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SYNTHESIS OF TWO KEY INTERMEDIATES REQUIRED FOR THE CONSTRUCTION OF THE BIS-SPIROACETAL MOIETY OF epi-17-DEOXY-(0-8)-SALINOMYCIN

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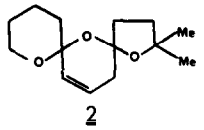
Abstract: The synthesis of two key intermediates required for the construction of the bis-spiroacetal moiety of epi-17-deoxy-(0-8)-salinomycin (1), namely, lactone (3) and acetylene (4), is described.

In an earlier communication[1] we reported the preparation of the novel unsaturated bis-spiroacetal (2) in which the stereochemistry was later established to be the same as that found in the bis-spiroacetal moiety of epi-17-deoxy-(0-8)-salinomycin (1)[2]. Using the same strategy for the synthesis of the model bis-spiroacetal (2), the bis-spiroacetal moiety of epi-17-deoxy-(0-8)-salinomycin (1) was envisaged to be derived from a lactone fragment (3) and an acetylenic fragment (4) (Scheme 1). The syntheses of these latter two building blocks are described.



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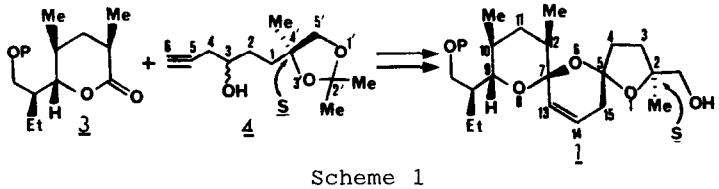

Scheme 1

The S configuration at C-2 in the bis-spiroacetal moiety of the natural product necessitated the synthesis of the acetylene (4) in which the configuration at C-4' was also S. Since C-3 of the acetylene is to be transformed into a spirocentre it was not necessary to control the stereochemistry at this carbon. The successful approach to the (4'S)-acetylene (4) involved the addition of the Grignard reagent of propargyl bromide to the (S)-aldehyde (5) (Scheme 2). The (S)-aldehyde (5) in turn was prepared in several steps from the simple intermediate (S)-(-)-lactonic acid (6) which was available *via* a 'classical' resolution. Large quantities of racemic lactonic acid (6) were prepared from levulinic acid (7) by cyanohydrin formation and acid hydrolysis according to the method of Iwanami and Kawai[3]. After resolution of its cinchonine salt[4] (S)-(-)-lactonic acid (6) was reduced with lithium

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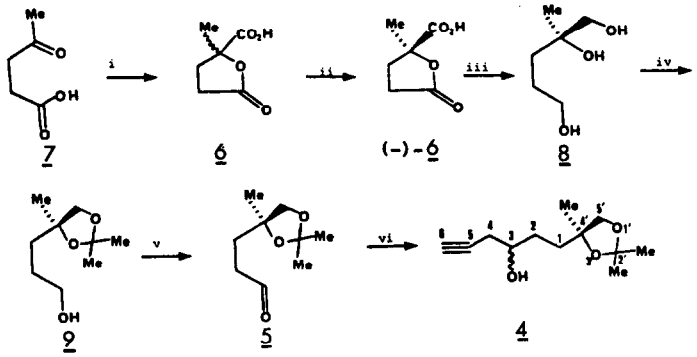
aluminium hydride in 53% yield to the (S)-triol (8) which afforded (S)-acetonide (9) in 83% yield upon treatment with acetone and p-toluene-sulphonic acid. The optical rotations of these latter two intermediates were in agreement with the literature values[4]. Oxidation of the (S)-alcohol (9) using dimethylsulphoxide activated with trifluroacetic anhydride at -60°C yielded the (S)-aldehyde (5) ($[\alpha]_D^{23}$+ 1.5° (c, 2.48, CCl_4)) in 68% yield which upon addition to the magnesium Grignard reagent of propargyl bromide gave the required (4'S)-acetylene (4) in 81% yield. The product was established to be a 1:1 mixture of the (3R, 4'S)- (3S, 4'S)-diastereomers from 360MHz 'H n.m.r.

