was added, and the solution was heated to reflux. After 2 h the reaction was complete, judging by the formation of an intensely absorbing product on TLC viewed by UV light. The reaction mixture was cooled in a water bath to room temperature and most of the solvent removed on a rotary evaporator. The reaction mixture was redissolved immediately in absolute ethanol and hydrogenated for 30 min with excess Raney nickel (1 g) as a catalyst. The hydrogenated product was then purified by column chromatography with benzene–diethyl ether (1:1), yielding 400 mg of syrupy **12** (65%) which exhibited the following data: TLC R_f 0.37 [benzene–diethyl ether (1:1)]; $[\alpha]^{23}_D$ −3.2° (*c* 3.7, chloroform); IR 3450 (s, br), 2950 (s), 2880 (s), 1720 (s, sh), 1455, 1360, 730 (s), 690 (s) cm^{-1}; NMR (220 MHz) δ 0.95 (t, 3, CH_2CH_3), 1.36–1.82 (m, 6), 2.09 (s, 3, $COCH_3$), 2.41 (m, 3, CH_2CO, OH), 3.27 (m, 1, H-6) 3.45 (m, 1, H-7), 4.47 (d of AB q, 1, $J_{A,B}$ = 11.0 Hz, OCH_AH_BPh), 4.61 (d of AB q, 1, $J_{A,B}$ = 11.0 Hz, OCH_AH_BPh), 7.35 (s, 5, OCH_2Ph); mass spectrum, *m/e* 205 (M^+ + 1 − CH_3COCH_3), 115 (M^+ − CH_3COCH_3 − $PhCH_2$).

(1*R*,5*S*,7*R*)-7-Ethyl-5-ethyl-16,8-dioxabicyclo[3.2.1]octane [(+)-*exo*-Brevicomin (7)]. The ketone **12** (350 mg, 1.33 mmol) was dissolved in absolute ethanol (10 mL) and hydrogenated over a catalytic amount of palladium (5% on carbon). After 36 h, TLC indicated a faster running non-UV-active material had formed. The TLC mobilities (R_f 0.51 and 0.57 in petroleum ether–ethyl acetate mixtures, 10:1 and 5:1, respectively) were identical with those of an authentic sample provided by Wasserman.[15] The reaction mixture was filtered through Celite, poured into pentane (15 mL), and washed three times with water (5 mL), and the material from the dried pentane solution was purified by preparative layer chromatography with ethyl acetate petroleum ether (1:5). The pheromone **5** was eluted with pentane and the solvent removed by passing a gentle stream of nitrogen over the solution. The infrared spectrum of the material obtained (130 mg, 64%) and that of the authentic sample[15] of the racemic **1** were identical in the "fingerprint" region; $[\alpha]^{23}_D$ +81.5° (lit.[17] +84.1°).

Acknowledgment. The work was supported by grants from the National Research Council of Canada and The Canadian Forestry Service (Environment Canada). We are deeply indebted to Dr. Iain Weatherston (then at the Insect Pathology Research Institute) for numerous helpful discussions.

Registry No. (+)-**1**, 20290-99-7; **4**, 80485-56-9; **7a**, 582-52-5; **7b**, 18685-18-2; **7c**, 22529-61-9; **7d**, 22331-19-7; **8**, 19877-13-5; α-**9a**, 80502-02-9; β-**9a**, 80502-03-0; α-**9c**, 80485-57-0; β-**9c**, 80485-58-1; α-**9d**, 80502-04-1; β-**9d**, 80502-05-2; **9e**, 80485-59-2; **11**, 80485-60-5; **12**, 80502-06-3.

Synthetic Routes to 6,8-Dioxabicyclo[3.2.1]octyl Pheromones from D-Glucose Derivatives. 3.† Synthesis of (−)-Frontalin

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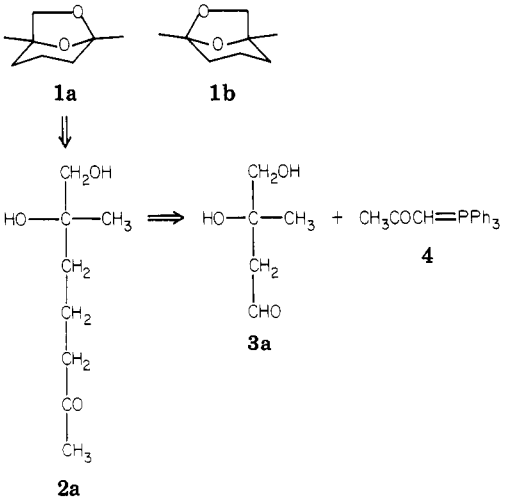
Received June 24, 1981

3-Deoxy-2-oxo glycosides with and without a C4 hydroxyl group are readily prepared from methyl α-D-glucopyranoside. Reaction with methylmagnesium iodide gives the C2 tertiary alcohol with an axially oriented methyl group. The epimeric tertiary alcohol can be obtained by methylenation of the ketone followed by oxymercuration–demercuration. The carbinol obtained by the latter route has been converted into (−)-frontalin, the major naturally occurring enantiomer of the pheromone, by a sequence which can also be applied to obtain the (+) enantiomer. The preferred route utilizes the 3,4-dideoxy precursor by benzylating the C2 tertiary alcohol and then hydrolyzing and reducing the anomeric center. The C5–C6 diol is then cleaved with periodate, and a Wittig condensation affords 1,3,4,5-tetradeoxy-6-*O*-benzyl-6-*C*-methyl-D-*glycero*-hexulose. Upon hydrogenolysis of the benzyl ether, cyclization to frontalin occurs spontaneously.

In the preceding paper[1] we described a synthesis of *exo*-brevicomin for which the starting material was commercially available,[2] 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose ("diacetone glucose"). In an earlier communication from this laboratory,[3] we described some of our studies on the preparation of frontalin (**1**) from readily obtained (commercially available[2]) derivatives of methyl α-D-glucopyranoside, and in this paper we give full details of this work.

