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8,11-EPOXY BRIDGED CEMBRANOLIDE DITERPENE FROM THE SOFT CORAL SINULARIA FLEXIBILIS[1)]

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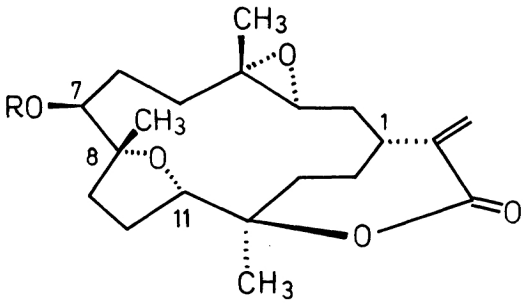
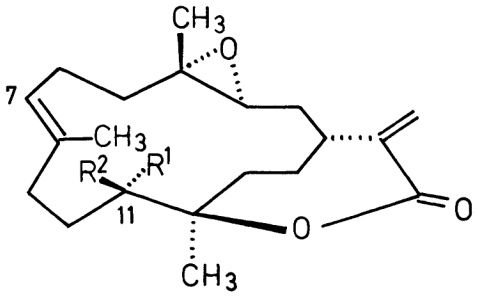
Two new cembranolide diterpenes have been isolated from the Japanese soft coral Sinularia flexibilis. Their structures have been elucidated on the basis of spectroscopic data and chemical transformations.

During the course of our investigation[2)] on the biologically active constituents from marine organisms, we have isolated new cembranolide diterpenes from the soft coral Sinularia flexibilis. Here we wish to describe the structure elucidation of a novel cembranolide 1 having an 8,11-epoxy bridge and 2 on the basis of spectroscopic data and chemical transformations.

Sinularia flexibilis (wet weight 1 kg), collected at the coral reef of Ginowan Bay (Okinawa), was freeze-dried (200 g) and was extracted with hexane then ethyl acetate. The AcOEt extract (20 g) was repeatedly chromatographed on a silica gel column to give the compound 1[3)] [0.16 g, $C_{22}H_{32}O_6$, $[\alpha]_D$ +31°(c 0.5, MeOH), mp 149-150°C] and 2 [0.05 g, $C_{20}H_{30}O_4$, $[\alpha]_D$ +19.7°(c 0.5, MeOH), mp 166.5-168.5°C], along with the seven cembranoid diterpenes which were previously isolated from the same animal; sinulariolide[4a)] (3), cembrene A,[4b)] flexibilene,[4c)] 11-dehydrosinulariolide,[4b)] 11-episinulariolide acetate,[4d)] flexibilide[4e)] and dihydroflexibilide.[4e)]





1 R = $COCH_3$ 4 R = H

2 R^1 = H, R^2 = OH

5 R = CO-C(Ph)(OCH3)(CF3) 6 R = CO-C(OCH3)(Ph)(CF3)

3 R^1 = OH, R^2 = H

The spectral data[5] for 1 showed the presence of an α-methylenelactone [IR 1720, 1622, 905 cm^{-1}, ^{1}H-NMR δ_{ppm} 5.44(1H,brs), 6.26(1H,brs), ^{13}C-NMR δ_{ppm} 123.6(t) 145.4(s), 169.5(s)], a trisubstituted three membered epoxide [^{1}H-NMR 3.40(1H,dd,J= 10.6,4 Hz), ^{13}C-NMR 59.9(s), 60.8(d)], an acetoxyl group [IR 1735 cm^{-1}, ^{1}H-NMR 2.06 (3H,s), ^{13}C-NMR 21.1(q), 171.2(s)] and an α,α,α′-trisubstituted tetrahydrofuranyl moiety [^{1}H-NMR 4.37(1H,dd,J=8.4,3.6 Hz), ^{13}C-NMR 83.4(d), 85.4(s)]. From these spectral data and the comparison of the data with those of sinulariolide (3), the structure of 1 was suggested as illustrated except for the stereochemistry. The structure was confirmed by the chemical transformation of sinulariolide (3), whose absolute structure had been established by X-ray diffraction method,[4a] into 1 as follows. Treatment of 3 with m-chloroperbenzoic acid in chloroform gave an alcohol 4 [mp 214-216°C, $C_{20}H_{30}O_5$, $[\alpha]_D$ +15.8°(c 1.0, MeOH) as a sole product in a quantitative yield. The stereochemistry at newly arisen chiral centers (C-7 and -8) was determined by converting 4 into S-MTPA ester 5[6] and R-MTPA ester 6,[6] respectively, and by measuring their lanthanide-induced ^{1}H-NMR spectra.[7] The lanthanide-induced shift of the methoxy signal(0.91 ppm,[Eu(fod)$_3$]/[MTPA ester]=1) in the S-MTPA ester 5 was larger than that for the R-MTPA ester 6(0.79 ppm), showing the 7-S configuration.[7] From the result, the stereochemistry at C-8 should be necessarily decided as R. Acetylation of 4 with acetic anhydride in pyridine gave an acetate. The physical properties of the acetate thus obtained were in agreement with those of 1 in every respect.

