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Xeniaoxolane: A New Xenicane-type Diterpenoid from the Okinawan Soft Coral, *Xenia* sp.; Absolute Configurations of Xeniaoxolane, Xeniolide-A and Xenialactol

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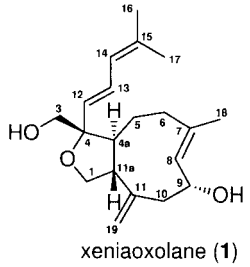
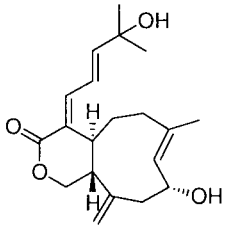
Abstract—A new xenicane-type diterpenoid, xeniaoxolane, containing tetrahydrofuran, was isolated from the Okinawan soft coral of the genus, *Xenia* along with xeniolide-A and xenialactol. The relative configuration of xeniaoxolane was determined based on spectroscopic analysis. The absolute configuration of xeniolide-A was determined using the modified Mosher's method and those of xeniaoxolane and xenialactol, by chemical conversions.

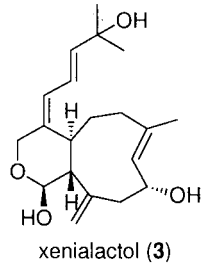
Various xenicane-type diterpenoids have been isolated from marine alga, gorgonian and soft coral[1] and many of these are of considerable interest from standpoints of unique structural features and biological activity.[2] Recently, the authors reported the isolation and structural determination of three xenicane-type diterpenoids from the Okinawan soft coral.[3] While engaged in study on the chemical constituents of Okinawan soft coral, a new xenicane-type diterpenoid xeniaoxolane (**1**) was isolated from the soft coral of the genus, *Xenia*, along with xeniolide-A[4] (**2**) and xenialactol[5] (xenialactol-C[6]) (**3**). The isolation and structural determination of xeniaoxolane (**1**) and absolute configurations of these compounds are presented in the following.



xeniaoxolane (**1**)



xeniolide-A (**2**)



xenialactol (**3**)

Specimens of soft coral (wet wt 5.5 kg), from the coral reef of Ishigaki Island, Okinawa, Japan, in December 1993, were immersed in MeOH and then EtOAc. The MeOH and EtOAc extracts were combined and partitioned between EtOAc and H_2O. The EtOAc-soluble portion (17.2 g) was repeatedly chromatographed on silica gel column to give xeniaoxolane (**1**) (0.83 % yield based on the EtOAc-soluble portion), xeniolide-A (**2**) (1.41 % yield) and xenialactol (**3**) (0.59% yield).

Xeniaoxolane (**1**) was shown to have the molecular formula $C_{20}H_{30}O_3$ based on high resolution EIMS. The IR spectrum of **1** indicated absorptions due to a hydroxyl group (3387 cm^{-1}) and conjugated diene group (1632 cm^{-1}). The conjugated diene group was also shown present by the UV spectrum [λ_{max} 242 nm (ϵ 18,300)]. All 20 carbons appeared in the ^{13}C NMR spectrum and the DEPT spectrum indicated the presence of three methyls, five sp^3 methylenes, one sp^2 methylene, three sp^3 methines, four sp^2 methines, one sp^3 quaternary carbon and three sp^2 quaternary carbons (Table 1). ^1H and ^{13}C NMR correlations were demonstrated by the HMQC spectrum. ^1H and ^{13}C NMR spectra showed the presence of one conjugated diene [δ_H 5.58 (1H, d, J=15.3 Hz), 6.55 (1H, dd, J=15.3, 11.0 Hz), 5.85 (1H, br d, J=11.0 Hz), δ_C 131.0 (CH), 126.0 (CH), 124.6 (CH), 136.1 (C)], one *exo* methylene [δ_H 4.89 (1H, br s), 5.05 (1H, br s), δ_C 143.2 (C), 119.2 (CH_2)], three olefinic methyls [δ_H 1.61 (3H, s), δ_C 18.8 (CH_3); δ_H 1.80 (3H, s), δ_C 18.5 (CH_3); δ_H 1.80 (3H, s), δ_C 26.0 (CH_3)], one oxygenated methine adjacent to trisubstituted olefin [δ_H 4.59 (1H, dt, J=4.9, 9.5 Hz), 5.21 (1H, d, J=9.5 Hz), δ_C 70.8 (CH), 129.6 (CH), 134.7 (C)] and oxygenated two methylenes [δ_H 3.62