Frontalin (**1**) was isolated[4] as a component of the aggregation pheromone of *Dendroctonus frontalis*, and by synthesizing both enantiomers, Mori[5] showed that the biologically active species was the 1*S*,5*R* form **1**, having $[\alpha]^{23}_D$ −52°. In addition, the molecule has been synthesized in racemic,[6] both enantiomeric,[7a] and unnatural (**1b**)[7b,c]



forms, and notably in the context of of our work, Ohrui and Emoto have achieved a synthesis of the natural ma-

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† For part 2 see ref 1.

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terial (**1a**)[8] beginning with D-glucose by a totally different route from that reported herein.

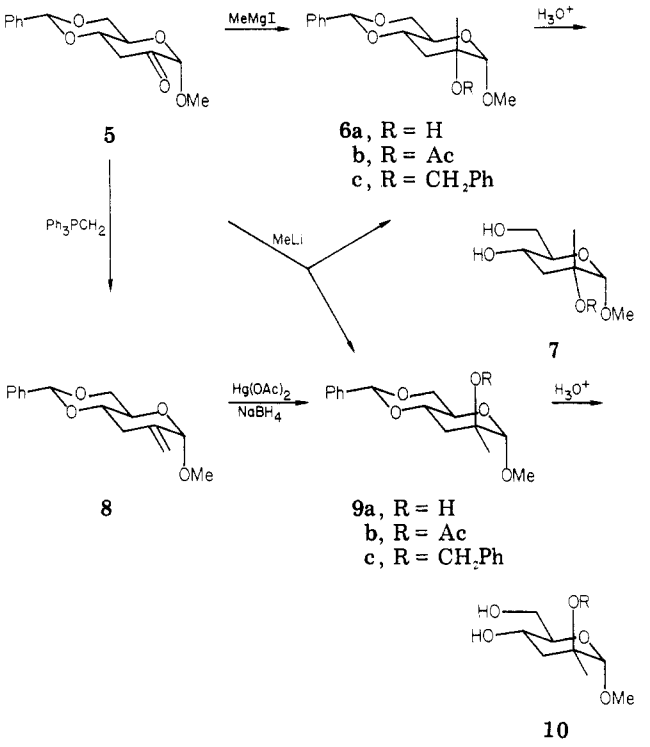
Although our primary interest was the naturally occuring enantiomer **1a**, we were particularly interested in exploring routes which could be tailored to give one enantiomer or the other with only minor variations in the basic synthetic strategy.[9] In keeping with our approach to *exo*-brevicomin,[1] our target was the acyclic form of **1a**, namely, **2** which is seen to have *S* chirality. This could be obtained from reaction of the tetrose **3** with the stabilized ylide 1-(triphenylphosphoranylidene)-2-propanone[10] (**4**) followed by hydrogenation. Thus our initial objective was to develop routes to the tetrose **3** and its mirror image.

The primary requirement was therefore the preparation of the tertiary alcohol center(s) of **3** and its enantiomer in known configuration(s). For this task the readily prepared ketone **5**[11] seemed a good starting point. The stereochemical outcome in additions to ketone **5** and the related olefin **8** were expected to be strongly influenced by the axial methoxyl group. Accordingly, Grignard addition to **5** (Scheme I) gave **6a** as the exclusive product, while oxymercuration/demercuration was equally selective, giving **9a** only. With methyllithium however, the reaction of **5** was much less specific, giving a 3:2 ratio of **6a** and **9a**.

Although the structures of **6** and **9** follow from the method of their formation, we sought confirmation by spectroscopic methods. Lemieux[12] and subsequently Lichtenthaler[13] have shown that for an epimeric pair of acetates on a pyranose ring, the methyl resonance of the axial member occurs to lower field in the ^{1}H NMR spectrum. Accordingly, the signal for **6b** was at δ 2.01 and that for **9b** at δ 2.08. The ^{13}C NMR spectra gave independent support for these assignments. Thus the equatorial methyl group in **9** should be shielded by the methoxyl in accordance with the γ effect;[14] accordingly, the C2 methyl of **9a** occurs at 20.93 ppm and that of **6a** at 23.1 ppm.

The benzyl ethers **6c** and **9c** were hydrolyzed to give the diols **7** and **10** respectively, also crystalline materials. The ^{1}H NMR spectra of these diols provided independent confirmation for the structures assigned above on the basis of the shielding effects of geminal protons by neighboring oxygen functions.[15] Thus in **7** both the axial and equatorial protons at C3 were coincident at 2.1 ppm; however, in **10** the equatorial H3 resonates at virtually the same position, 2.2 ppm, while the axial H3 is considerably further upfield at 1.6 ppm. Evidently in **7** the C2 oxygen shields both C3 protons, while in **10** the C2 oxygen deshields only the equatorial H3. The H4 signals also support these conclusions. Thus, H4 is more deshielded in **10** (4.1 ppm) than in **7** (~3.8 ppm).

Scheme I



With the structure of **10** secure, a path was investigated which could be applied to obtain the tetrose **3**. In theory, acid hydrolysis of the benzyl ether **9c** or **10c** should give the glycose **11a** (Scheme II). However, with dilute sulfuric or trifluoroacetic acid, recovery of **11a** was poor, there being evidence of a nonreducing substance. Although we did not confirm it, the latter was assumed to be the 1,6-anhydro sugar **12**, in keeping with ample precedent.[16] This problem was overcome in the usual way by acetolysis[17] of **10c**, whereupon the anomeric mixture of triacetates **11b** was formed.

Prolonged treatment of **11b** with sodium borohydride in ethanol gave the tetrol **13** which was freed of inorganic salts by repeated extraction with ethyl acetate. The syrupy material then was treated with sodium metaperiodate. The product proved to be a mixture of the tetrose **3b** and the hemiacetal **14** since both substances could be reduced to the same tetritol diacetate **15**. The former was therefore isolated by chromatography and treated immediately with the phosphorane **4**. The oily enone **17**, clearly a mixture of *E* and *Z* forms, was treated with hydrogen slightly above atmospheric pressure for 24–36 h. TLC gave no evidence of the independent existence of **2a** cyclization occurring in situ upon cleavage of the benzyl ether. After column chromatography with ether, careful evaporation afforded the pheromone **1** in ~60% yield from **3b**. The specific rotation and ^{1}H NMR spectrum were in excellent agreement with those reported for the previously synthesized material.[5]

Application of the route developed in Scheme II to the epimer **7** similarly afforded the (+)-frontalin, the enantiomer of **1**.

