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THE ENANTIOSPECIFIC SYNTHESIS OF (4S,5R)-AND (4S,5S)-4,5-DIHYDROXYDECANOIC ACID γ-LACTONES, PROPOSED AUTOREGULATORS FROM STREPTOMYCES GRISEUS

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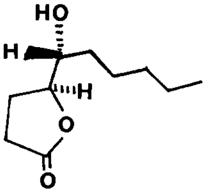
Summary - *Both the (4S,5R)- and (4S,5S)-isomers of 4,5-dihydroxydecanoic acid γ-lactone, natural products and proposed autoregulators of Streptomyces Griseus, have been synthesised directly and in high yield from D-ribose via a common intermediate.*

Recently, the isolation was reported of two novel natural products from strains of Streptomyces griseus, to which were assigned the structures 1 and 2, the (4S,5R)- and (4S,5S)- isomers respectively of 4,5-dihydroxydecanoic acid γ-lactone[1]. These compounds were originally claimed[1] to have autoregulatory properties, inducing the formation of aerial mycelium and the production of the anthracyclinone antibiotic leukaemomycin by mutant strains of S. griseus which had lost the ability to produce the antibiotic. This property is reminiscent of the behaviour of the well-established autoregulator A-factor 3[2] which



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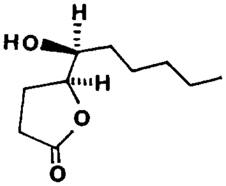

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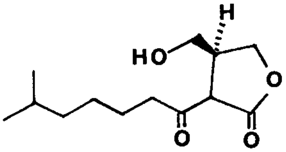

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induces streptomycin production by inactive mutants of *S.griseus.*

Very recently, however, the claim of biological activity for 1 and 2 has been retracted[3], although their status as novel natural products remains secure, and it seems likely that the autoregulatory activity observed was due to contamination of 1 and 2 by trace amounts of the highly potent A-factor 3. The original report of biological activity prompted us to develop a concise high-yielding synthetic route to both 1 and 2 in enantiomerically-pure forms. A multistep synthesis of the (4S,5R)-isomer 1, from triacetyl D-glucal, has been reported recently[4], as have some improvements on this route[5].

2,3-O-Isopropylidene-D-ribose (4), readily available in one step from the free sugar[6], underwent Wittig reaction with carboethoxymethylene triphenylphosphorane (CH_2Cl_2,R.T.,18h)[7] to give the *trans*-alkene 5, which, without rigorous purification, was treated with sodium periodate to give the somewhat unstable aldehyde 6[8,9] (94% from 4) as an oil. Addition of this aldehyde to butylidenetriphenylphosphorane (generated with BuLi, THF,0^o) gave the oily diene ester 7 (84%) as predominantly the 2E,6Z-isomer[9]. Hydrogenation proceeded virtually quantitatively to the saturated ester 8[9], which on exposure to TFA-water (4:1) gave after chromatography the oily (4S,5R)-γ-lactone 1 (91%, 68% from isopropylidene ribose 4), $[\alpha]_D$ + 8.6^o(c 0.9,CCl_4) [lit.[4]$[\alpha]_D$ + 11^o (c 1.37,CCl_4)], $\nu(CHCl_3)$ 1772 cm^{-1}, with spectroscopic properties in excellent agreement[9] with those reported previously[1,4].

The isomeric lactone 2 could also be prepared from intermediate 5. Catalytic hydrogenation followed by periodate cleavage gave the saturated aldehyde 9[9] (81% from 4). On treatment with K_2CO_3 in methanol[10], 9 underwent ready epimerisation to give the *trans*-disubstituted dioxolane system[11], and after reaction with butylidene triphenylphosphorane, alkene 10[9] was isolated in 79% yield. Hydrogenation to 11 (97%) and treatment with aqueous trifluoroacetic acid gave the (4S,5S)-lactone 2 (94%, 58% from 4) as an oil, $[\alpha]_D$ + 24.8^o(c 0.7,$CHCl_3$)$\nu(CHCl_3)$ 1775 cm^{-1} the n.m.r. spectrum of which was in complete agreement with that reported and illustrated[1] for the natural product. In particular, the signal for H-5 appeared at δ 3.56, with the complete absence of the absorbtion at δ 3.94 due to H-5 of the isomer 1.