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Table 1. NMR data for xeniaoxolane (**1**)

No.	Xeniaoxolane (**1**)	
	^{13}C NMR[a]	^{1}H NMR (J in Hz)[b]
1	70.9 (CH_2)	3.62 (m) 3.86 (t, 8.5)
3	64.5 (CH_2)	3.52 (br d, 11.4) 3.62 (br d, 11.4)
4	88.0 (C)	–
4a	50.3 (CH)	2.12 (m)
5	26.5 (CH_2)	1.44 (m) 1.78 (m)
6	40.1 (CH_2)	1.89 (dd, 12.6, 4.6) 2.12 (m)
7	134.7 (C)	–
8	129.6 (CH)	5.21 (d, 9.5)
9	70.8 (CH)	4.59 (dt, 4.9, 9.5)
10	40.5 (CH_2)	2.00 (ddd, 12.3, 9.5, 1.7) 2.51 (dd, 12.3, 4.9)
11	143.2 (C)	–
11a	57.0 (CH)	2.68 (q, 10.0)
12	131.0 (CH)	5.58 (d, 15.3)
13	126.0 (CH)	6.55 (dd, 15.3, 11.0)
14	124.6 (CH)	5.85 (br d, 11.0)
15	136.1 (C)	–
16	26.0 (CH_3)	1.80 (s)
17	18.5 (CH_3)	1.80 (s)
18	18.8 (CH_3)	1.61 (s)
19	119.2 (CH_2)	4.89 (br s) 5.05 (br s)

[a] 125 MHz, $CDCl_3$.
[b] 500 MHz, $CDCl_3$.

(1H, m), 3.86 (1H, t, J=8.5 Hz), δ_C 70.9 (CH_2); δ_H 3.52 (1H, br d, J=11.4 Hz), 3.62 (1H, br d, J=11.4 Hz), δ_C 64.5 (CH_2)]. The above functional groups were extended to the following partial structures by COSY spectrum (Fig. 1). These partial structures and quaternary carbon (C-4) were found to be connected based on HMBC spectrum; also observed were included the cross peaks: H-1/C-4, C-11; H-5/C-4a; H-6/C-4a, C-7, C-8; H-11a/C-5, C-10, C-11, C-19; H-12/C-3, C-4a; H-13/C-4 and Me-18/C-6, so that the xenicane skeleton including tetrahydrofuran could be constructed. *E* configuration of the carbon–carbon double bond (C-7) was indicated by ^{13}C chemical shift (δ_C 18.8, CH_3) of the olefinic methyl group (C-18)[7] and NOESY correlation between H-9 (δ_H 4.59) and H-18 (δ_H 1.61).

The relative configurations of all chiral centers in **1** were elucidated based on NOESY spectrum (Fig. 2). *trans*-Juncture of two rings was indicated by NOESY correlations between H-3 (δ_H 3.62) and H-11a (δ_H 2.68), and between H-5β (δ_H 1.44) and H-11a (δ_H 2.68) and between H-4a (δ_H 2.12) and H-12 (δ_H 5.58), which suggested H-3 and H-11a to be on the same face of the ring and H-4a and diene moiety to be on the opposite face to H-11a. The conformation of the 9-membered ring was inferred from NOESY correlations between H-4a and H-8 (δ_H 5.21) and between H-8 and H-10α (δ_H 2.00) and between H-11a and H-19 (δ_H 5.05). The stereochemistry of the hydroxyl group at C-9 was determined as an α configuration by NOESY correlations between H-19 (δ_H 4.89) and H-9 (δ_H 4.59) and between H-9 and H-18 (δ_H 1.61). The relative configuration of **1** was thus assigned to 4R^*, 4aS^*, 9R^* and 11aR^*.

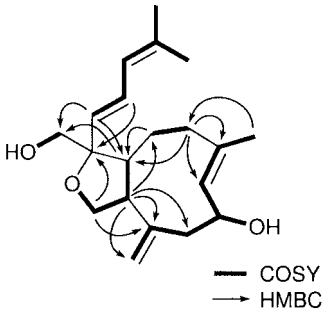


Figure 1. Planar structure of xeniaoxolane (**1**).

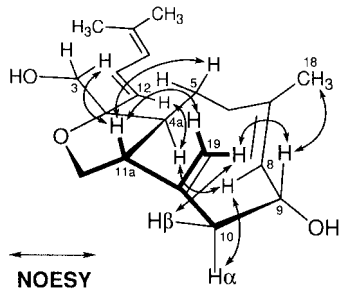


Figure 2. NOESY correlations of xeniaoxolane (**1**).

