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Enantiospecific Synthesis of (4*S*,5*S*)-5-Hydroxydecan-4-olide (L-Factor)

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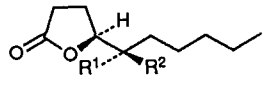
Starting from (2*R*,3*S*)-2,3-dihydroxybutanolide, (4*S*,5*S*)-5-hydroxydecan-4-olide (L-factor) was synthesized, the latter being an autoregulator in the biosynthesis of the anthracycline antibiotic leukaemomycin.

Gräfe isolated L-factors from a culture of *Streptomyces griseus* and identified them as (4*S*,5*R*)-5-hydroxydecan-4-olide **1a** and its (4*S*,5*S*) isomer **1b**.[1] The species were found to be autoregulating agents in the biosynthesis of the anthracycline antibiotic leukaemomycin.



1a; R^1 = H, R^2 = OH (4*S*, 5*R*)
b; R^1 = OH, R^2 = H (4*S*, 5*S*)

Synthetic procedures for the preparation of the (4*S*,5*R*)-, (4*S*,5*S*)- and (4*R*,5*R*)-stereoisomers of **1** from carbohydrates such as tri-*O*-acetyl-D-glucal, D-ribose and D-glucose, respectively, have been reported in the literature.[2–4] As far as non-carbohydrate approaches are concerned, it is worth mentioning the synthesis of all four stereoisomers from the product of asymmetric epoxidation of 1-octen-3-ol.[5]

In this communication we describe a simple scheme for the enantiospecific synthesis of (4*S*,5*S*)-L-factor **1b**. Following our scheme, the required product was obtained from easily available (2*R*,3*S*)-1,3-dihydroxybutanolide **2**.[6]

Lactone **2** reacted with Bu^tMe_2SiCl in a solution of *N*,*N*-

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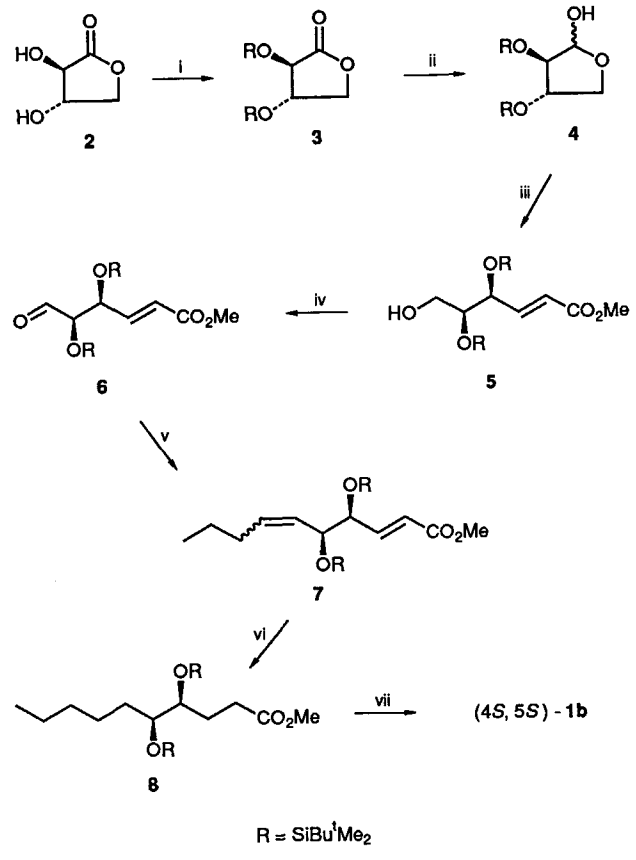

