Tetrahedron Vol. 40, No. 10, pp. 1713 to 1719, 1984
Printed in Great Britain.

0040-4020/84 $3.00 + .00

SYNTHESIS OF (4S,5R)-(+)-L-FACTOR, A PROPOSED AUTOREGULATOR OF ANTHRACYCLINE BIOSYNTHESIS

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(*Received in France* 16 *December* 1983)

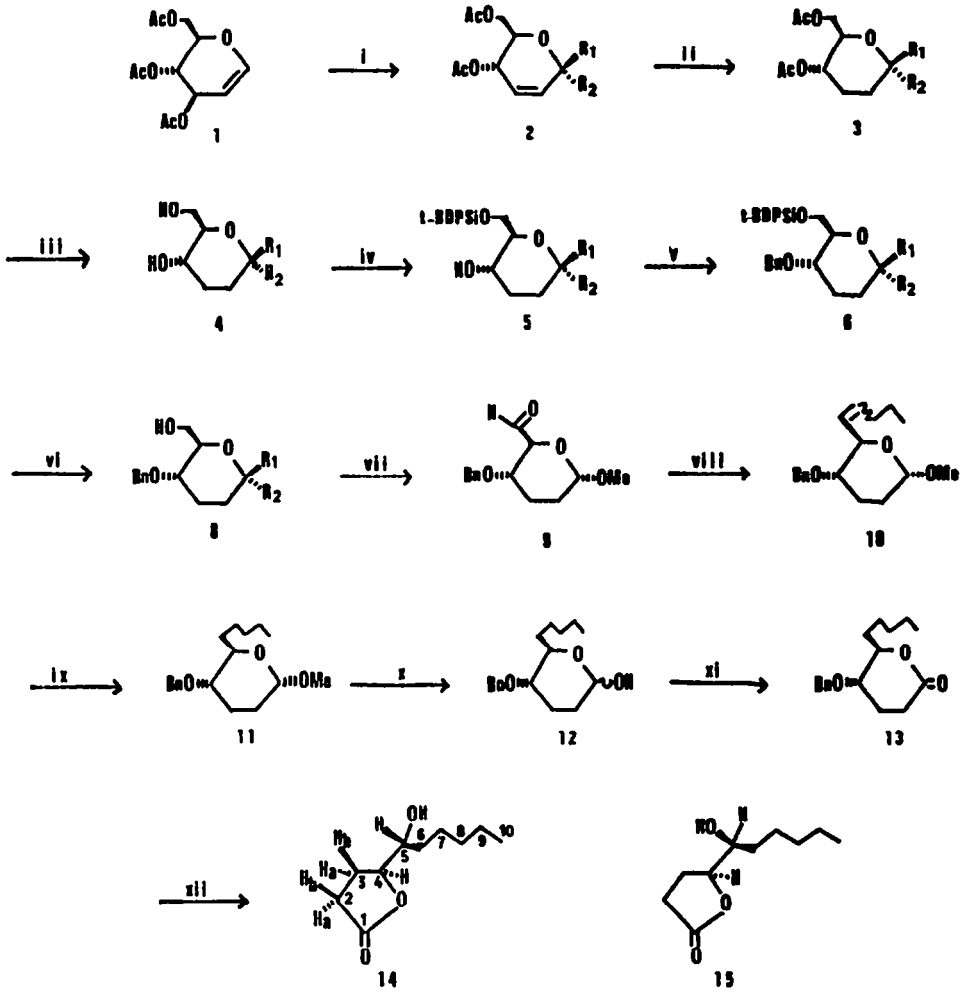
Abstract : A 12 steps synthesis of the 6-C-(n-butyl)-2,3,6-trideoxy-D-erythro-1,4-lactone **14** from commercial 2,3,6-tri-O-acetyl-D-glucal is described.

Morphological differentiation and production of antibiotics in Streptomyces are known to be regulated by common cellular signals such as the size of the metabolite pools, regulatory nucleotides and also by specific signals acting as triggers which are effective with a limited group of microorganisms only[1]. Examples of specific signals are the A-factor which induces formation of aerial mycelium and streptomycin production in certain strains of S. griseus[2], the C-factor, and the antibiotic pamamycin which induces cyto-differentiation in the asporogeneous strains of S. griseus[3] and S.alboniger[4],respectively. Two specific signal substances have recently been isolated[5] which, owing to their effects on the biosynthesis of leukaemycin were termed "L-factors". Structures **14** and **15** have been proposed[5] for these biologically active substances.

