Tetrahedron Letters,Vol.30,No.8,pp 985-988,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

SYNTHESIS OF (±)-TALAROMYCINS A, B, C AND E

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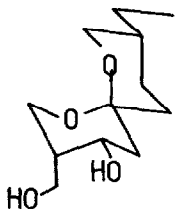
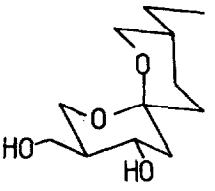
Summary - Two key unsaturated spiroacetals have been used in the synthesis of talaromycins A, B, C and E by routes involving chlorohydration and reductive dechlorination.

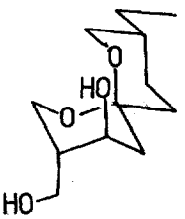
The talaromycins A (1) and B (2) were isolated from the fungus Talaromyces stipitatus which grows on woodshavings-based animal feedstuffs, and were shown to be avian toxins[1]. Their activity arises through the blocking of outward potassium fluxes in smooth muscle leading to muscle dysfunction. In a more detailed re-examination of extracts from Talaromyces stipitatus, Lynn and co-workers isolated four more spiroketals, talaromycins C-F[2] (3 - 6). Both enantioselective[3] and syntheses of the racemic talaromycins[4] have been reported. In this letter we report the stereodivergent synthesis of talaromycins A, B, C and E from common intermediates.



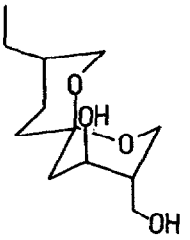
Talaromycin A (1)



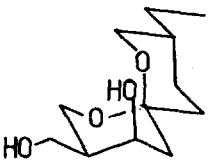
Talaromycin B (2)



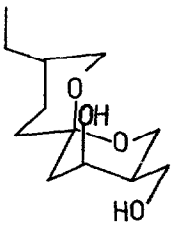
C (3)



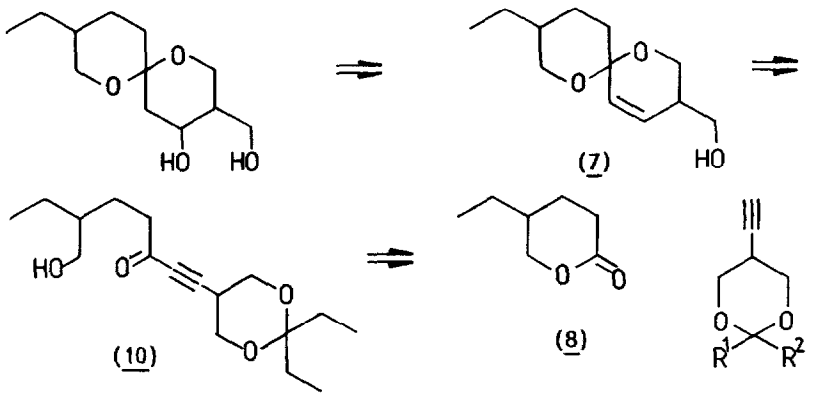
D (4)



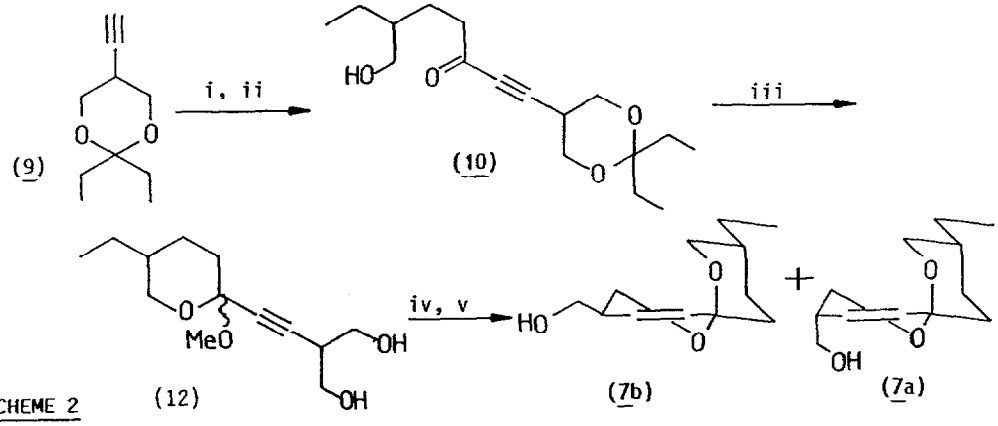
E (5)



