690 mg) according to the procedure of Tronchets[17] gave **20** (465 mg, 65% yield, mp 41–42 °C; lit.[17] mp 41–42 °C). The vinyl furanose **20** (250 mg) in CH_2Cl_2 (15 mL) was treated at −78 °C with ozone until a blue color developed. The mixture was treated with dimethyl sulfide and warmed to room temperature and the solvent removed (0.1 torr, 25 °C) to afford **21** (45 mg, 18%, clear oil): IR ($CHCl_3$) 1725 (RCHO); NMR ($CDCl_3$) δ 9.61 ppm (s, 1 H, CHO). Refluxing the above aldehyde **21** (35 mg) with anhydrous CH_3OH·HCl (15 h) followed by evaporation of the solvent (0.1 torr, 25 °C) and preparative TLC gave **9** (19 mg, 55%) as a clear oil. This product was the same by TLC and NMR as a sample of **9** prepared by similar treatment of acetal **8**.

Dithiane 22. To a solution of 1,3-dithiane (780 mg, 6.5 mmol) in THF (30 mL) at −30 °C was added *n*-butyllithium (4.3 mL, 1.5 M in hexane, 6.5 mmol). Ulose **19** (1.0 g, 6.2 mmol in 20 mL THF) was added dropwise to the above 2-lithio-1,3-dithiane[18] solution at 0 °C. After 18 h at 20–25 °C, the mixture was poured into ice water (100 mL), the aqueous solution was extracted (CH_2Cl_2), and the extracts were dried ($MgSO_4$) and concentrated (0.1 torr, 25 °C) to give a white amorphous solid which was recrystallized to give dithane **22** (1.25 g, 71% yield, mp 185–186 °C): NMR ($CDCl_3$) δ 5.85 ppm (d, 1 H, H-1, J_{1-2} = 3.7), 4.72 (d, 1 H, H-2, J_{2-1} = 3.7), 4.31 (d, 1 H, H-4a, J_{4a-4b} = 9.8), 4.05 (s, 1 H, H-5), 3.71 (d, 1 H, H-4b, J_{4b-4a} = 9.8), 2.96, 2.06 (2 m, 6 H, $(CH_2)_3$, 1.61, 1.41 (2 s, 6 H, $C(CH_3)_2$). Anal. Calcd for $C_{11}H_{18}O_4S_2$: C, 47.46; H, 6.52; S, 23.03. Found: C, 47.67; H, 6.34, S, 22.77.

Ulose Dimer 23. When the above reaction was carried out as above with the exception that an excess of *n*-butyllithium was used in making the 2-lithio-1,3-dithiane and that the solution had only 5 mL of THF for 500 mg of substrate (instead of 54 mL for 780 mg of substrate as above), then the product was the aldol dimer **23** (395 mg, 40% yield after crystallization from ethyl acetate/hexane, mp 175.5–179.0 °C, $[\alpha]^{20}_D$ +166° (*c* 1, $CHCl_3$); lit. for enantiomer[21] mp 174.5–175.5 °C, $[\alpha]^{18}_D$ −164° (*c* 0.7, $CHCl_3$). This product corresponded in IR, NMR, and C and H analysis with that reported[21] for the dimer of the enantiomer of ulose **19**. A sample of **23** upon storage at room temperature for several weeks changed. Preparative TLC gave the α,β-unsaturated ketone **24**: IR 1715 (C=CC=O); NMR ($CDCl_3$) δ 5.87, 4.87 (2 d, 2 H, H-1′, $J_{1'-2'}$ = 3.66), 5.79, 4.77 (2 d, 2 H, H-2, J_{2-1} = 3.97), 4.00 (d, 1 H, J_{4b-4a} = 9.15), 3.81 (dd, 1 H, H-4a, J_{4a-4b} = 9.15, J_{4b-2} = 1.53), 1.55, 1.36 (2 s, 6 $(CH_3)_2$), 1.45 (s, 6 H, $(CH_3)_2$).

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