We have now synthesized (4S,5R)-(+)-L-factor, namely 6-C-(n-butyl)-2,3,6-trideoxy-D-erythro-1,4-lactone **14** in pure optically active form, starting from commercially available 3,4,6-tri-O-acetyl-D-glucal. (Scheme I)

Our first concern was the synthesis of the glycoside **8**, a useful precursor for carbon-carbon bond formation at the C_6 position. Reaction of 3,4,6-tri-O-acetyl-D-glucal **1** with methanol as described by Ferrier et al.[6] gave methyl-4,6-di-O-acetyl-2,3-dideoxy-α,β-D-erythro-hex-2-enopyranoside **2** which was hydrogenated over Pt to yield the 2,3-dideoxy compound **3** as a mixture of anomers (α : β = 3 : 1, as shown by ^{1}H-n.m.r. spectroscopy). Deacetylation with methanol-water-triethylamine (5:4:1, v/v/v) gave a mixture of diols **4** (α and β) which could not be separated by silica gel chromatography. Diol **4** α and its diacetate were first prepared by A.Canas-Rodriguez et al. using another procedure[7a]. Diols **4** were routinely transformed into the t-butyldiphenylsilyl ethers **5**[8]. Subsequent benzylation of **5** yielded the fully protected glycosides **6**. Finally, desilylation using n-tetrabutylammonium fluoride in dry THF solution[9] afforded the intermediate **8**. On a large scale preparation, purification at this step allowed to isolate pure **8** α anomer in 48 % yield from **1**.

Our second concern was the introduction of a 4 carbons unit at the C_6 position of the deoxysugar. Oxidation of **8** α was best achieved according to Swern et al.[10]. The aldehyde **9** was immediately reacted with the butylidene phosphorane (generated in toluene from n-butyl triphenylphosphonium



R_1 = H, R_2 = OMe α anomer
R_1 = OMe, R_2 = H β anomer

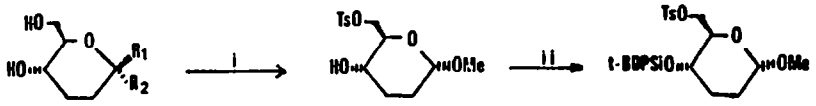
SCHEME I

i, MeOH, BF_3-Et_2O, PhH, 90mn, RT; ii, H_2, PtO_2, MeOH; iii, MeOH-H_2O-Et_3N (5/4/1);iv, t- BDPSiCl, Pyr., RT; v, BnBr, KH, THF, RT; vi, n-$Bu_4N^+F^-$, THF,RT; vii, $(COCl)_2$, DMSO, CH_2Cl_2, 15mn, -78°C then Et_3N; viii, Ph_3P^+-n-$C_4H_9Br^-$, n-BuLi, PhMe, -78°C to RT; ix, Raney Ni, MeOH; x, AcOH-H_2O (4/1), 90mn,75°C; xi,P C C , AcONa, 4Å M.S, CH_2Cl_2; xii, 10% Pd/C, MeOH.

bromide and n-butyl lithium). The insaturated compound 10, isolated in 61 % yield from 8 α was characterized using ^{1}H-n.m.r. and mass spectroscopy . Selective hydrogenation of the double bond in the presence of Raney Ni[11] gave compound 11 in 69 % yield.

Attempts to obtain directly 11 from 7b, synthesized from the known [7b] crystalline monotosylate 7a (Scheme II), failed or resulted in poor yield[12].

Hydrolysis of the deoxyglycoside 11 (80% aqueous acetic acid) gave the hemiacetal 12 (93%) which was oxidized to the corresponding lactone 13 using P C C in the presence of 4Å molecular sieves[13]. Finally, removal of the benzyl ether by catalytic hydrogenation yielded 6-C-(n-butyl)-2,3,6-trideoxy-D-erythro-



SCHEME II

4 7a 7b

R_1 = H, R_2 = OMe, α anomer; R_1 = OMe, R_2 = H, βanomer

i, 1.1 eq.TsCl, Pyr.,R.T., ii, 1.05 eq. t-BDPSiCl, DMF, imidazole, 45°C (20hr).

