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NARGENICIN MODEL STUDIES : DEHYDRATIVE REARRANGEMENT OF A DIHYDROXYOCTAHYDRONAPHTHALENE

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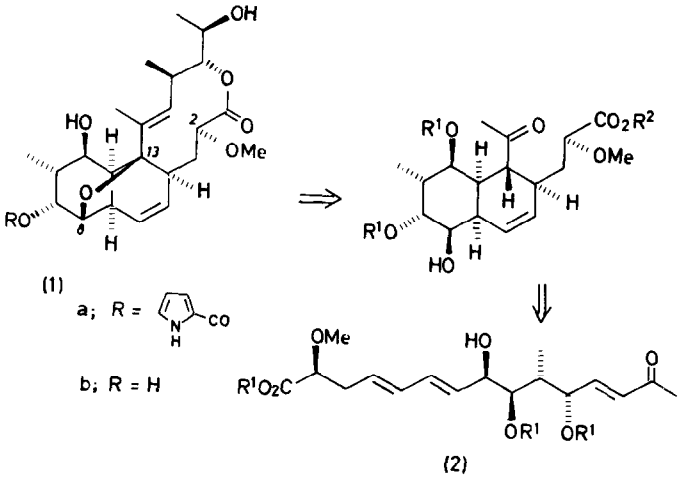
Summary - Cyclic ether formation by dehydration of a cis-fused 5-acetyl-1,5-dihydroxyoctahydronaphthalene occurs with rearrangement to give a 12-oxatricyclo[5.4.$1^{1,7}$.$0^{3,8}$]dodecene rather than the 11-oxatricyclo[4.4.$1^{1,6}$.$0^{2,7}$]undecene system of the nargenicin antibiotics.

The nargenicin antibiotics, represented by nargenicin A_1(1a) and nodusmicin(1b),[1] comprise a recently identified group of structurally fascinating macrolide antibiotics displaying significant antimicrobial activity. The novel structural features include a highly functionalised oxygen-bridged cis-octahydronaphthalene (11-oxatricyclo[4.4.$1^{1,6}$.$0^{2,7}$]undecene) nucleus. Recent reports of the synthesis of such a moiety,[2] and on the biosynthesis of (1a) and (1b),[3] have prompted us to report on our own synthetic studies in this area. The strategy we adopted (and which now may be regarded as biomimetic[3]) is outlined below and has as its central features (a) formation of a cis-octahydronaphthalene by intramolecular Diels-Alder cycloaddition of a highly functionalised triene (2), and (b) the subsequent closure of the C-8,13 ether linkage before macrolide elaboration.



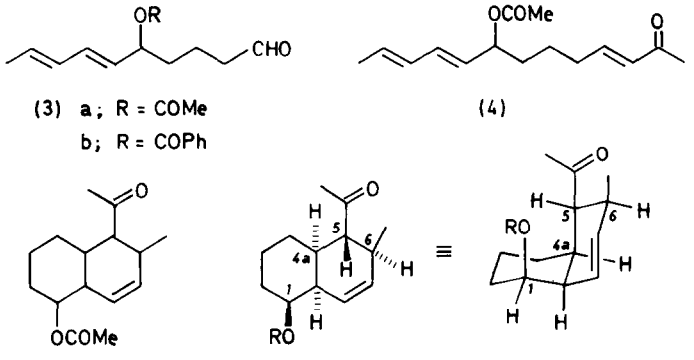
Although our expectation of a preference for the exo-mode of cycloaddition of (2), leading to the required cis-ring fusion, was well-precedented,[4] we chose to confirm this prediction and to examine methodology for the ether formation on a simplified model system. To this end the trienone (4) was prepared as follows. Addition of the Grignard reagent prepared from 4-bromobutanal diethyl acetal to (2E,4E)-hexa-2,4-dienal (THF, 0°C) afforded a hydroxy-acetal (83%)[4a] that was acetylated (Ac_2O, Et_3N, catalytic DMAP; 25°C, 4 h; 87%).[5] Hydrolysis of the acetal (5%$[CO_2H]_2$-H_2O; 25°C, 48 h) produced an aldehyde (3a) (94%)[5] which was condensed with 2-oxopropylidenetriphenylphosphorane (CH_2Cl_2; reflux, 4.5 h) to give the E,E,E-trienone (4) (69% after chromatography).[5]

The intramolecular Diels-Alder cycloaddition of trienone (4), could be accomplished by heating in oxygen-free dry xylene at 130°C. After 12 h chromatographic separation yielded the octahydronaphthalene cycloadduct (5)[5] as a mixture of stereoisomers (54%) and unchanged trienone (28%). A more efficient protocol for cycloaddition proceeded directly from the dienal (3a), which on heating with 2-oxopropylidenetriphenylphosphorane in xylene (100°C, 1 h, then 140°C, 5 h) afforded the cycloadduct (5) as the same mixture of isomers (90%). Further separation by preparative h.p.l.c. gave the octahydronaphthalene (6a)[5] with the desired cis-ring fusion and β-acetoxy stereochemistry as the major single isomer (37%).[6] Repetition of this sequence with the benzoate (3b)[5] gave similar results but a less convenient separation.

The assignment of the illustrated stereochemistry to this major adduct is based on ^1H n.m.r. studies at 250 MHz ($CDCl_3$) on both acetate (6a) and the alcohol (6b)[5] obtained from it after basic methanolysis [acetylation of (6b) regenerated (6a), excluding the possibility of epimerisation during hydrolysis]. These indicate inter alia the presence of axial protons at C-4a, 5, and 6, and an equatorial proton at C-1.[6] The relative configuration was confirmed as (6) by an X-ray crystal structure determination of alcohol (6b),[8] although the crystal conformation (Fig.1) is different to that observed in solution.