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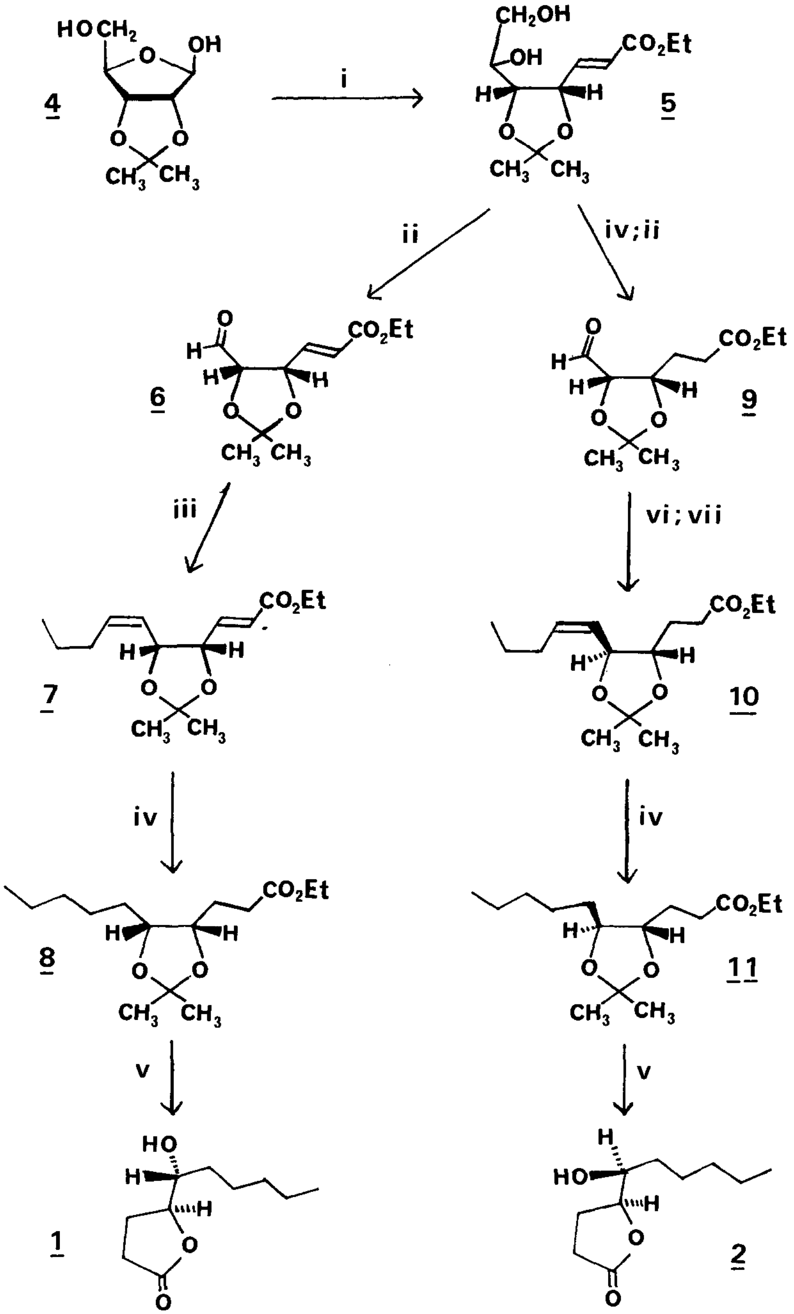

i, Ph_3PCHCO_2Et, CH_2Cl_2, RT, 18h; ii, $NaIO_4$, $MeOH/H_2O$; iii, Ph_3P-C_4H_9.Br, BuLi, THF, 0°, then add aldehyde; iv, H_2, Pd/C, MeOH; v, TFA-H_2O (4:1), RT, 1h; vi, K_2CO_3, MeOH, RT, 2h; vii, as iii, but 2 equiv. phosphorane.

