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Note

Enantiospecific synthesis of (+)-*exo*-brevicomin from D-xylose*

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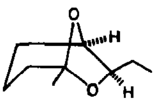
exo-Brevicomin (**1**) is a principal component of the sex attractant of the western pine beetle, *Dendroctonus brevicomis* (Coleoptera:Scolytidea), the pest of the ponderosa pine tree[1]. Due to its importance in the pest control of pine forests coupled with its novel morphological features, several syntheses of **1**, both racemic[2] as well as optically active[3], have appeared. In spite of the fact that **1** has a striking similarity to 1,6-anhydro-α-D-hexopyranoses, the utility of sugars in the chiral synthesis of **1** has not been fully exploited, as only two syntheses[4] of **1** from D-glucose have been reported so far. We now describe a synthesis of (+)-*exo*-brevicomin starting from D-xylose.



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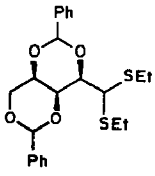

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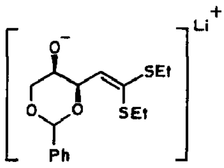

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2,4:3,5-Di-*O*-benzylidene-D-xylose diethyl dithioacetal[5] (**2**), when treated with butyl-lithium at −10°, gave an unstable ketene dithioacetal derivative **3**, which was reduced *in situ* with lithium aluminium hydride to afford the 2-deoxy derivative **4** (overall yield of 29%). The structure of **4** was demonstrated by the ^{1}H-n.m.r. data (loss of the signal for the benzylidene protons, m at δ 2.00 for H-2,2′).

Compound **4** was desulfurised with W-2 Raney nickel in refluxing ethanol to give 80% of the 1,2-dideoxy product **5**, the ^{1}H-n.m.r. spectrum of which contained signals characteristic of a CHEt group. Hydrogenolysis of **5** with aluminium chloride–lithium aluminium hydride (1:1) in refluxing dichloromethane gave a

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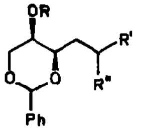
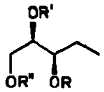
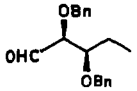
product which appeared to be chromatographically homogeneous but was a 1:1 mixture of isomeric diols (^{1}H-n.m.r. data).



4 R = H, R',R" = SEt
5 R,R',R" = H
6 R = Bn, R',R" = H



7 R,R' = Bn, R" = H
8 R = H, R',R" = Bn
9 R" = Ac, R',R = Bn



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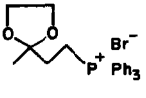
Compound **5** was conventionally *O*-benzylated to give 90% of **6** which, with aluminium chloride–lithium aluminium hydride, gave 50% of **7** and 6.25% of **8**, after chromatography. The structure **7** was assigned by comparing its ^{1}H-n.m.r. spectrum with that of the derived acetate **9**. The resonances for H-1,1' appeared in each spectrum as a doublet, but in that of **9** they were shifted downfield by 0.5 p.p.m., whereas the chemical shifts of all the other resonances were comparable, thereby indicating the presence of a primary hydroxyl group in **7**.

Swern oxidation[6] of **7** at −50° afforded 90% of the aldehyde **10**, which was immediately treated with the phosphonium salt **11** in the presence of butyl-lithium to yield an *EZ*-mixture of the Wittig product **12** (^{1}H-n.m.r. data). Hydrogenation of **12** in the presence of Raney nickel at normal pressure and temperature reduced the double bond and removed the benzyl groups to give 90% of the diol **13**. Brief treatment of **13** with toluene-*p*-sulfonic acid at −10° effected cyclisation to give 74% of (+)-**1**, the analytical and spectral data of which were comparable with those reported for *exo*-brevicomin.