1,4-lactone 14 as a colourless oil. When this sequence was worked out using the mixture of anomers obtained from Ferrier reaction, (4S,5R)-(+)-L-factor was isolated in an 20 % overall yield.

This compound showed a slow stimulation of aerial mycelium formation, reproductible in six independent assays. But the high concentration needed to perform the biological effect excludes that 14 possess a role as an autoregulator of cytodifferentiation. In contrast to A-factor there was not concomitant formation of anthracyclines[14].

EXPERIMENTAL

^{1}H-n.m.r. spectra were recorded on a Perkin-Elmer R-32 instrument. Chemical shifts are reported in p.p.m. downfield from TMS (δ) as internal standard. Following abbreviations are used for spin multiplicity: s = singlet, d = doublet, dd = doublet of doublet and m= multiplet . Mass spectra were determined on a Ribermag R-10-10C instrument in the chemical ionization mode. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter at ambient temp. I.R spectra were recorded on a Philips Pye Unicam SP3-100 spectrophotometer and are reported in wave numbers (cm^{-1}).

Analytical t.l.c. was performed on 0.25 mm pre-coated silica gel plates purchased from E. Merck.

Reagents and solvents were commercial grades and were used as supplied with the following exceptions:methylene chloride: distilled over phosphorus pentoxide; toluene and hexane : distilled over calcium hydride; ether and tetrahydrofuran (THF):distilled over sodium benzophenone ketyl; dimethylsulfoxide, pyridine and triethylamine:dried over calcium hydride.

All reactions sensitive to oxygen or moisture were conducted under an argon atmosphere.

Elemental analyses were obtained from the Service Central de Micro-Analyse du Centre National de la Recherche Scientifique (Vernaison, France).

Methyl-2,3-dideoxy-α, β-D-erythro-hexopyranoside 4

3,4,6-tri-O-acetyl-D-glucal 1 (26.2g, 96.3mM) was treated according to the procedure described by Ferrier and Prasad[6] to give after distillation (b.p. 122-124°C/ 0.2 mm Hg) 18.1 g (82 %) of the methyl 4,6-di-O-acetyl-2,3-dideoxy- α, β -D-erythro-hex-2-enopyranoside 2. This mixture of anomers was hydrogenated in methanol (90 ml) over PtO_2 (700 mg) to give 18.3 g(100 %) of 3 as a colourless oil[7a] which showed two methoxy proton resonances at 3.38 (major) and 3.60 (minor) indicative of the presence of α and β -anomers in the ratio 3/1[6]. Deacetylation (methanol:100 ml; water:80 ml; triethylamine:20 ml, overnight, room temp.) gave after removal of the solvent and coevaporation of the residue with toluene (3 x 40 ml) the syrupy methyl 2,3-dideoxy- α, β -D-erythro-hexopyranoside 4 (12 g, 100 %)[7a].

Methyl-6-O-(t-butyldiphenylsilyl)-2,3-dideoxy-α,β -D-erythro-hexopyranoside 5

To a cold (0°C) soln. of 4 (12 g, 73.5 mM) in dry pyridine (100 ml) was syringed dropwise t-butylchlorodiphenylsilane[8] (21.1 ml,

81 mM, 1.1 eq.) and the mixture was kept overnight with stirring. The soln. was concentrated then diluted with ether (500 ml) and successively washed with saturated $KHSO_4$, water, brine and dried over Na_2SO_4. After concentration crude 5 was isolated as a syrup (29.4 g) .A sample of this product was chromatographed by silica gel column [eluted with hexane-ethyl acetate (4:1) containing triethylamine (0.1%)] to give:

5 α: m.p. 55-57°C (from ethyl acetate-hexane); ^{1}H-n.m.r.($CDCl_3$):7.68 . (4H,m), 7.35 (6H,m), 4.58 (1H,broad s,H-1), 3.28 (3H,s,OMe), 1.08 (9H,s,t-Bu); i.r. (neat): 3450 (OH); $[\alpha]_D$= +46° (c 3.5, CCl_4); m.s. ($C_{23}H_{32}O_4Si$, M.W.: 400):369 (29), 401 (8), 418 (26); Anal. calcd. for $C_{23}H_{32}O_4Si$: C, 68.96; H, 8.05; found : C, 68.91; H, 8.14.

