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SPIROKETALS: A TOTAL SYNTHESIS OF (±)-TALAROMYCIN B VIA A STEREOSELECTIVE CATION-OLEFIN CYCLISATION STEP

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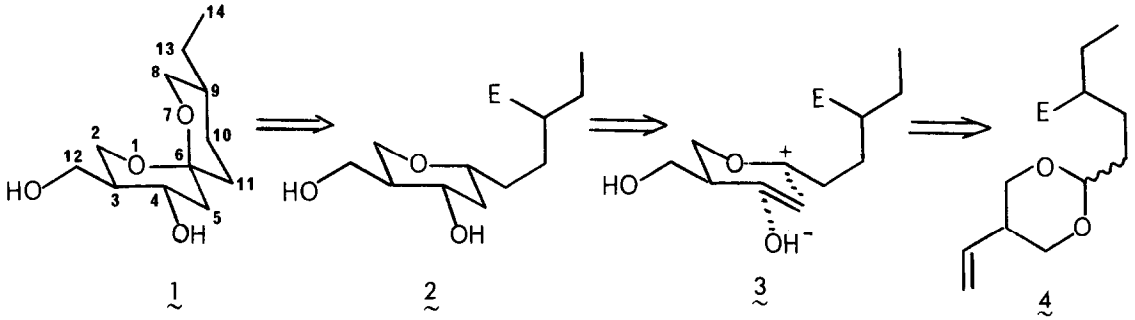
Summary: The acid catalysed rearrangement of an acetal derived from 2-hydroxymethyl-3-butene-1-ol proceeding via an intramolecular cation-olefin cyclisation provides access to a 4-hydroxytetrahydropyran and thence to (±)-talaromycin B.

In a previous paper[1] we described an approach to the synthesis of hydroxy-substituted spiroketals based on the stereoselective formation of 4-hydroxytetrahydropyrans formed via a cation-olefin cyclisation step.

Talaromycin B, 1, characterised by Lynn and co-workers[2] is an avian toxin obtained from cultures of Talaromyces stipitatus and has recently been synthesised for the first time by Schreiber and Sommer[3]. Because of the symmetry inherent in the 4-hydroxytetrahydropyran ring of this spiroketal a retro-synthetic analysis (SCHEME 1) based on our methodology seemed particularly appropriate to its synthesis. Thus we envisaged the key step to involve ring-opening of a symmetrically substituted acetal 4 followed by intramolecular capture of the cation by the olefin as in 3 to provide a stereoselective entry to the 4-hydroxytetrahydropyran 2.