To date, the absolute configurations of xeniolide-A (**2**) and xenialactol (**3**) have not been determined. The absolute configuration of **2** was determined by the application of modified Mosher's method.[8] Xeniolide-A (**2**) was converted to (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl (MTPA) ester and (*S*)-MTPA ester by treatment with (*R*)- or (*S*)-MTPA-Cl and DMAP, respectively. The ^{1}H NMR spectrum for each compound was measured and Fig. 3 shows Δδ ([δ of the (*S*)-MTPA ester]-[δ of the (*R*)-MTPA ester]). The signs are positive due to left-sided protons but negative owing to right-sided protons, thus demonstrating the 9*R* configuration based on the modified Mosher's method. The relative configuration of **2** has already been established and the present results indicate 4a*S*, 9*R* and 11a*R* configurations for xeniolide-A (**2**).

The absolute configurations of xeniaoxolane (**1**) and xenialactol (**3**) were determined by chemical conversions of xeniolide-A (**2**) (Scheme 1). Xeniolide-A (**2**) was reduced with DIBAL-H in THF at −78°C to give tetraol **4**, $[\alpha]_D^{27}$=−216° (*c* 0.90, MeOH). Tetraol **4** was treated with 1N HCl at room temperature to give xeniaoxolane (**1**).

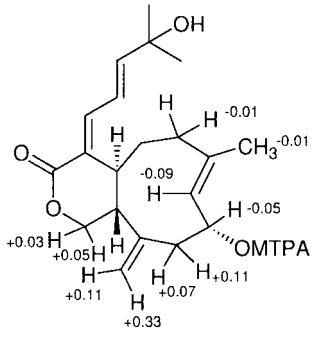
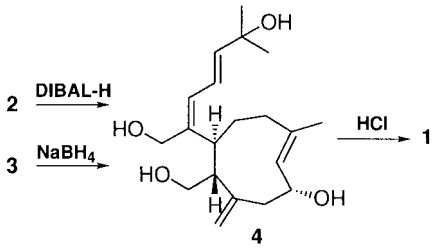


Figure 3. Δδ obtained for the MTPA esters of xeniolide-A (**2**).



Scheme 1.

Spectral data and the sign of optical rotation of semi-synthesized **1** were identical to those of natural xeniaoxolane (**1**). This conversion showed the absolute configuration of **1** to be 4*R*, 4a*S*, 9*R* and 11a*R*. Xenialactol (**3**) was reduced by $NaBH_4$ in MeOH at 0°C to give a product, $[\alpha]_D^{27}=-272°$ (*c* 1.03, MeOH), whose spectral data and the sign of optical rotation were identical to tetraol **4**, which was converted from **2**. The absolute configuration of **3** was thus shown to be 1*S*, 4a*S*, 9*R* and 11a*R*.

Xeniaoxolane (**1**) is a structurally unique xenicane-type diterpenoid possessing tetrahydrofuran moiety.[9] Xenicane-type diterpenoid possessing tetrahydrofuran moiety was presumed to be biosynthesized from xenicane-type diterpenoid having two hydroxymethyl groups, corresponding to tetraol **4**[9a,b] and the presumption was shown valid by the chemical conversion of tetraol **4** to xeniaoxolane (**1**) in this study.

Experimental

General experimental procedures

Optical rotations were measured with a JASCO DIP-360 automatic polarimeter. IR spectra were recorded with a Perkin–Elmer FT-IR 1710 spectrometer or JASCO A-302 spectrometer and ^1H and ^{13}C NMR spectra with a Bruker AM-400 or a Bruker AM-500. Chemical shifts are given on a δ (ppm) scale with tetramethylsilane (TMS) as the internal standard (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad). EIMS and high resolution EIMS (HREIMS) spectra were obtained with a VG Auto Spec spectrometer.