5 β : syrup; $[\alpha]_D$= -29° (c 1.52, CCl_4); m.s. ($C_{23}H_{32}O_4Si$, M.W.:400): 369 (17), 418 (100); Anal. calcd. for $C_{23}H_{32}O_4Si$: C, 68.96; H, 8.05; found : C, 68.98; H,8.15.

Methyl-4-O-benzyl-6-O-(t-butyldiphenylsilyl)-2,3-dideoxy- α,β -D-erythro-hexopyranoside 6

To a cold (-10°C) soln. of crude 5 (29.4 g, 73.5 mM) in dry THF (200 ml) containing benzyl bromide (9.6 ml, 1.1 eq.) was added by portions a dispersion of potassium hydride (35 wt.% in mineral oil) until the end of evolution of hydrogen. The mixture was then stirred for 4 hr. at 0°C and methanol was added in order to destroy the excess of reagents. The mixture was kept overnight at room temp. prior concentration to dryness. The residue was suspended in ether (600 ml), washed with water, brine and dried over Na_2SO_4. Concentration of the solution gave crude 6 (36 g). A sample was chromatographed by silica gel column [eluted with hexane-ethyl acetate (9:1) containing triethylamine(0.1%)] to give the two anomers :

6 α: syrup; ^{1}H-n.m.r. ($CDCl_3$): 7.65 (4H,m), 7.25 (11H,m), 4.63 (1H,broad s,H-1), 3.30 (3H,s,OMe), 1.08 (9H,s,t-Bu); $[\alpha]_D$= + 62° (c 1.01,CCl_4); m.s. ($C_{30}H_{38}O_4Si$, M.W.: 490) : 459 (100), 508 (31); Anal. calcd. for $C_{30}H_{38}O_4Si$: C, 73.43; H, 7.81; found: C, 73.98; H, 7.88.

6 β : syrup; ^{1}H-n.m.r. ($CDCl_3$) : 7.68 (4H,m), 7.28 (11H,m), 4.57 (1H,broad s,H-1), 4.50 (2H,s,$\underline{CH_2}$Ph), 3.33 (3H,s,OMe), 1.55 (4H,m,H-2,H-2' and H-3,H-3'), 1.08 (9H,s,t-Bu); $[\alpha]_D$= +30° (c 1.30, CCl_4); m.s. ($C_{30}H_{38}O_4Si$, M.W.:490): 459 (20), 508 (60); Anal. calcd.for $C_{30}H_{38}O_4Si$: C, 73.43; H, 7.81; found : C, 73.34; H, 7.96.

Methyl-4-O-(t-butyldiphenylsilyl)-2,3-dideoxy-6-O-p-toluenesulfonyl- α -D-erythro-hexopyranoside 7b.

To a soln. of the monotosylate 7a[7b] (1.98 g, 6.26 mM; obtained by monotosylation of the diol 4 and selective crystallization of the α anomer) in dry DMF (30 ml) was added imidazole (1g,15.6 mM, 2.5 eq.) and t-butylchlorodiphenylsilane (1.9 ml, 6.9mM, 1.05 eq.). The homogeneous mixture was kept overnight at 50°C then evaporated to dryness and the residue was diluted with ether (150 ml). The organic layer was successively washed with aqueous $NaHCO_3$, water, brine, dried over Na_2SO_4 and concentrated to give crude 7b. After column chromatography on silica gel [eluted with hexane-ethyl acetate (9:1) containing triethylamine (0.1 %)] pure 7b was isolated as a syrup (2.6 g, 74%). ^{1}H-n.m.r. ($CDCl_3$) :7.65 (6H,m), 7.30 (8H,m), 4.42 (1H,broad s,H-1), 3.25 (3H,s,OMe), 2.40 (3H,s,CMe), 1.60 (4H,m,H-2, H-2' and H-3, H-3'), 0.96 (9H,s,t-Bu); i.r. (neat) : 1360 and 1180 (OSO_2); $[\alpha]_D$= +54° (c 0.87, CCl_4); m.s. ($C_{30}H_{38}O_6SSi$, M.W.:554) : 572 (12); Anal. calcd. for $C_{30}H_{38}O_6Si$: C, 64.95;

H, 6.90; found : C, 64.86; H, 6.78.

