mL of tetrahydrofuran was added dropwise, and the reaction mixture was allowed to warm to room temperature. After being stirred for 1 h, the mixture was quenched with 1 mL of water and acidified to pH 2 with 3 N HCl. Saturated ammonium chloride solution (3 mL) was added, and the mixture was extracted with ether. The organic layer was extracted with dilute sodium carbonate solution, the basic extract was acidified to pH 2 with 3 N HCl, and the aqueous layer was extracted with ether. After the ethereal extract was washed twice with water, it was dried (Na_2SO_4), and the solvent was removed to yield 114 mg (80%) of **6** as a clear oil: IR (film) 3100 (br), 1720, 1655, 1600 cm^{-1}; UV (MeOH) λ_{max} 217 (ϵ 15600), 262 (12670); ^{13}C NMR δ 169.7, 166.8, 165.8, 155.2, 142.1, 138.3, 129.0, 124.2, 117.3, 62.7, 50.9, 39.31, 18.50. A small sample of **6** in ether was esterified with an excess of diazomethane, and the product was subjected to rapid chromatography on silica. Elution with ether–hexane (2:3) gave the diester **23** as a colorless oil: ^1H NMR ($CDCl_3$) δ 8.35 (1 H, dd, J = 11.16 Hz), 6.58 (1 H, t, J = 11 Hz), 6.03 (1 H, d, J = 16 Hz), 5.92 (1 H, d, J = 11 Hz), 5.70 (1 H, m), 4.30 (2 H, t, J = 7 Hz), 3.74 (3 H, s), 3.66 (3 H, s), 2.52 (2 H, t, J = 7 Hz), 2.22 (3 H, d, J = 1.5 Hz); mass spectrum, m/e 282.112 (M^+, calcd for $C_{14}H_{18}O_6$ 282.110).

Registry No. 5, 80514-95-0; **6**, 80514-96-1; **7**, 541-57-1; **8**, 590-90-9; **9**, 20705-59-3; **10**, 80514-97-2; **11**, 503-48-0; **12**, 2381-87-5; **14**, 32775-50-1; **15**, 80514-98-3; **16**, 80514-99-4; **17**, 2605-67-6; **18**, 35066-34-3; **19**, 35066-33-2; **20**, 35066-36-5; **21**, 80515-00-0; **22**, 80515-01-1; **23**, 80515-02-2; 2-furoic acid, 88-14-2; ethyl acetate, 141-78-6; α-bromoacetyl bromide, 598-21-0; triethyl phosphite, 122-52-1; trimethyl phosphite, 121-45-9.

Synthetic Routes to 6,8-Dioxabicyclo[3.2.1]octyl Pheromones from D-Glucose Derivatives. 2.‡ Synthesis of (+)-*exo*-Brevicomin

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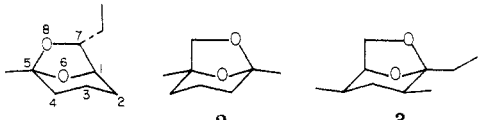
Received June 24, 1981

The hydrated, acyclic form of (+)-*exo*-brevicomin indicates that the chirality of the molecule resides in a D-threo glycol segment such as that found at C3 and C4 of D-glucose. Accordingly, "acyclic transfer" of this portion of the sugar into a suitable precursor is required; however, the synthetic route adopted has utilized all six carbons of D-glucose. Thus the C3-hydroxyl group of "diacetone glucose" is benzylated, and the 5,6-*O*-isopropylidene ring is selectively hydrolyzed. The resulting diol is disulfonated, and reductive elimination now gives the hex-5-enofuranose. Acid-induced methanolysis of the 1,2-*O*-isopropylidene ring affords the methyl furanoside, exposing the C2 hydroxyl which is then removed by the Barton–McCombie procedure. Gentle hydrolysis now gives the free furanose which reacts with the ylide from chloroacetone, the crude α-enone product being hydrogenated directly. Purification is effected at this stage, upon further treatment with hydrogen, the benzyl group of the saturated ketone is cleaved by hydrogenolysis, and cyclization occurs in situ to give (+)-*exo*-brevicomin.

