STUDIES OF AUSTRALIAN SOFT CORALS. XLV.[1] EPOXIDATION REACTIONS OF CEMBRANOID DITERPENES: STEREOCHEMICAL OUTCOMES≠

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Abstract - Epoxidation of the cembranoid diterpene (1) afforded the known 7S,8S-epoxide (2), the 7R,8R-epoxide (3), the 11R,12R-epoxide (4) and the 11S,12S-epoxide (5) in the ratio 1:3:3:10. Similar epoxidation of the cembranolide (1R,2R,3E,7E,11E)-cembra-3,7,11,15-tetren-17,2-olide (6) afforded the 7S,8S-epoxide (7), the 7R,8R-epoxide (8), the 11R,12R-epoxide (9) and the 11S,12S-epoxide (10) in the ratio of 1:5:6:8. Only one of the products (8), from the second epoxidation reaction was known. The other three compounds are reported for the first time. This study reveals a significant preference for epoxidation at the 11,12-double bond. No evidence of epoxidation at the 3,4-double bond was detected in either system.

We have recently reported[2] the isolation and structural determination of four isomeric monoepoxides of the cembranoid diterpene sarcophytonin (1),[3] presumably derived from biologically mediated epoxidation. It is interesting to note that these monoepoxides isolated from nature were the two epimeric 7,8-epoxides (2) and (3), and the two epimeric 11,12-epoxides (4) and (5).[2] No 3,4-epoxides of sarcophytonin were known.[4] We wondered whether this apparent regioselectivity was a feature of the conformational preferences of the cembrane ring, an indication of enzyme specificity, or merely a reflection of the fact that insufficient soft corals had been investigated. Because we had a supply of sarcophytonin (1) and of the cis-fused cembrenolide (6)[5] available to us, we decided to study the chemical epoxidation of these substrates in chloroform using m-chloroperbenzoic acid as oxidant. The reactions were carried out at room temperature in the presence of sodium carbonate, and terminated when more polar components (bis-epoxides) started to form (tlc).

≠ Dedicated to Professor Sir Derek H.R. Barton on the occasion of his 70th birthday.

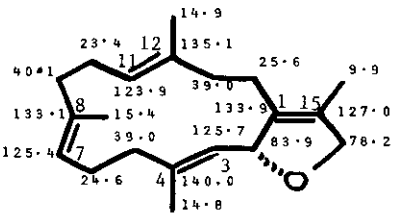
In the case of the epoxidation of sarcophytonin (1),[3] the reaction proceeded virtually to exhaustion of the substrate before significant quantities of bis-epoxides formed. The reaction was worked up and rapidly fractionated on silicic acid to give a fraction containing only the monoepoxides (2)-(5). Hplc analysis permitted identification of all components by comparison with authentic samples,[2] and afforded an approximate ratio of their relative abundances. Thus the ratio of the 7S,8S-epoxide (2), to the 7R,8R-epoxide (3), to the 11R,12R-epoxide (4), and to the 11S,12S-epoxide (5) was 1:3:3:10. The 11,12-epoxides predominated, and there was also a stereoselection between the epimeric epoxides at each site. No 3,4-epoxides were detected.

In the case of the epoxidation of cis-fused cembrenolide (6),[5] the onset of extensive bis-epoxide formation coincided with 50% reaction of the substrate. At this stage, the reaction was terminated and the fraction containing mono-epoxides (7)-(10) was isolated. Hplc analysis of this fraction showed the ratio of the 7S,8S-epoxide (7),[6] to the 7R,8R-epoxide (8),[7] to the 11R,12R-epoxide (9)[8] and to the 11S,12S-epoxide (10)[9] was 1:5:6:8. Assignments of regiochemistry to (9) and (10) were *based on extensive long and short range 2D* ^{13}C-^{1}H correlation experiments using a Bruker AM300 nmr spectrometer. The structure of (8) had been established in an earlier study,[7] and the minor metabolite (7) was identified by its ^{1}H and ^{13}C nmr properties. Stereochemical assignments were based on comparisons with the known compounds (2)-(5)[2] (Figure 1). There was no evidence for the production of 3,4-epoxycembranolide derivatives under these conditions.