With the processes in Schemes I and II accomplished, we had developed a procedure for preparing both enan-

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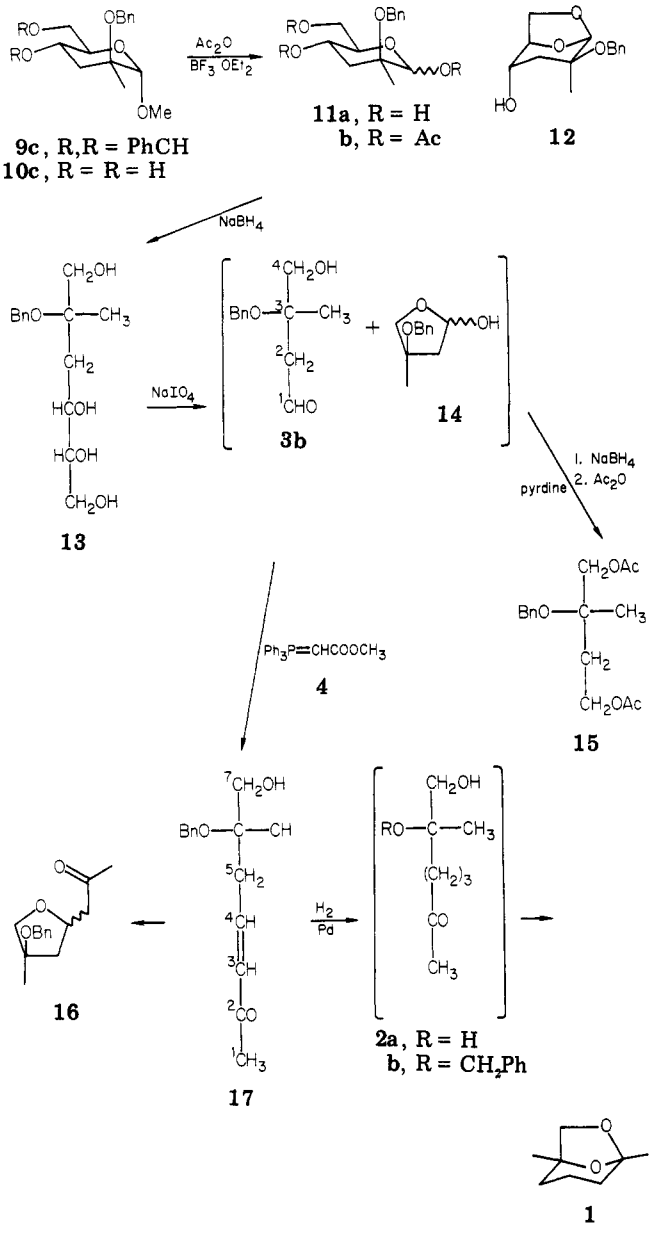
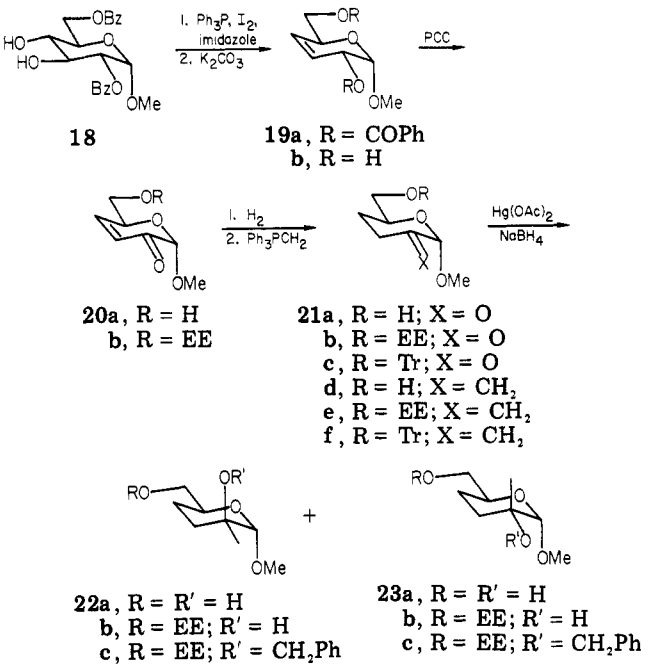
Scheme II



Scheme III



[a] EE = α-ethoxyethyl.

tiomers of frontalin from ketone **5**. However, handling of the key intermediate **3b** proved to be a problem. Formation of the hemiacetal **14** had been expected; however, since hemiacetals react with stabilized Wittig reagents[18] to give isolable[19] alkenes, we assumed that **14** would have also given the enone **17**. Indeed, there should be no need to separate **3b** from **14**. However, reaction of **14** with **4** required 3 days in refluxing dioxane for completion, and under these conditions, cyclization[17] to **16** occurred.

Had both hydroxyl groups of **3b** been benzylated, **16** could not have formed. With such a di-*O*-benzyl derivative, the final steps of the synthesis involving hydrogenolysis would remain the same; however, the earlier steps would have to be retooled to permit specific C1 benzylation of **13**, and this would have required several additional protection operations.

The alternative was to use a different 2-oxo sugar for the synthesis. The preparation of enone **20** has been described previously from our laboratory,[20] although the procedure indicated in Scheme III now utilizes the reductive elimination procedure of Garegg.[21] For the preparation of (−)-frontalin (**1**) from **20** based on the processes in Scheme II, we required the olefinic system **21**. In the light of the steps that follow, protection of the primary hydroxyl groups seemed superfluous; however, with the unprotected alkene, **21d** oxymercuration/demercuration gave both epimeric tertiary alcohols, **22a**, and **23a**, whereas with protection with the α-ethoxyethyl (EE) derivative **21e**, **22b** was obtained exclusively. Interestingly, with the trityl ether **21f**, no oxymercuration occurred!