Methyl-4-O-benzyl-2,3-dideoxy- α-D-erythro-hexopyranoside 8 α

To a cold soln. of crude **6** (36g, 73.5mM) in dry THF (200ml) was added via a double tip needle a freshly prepared soln. of n-tetrabutylammonium fluoride[9] in dry THF (1M soln.,147mM, 2 eq.) with stirring. After 4hr at room temp. the reaction mixture was concentrated, diluted with toluene (100ml) and filtered through silica gel. Elution with a mixture of toluene - ethyl acetate [(7:3), 300ml)] then evaporation yielded crude **8** which was purified by flash chromatography on silica gel [250g, eluted with hexane-ethyl acetate (7:3)] to give **8 α** (11.9g,48% from starting 3,4,6-tri-O-acetyl-D-glucal **1**) as a syrup.[1]H-n.m.r. ($CDCl_3$): 7.28 (5H,s,Ph), 4.65 (1H,broad s,H-1), 4.53 (2H,m,$\underline{CH_2}$Ph), 3.30 (3H,s,OMe), 2.47 (1H,broad s,OH, exchangeable with deuterium oxide); i.r. (neat) : 3440 (OH); $[\alpha]_D$= +129° (c 1.35, CCl_4); m.s.($C_{14}H_{20}O_4$, M.W.: 252) : 221 (66), 270 (17); Anal. calcd. for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99; found: C, 66.47; H, 8.03.

Methyl-4-O-benzyl-2,3-dideoxy-6-aldehydo-α-D-erythro-hexo-dialdo-1,5-pyranoside 9

To a cold (-78°C) soln. of oxalyl chloride (1.74ml, 20mM, 5eq.) in CH_2Cl_2 (30 ml) was added dropwise a soln. of dimethyl sulfoxide (3.1ml, 43.6mM) in CH_2Cl_2 (7ml)[10]. The mixture was stirred for 5 mn at -78°C and then a soln. of **8 α** (1.04g, 4mM) in CH_2Cl_2 (5ml) was added dropwise via double tip needle with stirring . After 15 mn at -78°C, Et_3N (12.6ml, 91mM) was added dropwise via syringe and stirring was continued for 15 mn at this temp. The mixture was allowed to warm to -30°C and partitioned between ether (150ml) and 1 N aq.HCl (60ml). The organic layer was washed with water, aq. $NaHCO_3$ soln., then brine, dried over $MgSO_4$, concentrated under reduced pressure to give 1g of crude aldehyde **9** which was not further purified .[1]H-n.m.r. ($CDCl_3$) :9.51 (1H,d,$J_{6,5}$:1.3Hz,H-6), 7.18 (5H,s,Ph), 4.58 (1H,broad s,H-1), 4.45 (2H,s, $\underline{CH_2}$Ph), 3.90 (1H,dd,$J_{5,4}$:9.0Hz,H-5), 3.28 (3H,s,OMe); i.r. (neat) : 1738 (C=O); m.s. ($C_{14}H_{18}O_4$, M.W. : 250) : 250 (12), 251 (15), 268 (7).