Animal material, extraction and isolation

The soft coral *Xenia* sp. was collected from the coral reef of Ishigaki Island (Okinawa, Japan) in December, 1993 at a depth of 1–3 m. A voucher specimen (SC-93-2) is deposited at this laboratory, School of Pharmacy, Tokyo University of Pharmacy and Life Science (Tokyo, Japan). Wet specimens (5.5 kg) were immersed in MeOH (4.5 L and 3.0 L×3) and the extracts were partitioned between EtOAc (750 mL×3) and H_2O (750 mL) to give EtOAc-soluble portion (17.2 g). The EtOAc-soluble portion was chromatographed on a silica gel column to give the following five fractions; fraction 1 (4.07 g) eluted with hexane–EtOAc=10:1, fraction 2 (3.20 g) eluted with hexane–EtOAc=5:1, fraction 3 (4.07 g) eluted with hexane–EtOAc=1:1, fraction 4 (2.56 g) eluted with EtOAc and fraction 5 (3.20 g) eluted with MeOH. Fraction 3 was subjected to flash silica gel column chromatography (eluted with hexane–EtOAc=1:1) to give xeniaoxolane (**1**) (143 mg). Fraction 4 was subjected to flash silica gel column chromatography (eluted with hexane–EtOAc=1:4) to give four fractions 4-1 (147 mg), 4-2 (406 mg), 4-3 (266 mg) and 4-4 (1.42 g). Fraction 4-2 was subjected to flash silica gel column chromatography (eluted with hexane–EtOAc=1:1) to give xeniolide-A (**2**) (242 mg). Fraction 4-3 was subjected to flash silica gel column chromatography (eluted with hexane–acetone=2:1) followed by recrystalization from EtOAc–hexane to give xenialactol (**3**) (102 mg).

Xeniaoxolane (1). Colorless oil; $[\alpha]_D^{25}=-140°$ (*c* 0.20, $CHCl_3$); IR (neat) ν_{max} 3387, 1632 cm^{-1}; UV (MeOH) λ_{max} 242 nm (ϵ 18,300); ^1H and ^{13}C NMR see Table 1; HMBC correlation (H/C) 3/1, 3/4, 3/4a, 3/12, 4a/3, 4a/4, 4a/5, 4a/6, 4a/11a, 4a/12, 6/4a, 6/5, 6/7, 6/8, 6/18, 8/6, 8/9, 8/18, 9/7, 9/8, 9/10, 10/8, 10/9, 10/11, 10/11a, 10/19, 11a/1, 11a/4, 11a/4a, 11a/10, 11a/11, 11a/19, 12/3, 12/4a, 12/13, 12/14, 13/4, 13/12, 13/14, 13/15, 14/13, 14/15, 14/15, 14/16, 16/14, 16/15, 16/17, 17/14, 17/15, 17/16, 18/6, 18/8, 19/10, 18/11a; NOESY correlation (H/H) 3/11a, 3/12, 4a/8, 9/18, 11a/19, 14/17, 18/19, EIMS *m/z* 318 $[M]^+$, 303 $[M-CH_3]^+$, 287; HREIMS *m/z* 303.1980 (calcd for $C_{19}H_{27}O_3$, 303.1960).

(*R*)-MTPA ester of xeniolide-A. To a solution of xeniolide-A (**1**) (6.0 mg, 18 mmol) in $CHCl_3$ (0.3 mL), Et_3N (0.1 mL), DMAP (1.0 mg) and (*R*)-MTPA-Cl (20.0 mg, 79.0 μmol) were added and the mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with ether and washed with H_2O and saturated NaCl aqueous solution. The organic layer was dried over $MgSO_4$ and concentrated under reduced presser. The residue was purified by silica gel column chromatography (eluted with hexane–EtOAc=2:1) to give (*R*)-MTPA ester (4.1 mg, 44% yield) as a colorless oil: $[\alpha]_D^{25}=-36.2°$ (*c* 0.53, $CHCl_3$); IR (neat) ν_{max} 3450, 1743, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.38 (3H, s), 1.39 (3H, s), 1.51–1.66 (2H, m), 1.80 (3H, s), 2.03 (1H, m), 2.24 (2H, m), 2.39 (1H, d, *J*=14.4 Hz), 2.51 (1H, dd, *J*=14.4, 6.6 Hz), 3.03 (1H, br d, *J*=9.4 Hz), 3.52 (1H, t, *J*=11.5 Hz), 3.61 (3H, s), 4.03 (1H, dd, *J*=11.5, 5.6 Hz), 4.63 (1H, s), 4.79 (1H, s), 5.40 (1H, d, *J*=8.0 Hz), 5.95 (1H, br t, *J*=6.6 Hz), 6.25 (1H, d, *J*=15.0 Hz), 6.49 (1H, dd, *J*=15.0, 11.5 Hz), 6.91 (1H, d, *J*=11.5 Hz), 7.42 (3H, m), 7.53 (2H, m); EIMS *m/z* 530 $[M-H_2O]^+$; HREIMS *m/z* 530.2274 (calcd for $C_{30}H_{33}O_5F_3$, 530.2280).