It was our hope to be able to incorporate all six carbons of the sugar into frontalin. Accordingly, **22b** was deprotected to **22a** and oxidized with Fetizon's reagent,[22] whereupon the crystalline lactone **24** was obtained (Scheme IV). The addition of 1 equiv of methyllithium or methylmagnesium halide would have given **25**, a highly promising precursor of frontalin. However, in spite of ample literature precedents,[23] the addition could not be stopped at **25**; thus the use of 1 equiv of the methyl reagent gave the tertiary alcohol **26** and unchanged lactone **24**.

In the light of this failure, alcohol **22b** was subjected to benzylation and acetolysis, and the anomeric acetates **27** were reduced and acetonated to give **28**. The latter was now benzylated, hydrolyzed, and cleaved with sodium periodate to the aldehyde **29**, which was treated with methoxyethylidene phosphorane,[24] the resulting enol ether mixture being hydrolyzed to ketone **30**. As before, hydrogenolysis was followed by in situ cyclization to give **1** identical with the material prepared in Scheme II.

In summary, the protected tertiary alcohols **10** (Scheme I) and **22** (Scheme III) afford routes to (−)-frontalin, but

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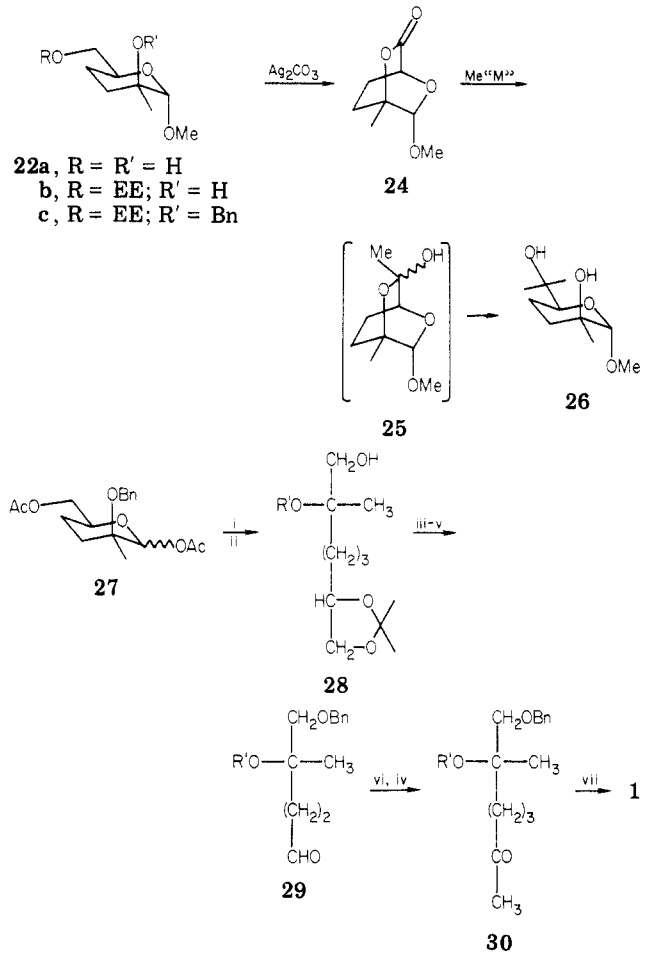
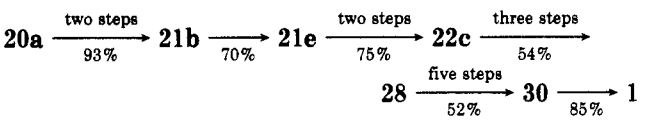
Scheme IV [a,b]



[a] R' = CH_2Ph. [b] (i) $LiAlH_4$, (ii) acetone/H_2SO_4, (iii) $PhCH_2Br$, (iv) H_3O^+, (v) $NaIO_4$, (vi) $Ph_3PC(OMe)CH_3$, (vii) H_2/Pd.

the latter is the preferred precursor because of the problems with the formation of **14** and **16** (Scheme II). As indicated below, all transformations go with good to excellent yields.



Experimental Section

For General Methods section, see the preceding paper.[1]

Methyl 2-*O*-Benzyl-4,6-*O*-benzylidene-2-deoxy-3-*C*-methyl-α-D-*ribo*-hexopyranoside (6c). (a) A solution of methylmagnesium iodide in dry diethyl ether was prepared by reacting clean dry magnesium (9.6 g, 0.4 mol), methyl iodide (15 mL), and dry ether (150 mL). The Grignard reagent was cooled to −65 °C in a dry ice/acetone bath, and methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*erythro*-hexopyranoside-2-uloside (**5**)[11] (11.0 g, 0.042 mol) was added. After 4 h the reaction mixture was poured into a separatory funnel and diluted with ether (100 mL). This solution was washed with saturated ammonium chloride (100 mL) and saturated bicarbonate (100 mL), dried over sodium sulfate, and taken to dryness. The tertiary alcohol **6a** (8.4 g, 73%) was recovered as a solid and recrystallized from chloroform/hexane: mp 152–153 °C; R_f 0.20 [ethyl acetate–petroleum ether (1:4)].

(b) Alternatively, ketone **5**[11] (0.264 g, 1 mmol) was dissolved in dry ether (10 mL) and cooled to −78 °C. Excess methyllithium (5.1 mmol) in THF was added, and after 15 min, TLC [ethyl acetate–petroleum ether (1:4)] showed that the reaction was complete and that two new products, **6a** and **9a** (R_f 0.15 and 0.20, respectively), had formed. A workup in the usual way afforded a syrup which was fractionated on a column by using the same solvent mixture to afford **6a** (0.130 g) and **9a** (0.085 g).

