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Note

An enantiospecific synthesis of (4*R*,5*R*)-5-hydroxy-4-decanolide from D-glucose*

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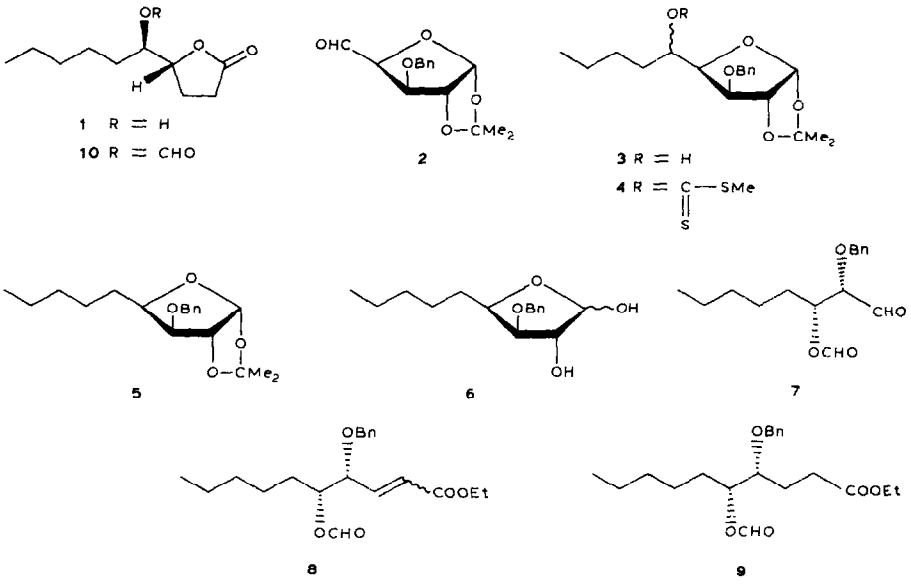
The proposed autoregulators for leukaemomycin biosynthesis, L-factors [(4*S*,5*S*)- and (4*S*,5*R*)-5-hydroxy-4-decanolides], were first isolated[1] from *Streptomyces griseus*. Although the earlier claim[2] of their biological significance has been questioned, asymmetric syntheses[3] from carbohydrate and non-carbohydrate precursors and syntheses[4] of all four diastereoisomers of L-factor have been reported. We now report an enantiospecific synthesis of the unnatural (4*R*,5*R*)-L-factor **1**, starting from D-glucose.



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Treatment of the aldehyde **2** (obtained[5] from D-glucose in four steps) with butylmagnesium bromide at room temperature afforded 77% of a mixture of 6-*C*-propyl-D-gluco-/L-ido-furanose derivatives (**3**). Deoxygenation at position **5** was achieved by the Barton–McCombie procedure[6]. Thus, treatment of **3** successively with sodium hydride, carbon disulfide, and methyl iodide afforded 86% of the xanthate derivative **4**, the ^{1}H-n.m.r. spectrum of which contained a singlet at 2.50 p.p.m. characteristic of an *S*-methyl group. The down-field shift (6.00 p.p.m.) of the resonances due to H-5 suggested that the xanthate group was present at this position. When **4** was heated under reflux with tributyltin hydride and α,α'-azobisisobutyronitrile in toluene, 81% of **5** was obtained.

The isopropylidene group in **5** was removed by treatment with 6M hydrochloric acid in tetrahydrofuran to give the hemiacetal **6**. Treatment of **6** with sodium metaperiodate yielded the unstable aldehyde **7**, which was treated immediately with ethoxycarbonylmethylenetriphenylphosphorane in benzene to give the *E*/*Z*-α,β-unsaturated ester **8**, which was hydrogenated in the presence of excess of Raney nickel to yield **9**, the ^{1}H-n.m.r. spectrum of which contained resonances characteristic of ethoxycarbonyl, *O*-benzyl, and *O*-formyl groups.

Debenzylation of **9** and then lactonisation, using[7] boron trifluoride etherate–dimethyl sulfide, gave 67% of **10**, which showed i.r. absorptions for lactone and *O*-formyl groups. In addition, the ^{1}H-n.m.r. spectrum of **10** contained a signal (s, 8.12 p.p.m.) for the formyl proton, whereas H-4, due to the presence of the formyl group, resonated in the down-field region at 5.23 p.p.m. Treament of **10** with sodium hydroxide in methanol afforded (4*R*,5*R*)-5-hydroxy-4-decanolide[4] (**1**).