Sugar derivatives possessing the 6,8-dioxabicyclo-[3.2.1]octyl skeleton, most commonly encountered as 1,6-anhydro-β-D-hexopyranoses, are readily obtainable,[1-5] and a sizeable body of knowledge about their chemistry exists.[6] However, the first natural products found to contain this ring system were the beetle pheromones *exo*-brevicomin,[7] frontalin,[8] and α-multistriatin,[9] shown as their (major) naturally occurring enantiomers **1–3** respectively. The

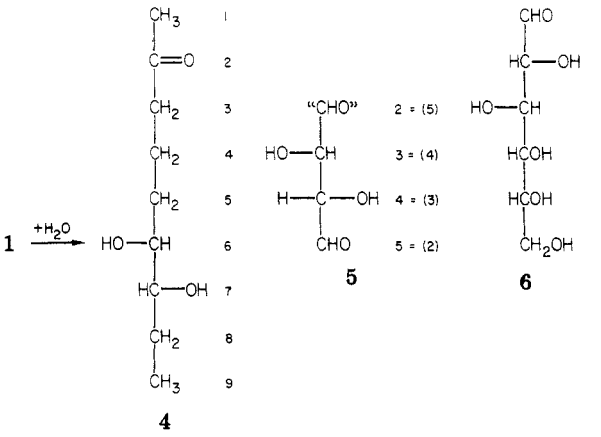


1 **2** **3**

first of these, *exo*-brevicomin (**1**), was isolated only in 1969 by Silverstein.[7] Subsequently, frontalin (**2**)[8] and multistriatin (**3**)[9] were added. We have studied the preparation of all three from derivatives of D-glucose and now report our results, some of which have appeared in preliminary form.[10,11] In this paper we describe our work on *exo*-brevicomin (**1**), and in the accompanying papers we discuss frontalin (**2**)[12] and α-multistriatin (**3**).[13]

Dendroctonus brevicomins, the western pine beetle, is a principal pest in timber regions on the western coast of North America. The beetle emits an aggregation pheromone system that attracts other beetles of the same species to the host tree which they inoculate with a pathogenic

Scheme I



4 **5** **6**

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† From the M.Sc. Thesis of A.E.S. University of Waterloo, 1978.

‡ Reference 10 is considered part 1 of this series.

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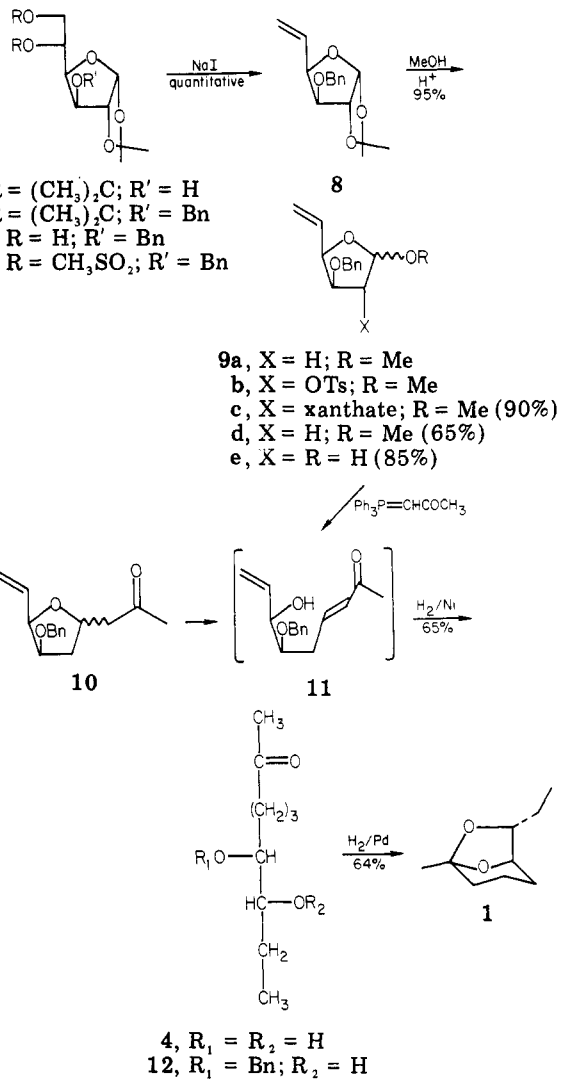
0022-3263/82/1947-0932$01.25/0

