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EPOXIDES IN SYNTHESIS. STUDIES TOWARDS THE AUROVERTINS

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Summary: A synthesis of the 2,6-dioxabicyclo[3.2.1] octane ring system(16) found in the natural aurovertins e.g.(1), based on a biogenetic model (Scheme 1) and using two key epoxide cyclisation steps viz(12)→(13) and (14)→(16a), is described.

The aurovertins, exemplified by aurovertin A(1), are a family of unusual polyenepyrone substituted 2,6-dioxabicyclo[3.2.1]octanes which are produced by the fungus Calcarisporium arbuscula[1]. They are related structurally, and show a similar biological profile, to the citreoviridinoid group of toxins e.g. citreoviridin(2), found in Penicillium citreoviride[2]. Both classes of natural compound are potent inhibitors of ATP-synthesis and ATP-hydrolysis catalysed by mitochondrial enzyme systems. In addition, citreoviridin(2) has been shown to inhibit oxygen uptake in pea root segments, thereby suggesting that the molecules (1) and (2) are likely to be herbicidal or fungicidal or both[3]. Asteltoxin(3), found in Aspergillus stellatus[4] is also related both structurally and biogenetically to aurovertin A(1). Furthermore, asteltoxin has been shown to have a similar inhibiting effect to (1) and (2) on the activity of E coli ATP-ase.

It seems probable that the intriguing 2,6-dioxabicyclo[3.2.1]octane ring system present in the aurovertins is derived in Nature by cyclisation of a tris(1,2-, 3,4-, 5,6-)epoxide intermediate produced by stepwise epoxidation of a pyrone substituted triene precursor molecule (see Scheme)[5]. In this Letter, we describe a synthesis of the 2,6-dioxabicyclo[3.2.1]octane system viz (16b) in aurovertin A, which is based on this biogenetic model, and uses the two key epoxide cyclisation steps (12)→(13), and (14)→(16a).

Thus, the aldehyde (5b) was first elaborated from ethyl E-2-methylpent-2-enoate following oxidation to the vicinal-diol(4) (OsO_4, NMMO, Me_2CO-H_2O; 80%), acetonide formation [$Me_2C(OMe)_2$, p-TSA; 96%], reduction to (5a) ($LiAlH_4$, 98%), and finally oxidation (PCC, celite, 76%). A Wittig condensation between the aldehyde (5b) and ethoxycarbonylethylidenetriphenylphosphorane(25°C, 48h) then provided the E-unsaturated ester(6)[6] exclusively (75%), which by

successive reduction ($LiAlH_4$) and oxidation (MnO_2) was next converted into the E-enal(7). A Wadsworth-Emmons condensation between (7) and the phosphonate ester (8) (NaH, THF, 0°-25°C, 1h) then produced the all-E trienoate (9;66%), whose geometry followed conclusively from examination of its high field p.m.r., together with c.m.r. data[6].

Interaction between (9) and one equivalent of meta-chloroperbenzoic acid in dichloromethane at 25°C for 7h, led to a 3:1 mixture (76%) of the β- and α-epoxides (10) and (11) respectively, resulting from regiospecific epoxidation of only the C6-C7 double bond in (9). Treatment of the separated β-epoxide (10)[7] with 50% aqueous trifluoroacetic acid (25°C, 72h) then resulted in smooth de-ketalisation and concomitant cyclisation of the resulting epoxy-diol (12), leading to the substituted tetrahydrofuran (13; 36%). The relative stereochemistry of (13) followed unambiguously from inspection and comparison of its p.m.r. and c.m.r. data with those of related molecules in the citreoviridinoid family of metabolites[2,7].

The synthesis of the 2,6-dioxabicyclo[3.2.1]octane ring system present in the aurovertins, was then completed via a second epoxy-alcohol cyclisation involving the β-epoxide (14). Interestingly, the epoxidation of (13) was found to be unusally difficult, with normal oxidising agents [mcpba, MoO_5, $VO(acac)_2$] leaving the diene largely unaffected. Using the more reactive 3,5-dinitroperbenzoic acid[8], however, the epoxidation of (13) proceeded reasonably smoothly, leading to both the β- and α-epoxides (14) and (15)(60%). Treatment of each of the epoxy-alcohols (14) and (15) with p-toluenesulphonic acid then gave rise to the corresponding isomeric 2,6-dioxabicyclo[3.2.1] octanes (16a;15%) and (17a;67%) respectively[9]. Acetylation of the isomer (16a) (Ac_2O,C_5H_5N, 25°C, 18h) produced the diacetate (16b) which showed p.m.r. spectral data closely similar to those found for corresponding signals in the p.m.r. spectum of natural aurovertin A[10].