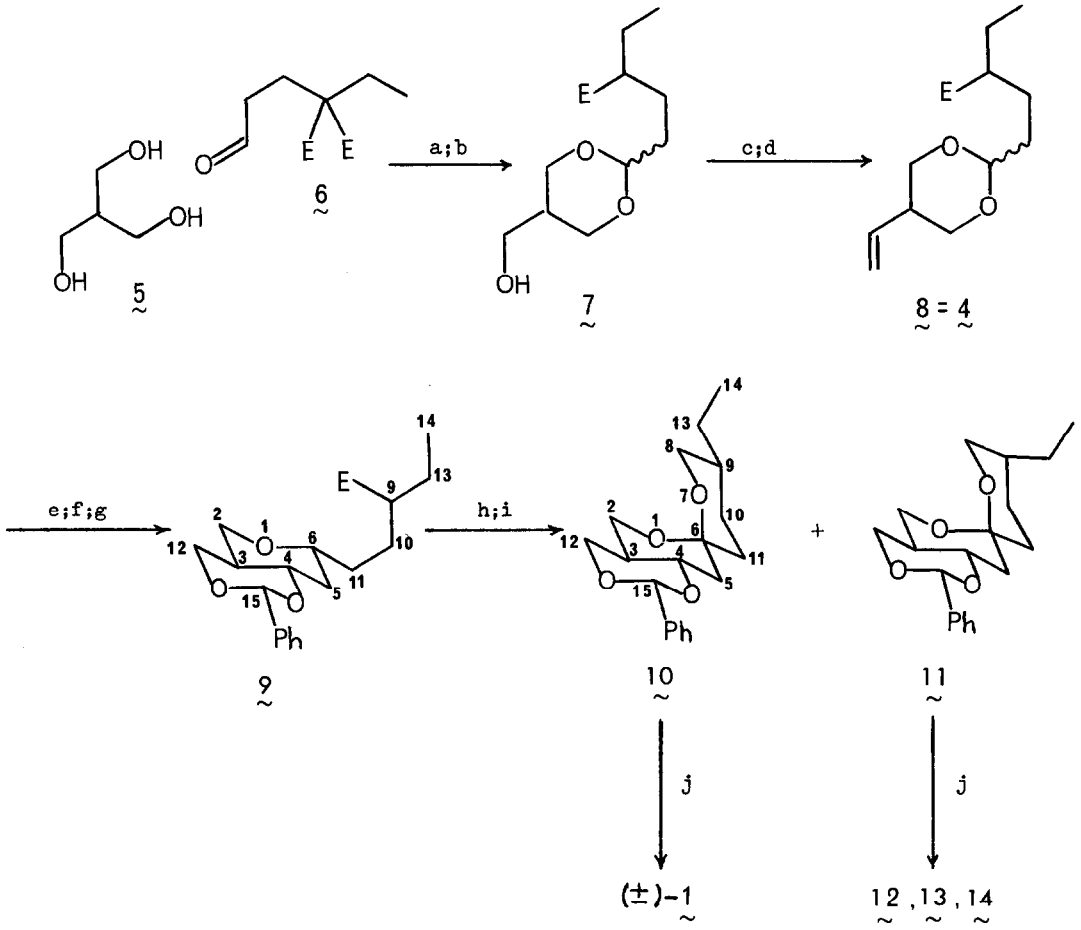


1 2 3 4

SCHEME 1 (E=CO_2Et)

In view of our earlier work[1] we felt assured that the 4-hydroxy and 6-pentyl substituents of 2 would have the correct relative stereochemistry but were less sure of that of the 3-hydroxymethyl group. However, since it is known[2] that talaromycin A, the 3-epimer of talaromycin B, undergoes complete isomerisation to the latter in the presence of acid it was felt that this objection was of little moment. A greater potential drawback to the analysis in SCHEME 1 is the lack of stereochemical control of the 9-ethyl substituent so elegantly overcome by Schreiber and Sommer. Our route does indeed suffer from this fault but gave us an opportunity to examine the 9-epimer of talaromycin B with interesting results.

Our route to (±)-talaromycin B (and its 9-epimer) is shown in SCHEME 2. The decarbethoxylation of the acetal derived from the triol[4] 5 and the aldehyde[5] 6 gave (91%) the dioxane 7 as a 1:1 mixture of cis- and trans- isomers. Oxidation of this using PCC gave the aldehyde which was condensed with Lombardo's reagent[6] to give (35%) the desired olefin 8. Gratifyingly, the exposure of the acetal 8 to a 1:1 mixture of TFA-TFAA at 20° for 24h followed by removal of the trifluoroacetyl groups with MeOH-K_2CO_3 gave a nearly quantitative yield of the anticipated diol 2.



5 6 7 8 = 4 9 10 11 (±)-1 12, 13, 14

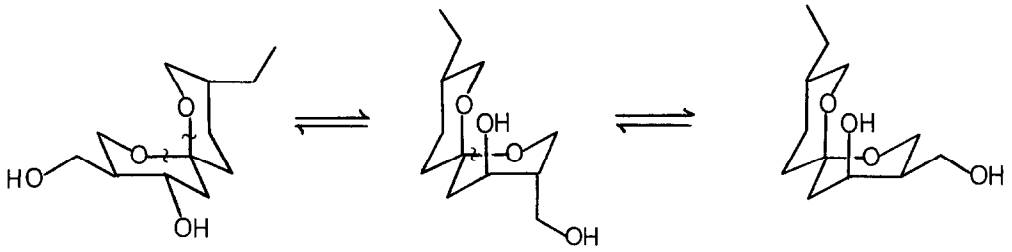
Reagents: a) Toluene, p-TsOH; b) NaCl DMSO 150°/24h; c) PCC; d) $Zn/CH_2Br_2/TiCl_4$; e) TFA-TFAA 20°/24h; f) MeOH-K_2CO_3; g) PhCHO p-TsOH; h) LAH; i) HgO/I_2 CCl_4 20°/24h; j) 4:1 TFA-water/2h

SCHEME 2 (E=CO_2Et)

Protection of the diol with benzaldehyde gave the acetal 9 as a single ring isomer[7] having the anticipated stereochemistry as shown. LAH-Reduction of this ester followed by spirocyclisation of the derived alcohol via its hypoidite[8] gave (55%) a 3:1 mixture of the benzal acetal 10 of (±)-talaromycin B and its 9-epimer 11. Separation of the mixture was readily accomplished by hplc[9] and gave the pure isomers[10]. Treatment of 10 with TFA-water

gave (±)-talaromycin B[11] the 400 MHz ^{1}H-NMR spectrum of which was identical to that reported[2,12] for the natural product.