fungus eventually leading to its death.[14] The pheromone (+)-(*R*)-*exo*-brevicomin (1) was first prepared in racemic form by Wasserman,[15] and since then there have been several other syntheses of the racemic substance **3b**[16] as well as one of the naturally occurring enantiomer.[16] A synthesis of 1 from D-glucose has also been achieved by Ferrier.[18]

The Fischer projection 4 is the hydrated form of 1, and the chiral component is thereby seen to be a D-threo glycol. Juxtaposition of 4 with the Fischer projection of D-glucose 6 (Scheme I) inidicates that the required D-threo relationship exists at C3 and C4 of D-glucose. What is required, therefore, is a derivative that permits "acyclic transfer"[19] of the intact C3–C4 portion of D-glucose into a suitable precursor of 4. The synthon 5 is the equivalent of what is required, and addition of two- and four-carbon fragments at the "ends" would lead to the formation of 4. Because of the symmetry of 5 there is the option of adding either fragment to either "end" of 5. For this purpose, 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose (diacetone glucose)[20] seemed ideal, since the C3 OH is available for protection, and the C4 OH is sequestered as the ring oxygen. Compound **7a** could be processed to furnish aldehydic groups at C5 and C2 by sequential hydrolysis of the two isopropylidene groups followed by cleavage with sodium periodate. This format would, however, mean the loss of two of the six carbons of glucose and was therefore rejected in favor of an alternative that would preserve all six carbons of the sugar.

In the light of this constraint, the alkene 8 was chosen for investigation since one of the unwanted hydroxyl groups (that at C5) has already been removed (see Scheme II), and the vinyl group would eventually become the C8–C9 ethyl group of 4. For the preparation of 8 the simple method of Jones and Thompson[21] was utilized. Benzylation of **7a** to give **7b** was followed by selective hydrolysis to **7c** and disulfonation to give **7d**. Treatment with sodium iodide[21] then led to alkene 8. Treatment of the 8 with methanolic hydrogen chloride cleaved the acetonide with concomitant formation of the glycoside **9a**, thereby exposing the other unwanted hydroxyl group at C2. Removal of the latter functionality was expected to be problematic in view of the known difficulty for nucleophilic displacement at C2 of normal glycosides. Thus

Scheme II



treatment of the sulfonate **9b** with lithium aluminum hydride regenerated the alcohol **9a**. Presumably hydride attack occurred on sulfur rather than on carbon.

The Barton–McCombie deoxygenation[22] which does not involve nucleophilic displacement provided a ready solution to the problem. Thus **9a** was converted into the xanthate ester **9c**, which upon reaction with tri-*n*-butyltin hydride in refluxing toluene for 5 days gave the 2-deoxy sugar **9d** in 65% overall yield.

As expected, the 2-deoxy glycoside **9d** underwent facile hydrolysis to give the lactol **9e** which now only required a 3-carbon extension to afford the skeleton of 4. Compound **9e** reacted readily with the ylide derived from chloroacetone;[23] however, attempts to purify the product chromatographically caused cyclization to the furan **10**. We attempted to utilize the latter by treatment with base in the presence of hydrogen and palladium in the hope that a retro-Michael reaction to 11 would occur, followed by hydrogenation to give 4 and then by hydrogenolysis leading to *exo*-brevicomin (1). However, a variety of bases were tried without success.