Methyl-4-O-benzyl-6-C-(n-butylidene)-2,3,6-trideoxy- α -D-erythro-hexopyranoside 10

After coevaporation with dry toluene (3 x 10 ml), aldehyde **9** was dried under vacuum (30 mn) and immediately used for the Wittig reaction. Dry n-butyl triphenyl phosphonium bromide (4.7g,12mM,3eq.) was suspended in dry toluene (35 ml). A soln.of n-butyl lithium in hexane (1.7M,5.7 ml,10 mM,2.5eq.) was added dropwise at 0°C with stirring . The deep orange soln. was further stirred for 15 mn, the lithium bromide allowed to deposite and the phosphorane was cooled to -78°C. To a cold (-78°C) soln. of **9** in dry toluene (10 ml) was added dropwise via double tip needle the phosphorane until the orange colour persisted.The mixture was then allowed to warm to room temp. Excess of phosphorane was destroyed with acetone (0.5 ml), and the mixture was filtered through silica gel under vacuum and eluted with ether (150 ml) . The filtrate was concentrated under reduce pressure to afford crude **10** which was chromatographed by silica gel column [eluted with hexane-ether(15:1)]. Syrupy **10** was isolated (700mg,61% from **8**) as a mixture of cis and trans isomers. [1]H-n.m.r (C_6D_6) : 7.16 (5H,m,Ph), 5.56 (2H,m,ethylenic H), 4.50 (1H,broad s,H-1), 4.38 (2H,s,$\underline{CH_2}$Ph), 3.21 (3H,s,OMe), 2.15 (2H,m,vinylic $\underline{CH_2}$), 0.86 (3H,d,J:7.0Hz,CH_3); $[\alpha]_D$= +51° (c 0.57, CCl_4); m.s. ($C_{18}H_{26}O_3$, M.W.: 290) : 259 (69), 276 (100), 290 (4), 308 (31); no satisfactory analysis of this product has been obtained.

Methyl-4-O-benzyl-6-C-(n-butyl)-2,3,6-trideoxy-α-D-erythro-hexopyranoside 11

To a soln. of 10 (446mg,1.53 mM) in methanol (2 ml) was added a suspension of Raney Ni (washed with methanol,10 ml) and hydrogen was bubbled for 3 hr at room temp.[11]. The mixture was then filtered and the catalyst washed thoroughly with toluene (60 ml) . Concentration of the combined filtrates afforded crude 11 (423 mg) which was further purified by silica gel column chromatography [eluted with hexane-ether (10:1)] to give pure 11 (312 mg, 69%) as a syrup. ^{1}H-n.m.r. ($CDCl_3$):7.25 (5H,s,Ph), 4.45 (1H,broad s,H-1), 3.30 (3H,s,OMe); $[\alpha]_D$= +133° (c 1.37, CCl_4), m.s.($C_{18}H_{28}O_3$, M.W.:292) : 261 (15), 278 (86), 310 (100); Anal. calcd. for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65; found : C, 74.15; H, 9.54.

4-O-benzyl-6-C-(n-butyl)-2,3,6-trideoxy-D-erythro-hexopyranoside 12

A soln. of the glycoside 11 (311.6mg, 1.07mM) in a mixture of acetic acid-water (8:2,v/v,30 ml) was heated for 90 mn at 75°C. After this time, the soln. was concentrated to dryness and the oily residue was coevaporated with toluene (3 x 10 ml) to give crude 12 (323 mg) . Chromatography on silica gel column [eluted with hexane-ethyl acetate (4:1)] gave the hemiacetal 12 (276 mg, 93%) as a colourless syrup. ^{1}H-n.m.r. ($CDCl_3$) :7.3 (5H,s,Ph), 5.1(1H,broad s,H-1), 4.54 (2H,m,$\underline{CH_2}$Ph),0.90 (3H,broad d,CH_3); i.r.(neat) : 3450 (OH); $[\alpha]_D$= +88° (c 0.51 (CCl_4); Anal. calcd. for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41; found : C, 73.20; H, 9.49