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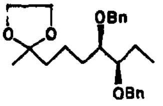

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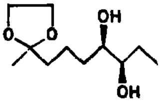

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EXPERIMENTAL

All evaporations were performed under diminished pressure. ^{1}H-N.m.r. spectra were recorded for solutions in $CDCl_3$ (internal Me_4Si) with a Varian FT-80A or Bruker WH-90 spectrometer. Optical rotations were measured with a JASCO DIP-181 polarimeter. All solvents were purified and dried. E.i.-mass spectra were obtained using an AEI MS-30 spectrometer. Column chromatography was performed on silica gel (Acme) (60–120 mesh).

*3,5-O-Benzylidene-2-deoxy-*D-threo-*pentose diethyl dithioacetal* (**4**). — Butyl-lithium (100 mL, 2M solution in hexane) was added to a solution of **2** (43.2 g, 100 mmol) in tetrahydrofuran (300 mL) at −10°. The mixture was stirred for 2 h, lithium aluminium hydride (1.9 g, 50 mmol) was added, and, after further reaction for 4 h at the same temperature, the mixture was quenched with saturated aqueous sodium hydrogencarbonate (20 mL). The precipitate was collected and the solvent was distilled off. Column chromatography (1:4 ethyl acetate–benzene) of the gummy product gave **4** (9.51 g, 29%), $[\alpha]_D^{28}$ +16° (*c* 2.9, chloroform); ν_{max}^{Nujol} 3450 cm^{-1} (OH). Mass spectrum: *m/z* 328 (M^{+}). ^{1}H-N.m.r. data: δ 1.25 (t, 6 H, 2 CH_3), 2.15 (m, 2 H, H-2,2′), 2.65 (q, 4 H, 2 CH_2), 3.45 (bs, OH), 3.60 (bs, 1 H, H-1), 3.90–4.50 (m, 4 H, H-3,4,5,5′), 5.65 (s, 1 H, PhC*H*), 7.43 (m, 5 H, Ph).

Anal. Calc. for $C_{16}H_{24}O_3S_2$: C, 58.52; H, 7.37; S, 19.49. Found: C, 58.60; H, 7.25; S, 19.70.

(4R,5R)-4-Ethyl-2-phenyl-1,3-dioxan-5-ol (**5**). — A mixture of **4** (6.56 g, 20 mmol), ethanol (50 mL), and W-2 Raney nickel (30 g) was boiled under reflux for 6 h, then filtered, and concentrated under reduced pressure to yield **5** as a colourless oil (3.33 g, 80%), $[\alpha]_D^{28}$ −2.5° (*c* 1, chloroform); ν_{max}^{liq} 3450 cm^{-1} (OH). Mass spectrum: *m/z* 208 (M^{+}). ^{1}H-N.m.r. data: δ 1.02 (t, 3 H, CH_3), 1.70 (m, 2 H, CH_2), 2.64 (bs, OH), 3.45 (bs, 1 H, H-4), 3.75–4.10 (m, 3 H, H-3,5,5′), 5.50 (s, 1 H, H-2), 7.35–7.65 (m, 5 H, Ph).

Anal. Calc. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.05; H, 7.80.

(4R,5R)-5-Benzyloxy-4-ethyl-2-phenyl-1,3-dioxane (**6**). — To a suspension of sodium hydride (0.264 g, 11 mmol) in tetrahydrofuran (10 mL) were added, sequentially, solutions of **5** (2.0 g, 9.6 mmol) in tetrahydrofuran (10 mL) and benzyl bromide (1.9 g, 11 mmol) in tetrahydrofuran (10 mL), and the reaction was continued for 2 h. Water (10 mL) was added, the mixture was extracted with ether (4 × 25 mL), the combined extracts were concentrated, and the residue was crystallised from light petroleum to give **6** (2.6 g, 90%), m.p. 90°, $[\alpha]_D^{28}$ −20° (*c* 1.4, chloroform). Mass spectrum: *m/z* 298 (M^{+}). ^{1}H-N.m.r. data: δ 0.88 (t, 3 H, CH_3), 1.70 (m, 2 H, CH_2), 3.50–3.90 (m, 2 H, H-4,5), 4.50 (m, 2 H, H-6,6′), 4.60 (s, 2 H, PhC*H*$_2$), 5.50 (s, 1 H, H-2), 7.25 (m, 10 H, 2 Ph).