In view of this failure, purification of the Wittig adduct of **9e** was postponed. After the condensation was complete, the acetonitrile solvent was evaporated, the residue dissolved in ethanol, and the crude sample of 11 was hydro-

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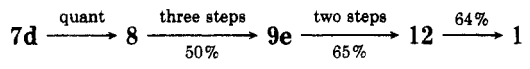
genated over excess Raney nickel for 30 min, whereupon the saturated product **12** was obtained. Purification by column chromatography was effected, and the material was then exposed to hydrogen and palladium. The benzyl ether of **12** was thereby cleaved to give **4**, and cyclization to *exo*-brevicomin (**1**) occurred in situ. The progress of these transformations beginning with **12** could be followed conveniently on thin-layer chromatograms by noting the formation of the polar diol **4** which eventually gave way to the nonpolar substance **1**. The infrared and mass spectrum of **1** were identical with an authentic sample of the racemic pheromone obtained from Professor Wasserman.[15] The specific rotation was (+) 80.7° in good agreement with the literature value of +84.1°.[17]

In summary, *exo*-brevicomin can be readily obtained as its naturally occurring antipode, **1**, from the disulfonate **7d** prepared in four simple steps from "diacetone glucose". The following summary equation shows that beginning with the disulfonate, seven steps are required for an overall yield of 21%.



Experimental Section

General Methods. Melting points were determined in capillary tubes in a Buchi Model SMP-20 melting point apparatus and are uncorrected. Elemental analyses were performed by Microanalyses Laboratory. Nuclear magnetic resonance (NMR) spectra, unless otherwise stated, were determined in deuteriochloroform containing 1% tetramethylsilane as an internal standard with either a Perkin-Elmer R-12B (60 MHz) or a Varian HR-220 spectrometer. Coupling constants were obtained by measuring the spacings of spectra judged to be first order. Infrared (IR) spectra were determined on a Beckman Model IR-10 spectrometer by using 0.1-mm sodium chloride cells and chloroform as the solvent or sodium chloride plates for thin-film smears. Low-resolution mass spectra were determined on a Varian MAT CH7 mass spectrometer. High-resolution mass spectra were determined on a VG 7070F.

Optical rotations were measured on a Carl Zeiss Model LEP nur 370740 Lichtelektrisches Präzisionpolarimeter at 23 °C.

All gas–liquid chromatography (GLC) was performed on an Aerograph model 1520 with an Ultrabond packed steel coil (6 ft × $^1/_8$ in.). The column temperature will be specified while the detector temperature was 260 °C and the injector temperature was 230 °C. The helium flow rate was 25 mL/min. Ratios were determined by measuring the peak heights of the spikes or by cutting out and weighing broad peaks.

The progress of all reactions was monitored by thin-layer chromatography (TLC) which was performed on 1.3 cm × 6.6 cm aluminum sheets precoated with silica gel 60 (HF-254, E. Merck) to a thickness of 0.25 mm. The developed chromatograms, unless otherwise stated, were viewed under an ultraviolet light, sprayed with concentrated sulfuric acid, and briefly heated to a temperature greater than 100 °C under a hot air gun. For column chromatography, E. Merck silica gel (0.063–0.20 mm, 70–230 mesh ASTM) was used. Preparative thick-layer chromatography was done on glass plates (20 cm × 20 cm) coated with silica gel 60 (HF-254, E. Merck) to a thickness of 2.0 mm.

Unless otherwise stated, all solvents were evaporated on a rotary evaporator under reduced pressure and the residues dried under high vacuum.

3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (8). 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (diacetone glucose,[20] **7a**) was benzylated to give **7b** and then selectively hydrolyzed to **7c** according to the literature procedure.[24] The derived dimesylate **7d** (44 g, 0.09 mol) was then treated with sodium iodide (44 g, 0.3 mol) in butanone (500 mL) and refluxed for 24 h as described by Jones and Thompson.[21] The alkene **8** (27 g) was obtained in quantitative yield.