EXPERIMENTAL

3-O-Benzyl-6-deoxy-1,2-O-isopropylidene-6-C-propyl-α-D-gluco-/L-ido-furanose (**3**). — To magnesium (0.26 g, 11 mmol) in ether (10 mL) at 15° was added butyl bromide (1.5 g, 11 mmol) in ether (10 mL) under nitrogen. The mixture was stirred for 1 h at room temperature and then cooled to 0°, and 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose[5] (**2**; 2.78 g, 10 mmol) in ether (25 mL) was added during 20 min. The mixture was stored for 4 h at room temperature, saturated aqueous ammonium chloride was added, the aqueous layer was extracted with ether, and the combined ether layers were washed with brine, then dried, and concentrated. Column chromatography (silica gel; ethyl acetate–light petroleum, 1:3) of the residue afforded **3** (2.6 g, 77%), ν_{max} 3500 cm^{-1} (OH). ^{1}H-N.m.r. data ($CDCl_3$): δ 0.95 (t, 3 H, CH_3), 1.32, 1.52 (2 s, 6 H, Me_2C), 1.1–1.6 (m, 6 H, 3 CH_2), 2.25 (bs, 1 H, OH, D_2O exchangeable), 4.0 (m, 2 H, H-3,5), 4.3–4.8 (m, 4 H, H-2,4 and PhCH_2), 5.95 (d, 1 H, *J* 3 Hz, H-1), 7.25 (s, 5 H, Ph).

Anal. Calc. for $C_{19}H_{28}O_5$: C, 67.8; H, 8.4. Found: C, 67.6; H, 8.0.

3-O-Benzyl-5-C-butyl-5-deoxy-1,2-O-isopropylidene-α-D-xylofuranose (**5**). — Sodium hydride (0.96 g, 50% oil dispersion, 20 mmol) was washed with dry hexane and then suspended in dry tetrahydrofuran (20 mL). A solution of **3** (3.36 g, 10

mmol) in tetrahydrofuran (10 mL) was gradually added. After 1 h at room temperature, carbon disulfide (1.5 mL) was added followed by methyl iodide (1.5 mL). The mixture was stirred overnight, then decomposed with methanol (2 mL), and concentrated. The residue was partitioned between water and ether. The ether layer was washed with water, dried, and concentrated. Short-column chromatography (ethyl acetate–light petroleum, 1:5) of the residue gave 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-6-*C*-propyl-α-D-gluco-/L-ido-furanose 5-(*S*-methyl dithiocarbonate) (**4**; 3.7 g, 86%). ^{1}H-N.m.r. data ($CDCl_3$): 0.9 (distorted t, 3 H, CH_3), 1.34, 1.52 (2 s, 6 H, CMe_2), 1.1–1.6 [m, 6 H, $(CH_2)_3$], 2.50 (s, 3 H, SMe), 3.8–4.9 (m, H-2,3,4 and PhCH_2), 5.95 (d, 1 H, *J* 3 Hz, H-1), 6.1 (m, 1 H, H-5), 7.25 (s, 5 H, Ph).

A mixture of **4** (2.13 g, 5 mmol), α,α′-azobisisobutyronitrile (10 mg), and toluene (25 mL) was boiled gently under reflux under nitrogen, and freshly prepared tributyltin hydride (3 mL) was introduced. After 10 h, the mixture was concentrated. Column chromatography (ethyl acetate–light petroleum, 1:10) of the residue gave **5** (1.3 g, 81%), $[\alpha]_D$ −40° (*c* 2, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 0.9 (distorted t, 3 H, CH_3), 1.25, 1.40 (2 s, 6 H, Me_2C), 1.1–2.5 [m, 8 H, $(CH_2)_4$], 3.66 (d, 1 H, *J* 3 Hz, H-3), 4.0 (m, 1 H, H-4), 4.46 (d, 1 H, *J* 3 Hz, H-2), 4.50 (ABq, 2 H, PhCH_2), 5.76 (d, 1 H, *J* 3 Hz, H-1), 7.30 (s, 5 H, Ph).

Anal. Calc. for $C_{19}H_{28}O_4$: C, 71.2; H, 8.8. Found: C, 71.2; H, 8.9.