The structure 2 for the second cembranolide was elucidated by the spectral data,[8] and acetylation to give known 11-episinulariolide acetate.

The compound 1 showed a cytotoxic activity against DBA/MC fibrosarcoma at a concentration of 100 μg/ml.

References

1) This paper constitutes Part XI of "Studies on Marine Natural Products".

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3) All new compounds gave satisfactory elemental analysis or high resolution mass measurement.

4) a) B.Tursch,J.C.Braekman,D.Daloze,M.Herin,R.Karlsson,and D.Losman, Tetrahedron, 31, 129(1975); b) M.Herin and B.Tursch, Bull.Soc.Chim.Belg., 85, 707(1976); c) M.Herin,M.Colin,and B.Tursch, ibid., 85, 801(1976); d) Y.Kashman, M.Bodner, Y.Loya,and Y.Bernayahu, Israel.J.Chem., 16, 1 (1977); e) R.Kazlauskas,P.T.Murphy,R.J.Wells,P.Schönholzer,and J.C.Coll,Aust.J.Chem.,31,1817 (1978).

5) 1: IR($CHCl_3$) 1735,1720,1622,905 cm^{-1}. ^{1}H-NMR(270 MHz,$CDCl_3$) δ_{ppm} 1.16(3H,s),1.24(3H,s),1.25(3H, s),2.06(3H,s),2.58(1H,tt,J=11,6 Hz),3.23(1H,dt,J=6,11 Hz),3.40(1H,dd,J=10.6,4 Hz),4.37(1H,dd, J=8.4,3.6 Hz),5.17(1H,d,J=8.9 Hz),5.44(1H,brs),6.26(1H,brs). ^{13}C-NMR(67.8 MHz,$CDCl_3$) δ_{ppm} 16.4(q),17.1(q),21.1(q),26.7(t),27.3(t),29.3(q),29.8(t),33.2(t),33.6(t),34.3(t),34.9(t),35.7 (d),59.9(s),60.8(d),77.9(d),83.4(d),85.4(s),88.2(s),123.6(t),145.4(s),169.5(s),171.2(s).

6) The MTPA esters were prepared by treatment of 4 with S-(-)- or R-(+)-MTPA chloride in pyridine. 5: ^{1}H-NMR(270 MHz,$CDCl_3$) δ_{ppm} 1.14(3H,s),1.23(3H,s),1.26(3H,s),3.49(3H,s),5.34(1H,brd,J=8.9 Hz), 5.44(1H,brs),6.27(1H,brs). 6: ^{1}H-NMR(270 MHz,$CDCl_3$) δ_{ppm} 1.09(3H,s),1.28(6H,s),3.51(3H,s),5.35 (1H,brd,J=8.9 Hz),5.45(1H,brs),6.28(1H,brs).

7) S.Yamaguchi and F.Yasuhara, Tetrahedron Lett., 1977, 89.

8) 2: IR($CHCl_3$) 3560,1690 cm^{-1}. ^{1}H-NMR(270 MHz,$CDCl_3$) δ_{ppm} 1.27(3H,s),1.38(3H,s),1.69(3H,brs),2.95 1H,dd,J=10.5,3.6 Hz),4.23(1H,m),5.15(1H,t,J=5 Hz),5.50(1H,brs),6.28(1H,s). ^{13}C-NMR(67.8 MHz, $CDCl_3$) δ_{ppm} 17.6(q),17.7(q),23.1(q),23.6(t),28.2(t),29.7(t),32.3(t),32.6(t),33.9(t),35.0(d), 36.5(t),60.0(s),61.5(d),71.2(d),90.6(s),125.0(t),125.0(d),135.6(s),143.4(s),168.7(s).

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