4-O-benzyl-6-C-(n-butyl)-2,3,6-trideoxy-D-erythro-1,5-lactone 13

To a suspension of pyridinium chlorochromate (1.2g, 5.58mM, 6eq.), sodium acetate (1g) and 4 Å powdered molecular sieves (300mg) in dry CH_2Cl_2 (20 ml) was added a soln. of the compound 12 (276mg, 0.93mM) in dry CH_2Cl_2 (5ml)[13]. The mixture was stirred at room temp. for 2 hr then diluted with ether (15ml) and the suspension was then filtered through silica gel . Elution with hexane-ethyl acetate (8:3) gave, after concentration of the solvent, pure lactone 13 (202mg, 74%), as a colourless oil. ^{1}H-n.m.r. ($CDCl_3$) : 7.28 (5H,s,Ph), 4.52 (2H,m,$\underline{CH_2}$Ph), 4.25 (1H,m,$J_{4,5}$:10.0Hz,$J_{4,3ax}$:7.0 Hz,H-4), 3.50 (1H,dd,$J_{5,4}$:10.0 Hz,$J_{5,6}$: 6.0 Hz,H-5), 2.65 (1H,m,$J_{2ax,3eq}$:2.0 Hz,$J_{2ax,3ax}$:9.0 Hz,$J_{2ax,2eq}$:14.0 Hz,H-2ax), 2.35 (1H,m,$J_{2eq,3ax}$:5.0 Hz,H-2eq.), 1.98 (2H,m,H-3ax and H-3eq.), 1.70-1.10 (8H,broad m,CH_2), 0.90 (3H,broad s,CH_3); i.r. (neat) : 1730 (C=O); $[\alpha]_D$= +106° (c 0.69,CCl_4); Anal. calcd. for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75; found: C, 73.53; H, 8.70.

6-C-(n-butyl)-2,3,6-trideoxy-D-erythro-1,4-lactone 14

A soln. of the lactone 13 (202mg, 0.72mM) in methanol (20 ml) was hydrogenated over 10% Pd/C. The reaction was carefully monitored by t.l.c. [elution with hexane-ethyl acetate (1:1)] until desappearance of the starting lactone 13 (Rf. 0.70) and formation of a single product (Rf. 0.45). After 48hr two products were present, probably due to the formation of the pyranoïd (Rf. 0.40) and furanoïd (Rf. 0.45) lactones and the reaction was allowed to go to completion.

After 96hr, a single product (Rf. 0.45) was isolated after filtration and evaporation of the soln . Purification by chromatography over silica gel [elution with hexane-ethyl acetate (7:3)] yielded 14 as a colourless oil (126 mg,93%). ^{1}H-n.m.r. ($CDCl_3$, 250 MHz):4.45 (1H,m,$J_{4,3a}$:7.3 Hz, $J_{4,3b}$:6.2 Hz, $J_{4,5}$:3.5 Hz,H-4), 3.90 (1H,m,$J_{5,6}$:6.5 Hz,H-5), 2.60 (1H,m,$J_{2a,2b}$:18.0 Hz,$J_{2a,3a}$: 10.0Hz,$J_{2a,3b}$:8.5Hz,H-2a), 2.50 (1H,m, $J_{2b,3a}$:8.4Hz, $J_{2b,3b}$:9.5Hz,H-2b), 2.25 (1 H,m,$J_{3a,3b}$:13.0Hz, $J_{3a,4}$:7.2 Hz, H-3a), 2.15 (1 H,m,$J_{3b,4}$:6.2Hz,H-3b); ^{13}C-n.m.r.

(C_6D_6, WP-80 Brucker) : 177.43 (C-1), 83.02 (C-4), 71.55 (C-5), 32.47 (C-6), 32.15 (C-8), 28.71 (C-2),25.71 (C-7), 22.98 (C-9), 21.18 (C-3), 14.24 (C-10); i.r. (5 mg/ml in $CDCl_3$): 3605 (OH), 1770 (C=O); $[\alpha]_D$= +11° (c 1.37,CCl_4); m.s. ($C_{10}H_{18}O_3$, M.W.:186) [C.I, NH_3], 186 (13), 187 (46), 204 (100); [E.I.] 158 (M^+-CO, $C_9H_{18}O_2$), 101 (side chain,$C_6H_{13}O$), 86 (butyrolactone moiety, $C_4H_6O_2$); Anal. calcd. for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74; found : C, 64.70; H, 9.81.

Acknowledgment - Dr. J.Y. Lallemand (I.C.S.N., Centre National de la Recherche Scientifique, Gif-Sur-Yvette) for ^1H. 250 MHz n.m.r., G. Keravis for m.s. and Dr. U. Gräfe (Akademie der Wissenschaften der D.D.R., Iena) for biological assays are gratefully acknowledged.

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