A portion of the alcohol **6a** (3.2 g, 11.4 mmol) was dissolved in dry dimethylformamide (50 mL), sodium hydride (1.2 g) was added, and after the mixture was heated at 45 °C for 30 min, benzyl chloride (6 mL) was added with stirring. After 3 h methanol (4 mL) was added, and the mixture was stirred for a further 30 min. The reaction mixture was poured into a separatory funnel, diluted with ether (100 mL), wand washed with water (3 × 100 mL). The ethereal layer was dried over sodium sulfate and taken to dryness. The reaction was chromatographed on a silica gel column by eluting with 10% ethyl acetate in petroleum ether (bp 30–60 °C). The benzyl ether **6c** (3.6 g, 85%) was recovered as a solid and recrystallized from ether: mp 95.5–96 °C; R_f 0.49 [ethyl acetate–petroleum ether (1:4)]; $[\alpha]^{23}_D$ +107.4 (*c* 1.78, methanol); ^1H NMR (60 MHz) δ 1.51 (s, 3, CH_3), 2.25 (m, 2, H3, H3′), 3.51 (s, 3, OCH_3) 4.51 (s, 1, H1), 4.6 (br s, 2, CH_2Ph) 5.57 (s, 1, CHPh), 7.4 (m, 10, phenyl). Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.07. Found: C, 71.35; H, 6.55.

Methyl 2-*O*-Benzyl-4,6-*O*-benzylidene-3-deoxy-2-*C*-methyl-α-D-*arabino*-hexopyranoside (9c). (a) *O*-Methyltriphenylphosphonium bromide (12.9 g, 0.036 mol) and anhydrous dimethoxyethane (100 mL) were placed in a dry 500-mL three-necked flask flushed with dry nitrogen. To this mixture was added *n*-butyllithium solution (15.3 mL, 0.036 mol), and the reaction mixture was stirred at room temperature for 30 min. The ketone **5**[11] (4.78 g, 0.081 mol) in dry dimethoxyethane (20 mL) was added and the reaction mixture stirred for 3 h. Dilution with ether (300 mL) was followed by filtration through Celite, and the filtrate was evaporated to dryness. The residue was chromatographed on silica gel by eluting with 10% ethyl acetate in petroleum ether (bp 30–60 °C). The olefin [methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-*C*-methylene-α-D-*erythro*-hexopyranoside (**8**), 4.6 g (95%)] was recovered as a syrup, R_f 0.38 [ethyl acetate petroleum ether (1:9)]. ^1H NMR shows an *exo*-methylene signal at 4.87 ppm. To the olefin **8** (3.8 g, 0.0140 mol) in tetrahyhdrofuran (21 mL) and water (25 mL), was added mercuric acetate (4.91 g), and the mixture was stirred at room temperature for 24 h. The addition of 3 M sodium hydroxide solution (34 mL) and a 0.5 M solution of sodium borohydride in 3 M sodium hydroxide (19 mL) was followed by further stirring for 15 min. The mixture was poured into a separatory funnel and extracted with chloroform (3 × 50 mL). The chloroform layer was dried over sodium sulfate and taken to dryness to give the tertiary alcohol **9a** (3.2 g, 78%) which was recrystallized from chloroform/hexane: mp 173–174 °C; R_f 0.15 [ethyl acetate petroleum ether (1:4)].

The alcohol **9a** was benzylated (as described above for the epimer **6a**) to afford **9c**: R_f 0.51 [ethyl acetate–petroleum ether (1:4)]; mp 118–119 °C; $[\alpha]^{23}_D$ −65.8° (*c* 1.82, methanol); ^1H NMR (60 MHz) δ 1.32 (s, 3, CH_3), 2.15 (m, 2, H3, H3′), 3.40 (s, 3, OCH_3), 4.55 (s, 3, H1 and CH_2Ph), 5.55 (s, 1, **CHPh**), 7.4 (m, 10, phenyl). Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.07. Found: C, 72.17; H, 6.94.

Methyl 2-*O*-Benzyl-2-*C*-methyl-α-D-*ribo*-hexopyranoside (7). The benzyl ether **6c** (3.6 g, 9.7 mol) was dissolved in dioxane (40 mL), and 10% sulfuric acid (10 mL) was added. The mixture was stirred at room temperature for 18 h, neutralized with solid sodium bicarbonate, and evaporated to dryness. The residue was extracted with hot ethyl acetate and filtered, and the solvent was evaporated. The diol **7** (2.42 g, 86%) was obtained as a solid which was recrystallized from chloroform/hexane: R_f 0.08 [ethyl acetate–petroleum ether (1:1)]; mp 127–128 °C; $[\alpha]^{23}_D$ +80.7° (*c* 2.15, methanol); ^1H NMR (60 MHz) δ 1.40 (s, 3, CH_3), 2.1 (d, 2, H3a, H3e), 2.6 (variable, br, 2, OH), 3.47 (s, 3, CH_3), 3.7–3.9 (m, 4, H4, H5, H6, H6′), 4.4 (s, 1, H1), 4.5 (s, 2, CH_2Ph); 7.4 (s, 5, phenyl). Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.65; H, 7.80.

Methyl 2-*O*-Benzyl-2-*C*-methyl-α-D-*arabino*-hexopyranoside (10). The benzyl ether **9c** was hydrolyzed as described above for the 2 epimer **6c**. The product **10** was similarly crystallized from chloroform/hexane: R_f 0.11 [ethyl acetate–petroleum ether (1.1)]; mp 101–102 °C; $[\alpha]^{23}_D$ +81.5° (*c* 0.98, (methanol); ^1H NMR (60 MHz) δ 1.21 (s, 3, CH_3), 1.60 (dd, 1, H3a, $J_{3e,3a}$ = 6.0 Hz, $J_{3a,4}$ = 8 Hz), 2.2 (dd, 1, H3e, $J_{3e,4}$ = 2 Hz), 2.9 (variable, br, 2, OH), 3.60 (s, 3, CH_3), 3.65–3.95 (m, 3, H5, H6,

H6'), 4.1 (dd, 1, H4), 4.6 (s, 3, H1 and CH_2Ph overlapping), 7.4 (s, 5, phenyl). Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.80; H, 7.81.