Further work is now in progress to develop this sequential epoxy-alcohol cyclisation approach in the chiral series, and to apply it to the synthesis of a range of natural aurovertins.

We thank Dr. R. Vleggaar for a generous sample of naturally derived aurovertin B, and Dr. J. M. Clough (I.C.I. Plant Protection) for his interest in this work. One of us (J.E.F.) also thanks the S.E.R.C. for a studentship, and the Society of Chemical Industry for their first Messel Scholarship.

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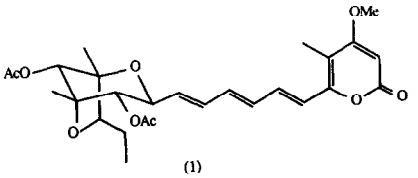
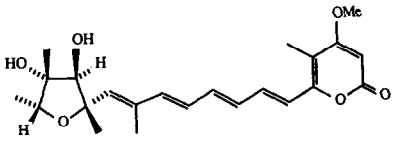
2. For bibliography see: M.C. Bowden, P. Patel and G. Pattenden,



(1)



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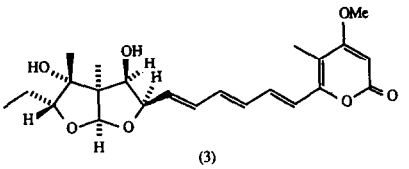

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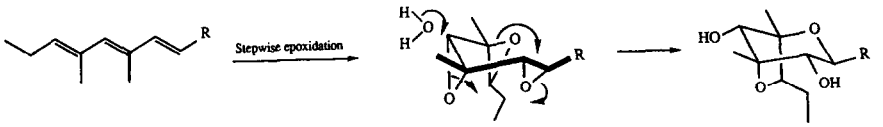
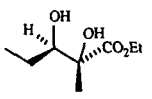


Scheme



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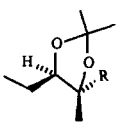
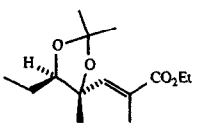
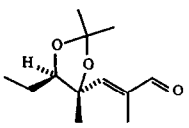


(5)



(6)

a R = CH_2OH
b R = CHO



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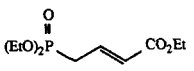
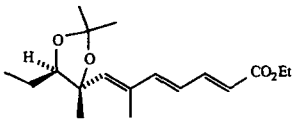
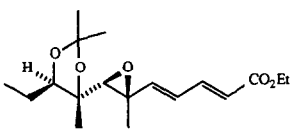


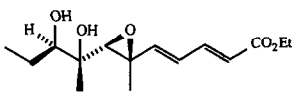
(8)



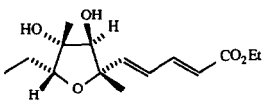
(9)



(10) ß-epoxide
(11) α-epoxide



(12)



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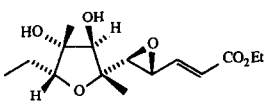
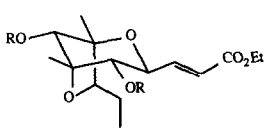
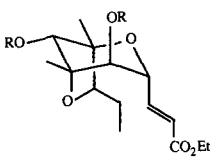


(14) ß-epoxide
(15) α-epoxide



(16)
a R = H; *b* R = Ac



(17)

Tetrahedron Letters, 1985, 26, 4793.