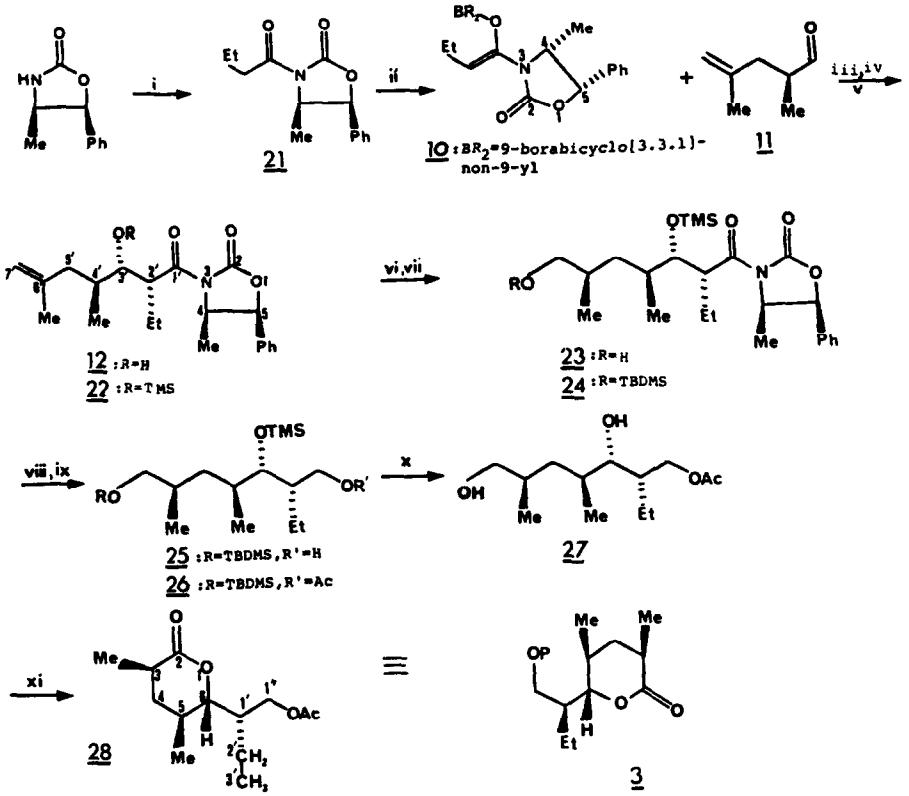


Reagents: i) NaCN, H_2O, 0.5h., R.T., then HCl(conc.), Δ, 4h. 83%; ii) cinchonine, recrystallisation and separation, then 10% HCl, continuous extraction (Et_2O), 48h.; iii) $LiAlH_4$, R.T., 15h., 53%; iv) acetone, p-TSA, R.T., 15h., 83%; v) DMSO, TFAA, Et_3N, -60°C, CH_2Cl_2, 68%; vi)  Br, Mg, $HgCl_2$(cat.), 81%.

Scheme 2

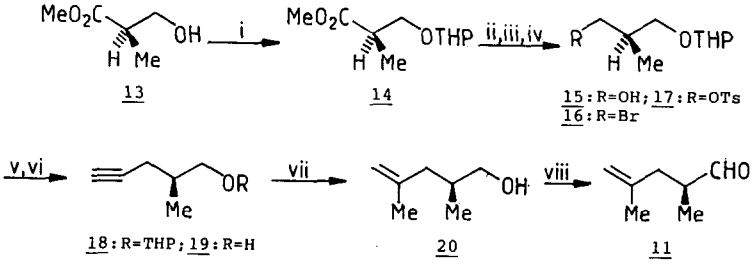
The key step in the synthesis of lactone (3) was the directed aldol condensation of the (Z)-boron enolate (10) with the optically active aldehyde (11) (Scheme 3). This was expected to give the required 2',3'-erythro, 3',4'-threo product (12) based on a similar aldol condensation used by Evans and Bartroli[5] in their synthesis of (+)-Prelog Djerassi lactone. Large quantities of (S)-aldehyde (11) were easily obtained from the optically active building block (R)-3-hydroxy-2-methylpropionate (13) (Scheme 4). After protection of the alcohol (13) as a tetrahydropyranyl ether (14) reduction of the ester group with lithium aluminium hydride afforded the alcohol (15) which was converted in high yield to the corresponding bromide (16) via the tosylate (17). Addition of the bromide (16) to an excess of lithium acetylide afforded the acetylene (18) in 60% yield which after deprotection to the alcohol (19) underwent carboalumination[6] with trimethylaluminium and zirconocene dichloride for 15h at room temperature to the alkene (20) in 82% yield. The material isolated exhibited an optical rotation in agreement with the literature[5]. Subsequent oxidation using pyridine-sulphur trioxide provided the required (S)-aldehyde (11) in 64% yield.