Methyl 3-*O*-Benzyl-5,6-dideoxy-α,β-D-*xylo*-hex-5-enofuranoside (9a). The olefinic acetonide **8** (25.0 g, 90.6 mmol) was dissolved in 2% methanolic hydrogen chloride (400 mL) and heated to reflux. After 45 min, TLC indicated that the reaction was complete. The reaction mixture was neutralized with saturated sodium bicarbonate and the product extracted into methylene chloride (3 × 150 mL). The extracts were collected, washed with water, and dried over sodium sulfate. The solvent was removed to give the mixture of anomers **9a** (21 g, 95%) having the following data: TLC R_f 0.35, 0.45 [for the two anomers; in benzene–diethyl ether (1:1)]; $[\alpha]^{23}_D$ +17.1° (*c* 0.9, chloroform); IR 3450 (br), 2910 (s), 1500 (m), 1455 (m), 730 (s), 690 (s) cm^{-1}; NMR (220 MHz) δ 2.79 (br s, 1, OH), 3.40 and 3.45 (2 s, 3, OMe ((α and β)), 4.55 (m, 2, OC**H**$_2$Ph), 4.76 (d, 0.5, $J_{1\beta,2}$ = 2 Hz, $H_{1\beta}$), 4.95 (d, 0.5, $J_{1\alpha,2}$ = 4.5 Hz, $H_{1\alpha}$), 7.30 (s, 5, OCH$_2$**Ph**); mass spectrum, *m/e* 250 (M^+) 160 (M^+ – CH_2Ph).

Methyl 3-*O*-Benzyl-5,6-dideoxy-2-*O*-[(methylthio)thiocarbonyl]-α,β-D-*xylo*-hex-5-enofuranoside (9c). The anomeric mixture of methyl furanosides **9a** (22.0 g, 88.0 mmol) was dissolved in dry ether (250 mL), and sodium hydride (6.0 g), washed twice with pentane, was added over 30 min at room temperature. After the addition was complete, the reaction mixture was heated to reflux, and carbon disulfide (13.5 mL, 224 mmol) and iodomethane (14.5 mL, 233 mmol) were added dropwise to the solution after 2 and 5 h, respectively. After 9 h of total reflux time, TLC indicated that the reaction was complete. Dropwise addition of water destroyed the excess sodium hydride, and the mixture was then transferred to a separatory funnel and washed successively with dilute hydrochloric acid, saturated sodium bicarbonate, and distilled water. The ethereal layer was dried over sodium sulfate and the solvent removed to give **9c** as a syrup (27 g, 90%) exhibited the following characteristics: TLC R_f 0.61 [benzene–diethyl ether (1:1)]; $[\alpha]_D$ +32° (c 1.6, chloroform); IR 1205 (s), 1070 (s), 1010 (s) cm^{-1}; NMR (60 MHz) δ 2.77 (s, 3, SCH_3), 3.41 (2 s, 3, OCH_3), 7.30 (s, 5, OCH_2Ph); mass spectrum, *m/e* 340 (M^+) 309 (M^+ – OCH_3).

Methyl 3-*O*-Benzyl-2,5,6-trideoxy-α,β-D-*threo*-hex-5-enofuranoside (9d). The xanthate ester **9c** (26.4 g, 77.6 mmol) was dissolved in dry toluene (400 mL), and the solution brought to reflux under an atmosphere of argon. Freshly distilled tri-*n*-butyltin hydride (270 mL, 92.9 mmol) dissolved in dry toluene (100 mL) was added dropwise to the refluxing solution over a 10-h period. After 5 days, no further changes were observed on TLC, and the reaction was terminated. The solvent was removed by rotary evaporation, and the product was purified directly by column chromatography with a solvent mixture of benzene and diethyl ether ranging from 19:1 to 2:1. The product **9d** (12 g, 65%) was contaminated by a small amount of inseparable reduction byproducts but was suitable for use in the next step.