Ethyl (4R,5R)-4-benzyloxy-5-formyloxydecanoate (**9**). — A mixture of **5** (3.2 g, 10 mmol), 6M hydrochloric acid (3 mL), and tetrahydrofuran (25 mL) was stirred for 3 h, then neutralised (Na_2CO_3), filtered, and concentrated. A solution of the residue in ether was washed with brine, dried, and concentrated to afford **6** (1.95 g, 67%). To a solution of **6** (2.89 g, 10 mmol) in acetone (30 mL) was added water (1 mL) and sodium metaperiodate (4.28 g, 20 mmol). The mixture was stirred at room temperature for 1 h and then concentrated, and the residue was extracted with ether. The extract was washed with brine, dried, and concentrated to afford **7**, which was stirred overnight with benzene (25 mL) and ethoxycarbonylmethylenetriphenylphosphorane (3.48 g, 10 mmol). The benzene was removed under reduced pressure and the residue (*EZ*-**8**) was reduced with Raney nickel (5 g) in ethanol (20 mL) under normal temperature and pressure. After 4 h, the catalyst was collected on Celite and washed with ethanol, and the combined filtrate and washings were concentrated. Column chromatography (ethyl acetate–light petroleum, 1:4) of the residue gave **9** (1.2 g, 54%), $[\alpha]_D$ +31° (*c* 2, chloroform): ν_{max} 1740 cm^{-1} (C=O). ^{1}H-N.m.r. data ($CDCl_3$): δ 0.9–2.5 (m, 18 H), 3.50 (m, 1 H, H-4), 4.04 (q, 2 H, OCH_2CH_3), 4.55 (s, 2 H, PhCH_2), 5.0 (m, 1 H, H-5), 7.30 (s, 5 H, Ph), 8.05 (s, 1 H, O–CHO).

Anal. Calc. for $C_{20}H_{30}O_5$: C, 68.5; H, 8.6. Found: C, 68.7; H, 8.4.

(4R,5R)-5-Formyloxy-4-decanolide (**10**). — To a solution of **9** (0.35 g, 1 mmol) in dichloromethane (3 mL) was added dimethyl sulfide (3 mL) and boron trifluoride etherate (1.42 g). The mixture was stored for 8 h at room temperature

and then diluted with water, and the aqueous layer was extracted with dichloromethane. The combined organic solutions were washed with water, dried, and concentrated. Column chromatography of the residue on silica gel (ethyl acetate–light petroleum, 1:3) gave **10** (0.19 g, 67%), $[\alpha]_D$ +45° (*c* 2, chloroform); ν_{max} 1740, 1790 cm^{-1} (C=O). ^{1}H-N.m.r. data ($CDCl_3$): δ 0.9–2.8 (m, 15 H), 4.5 (m, 1 H, H-4), 5.23 (m, 1 H, H-5), 8.12 (s, 1 H, O–CHO).

Anal. Calc. for $C_{11}H_{18}O_4$: C, 61.7; H, 8.5. Found: C, 61.4; H, 8.7.

(4R,5R)-5-Hydroxy-4-decanolide (**1**). — To a solution of **10** (0.21 g, 1 mmol) in methanol (5 mL) was added a solution of sodium hydroxide (0.5 g) in water (1 mL). The mixture was stored at room temperature for 4 h, then acidified with dilute hydrochloric acid, and extracted with ether. The extract was washed with water, dried, and concentrated. Column chromatography (ethyl acetate–light petroleum, 1:3) of the residue gave **1** (0.15 g, 83%), m.p. 40° (from ethanol), $[\alpha]_D$ −32° (*c* 2, chloroform) {lit.[4] m.p. 42–44°, $[\alpha]_D$ −33.1° (*c* 1.64, chloroform)}; ν_{max} 1770 (C=O), 3470 cm^{-1} (HO). ^{1}H-N.m.r. data ($CDCl_3$): δ 0.9 (t, 3 H, CH_3), 1.2–2.7 (m, 13 H), 3.6 (m, 1 H, H-5), 4.45 (m, 1 H, H-4). Mass spectrum: *m/z* 186 (M^+).

Anal. Calc. for $C_{10}H_{18}O_3$: C, 64.5; H, 9.7. Found: C, 64.3; H, 9.6.

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