With the aldehyde (11) in hand, condensation with the (Z)-boron enolate (10) prepared by treatment of butanoyl oxazolidinone (21) with 9-borabicyclo [3.3.1]nonyl trifluoromethanesulphonate (1.1 eq) and diisopropylethylamine (1.2 eq) at 0°C for 0.5h afforded the diasteromerically homogeneous aldol adduct (12) in 84% yield after purification by 'flash' chromatography[7]. Treatment of the derived trimethylsilyl ether (22) with thexylborane in tetrahydrofuran at 0°C for 5h followed by bicarbonate peroxide oxidation afforded the alcohol (23) in 69% yield. The stereochemistry assigned to C-6' was based on the stereochemical outcome of the analogous hydroboration step in Evans' synthesis of (+)-Prelog-Djerassi lactone and was confirmed at a later stage in the synthesis. Formation of the tert-butyldimethylsilyl ether (24) followed by removal of the chiral auxiliary with lithium borohydride afforded the alcohol (25) in 71% yield. After formation of the acetate



Reagents: i) Bu^nLi, THF, -78°C, $CH_3(CH_2)_2COCl$, 91%; ii) BR_2OTf (1.1eq), Pr^iEtN (1.2eq), 0°C, 0.5h, CH_2Cl_2; iii) (11), -78°C to 25°C, 2h; iv) MeOH H_2O_2, 1h, 0°C, 84% overall; v) Me_3SiNEt_2 (1.5eq), DMAP (0.2eq), CH_2Cl_2, RT, 15h, 85%; vi) $C_6H_{13}BH_2$ (2eq), THF, 0°C, 5h, then aq $NaHCO_3$, H_2O_2, RT, 12h, 69%; vii) TBDMSOTf (1.5eq) 2,6-lutidine (2.2eq), 0.25h, 0°C, 94%; viii) $LiBH_4$ (1eq), THF, RT, 15h, 71%; ix) Ac_2O (1eq), Et_3N (2eq), DMAP, RT, 2h, 92%; x) MeOH, Amberlite IR 118, RT, 1.5h; xi) N-methylmorpholine-N-oxide (2eq), $RuCl_2(PPh_3)_3$ acetone, RT, 3h, then Ag_2CO_3 on celite, toluene, Δ, 1h, 68% overall.

(26), the silicon protecting groups were easily removed using Amberlite IR 118 in methanol affording the diol (27), which was directly oxidized to the lactone (28) using N-methylmorpholine-N-oxide catalysed by $RuCl_2(PPh_3)_3$ followed by silver carbonate on celite ($[\alpha]_D^{21}$+ 77.6° (c, 0.51, CCl_4); δ_H (360 MHz, $CDCl_3$) 0.93 (3H, d, J 6.3 Hz, 5-Me), 0.95 (3H, t, J 7.6 Hz, $-CH_2CH_3$), 1.24 (3H, d, J 7.1 Hz, 3-Me), 1.39 (1H, q, J 12 Hz, 4ax-H), 1.48-2.04 (5H, m, 4eq-H, 5ax-H, -CH(Et), and $-CH_2CH_3$), 2.06 (3H, s, $-COCH_3$), 2.43-2.55 (1H, m, 3ax-H), 4.06 (1H, t, J 11 Hz, $-CH_AH_BOAc$), 4.14 (1H, d, J 11 Hz, $-CH_AH_BOAc$), and 4.32 (1H, dd, $J_{1',6}$ 5.3 and $J_{5,6}$ 10.6 Hz, 6ax-H); ν_{max} (thin film) 2970, 2940, 2880, 1740, 1380 and 1240 cm^{-1}). The axial proton attached to C-4 resonated as a quartet at δ_H 1.39 with the coupling constant J 12 Hz establishing that the methyl substituents at C-3 and C-5 occupied equatorial positions. Similarly, the proton attached to C-6 resonated as a double doublet at δ_H 4.32 with the coupling constants $J_{5,6}$ 10.6 Hz and $J_{1',6}$ 5.3 Hz, indicating that the substituent at C-6 also occupied an equatorial position.



Reagents: i) DHP, p-TSA, R.T., THF, 100%; ii) $LiAlH_4$, Et_2O, 0°C, 15h, 90%; iii) TsCl, py, 0°C, 100%; iv) LiBr (4 equiv.), $NaHCO_3$, THF, Δ, 92%; v) $Li^{+-}C{\equiv}CH$ (5 equiv.) liq.NH_3, 15h, 60%; vi) MeOH, Amberlite IR 118, room temp., 15h, 92%; vii) Me_3Al, Cl_2ZrCp_2, $Cl(CH_2)_2Cl$, R.T., 15h, aqueous work-up, 82%; viii) py, SO_3, DMSO, Et_3N, 25°C, 3h, 64%.

Scheme 4

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