References and Notes

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4. L. Stamatatos, P. Sinaÿ, and J.-R. Pougny, *Tetrahedron*, 40, 1713 (1984).
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7. c.f. P.D. Kane and J. Mann, *J. Chem. Soc., Chem. Commun.*, 224 (1983).
8. Satisfactory spectroscopic and analytical data were obtained on all new compounds.
9. Selected ^{1}H n.m.r. data ($CDCl_3$): 6 (100 MHz) δ1.48, 1.64(each 3H, s), 4.25 (2H, q, $-OCH_2CH_3$), 4.84(1H, dd, J 8, 3 Hz, H-5), 5.90(1H, t, J $\sim$8 Hz, H-4), 6.04(1H, d, J 12 Hz, H-2), 6.30 (1H, dd, J 12, 8 Hz, H-3), 9.64(1H, d, J 3 Hz, CHO). 7 (200 MHz) δ1.41, 1.53 (each 3H, s), 2.08 (2H, m), 4.18 (2H, q), 4.71 (1H, td, J $\sim$6.2 and 1.4 Hz), 5.06 (1H, t, J $\sim$7 Hz), 5.33 (1H, m, H-6), 5.63(1H, dt, J 11.0 and 7.45 Hz, H-7), 6.04(1H, dd, J 15.6 and 1.5 Hz, H-2), 6.79 (1H, dd, J 15.6 and 5.6 Hz, H-3). 8 (200 MHz)δ 1.33 and 1.42 (each 3H, s), $\sim$1.4 (8H, m), 1.75(2H, q, H-3), 2.45 (2H, m, H-2), 4.05 (2H, m, H-4, H-5), 4.12 (2H, q, ethyl). 1 (360 MHz)δ 2.13(1H, dddd, J 12.8, 9.7, 7.4, 5.4 Hz, H-3a), 2.26 (1H, dddd, J 12.8, 10.0, 8.5, 7.2 Hz, H-3b), 2.52(1H, ddd, J 17.8, 9.7, 8.5 Hz, H-2a), 2.59(1H, ddd, J 17.8, 10.0, 5.4 Hz, H-2b), 3.94 (1H, dt, J 6.4, 3.3 Hz, H-5), 4.42 (1H, dt, J 7.3, 3.3 Hz, H-4). 9 (100 MHz) δ 1.36, 1.52 (each 3H, s), 1.8(2H, m), 2.35(2H, m), 4.08 (2H, q), 4.3 (2H, m), 9.60(1H, d, J 3 Hz). 10 (200 MHz)δ 1.37 (6H, s, CMe_2), 3.6 (1H, m, H-4), 4.11(2H, q, ethyl), 4.36(1H, t, J $\sim$8.5 Hz, H-5), 5.33 (1H, dd, J 10.8, 9.2 Hz, H-6), 5.66 (1H, dt, J 10.8, 7.5 Hz, H-7). 11 (200 MHz)δ1.35 (6H, s, CMe_2), 1.5, 1.9, 2.4 (each 2H, m), 3.59(2H, m, H-4, H-5), 4.12 (2H, q, ethyl). 2 (360 MHz),δ 2.10(1H, dddd, J 12.8, 9.9, 8.9, 7.5 Hz, H-3a) 2.24(1H, dddd, J 12.8, 9.5, 7.4, 5.2 Hz, H-3b), 2.52 (1H, ddd, J 17.8, 9.5, 8.9 Hz, H-2a), 2.60(1H, ddd, J 17.8, 9.9, 5.2 Hz, H-2b), 3.56(1H, m, H-5), 4.40(1H, dt, J 7.4, 4.6 Hz, H-4).
10. cf. A.W.M. Lee, V.S. Martin, S. Masamune, K.B. Sharpless, and F.J. Walker, *J. Am. Chem. Soc.*, 104, 3515 (1982).
11. The nature of the material after the epimerisation is not completely clear. The aldehyde signal in the ^{1}H n.m.r. is weak, and extra signals ascribable to methoxy groups are present. It is likely that the material is predominantly a mixture of diastereomeric hemi-acetals.[10] Reaction with *2 equivalents* of phosphorane gives 10 in high yield.

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