3-*O*-Benzyl-2-deoxy-3-*C*-methyl-D-*glycero*-tetrose (9b). The diol **10** (2.0 g, 7.1 mmol) was dissolved in acetic anhydride (14 mL) and cooled to 0 °C in an ice bath. Freshly distilled boron trifluoride etherate (0.56 mL) was added to the solution. The reaction mixture was stirred at 0 °C for 4 h, and then transferred to a separatory funnel containing a cold solution of sodium bicarbonate (50 mL). The solution was extracted with chloroform (30 mL), and the extract was washed with bicarbonate (50 mL), dried over sodium sulfate, and taken to dryness. The resulting anomeric mixture **11b** [m/e 343 ($M^+ - 1$); R_f 0.60 in petroleum ether–ethyl acetate (1:1)] was azeotroped with toluene (2 × 50 mL), taken up in absolute ethanol (20 mL), and cooled to 0 °C. Sodium borohydride (2.5 g) was added and the reaction mixture stirred overnight at room temperature. The solution was cooled to 0 °C, acetic acid (60 mL) added, and the mixture stirred at 0 °C for 1 h. The mixture was then evaporated to dryness and the residue extracted with hot ethyl acetate. The solution was filtered and evaporated, the residue (**13**), still containing some salts, was dissolved in water (50 mL) and dioxane (50 mL), and sodium bicarbonate (1.2 g) was added. This mixture was stirred at room temperature, and sodium periodate (3 × 1.2 g) was added at 15-min intervals. After 12 h the reaction mixture was filtered through Celite, the filter cake being washed with chloroform. The aqueous layer was extracted with chloroform, and the combined chloroform solutions were dried over sodium sulfate and evaporated to dryness. TLC of the residue in ethyl acetate–petroleum ether (1:1) showed two components, **14** and **3b** with R_f values 0.68 and 0.44, respectively. Reduction of the mixture with sodium borohydride and acetylation of the product with acetic anhydride and pyridine gave a single product assigned as the diacetate **15**: ^1H NMR (60 MHz) δ 1.2 (s, 3, CH_3) 1.9 (overlap CH_2CH_2O), 2.00 (s, 3, $COCH_3$), 2.01 (s, 3, $COCH_3$), 4.2 (q, 4, $2CH_2O$), 4.51 (s, 2, CH_2Ph), 7.3 (s, 5, phenyl); mass spectrum, m/e 294 (M^+), 217 ($M^+ - PhCH_2$). The mixture of **14** and **3b** was fractionated on silica gel by eluting with ethyl acetate/petroleum ether (bp 30–60 °C) (1:1) as the solvent. The aldehyde **3b** (0.782 g, 55%) was recovered as an oil: R_f 0.68 [ethyl acetate–petroleum ether (2:3)]; $[\alpha]^{23}_D$ +48.6° (c 2.3, chloroform); ^1H NMR (60 MHz) δ 1.5 (s, 3, CH_3), 2.7 (dd, 2, CH_2CHO), 4.15 (dd, 2, CH_2OH), 4.5 (s, 2, CH_2Ph), 7.3 (s, 5, phenyl), 9.7 (m, 1, CHO). IR 3500, 1720 cm^{-1}.

1,3,4,5-Tetradeoxy-6-*C*-methyl-D-*glycero*-hept-3-enulose (17). The tetrose **3b** (0.253 g, 1.21 mmol) and the ylide **4**[10] derived from chloroacetone (0.402 g, 1.26 mmol) were dissolved in tetrahydrofuran (10 mL) and refluxed for 12 h. The reaction mixture was evaporated to dryness and the residue passed through a silica gel column with 35% ethyl acetate in petroleum ether (bp 30–60 °C) as the eluting solvent. The enone **17** (0.220 g, 73%) was recovered as an oil: R_f 0.47 [ethyl acetate–petroleum ether (2:3)]; $[\alpha]^{23}_D$ +52.1° (c 3.4, chloroform); ^1H NMR (60 MHz) δ 1.35 (s, 3 H, C-CH_3), 2.25 (s, 3 H, CH_3CO), 2.5 (d, J = 8 Hz, 2 H, CH_2), 4.25 (d, J = 1.5 Hz, 2 H, CH_2OH), 4.55 (s, 2 H, CH_2Ph), 6.5 (d, J = 16 Hz, 1 H, C=CH), 6.8 (m, 1 H, C=CH), 7.35 (m, 5 H, phenyl); IR 3500, 1680, 1010 cm^{-1}; mass spectrum m/e 236(M^+), 159 ($M^+ - CH_2Ph$).

Methyl 3,4-Dideoxy-α-D-*erythro*-hex-3-enopyranoside (19b). Methyl 2,6-di-*O*-benzoyl-α-D-glucopyranoside (**18**;[20,25] 100 g, 0.25 mol) triphenylphosphine (262 g, 1 mol), and imidazole (68 g, 1 mol) were refluxed in toluene (1500 mL) with vigourous stirring. Iodine (194 g, 0.77 mol) was added in small quantities over a period of 1 h, and the reaction mixture was refluxed for an additional hour. The reaction mixture was decanted into a saturated sodium bicarbonate solution (1500 mL). Toluene (3 × 50 mL) was used to extract the black, tarry residue in the bottom of the flask, and these toluene extracts were added to the bicarbonate mixture. The toluene phase was washed with aqueous sodium thiosulfate until the iodine was consumed and was then washed with distilled water (2 × 500 mL) and dried with magnesium sulfate. The residue obtained upon evaporation was stirred with diethyl ether and the insoluble triphenylphosphine oxide filtered off. The ether was evaporated, the crude dibenzoate **19a** [R_f 0.33 in ethyl acetate–petroleum ether (1:4)] was dissolved in methanol (2 L), potassium carbonate (30 g) was added, and the mixture was stirred at room temperature overnight when TLC indicated that debenzylation was complete. The solids were removed by filtration and the filtrate evaporated. The residue was taken up in water and extracted repeatedly with benzene to remove methyl benzoate and triphenylphosphine. Evaporation of the aqueous phase afforded **19b** [27 g (70%); R_f 0.01 (ethyl acetate–petroleum ether, 1:1)] which was identified by comparison with the previously reported material[20] and was suitable for use in the next step.