Anal. Calc. for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.00; H, 7.20.

(2R,3R)-2,3-Dibenzyloxypentan-1-ol (**7**). — To an ice-cooled mixture of aluminium chloride (1.50 g), lithium aluminium hydride (1.50 g), and ether (20 mL) was added a solution of **6** (2.98 g, 10 mmol) in dichloromethane (30 mL). The mixture was stirred for 6 h at ambient temperature, saturated aqueous sodium carbonate (3 mL) was added, and insoluble material was collected and washed with dichloromethane. The combined filtrate and washings were concentrated, and column chromatography (1:20 acetone–light petroleum) of the residue (2.50 g) afforded (2*R*,3*R*)-1,2-dibenzyloxypentan-3-ol (**8**; 0.19 g, 6.25%), isolated as a syrup, $[\alpha]_D^{28}$ −12° (*c* 1, chloroform). ^{1}H-N.m.r. data: δ 0.90 (t, 3 H, CH_3), 1.45 (m, 2 H, CH_2), 2.20 (bs, 1 H, OH), 3.40–3.70 (m, 3 H, H-1,1′,2), 4.50 (s, 2 H, PhC*H*$_2$), 4.55 (m, 1 H, H-3), 4.65 (ABq, 2 H, PhC*H*$_2$), 7.30 (bs, 10 H, 2 Ph).

Anal. Calc. for $C_{19}H_{24}O_3$: C, 76.00; H, 8.00. Found: C, 76.18; H, 8.00.

Eluted second was **7**, isolated as a syrup (1.50 g, 50%), $[\alpha]_D^{28}$ −3.5° (*c* 1, chloroform). ^{1}H-N.m.r. data: δ 0.90 (t, 3 H, CH_3), 1.55 (m, 2 H, CH_2), 2.10 (bs, 1 H, OH), 3.35–3.80 (m, 4 H, H-1,1′,2,3), 4.58, 4.65 (2 s, 4 H, 2 $PhCH_2$), 7.28 (bs, 10 H, 2 Ph).

Anal. Calc. for $C_{19}H_{24}O_3$: C, 76.00; H, 8.00. Found: C, 76.10; H, 8.00.

(2R,3R)-2,3-Dibenzyloxypentanal (**10**). — To a mixture of dichloromethane (10 mL), oxalyl chloride (0.504 g, 4 mmol), and methyl sulfoxide (0.312 g, 4 mmol) at −60° was added a solution of **7** (1.00 g, 3.3 mmol) in dichloromethane (5 mL). After 15 min, a solution of triethylamine (0.404 g, 4 mmol) in dichloromethane (2 mL) was added, the mixture was allowed to attain room temperature, and water (10 mL) was added. The mixture was extracted with dichloromethane (4 × 15 mL), and the combined extracts were washed with aqueous 10% HCl (10 mL), dried, and concentrated to give **10** as a syrup (0.90 g, 90%), $[\alpha]_D^{28}$ −3° (*c* 1.5, chloroform); ν_{max}^{liq} 1725 cm^{-1} (C=O). Mass spectrum: *m/z* 298 (M^+). ^{1}H-N.m.r. data: δ 0.85 (t, 3 H, CH_3), 1.60 (m, 2 H, CH_2), 3.60 (m, 1 H, H-3), 3.75 (dd, 1 H, *J* 6.5 and 2.0 Hz, H-2), 4.50 (s, 2 H, $PhCH_2$), 4.60 (ABq, $PhCH_2$), 7.25 (bs, 10 H, 2 Ph), 9.60 (d, 1 H, *J* 2.0 Hz, H-1).