Scheme 1 *Reagents and conditions*: i, Me_2Bu^tSiCl, DMF, imidazole, 25 °C, 5 h; ii, DIBAH, CH_2Cl_2, −78 °C, 2 h; iii, $Ph_3PC{=}CH{-}CO_2Me$, THF, 65 °C, 12 h; iv, $CrO_3 \cdot 2Py/SiO_2$, CH_2Cl_2, 25 °C, 2 h; v, $(Bu^n)^+ PPh_3\ ^-Br$, Bu^nLi; THF, −60 °C, 1 h; vi, H_2, 10% Pd/C, MeOH, 25 °C, 3 h; vii, $Bu^+_4\ NF^-$, THF, 1 h

dimethylformamide (DMF) in the presence of imidazole to give a 98% yield of silyl ether **3**. The latter was treated with diisobutylaluminium hydride (DIBAH) in a solution of CH_2Cl_2, which resulted in an 85% yield of lactol **4**. The lactol was carbomethoxyalkenated to give (4*S*,5*S*)-4,5-di-*O*-(*tert*-butyldimethylsilyl)-6-hydroxy-2*E*-hex-2-enoate **5** in 65% yield.† (4*S*,5*R*)-Aldehyde **6** was produced in 80% yield after oxidation of **5** with $CrO_3 \cdot 2Py$ on silica gel. Smooth condensation of **6** with n-butylidenetriphenylphosphorane resulted in a 74% yield of dienoate **7** as a mixture of isomers according to their geometry at C-7 (*Z*:*E* = 4:1 according to the ^1H NMR spectroscopic data). Compound **7** was hydrogenated on 10% Pd/C in MeOH to give (4*S*,5*S*)-4,5-di-*O*-(*tert*-butyldimethylsilyl)decanoate **8**.‡ Finally, a single-step treatment of **8** with Bu_4NF in tetrahydrofuran (THF) led to the desired (4*S*,5*S*)-5-hydroxydecan-4-olide **1b** in 70% yield.

Thus, (2*R*,3*S*)-2,3-dihydroxybutanolide **2** is a convenient starting compound for the synthesis of optically active natural δ-hydroxy-γ-butyrolactones, in particular (4*S*,5*S*)-5-hydroxydecan-4-olide.§

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† Characterization data for **6**: $[\alpha]_D^{25}$ −54.4° (*c* 0.82, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.07, 0.11, 0.12, 0.14 (4s, 12H, 4Me), 0.9, 0.96 (2s, 18H, $2CMe_3$), 3.72 (s, 3H, OMe), 4.04 (dd, 1H, 5-H, $J_{5,4}$ 4.7, $J_{5,6}$ 1.3 Hz), 4.56 (ddd, 1H, 4-H, $J_{4,2}$ 1.8, $J_{4,3}$ 4.1, $J_{4,5}$ 4.7 Hz), 6.09 (dd, 1H, 2-H, $J_{2,3}$ 15.7, $J_{2,4}$ 1.8 Hz), 7.05 (dd, 1H, 3-H, $J_{3,2}$ 15.7, $J_{3,4}$ 4.1 Hz), 9.61 (d, 1H, 6-H, $J_{6,5}$ 1.3 Hz).

‡ Compound **8**: $[\alpha]_D^{23}$ −44.4° (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.06, 0.09, 0.12, 0.13 (4s, 12H, 4Me), 0.9, 0.92 (2s, 18H, $2CMe_3$), 0.95 (t, 3H, 10-H_3, *J* 6.9 Hz), 1.21–1.38 (m, 5H, 6-Ha, 7-H_2-9-H_2), 1.47 (m, 1*H*, 6-Hb), 1.62 (m, 1H, 3-Ha), 1.98 (m, 1H, 3-Hb), 2.29 (ddd, 1H, 2-Ha, $J_{2a,3a}$ 7.11, $J_{2a,3b}$ 9.1, $J_{2a,2b}$ 16.1 Hz), 2.45 (ddd, 1H, 2-Hb, $J_{2b,3a}$ 6.11, $J_{2b,3b}$ 11.7, $J_{2b,2a}$ 16.1 Hz).

§ Compound (4*S*,5*S*)-**1b**: $[\alpha]_D^{25}$ +34.5° (*c* 0.45, $CHCl_3$); lit.[3] $[\alpha]_D$ +24.8° (*c* 0.7, $CHCl_3$); lit.[5] $[\alpha]_D^{21}$ +33.2° (*c* 1.11, $CHCl_3$).