Methyl 3,4-Dideoxy-α-D-*glycero*-hex-3-enopyranosid-2-ulose (20a). The diol **19b** (15 g, 93.75 mmol) was dissolved in 500 mL of CH_2Cl_2, and Celite (52.5 g) and pyridinium dichromate[26] (52.5 g) were added with stirring. After 12 h, TLC in ethyl acetate–petroleum ether (1:1) showed enone **20a** as the main product with some unreacted **19b** and side products. (Longer reaction times led to a greater number of side products.) The material was recovered by filtration and evaporation, and after column chromatography on silica with ethyl acetate–petroleum ether (1:2), **20a** (9.7 g) was isolated and was identical with the previously reported material.[20]

Methyl 2-*C*-Methyl-3,4-dideoxy-α-D-*threo*-hexopyranoside (22a). Enone **20a** (9 g, 57 mmol) was dissolved in CH_2Cl_2 (100 mL) and treated with ethyl vinyl ether (5.6 mL) and pyridinium *p*-toluenesulfonate[27] (100 mg) for 16 h, when TLC indicated completion. The mixture was passed through a short column of alumina, and evaporation of the eluate gave 12.4 g (95%) of **20b**: R_f 0.85 [ethyl acetate–petroleum ether (1:1)]; ^1H NMR (60 MHz) δ 4.20 (s, 1, H1), 6.15 (dd, 1, $J_{3,4}$ = 11.0 Hz, $J_{4,5}$ = 2.5 Hz, H4), 7.05 (m, 1, $J_{3,5}$ = 1.8 H, H3), 4.77 (q, 1, J = 5.4 Hz, $OCH(CH_3)O$); IR 1670 c^{-1}. The enone **20** b (12.0 g) was dissolved in EtOAc, 5% Pd/C (200 mg) was added, and the mixture was shaken with H_2 at 50 psi by using a Parr hydrogenator. Uptake ceased after 15 min, and TLC showed no UV-active substances, indicating the absence of starting material. Filtration and evaporation gave **21b** (11.8 g, 98%). This ketone (9.3 g, 40 mmol) was dissolved in C_6H_6 (50 mL) and added to the ylide prepared from *O*-methyltriphenylphosphonium bromide (21.4 g, 60 mmol) and *n*-butyllithium (23.6 mL) in C_6H_6. After the mixture was stirred at room temperature for 2 h, excess ammonium chloride solution was added, and the benzene layer was recovered and processed. Column chromatography with petroleum ether–ethyl acetate (9:1) afforded **21e**: 6.4 g (70%); R_f 0.75 [ethyl acetate–petroleum ether (1:4)]; ^1H NMR δ 4.85 (H-1 and methylene overlapping); IR ν_{max} 1660 cm^{-1}. The alkene **21e** (5.5 g, 23.9 mmol) was dissolved in tetrahydrofuran (44 mL) and water (25 mL), and mercuric acetate (10 g) was added. After the mixture was stirred for 1.5 h, when TLC showed that the reaction was complete, 3 M sodium hydroxide solution (70 mL) and 0.5 M sodium borohydride (40 mL) were added with stirring for 15 min. The mixture was extracted with chloroform, and the syrupy product **22b** (5.0 g, 85%) was treated directly with MeOH (100 mL) and pyridinium *p*-toluenesulfonate[27] (200 mg) for 3 h, the diol **22a** (3.2 g, 94%) being isolated by column chromatography with petroleum ether–ethyl acetate (2:1): R_f 0.25 [ethyl acetate–petroleum ether (1:1)]; $[\alpha]^{23}_D$ +49.1° (c 2.65, chloroform); ^1H NMR δ 4.27 (s, 1, H1), 3.25, (s, 3, OCH_3), 1.13 (s, 3, CH_3), 1.25–2.0 (m, 4, CH_2CH_2); IR ν_{max} 3400 cm^{-1}; mass spectrum, m/e 145 ($M^+ - CH_2OH$), 127 (145 - H_2O).

Methyl 2-*C*-Methyl-3,4-dideoxy-α-D-*threo*-pyranosid-urono-δ-lactone (24). The diol **22a** (352 mg, 2.0 mmol) was dissovled in toluene (15 mL) and refluxed with Ag_2CO_3 in Celite[21] added in ~200 mg portions at 0.5-h intervals. After 12 h, when TLC indicated completion, the mixture was filtered, the residue was washed wtih EtOAc, and the combined organic layers were evaporated to dryness. Lactone **24** was isolated by chromatography with petroleum ether/ethyl acetate (4:1); 250 mg, (73%). The material was recrystallized from same solvent system: mp 89–90 °C; $[\alpha]^{23}_D$ +101.7° (c 2.29, methanol); ^1H NMR (60 MHz) δ 4.63 (s, 1, H1), 3.48 (s, 3, OCH_3), 1.38 (s, 3, CH_3); IR ν_{max} 1770 cm^{-1}; mass spectrum, m/e 141 ($M^+ - CH_3O$), 128 ($M^+ - CO_2$), 97 (128 - CH_3O or 141 - CO_2). Anal. Calcd for $C_8H_{12}O_4$: C, 55.81;

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H, 7.02. Found: C, 55.58; H, 7.00.