In contrast to the findings for 10, acid treatment of the isomer 11 produced a readily separable[13] mixture (SCHEME 3) of three isomeric spiroketals. These isomers 12, 13, 14[14] were formed in the ratio 1:1:2[15] and their structures readily assigned by analysis of their 400 MHz ^{1}H-NMR spectra[16]. We presume these isomers to be formed by acid-catalysed ring opening of the spiroketal followed by recyclisation in alternative stereochemical modes and with the preservation of anomeric stabilisation[17]. That 10 gives but one product on acid treatment reflects the greater thermodynamic stability of the all-equatorially substituted spiroketal[18].



12 13 14

SCHEME 3

We thank Mr. M. R. Kipps for invaluable help in determining the NMR spectra.

References and notes

1. I.T.Kay and E.G.Williams, Tetrahedron Lett., 5915 (1983).
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3. S.L.Schreiber and T.J.Sommer, Tetrahedron Lett., 4718 (1983); see also reference 19.
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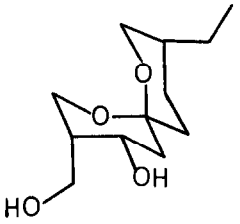
5. D.T.Warner and O.A.Moe, J.Am.Chem.Soc., 70, 3470 (1948).
6. L.Lombardo, Tetrahedron Lett., 4293 (1982).
7. ^{1}H-NMR (400 MHz), δ($CDCl_3$):0.88,3H$_{14}$,t,J=7Hz;1.24,3H$_E$,t,J=7Hz;1.38-1.80,7H$_{5a,10,11,13'}$,m;1.90-1.98,1H$_{5e}$,m;2.00-2.12,1H$_{3a}$,m;2.18-2.42,1H$_9$,m;3.08,1H$_{2a}$,t,J=10Hz;3.34-3.45,1H$_{6a}$,m;3.56,1H$_{12a}$,t,J=10Hz;3.64-3.83,2H$_{4a,2e}$,m;4.04-4.20,3H$_{12e,E}$,m;5.60,1H$_{15}$,s;7.10-7.90,5H,m.
8. M.L.Mihailovic, S.Gojkovic, and S.Konstantinovic, Tetrahedron, 3675 (1973).
9. Kieselgel 60 (450x25mm),4:1 n-hexane,diethyl ether.
10. 10: M.p.102-103° (hexane). ^{1}H-NMR (400 MHz),δ($CDCl_3$):0.9,3H$_{14}$,t,J=7Hz;1.18,2H$_{13}$,m,J=7Hz;1.36-1.80,6H$_{5a,9a,10a,10e,11a,11e}$,m;2.00-2.18,2H$_{5e,3a}$,m;3.27,1H$_{8a}$,t,J=10Hz;3.38,1H$_{2a}$,t,J=10Hz;3.50-3.60,2H$_{2e,8e}$,m;3.66,1H$_{12a}$,t,J=10Hz;4.06-4.16,2H$_{4a,12e}$,m;5.60,1H$_{15}$,s;7.20-7.50,5H,m.
11: M.p.84-85° (hexane). ^{1}H-NMR (400 MHz),δ($CDCl_3$):0.93,3H$_{14}$,t,J=7Hz;1.35-1.75,

$7H_{5a,9e,10e,11a,e,13}$,m;1.95-2.04,$1H_{10a}$,m;2.07-2.14,$2H_{3a,5e}$,m;3.39-3.47,$2H_{8e,2a}$,m; 3.52-3.58,$1H_{2e}$,dd,J=5Hz,10Hz;3.62-3.69,$1H_{12a}$,t,J=10Hz;3.78-3.84,$1H_{8a}$,dd,J=4Hz,10Hz; 4.05-4.15,$2H_{4a,12e}$,m;5.60,$1H_{15}$,s;7.20-7.50,5H,m.

11. M.p. 127-128° (CH_2Cl_2-hexane).
12. W.C.Hutton, N.J.Phillips, D.W.Graden, and D.G.Lynn, J.C.S.Chem.Comm., 864 (1983).
13. Spherisorb S5W (250x8mm),85:15 CH_2Cl_2, Me_2CO.
14. Only one enantiomer shown for each spiroketal.
15. Each of the isomers taken separately and treated with TFA-water gave the same ratio of products.
16. We could find no evidence for the formation of the fourth isomer (below):



17. A.J.Kirby, "The Anomeric Effect and Related Stereoelectronic Effects at Oxygen", Springer-Verlag, New York, 1983.
18. R.Baker, R.H.Herbert, and A.H.Parton, J.C.S.Chem.Comm., 601 (1982).
19. Since the preparation of this paper two further synthetic routes to (±)-talaromycin B have been reported: P. Kocienski and C. Yeates, J.C.S.Chem.Comm., 151 (1984); A.P.Kozikowski and J.G.Scipko, J.Am.Chem.Soc., 106, 353 (1984).

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