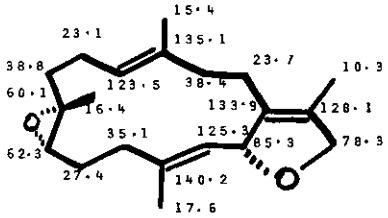
The only clear diagnostic feature of the ^{1}H nmr spectra of cembranes (1)-(10)[2,3,5-9] was that the 7,8-epoxymethine protons were triplets ($J \sim 5$ Hz, n = 4) while 11,12-epoxymethine protons were double doublets ($J \sim 3,10$ Hz, n = 4), a clear reflection of conformation restrictions imposed by the presence of the epoxide group.

As Figure 1 reveals, ^{13}C nmr data discriminates between the 7R,8R- and 7S,8S-epoxides (at C5 and C6) as also between the 11R,12R- and 11S,12S-epoxides (especially at C13 and C14). However unless both epimers are available, it would be unwise to make stereochemical assignments purely on the basis of these differences. What these experiments do reveal is that the conformation of the cembrane ring is such that (a) access to the 7,8-double bond is less facile than access to the 11,12-double bond in the two related systems, and (b) that one face of the 7,8-double bond (and to a lesser extent the 11,12-double bond) is preferentially exposed to the entering oxidant. Modelling studies are in progress to ascertain the reasons for these preferences.[10] The electron withdrawing effect of the C2 oxygen function presumably precludes 3,4-epoxidation in these systems.

Figure 1:
Structural formulae and ^{13}C nmr assignments



(1)



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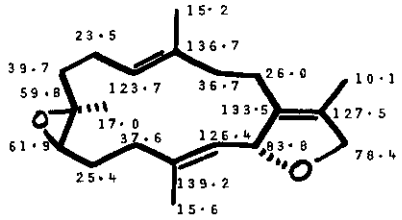

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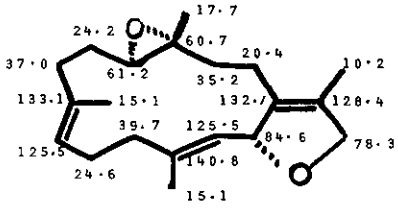

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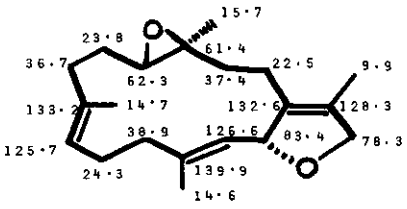

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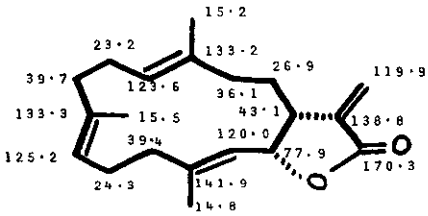
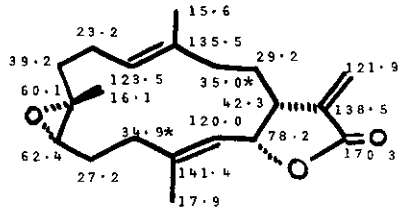


(6)



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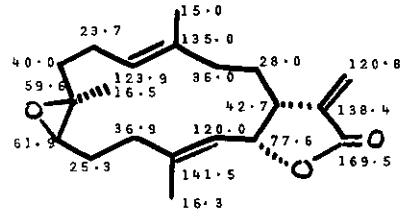

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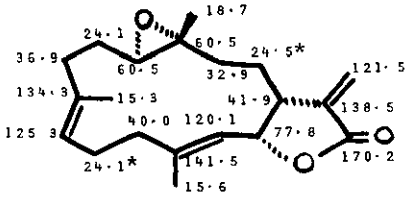
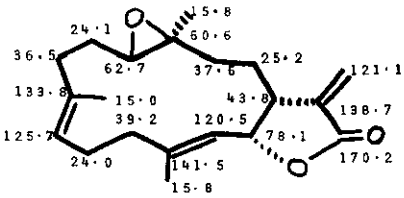


(9)

* may be interchanged



(10)

ACKNOWLEDGEMENTS

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3. M. Kobayashi, T. Nakagawa, and H. Mitsuhashi, Chem. Pharm. Bull., 1979, 27, 2382.