The introduction of suitable functionality at C-5 for ether formation was initially unsuccessful. Treatment of (6b), for example, with $Pb(OAc)_4$ did not give the desired hydrogen abstraction from C-5 but instead the intermediate alkoxy radical fragmented to afford a cyclohexene derivative (7)[5] (or its allylic regioisomer). Attempted halogenation of (6a) by various methods[9] afforded only the undesired monobromo regioisomer (8)[5]. Functionalisation at C-5 was eventually achieved by base-catalysed oxygenation of acetate (6a) (Bu^tOK, Bu^tOH, O_2; 35°C, 20 min. then Zn, AcOH) to give the diol (9) (40%)[5] and recovered alcohol (6b) (33%); the oxygen insertion was assumed to be from the less hindered convex face.[10]

Acid-catalysed dehydration of (9) (HCl, CH_2Cl_2; 25°C, 16 h) did lead to ether formation, but instead of the required 11-oxatricyclo[4.4.$1^{1,6}$.$O^{2,7}$]-



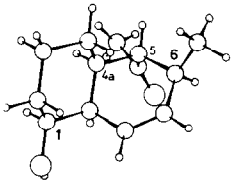
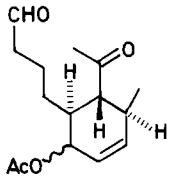
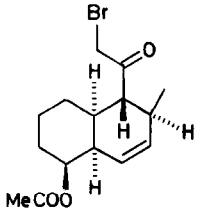
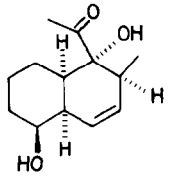
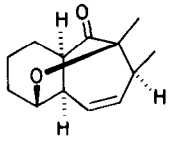


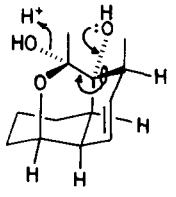
Fig. 1











undecene system,rearrangement occurred to afford (10) (58%).[5] This 12-oxatricyclo[5.4.$1^{1,7}$.$o^{3,8}$]dodecene formulation is supported by n.O.e. studies. A reasonable pathway for the production of this novel system invokes a 1,2-shift in the hemi-acetal (11).[11] Studies on the scope of this rearrangement and further efforts to close the ether bridge without rearrangement are presently underway.

References and Notes

1. (a) W.D. Celmer, G.N. Chmurny, C.E. Moppett, R.S. Ware, P.C. Watts, and E.B. Whipple, J.Am.Chem.Soc., 1980, 102, 4203; (b) H.A. Whaley, C.G. Chidester, S.A. Mizsak, and R.J. Wnuk, Tetrahedron Lett., 1980, 21, 3659. The stereochemistry illustrated in (1) is based on the X-ray structure shown in ref.1(b). In particular, the method of drawing the configuration at C-2 differs from that usually employed, but we feel it better represents the three-dimensional structure. This has also been noted elsewhere.[3c]

2. J. Kallmerten, Tetrahedron Lett., 1984, 25, 2843.

3. (a) D.E. Cane and C. Yang, J.Am.Chem.Soc., 1984, 106, 784; W.C. Snyder and K.L. Rinehart, ibid., p.787; (c) D.E. Cane and C. Yang, J.Antibiot., 1985, 38, 423.

4. (a) W.R. Roush, and S.E. Hall, J.Am.Chem.Soc., 1981, 103, 5200, (b) R.L. Funk and W.E. Zeller, J.Org.Chem., 1982, 47, 180.

5. All new compounds gave spectra (IR, UV, NMR, MS) consistent with the assigned structure, and satisfactory combustion analysis or accurate mass measurement. Purity was also assessed by t.l.c. examination.

6. The signal for H-5 in (6a) (δ2.84, dd) showed J 9.1 and 10.8 Hz, whilst that in (6b) (δ3.05, dd) had J 9.5 and 11.3 Hz. The resonance for H-1 in (6a) and (6b) showed no spin-spin coupling of sufficient magnitude to represent an axial-axial arrangement.

7. Also isolated were the α-acetoxy epimer of (6a)(13%), and a mixture of two trans-fused isomers.

8. This determination was kindly performed by Dr. M.J. Begley (Nottingham) and full details will be reported separately. Alcohol (6b), $C_{13}H_{20}O_2$, crystallised in the triclinic system, space group $P\bar{1}$, cell dimensions a = 6.411(1), b = 8.207(1), c = 12.230(2)Å, α = 98.97(1)°, β = 97.12(1)°, and γ = 110.41(1)° with two molecules per unit cell. The structure was determined from 1643 observed reflections by direct methods using the MULTAN program and refined to R = 5.19%.

9. These included pyrrolidine hydrotribromide, Br_2-AcOH, and $CuBr_2$. Inclusion of a halogen at an earlier stage, by using 1-halo-2-oxopropylidenetriphenylphosporanes in the olefination-cycloaddition sequence with dienal (3a), led to decomposition in the bromo-series; the major cycloadduct in the chloro-series was assigned the undesired trans-ring fused configuration.

10. E.J. Bailey, D.H.R. Barton, J. Elks, and J.F. Templeton, J.Chem.Soc., 1962, 1578.

11. The hemi-acetal (11) is chosen on the basis of stereoelectronic effects; the migrating C-C bond and a lone pair on the bridging oxygen atom are both antiperiplanar to the breaking C-O bond (see P.Deslongchamps, 'Stereoelectronic Effects in Organic Chemistry,' Pergamon Press, Oxford, 1983).

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