F (6)



SCHEME 1

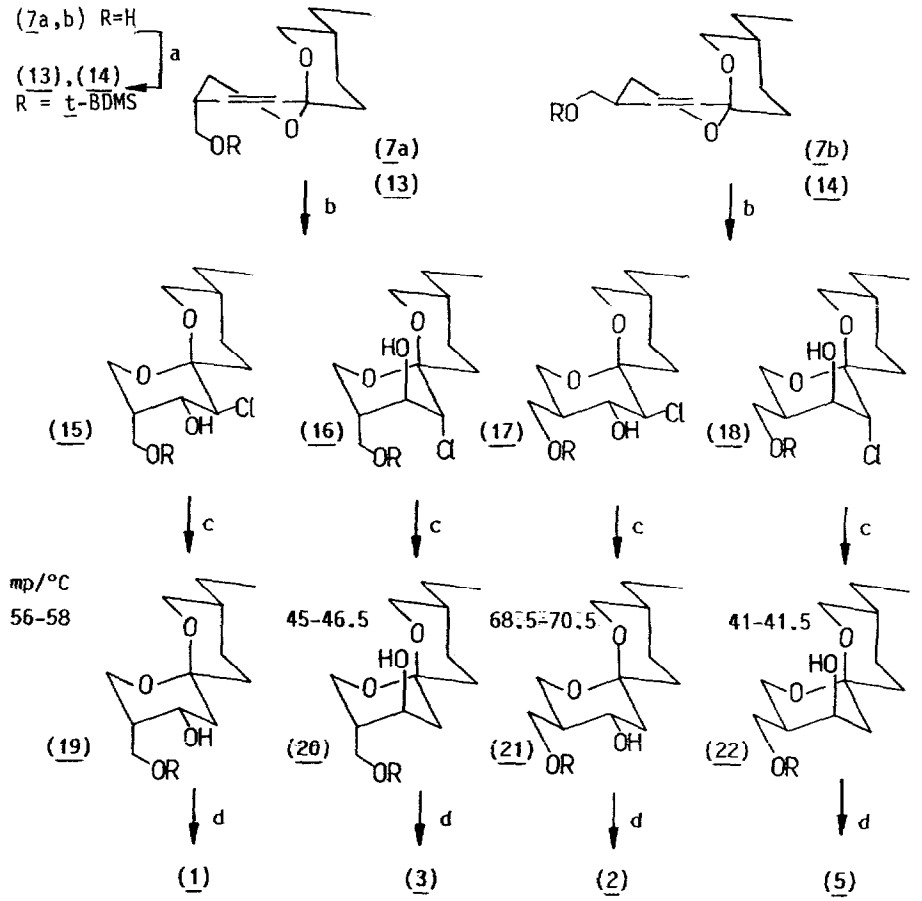


SCHEME 2

Reagents: i) n-BuLi, THF, -78°C; ii) (8), 78%; iii) MeOH, Amberlyst-15, 100%
iv) H_2/Pd/$CaCO_3$/Pb, MeOH; v) dl-camphorsulphonic acid, CH_2Cl_2, 78%

Retrosynthetic analysis indicated the olefinic spiroacetal (7) to be an important intermediate. This spiroacetal could be prepared by the addition of a substituted δ-valerolactone (8) to the lithium anion of a suitably protected acetylenic diol (9), followed by partial hydrogenation of the keto-acetylene (10) to the Z-olefin and acid catalysed spirocyclisation[5] (Scheme 1). The acetylene (9) was prepared in 27% overall yield from diethyl malonate in seven steps and was obtained as a colourless oil (bp 40-45°C @ 2mmHg)[6].