4. D.J. Faulkner, Nat. Prod. Rep., 1984, 1, 552; ibid., 1986, 3, 1; ibid., 1987, 4, 539.

5. J.C. Coll, S.J. Mitchell, and G.J. Stokie, Aust. J. Chem., 1977, 30, 1859.

6. 7S,8S-epoxide (7): mp 76-81°C; $[\alpha]_D$ -32° (c, 0.44, $CHCl_3$); ^1H nmr ($CDCl_3$, 300 MHz): δ0.90, m; 1.14, dt, J 3.6, 12.5 Hz; 1.29, s; 1.57, s; 1.78, s; 2.70, t, J 5.5 Hz; 3.25, m; 5.18, br.t, J 7 Hz; 5.35, dq, J ~1, 8.8 Hz; 5.37, dd, 7.1, 8.8 Hz; 5.61, d, J 2.4 Hz; 6.32, d, J 2.7 Hz. ^{13}C nmr: see Figure 1.

7. B.F. Bowden, J.C. Coll, L.M. Engelhardt, G.V. Meehan, G.G. Pegg, D.M. Tapiolas, A.H. White, and R.H. Willis, Aust. J. Chem., 1986, 39, 123. ^1H Nmr ($CDCl_3$, 300 MHz): δ0.85, m; 0.94, dt, J 3.4, 17.0 Hz; 1.25, s; 1.60, s; 1.84, s; 2.69, t, J 4.5 Hz; 3.13, m; 5.05, t, J 8 Hz; 5.12, d, J 10.5 Hz; 5.46, dd, J 8.2, 10.5 Hz; 5.53, d, J 3.2 Hz; 6.28, d, J 3.5 Hz.

8. 11R,12R-epoxide (9): mp 122-124°C; $[\alpha]_D$ +25° (c, 0.45, $CHCl_3$): ν_{max} 1755, 1660, 1420, 1080, 950 cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz): δ1.18, s; 1.58, s; 1.72, s; 2.75, dd, J 2.7, 10.3 Hz; 3.06, m; 4.99, t, J 6.4 Hz; 5.07, d, J 9.5 Hz; 5.30, dd, J 8.0, 9.5 Hz; 5.54, d, J 2.7 Hz; 6.26, d, J 3.0 Hz. ^{13}C Nmr: see Figure 1. Mass spectrum: m/z 316 ($M^{\cdot+}$, 5%), 298 (5), 217 (20), 212 (15), 163 (10), 161 (10), 151 (15), 133 (10), 121 (15), 119 (20), 105 (25), 95 (50), 93 (50), 91 (40), 81 (65), 79 (50), 55 (80), 53 (65), 43 (75), 41 (100). [Found 316.20350 $C_{20}H_{28}O_3$ requires 316.20383.]

9. 11S,12S-epoxide (10): mp 155-6°C; $[\alpha]_D$ +64° (c, 0.25; $CHCl_3$); ν_{max} 1755, 1660, 1460, 1378, 1340, 1280, 1230, 1165, 1150, 1080, 1000, 985, 965, 820 cm^{-1}. ^1H Nmr ($CDCl_3$, 300 MHz): δ0.82, td, J 3.2, 13.0 Hz; 1.25, s; 1.58, s; 1.64, s; 2.50, dd, J 3.2, 10.4 Hz; 2.94, m; 5.02, m; 5.08, d, J 9.1 Hz; 5.30, dd, J 7.4, 9.1 Hz; 5.54, d, J 2.8 Hz; 6.27, d, J 2.7 Hz. ^{13}C Nmr: see Figure 1. Mass spectrum: m/z 316 ($M^{\cdot+}$, 7%), 298 (6), 283 (5), 270 (4), 217 (40), 161 (25), 151 (40), 133 (35), 119 (40), 105 (50), 93 (65), 91 (65), 81 (80), 79 (75), 67 (75), 55 (80), 53 (80), 43 (80), 41 (100), 39 (65). [Found 316.20500 $C_{20}H_{28}O_3$ requires 316.20383.]

10. Y. Uchio, personal communication.

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