2-*O*-Benzyl-3,4-dideoxy-5,6-*O*-isopropylidene-2-*C*-methyl-D-*threo*-hexitol (28). The monoalcohol **22b** (2.76 g, 11.14 mmol) was dissolved in THF (10 mL) and treated with oil-free NaH (395 mg) in THF (40 mL). After the mixture was stirred for 15 min, $PhCH_2Br$ (1.81 mL) and Bu_4NI (50 mg) were added, and the mixture was left for 12 h, when TLC indicated that benzylation was complete. The product **22c** (3.21 g) was isolated in the usual way, and a portion (380 mg) was dissolved in Ac_2O (5 mL), the mixture was cooled to 0 °C, and freshly distilled $BF_3{\cdot}Et_2O$ (0.2 mL) was added. After being stirred at 0 °C for 6 h, the mixture was worked up as described above (for **11b**), and the crude product **27** was dissolved in Et_2O and treated with $LiAlH_4$ (150 mg) for 3 h at room temperature. Water was added, and reduced material was recovered in the usual way and then passed through a short column to remove salt. The glassy product, after being dried overnight under vacuum, was dissolved in dry purified acetone (50 mL) containing 1 drop of H_2SO_4. After 3 h at room temperature, TLC showed the reaction to be complete. After neutralization with Et_3N, the product was recovered and purified by chromatography on a column of silica gel to yield 150 mg of **28**: $[\alpha]^{23}_D$ +0.8 (*c* 2.50, methanol); ^1H NMR (60 MHz) δ 1.23 (s, 3, CH_3), 1.35 (s, 3, CH_3), 1.42 (s, 3, CH_3), 1.65 (m, 4, CH_2CH_2), 2.33 (s, 1-OH), 3.48 (br s, 2, CH_2OH), 4.00 (m, 3, H5, H6, H6'), 4.40 (s, 2-CH_2Ph), 730 (s, 5, phenyl); mass spectrum, *m/e* 294 (M^+ - 15), 279 (M^+ - 15), 263 (M^+ - CH_2OH).

(-)-Frontalin (1). (a) The enone **17** (0.204 g, 0.82 mmol) was dissolved in absolute ethanol (10 mL), 10% Pd/C (0.020 g) added, and the mixture stirred at room temperature under hydrogen at atmospheric pressure. After 36 h the solution was filtered through Celite and the volume reduced to approximately 0.5 mL. The product was purified by silica gel column chromatography, eluting with diethyl ether. Frontalin (1; 0.07 g, 60%) was recovered by evaporating the ether with a gentle stream of nitrogen. Care must be taken because of the volatility of the product. The frontalin had the following characteristics: $[a]^{23}_D$ +50.7° (*c* 10.5, chloroform) (lit.[5] $[\alpha]_D$ -52.0°); ^1H NMR (60 MHz) δ 1.32 (s, 3 H, C-CH_3), 1.42 (s, 3 H, C-CH_3), 1.65 (m, 6 H, $(CH_2)_3$), 3.5, 3.95 (J_{AB} = 7.0 Hz, 2 H, CH_2O).

(b) Compound **28** (125 mg, 0.425 mmol) was benzylated in the usual way (see preceeding procedure), and the crude dibenzyl derivative was treated with MeOH (2 mL) containing 1 drop of H_2SO_4 for 6 h. After neutralization with Et_3N, column chromatography with petroleum ether–ethyl acetate (2:1) afforded 101.3 mg (0.29 mmol) of diol [^1H NMR δ 1.23 (s, CH_3), 4.60 and 4.63 (dd, CH_2Ph), 7.28 (s, Ph)] which was dissolved in 50% dioxane–water (2 mL). $NaHCO_3$ (14 mg) and $NaIO_4$ (62 mg, 0.29 mmol) were added, and the reaction mixture was stirred at room temperature for 1 h, when TLC indicated formation of **29**. The product (71.3 mg, 0.23 mmol) was isolated by chromatography with petroleum ether–ethyl acetate (4:1) [^1H NMR δ 9.71 (t, CHO)], was dissolved in Et_2O (2 mL), and was treated at -40 °C with the ylide prepared from $Ph_3PCH(OCH_3)CH_3Cl$[24] (230 mg, 0.5 mmol) and *n*-BuLi in Et_2O at -40 °C. After 1 h at -40 °C the mixture was allowed to warm to room temperature, NH_4Cl solution was added, and the product was recovered by extraction into ether and the usual processing. The material was dissolved in dioxane (1 mL) and 0.1 M HCl (1 mL), and after 12 h Na_2CO_3 was added to neutrality. The mixture was filtered, evaporated to dryness, and chromatographed with benzene (to remove phosphorous species) followed by petroleum ether–ethyl acetate (2:1). The product **30** [55 mg (81%); ^1H NMR δ 2.15 (s, $COCH_3$)] was dissolved in EtOH, 5% Pd/C (10 mg) was added, and the mixture was subjected to hydrogenation in a Parr apparatus at 50 psi of H_2 for 2 h. The solvent was removed under vacuum below 20 °C, and the residue was chromatographed on a silica column with ether as the eluent. Careful evaporation left 12.1 mg (85%) of material identical with substance **1** prepared in part a.

(+)-Frontalin. (+)-Frontalin, the enantiomer of **1**, was prepared from the diol **7** in exactly the manner as outlined above for the conversion of **10** into **1**. The enantiomer thus obtained was identical except for $[\alpha]^{23}_D$ +51.3° [lit.[5] $[\alpha]_D$ +50.7°].

Acknowledgment. This work was supported by grants from the National Research Council of Canada and The Canadian Forestry Service (Environment Canada). We are deeply indebted to Dr. Iain Weatherstron (then at the Insect Pathology Research Institute) for numerous helpful discussions.

Registry No. (-)-**1**, 28401-39-0; (+)-**1**, 57917-96-1; **3b**, 62222-33-7; **5**, 19272-50-5; **6a**, 62222-26-8; **6b**, 80532-13-4; **6c**, 62222-28-0; **7**, 62222-30-4; **8**, 80581-18-6; **9a**, 62222-27-9; **9b**, 80532-14-5; **9c**, 62222-29-1; **10c**, 62222-31-5; **11b**, 80532-15-6; **13**, 80532-16-7; **14**, 62222-32-6; **15**, 80532-17-8; **16**, 80532-18-9; **17**, 62222-35-9; 18, 26927-44-6; **19a**, 34254-52-9; **19b**, 51385-38-7; **20a**, 35303-95-8; **20b**, 80532-19-0; **21b**, 80532-20-3; **21d**, 80532-21-4; **21e**, 80532-22-5; **21f**, 80532-23-6; **22a**, 80532-24-7; **22b**, 80532-25-8; **22c**, 80532-26-9; **23a**, 80532-27-0; **24**, 80532-28-1; **26**, 80532-29-2; **27**, 80532-30-5; **28**, 80532-31-6; **29**, 80532-32-7; **30**, 80532-33-8.