The mixture of anomers (**9d**) gave the following data: TLC R_f 0.33 [benzene–diethyl ether (3:1)]; $[\alpha]^{23}_D$ +5.26° (*c* 0.89, chloroform); IR 1210 (m), 1085 (s), 1035 (s), 730 (m), 690 (m) cm^{-1}; NMR (220 MHz) δ 2.18 (m, 2, H-2, H-2′), 3.35 and 3.41 (s, 3-OCH_3), 4.5 (m, 2, OC**H**$_2$Ph), 7.27 (s, 5, OCH$_2$**Ph**); mass spectrum, *m/e* 234 (M^+), 143 (M^+ – CH_2Ph).

3-*O*-Benzyl-2,5,6-trideoxy-D-*threo*-hex-5-enofuranose (9e). The anomeric mixture of 2-deoxy furanosides **9d** (11.2 g, 47 mmol) was dissolved in dioxane (100 mL). Glacial acetic acid (250 mL) and water (150 mL) were added, and the solution was stirred for 12 h. The solvent was removed on a rotary evaporator, and the residue was azeotroped with toluene to remove the last traces of solvent. The reaction product was then purified by column chromatography with a benzene–diethyl ether (1:1) mixture to afford the syrupy glycose **9e** (9.0 g, 85%) which gave the following data: TLC R_f 0.37 [benzene–diethyl ether (1:1)]; $[\alpha]^{23}_D$ –7.7° (*c* 2.6, chloroform); IR 3420 (s, br, OH), 2930 (s), 1502 (m), 1455 (m, sh), 1350 (m), 730 (s), 690 (s) cm^{-1}; NMR (220 MHz) δ 2.07 (m, 1, H-2′), 2.25 (m, 1, H-2), 4.03 (ddd, 1, $J_{3,2'}$ = 3.5 Hz, $J_{3,2}$ = 5.5 Hz, $J_{3,4}$ = 4.3 Hz, H-3), 4.32 (dd, 1, $J_{3,4}$ = 4.3 Hz, $J_{4,5}$ = 7.5 Hz, H-4), 4.55 (s, 2, OC**H**$_2$Ph), 5.32 (m, 2, H-6, H-6′), 5.68 (m, 1, H-1), 7.25 (s, 5, OCH$_2$**Ph**).

(3*R*,4*R*)-4-*O*-(Benzyloxy)-8-oxo-3-nonanol (12). The lactol **9e** (535 mg, 2.43 mmol) was dissolved in acetonitrile (40 mL), 1-(triphenylphosphoranylidene)-2-propanone[23] (2.2 g, 6.92 mmol)

(24) Whistler, R. L.; Lake, W. C. *Methods Carbohyd. Chem.* **1972**, *6*, 286.

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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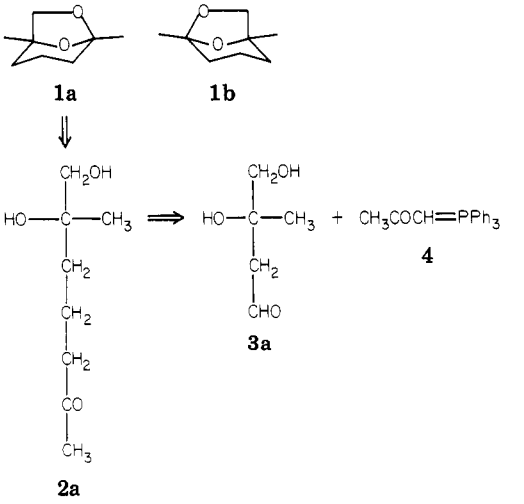
3-Deoxy-2-oxo glycosides with and without a C4 hydroxyl group are readily prepared from methyl α-D-glucopyranoside. Reaction with methylmagnesium iodide gives the C2 tertiary alcohol with an axially oriented methyl group. The epimeric tertiary alcohol can be obtained by methylenation of the ketone followed 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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