Anal. Calc. for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.00; H, 7.25.

2-[(4R,5R)-4,5-Dibenzyloxyhept-2-enyl]-2-methyl-1,3-dioxolane (**12**). — A mixture of 2-(2-bromoethyl)-2-methyl-1,3-dioxolane[7] (0.225 g, 1.1 mmol), triphenylphosphine (0.4 g, 1.5 mmol), and benzene (10 mL) was boiled under reflux and treated with tetrahydrofuran (10 mL) followed by butyl-lithium (0.5 mL, 1.1 mmol) at −10°. The resulting orange-coloured phosphorane was treated with a solution of **10** (0.298 g, 1 mmol) in tetrahydrofuran (5 mL). After 3 h, the mixture was poured into water (10 mL) and extracted with ethyl acetate (3 × 20 mL), and the combined extracts were concentrated. Column chromatography (light petroleum–acetone, 20:1) gave *EZ*-**10** (0.3 g, 75%), isolated as a syrup. Mass spectrum: *m/z* 396 (M^+). ^{1}H-N.m.r. data: δ 0.90 (t, 3 H, CH_3), 1.30 (s, 3 H, CH_3), 1.60 (m, 2 H, CH_2), 2.35 (dd, 2 H, *J* 7.5 and 3 Hz, allylic protons), 3.35 (m, 1 H, H-5′), 3.90 (s, 4 H), 4.20 (dd, 1 H, *J* 9 and 7 Hz, 1 H, H-4′), 4.50 (ABq, $PhCH_2$), 5.35–5.90 (m, 2 H, olefinic protons), 7.30 (bs, 10 H, 2 Ph).

Anal. Calc. for $C_{25}H_{32}O_4$: C, 75.72; H, 8.16. Found: C, 75.10; H, 8.00.

2-[(4R,5R)-4,5-Dihydroxyheptyl]-2-methyl-1,3-dioxolane (**13**). — A solution of **12** (0.12 g, 0.5 mmol) in ethanol was hydrogenated in the presence of W-2 Raney nickel (1 g) until 3 mol of hydrogen had been absorbed (2 h). The insoluble material was collected and washed with ethanol, and the combined filtrate and washings were concentrated under reduced pressure to give **13** (0.1 g, 90%) as an oil, $[\alpha]_D^{28}$ +15° (*c* 3, chloroform); ν_{max}^{liq} 3500 cm^{-1} (OH). Mass spectrum: *m/z* 200 ($M^+ - 18$). ^{1}H-N.m.r. data: δ 1.00 (t, 3 H, CH_3), 1.30 (s, 3 H, CH_3), 1.50 (m, 8 H, 4 CH_2), 2.6 (bs, 2 OH), 3.40 (m, 2 H), 3.95 (s, 4 H, 2 CH_2).

Anal. Calc. for $C_{11}H_{22}O_4$: C, 60.52; H, 10.16. Found: C, 60.10; H, 9.70.

(+)-exo-*Brevicomin* (**1**). — To a moist solution of **13** (0.10 g, 0.46 mmol) in ether was added toluene-*p*-sulfonic acid (0.01 g) at −10°. After 3 h, the reaction was quenched with solid sodium hydrogencarbonate, filtered, and concentrated. Distillation of the residue at 180° (bath) gave **1** (53 mg, 74%) as a colourless liquid, $[\alpha]_D^{28}$ +75° (*c* 1.5, ether). Mass spectrum: *m/z* 156 (M^{+}). ^{1}H-N.m.r. data: δ 0.87 (t, 3 H, *J* 7.0 Hz, CH_3), 1.30 (s, 3 H, CH_3), 1.45 (m, 8 H, 4 CH_2), 3.78 (t, 1 H, 7 Hz, H-7), 3.98 (bs, 1 H, H-1).

Anal. Calc. for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.10; H, 10.20.

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