Addition of the lactone[7] (8) to the lithium anion of acetylene (9) (Scheme 2) gave the hydroxyketo-acetylene (10) in 79% yield as an oil (bp 117°C @ 0.06mmHg); ν_{max} 2220cm^{-1} (C≡C) and 1680cm^{-1} (α,β-unsaturated carbonyl). Formation of the mixed methoxyacetal was accompanied by cleavage of the 1,3-dioxane ring to yield the acetylenic diol (12) in 87% yield as a 3:1 mixture of axial and aquatorial anomers which could be separated by flash chromatography on elution with EtOAc:petroleum (3:2→4:1) to afford the equatorial anomer as a colourless oil and the crystalline axial anomer (mp 73.5-74.5°C). Partial hydrogenation of the acetylenic diol (12) and acid catalysed



SCHEME 3
Reagents: i) t-BDMSCl, imidazole, DMF, 84% ii) t-BuOCl, acetone, H_2O (10:1); iii) n-Bu_3SnH, AIBN (cat.), toluene; iv) n-Bu_4NF, THF

spirocyclisation gave the olefinic spiroacetals (7a,b) as a 2:1 mixture of inseparable diastereomers (bp 62-64°C @ 0.04mmHg). The equatorial orientation of the ethyl group at C-9 was assigned from the large coupling constants (10.8Hz) observed between H-8_{ax} and H-9_{ax}, for both (7a) and (7b)). The H-8_{ax} signal was a characteristic of subsequent spiroacetals in this communication. Formation of the tert-butyldimethylsilyl ethers (13) and (14) followed by careful flash chromatography (Et_2O:petrol; 1:19); enabled each of the diastereomers (13) and (14) to be isolated in a combined yield of 84% (13) Rf = 0..13 (bp 97-99°C @ 0.2mmHg), (14) Rf = 0.18 (bp 97-99°C @ 0.2mmHg) (Scheme 3).

The olefinic spiroketal (13) was chlorohydrated to give the diastereomeric chlorohydrins (15) and (16) in a 1:4 ratio which were separated by flash chromatography in 73% combined yield [(15) Rf = 0.28, Et_2O:petroleum, 1:4, H-4_{ax}, δ = 4.19, ddd, $J_{4a,OH}$ = $J_{4a,3e}$ = 5Hz, $J_{4a,5a}$ = 10.8Hz; (16) Rf = 0.23, Et_2O:petroleum, 1:4. H-4_{eq}, δ = 3.78-3.72, m, including $J_{4e,OH}$ = 5.2Hz]. Similarly, chlorohydration of (14) gave the trans-diequatorial and trans-diaxial chlorohydrins (17) and (18) which were obtained as colourless oils after flash chromatography (Et_2O:petroleum, 3:17, (17) Rf = 0.21; (18) Rf = 0.39) in a ratio of 1.4:1 and a combined yield of 60%. The large trans-diaxial coupling observed between H-3_{ax} and H-5_{ax} and H-4_{ax} in (17) was particularly informative in assigning the relative stereochemistry at the three contiguous centres C-3 to C-5 [(17), H-4_{ax}, δ = 3.89, t, $J_{4a,5a}$ = $J_{4a,3a}$ = 9.9Hz; (18), H-4_{eq}, δ = 3.97, dt, $J_{4e,OH}$ = 10.8Hz, $J_{4e,5e}$ = $J_{4e,3a}$ = 2.8Hz]. Both trans-diaxial chlorohydrins (16) and (18) exhibited sharp absorptions in their i.r.

spectra at ν_{max} 3480cm^{-1} and 3510cm^{-1} respectively, indicative of an intramolecular hydrogen bond between the axial hydroxyl at C-4 and the O-7 in the adjacent tetrahydropyran ring, a phenomenon commonly observed in 4-hydroxy-1,7-dioxaspiro[5.5] undecanes[8].

Reductive de-chlorination[9] of the individual chlorohydrins (15 - 18) gave the corresponding alcohols (19 - 22) as white crystalline solids mp's 56-58°C, 45-46.5°C, 68.5-70.5°C and 41-41.5°C respectively and in yields of 60-80%. Finally, deprotection of the t-BDMS ethers (19 - 22) gave the talaromycins A, B, C and E; all spectral data was in accordance with published data. Talaromycin B was isolated as a white crystalline solid mp 129.7-130.5°C [(CH_2Cl_2:hexane; 1:3), Lit[4] 127-128°C], whereas the other three talaromycins were isolated as colourless oils. This route to the talaromycins A, B, C and E via the olefinic spiroketals (13) and (14) would be applicable to synthesis of the enantiomerically pure natural products by use of C-5 (R)-lactone (8).

Acknowledgements

We gratefully acknowledge financial support from the SERC and a CASE Award from Sigma Chemicals Company Ltd., (Poole).

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(Received in UK 30 December 1988)