3. M. Bellando, A. Trotta and R.C. Lomagno, Phytopathol.Mediterr. 1980, 19, 199 (Chem.Abs., 95, 198682b).
4. G.J. Kruger, P.S. Steyn, R. Vleggaar and C.J. Rabie, J.Chem.Soc., Chem.Commun., 1979, 441.
5. This proposition was first communicated by one of us at the Oxford Synthesis Meeting, July 1985. For biosynthetic investigations pertinent to the proposal see: P.S. Steyn and R. Vleggaar, J.Chem.Soc., Chem.Commun., 1985, 1531; A.E. de Jesus, P.S. Steyn and R. Vleggaar, ibid, 1985, 1633.
6. Satisfactory spectroscopic data, together with microanalytical or mass spectral data were obtained for all new compounds. Triene(9) showed: δ_H 1.05(t, J7, $CH_2\underline{CH}_3$), 1.23(Me), 1.3(t, J7, $CH_2\underline{CH}_3$), 1.35(Me), 1.45(Me), 1.52(m, 2H), 2.04(:C<u>Me</u>), 3.78(dd, J4 and 9, $CH_2\underline{CH}O$), 4.2(q, J7, $O\underline{CH}_2CH_3$), 5.58(:C<u>H</u>), 5.89(d, J15, :C<u>H</u>), 6.32(dd, J11 and 15, :C<u>H</u>), 6.52(d, J15, :C<u>H</u>), 7.33(dd, J11 and 15, :CH); δ_C 11.4(q), 13.1(q), 14.3(q), 22.4(q), 22.5(t), 26.4(q), 28.7(q), 60.2(t), 82.2, 84.4(d), 107.5, 120.6(d), 125.2(d), 135.4, 138.4(d), 144.9(d), 146.3(d), 167.2.
7. The β-epoxide(10) showed: δ_H 1.01(t, J7, $CH_2\underline{CH}_3$), 1.05(Me), 1.22(t, J7, $CH_2\underline{CH}_3$), 1.28(Me), 1.35(Me), 1.47(m, 2H), 1.61(Me), 2.53(1H), 3.96(dd, J4 and 9, 1H), 4.12(q, J7, $O\underline{CH}_2CH_3$), 5.83(d, J15, :C<u>H</u>), 5.85(d, J15, :C<u>H</u>), 6.31(dd, J11 and 15, :C<u>H</u>), 7.17(dd, J11 and 15, :C<u>H</u>) p.p.m. whereas the tetrahydrofuran(13) exhibited δ_H 1.07(t, J7, $CH_2\underline{CH}_3$), 1.24(Me), 1.29(t, J7, $CH_2\underline{CH}_3$), 1.3(Me), 1.58(m, 2H), 3.69(t, J6, 1H), 3.81(1H), 4.19(q, J7, $O\underline{CH}_2CH_3$), 5.9(d, J15, :C<u>H</u>), 6.3(d, J15, :C<u>H</u>), 6.49(dd, J10 and 15, :C<u>H</u>), 7.26(dd, J10 and 15, :C<u>H</u>).
8. W.H. Rastetter, T.J. Richard and M.D. Lewis, J.Org.Chem., 1978, 43, 3163. Caution should be exercised in the handling and storage of this reactive peracid.
9. The 2,6-dioxabicyclo[3.2.1]octane (16a) showed: δ_H 3.52(d, J6, 1H), 3.66(m, 2H), 4.21(q, J7, $OCH_2\underline{CH}_3$), 4.31(m, 1H), 6.12(d, J15, :C<u>H</u>), 7.03 (dd, J15 and 5, :C<u>H</u>), and the isomer (17a), δ_H 3.54(d, J5, 1H), 3.68 (dd, J5 and 8, 1H), 4.1(m,1H), 4.2(q, J7, $OCH_2\underline{CH}_3$), 4.2(m, 1H), 6.12(dd, J15 and 1, :C<u>H</u>), 6.99(dd, J15 and 5, :C<u>H</u>). These data correlate with those of the corresponding mono-acetates synthesised in contemporaneous studies by Yamamura et al; S. Nishiyama, H. Toshima, H. Kanai and S. Yamamura, Tetrahedron Letters, 1986, 27, 3643.
10. Aurovertin A(1) was produced from natural aurovertin B (Ac_2O, C_5H_5N) and showed: δ_H 4.81(d, J8, C<u>H</u>OAc), 4.9(C<u>H</u>OAc). cf. δ 4.79(d, J8, C<u>H</u>OAc), 4.87(C<u>H</u>OAc) for (16b) and δ 4.93(d, J8, C<u>H</u>OAc), 5.54(C<u>H</u>OAc) for (17b).

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