(*S*)-MTPA ester of xeniolide-A. To a solution of xeniolide-A (**1**) (6.0 mg, 18 μmol) in $CHCl_3$ (0.3 mL), Et_3N (0.1 mL), DMAP (1.0 mg) and (*S*)-MTPA-Cl (20.0 mg, 79.0 μmol) were added and the mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with ether and washed with H_2O and saturated aqueous NaCl solution. The organic layer was dried over $MgSO_4$ and concentrated under reduced presser. The residue was purified by silica gel column chromatography (eluted with hexane–EtOAc=2:1) to give (*S*)-MTPA ester (4.2 mg, 43 % yield) as a colorless oil: $[\alpha]_D^{25}=-73.5°$ (*c* 0.46, $CHCl_3$); IR (neat) ν_{max} 3451, 1743, 1641 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.39 (3H, s), 1.39 (3H, s), 1.51–1.63 (2H, m), 1.79 (3H, s),

2.07 (1H, m), 2.24 (2H, m), 2.50 (1H, d, J=14.4 Hz), 2.58 (1H, dd, J=14.4, 6.6 Hz), 3.06 (1H, br d, J=9.4 Hz), 3.57 (1H, t, J=11.5 Hz), 3.56 (3H, s), 4.06 (1H, dd, J=11.5, 5.6 Hz), 4.90 (1H, s), 4.96 (1H, s), 5.31 (1H, d, J=8.0 Hz), 5.90 (1H, br t, J=6.6 Hz), 6.26 (1H, d, J=15.0 Hz), 6.50 (1H, dd, J=15.0, 11.5 Hz), 6.93 (1H, d, J=11.5 Hz), 7.42 (3H, m), 7.56 (2H, m); EIMS m/z 530 $[M-H_2O]^+$; HREIMS m/z 530.2276 (calcd for $C_{30}H_{33}O_5F_3$, 530.2280).

DIBAL-H reduction of xeniolide-A. To a cold (−78°C) solution of xeniolide-A (**1**) (18.0 mg, 54 μmol) in THF (1.0 mL), DIBAL-H (400 μL, 372 μmol, 0.93 M in hexane) was added. The mixture was stirred for 1 h, treated with MeOH (20 mL), diluted with Et_2O, treated with saturated aqueous NaCl solution and stirred at room temperature for 5 h. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with hexane–acetone=1:2) to give tetraol **4** (6.0 mg, 33 % yield) as a colorless oil: $[\alpha]_D^{27}=-216°$ (c 0.90, MeOH); IR (neat) ν_{max} 3420, 1635 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.37 (3H, s), 1.37 (3H, s), 1.65 (3H, s), 1.70 (2H, m), 1.86 (1H, m), 1.99 (1H, m), 2.24 (1H, m), 2.46 (1H, m), 2.59 (1H, dd, J=12.6, 4.9 Hz), 3.06 (1H, br d, J=8.4 Hz), 3.32 (1H, t, J=11.4 Hz), 3.44 (1H, dd, J=11.4, 4.9 Hz), 4.17 (1H, d, J=14.4 Hz), 4.22 (1H, d, J=14.4 Hz), 4.65 (1H, m), 5.02 (1H, s), 5.06 (1H, s), 5.34 (1H, d, J=10.0 Hz), 5.91 (1H, d, J=15.0 Hz), 6.18 (1H, d, J=10.8 Hz), 6.66 (1H, dd, J=15.0, 10.8 Hz); ^{13}C NMR (CD_3OD, 100 MHz) δ 19.9 (q), 30.0 (q), 30.1 (q), 33.8 (t), 39.2 (t), 40.8 (t), 41.0 (d), 56.5 (d), 62.7 (t), 63.2 (t), 71.2 (d), 71.2 (s), 120.4 (t), 122.9 (d), 124.7 (d), 129.6 (d), 136.7 (s), 142.8 (s), 145.0 (d); EIMS m/z 287 $[M-H_2O-CH_2OH]^+$; HREIMS m/z 287.1985 (calcd for $C_{19}H_{27}O_2$, 287.2011).

Conversion of tetraol 4 to xeniaoxolane (1). To a solution of tetraol **4** (9.4 mg, 28 μmol) in MeOH (1.0 mL), 1N HCl (0.1 mL) was added and the mixture was stirred at room temperature for 5 min. A saturated aqueous $NaHCO_3$ solution was added to the reaction mixture and concentrated under reduced pressure. The residue was diluted with EtOAc, washed with H_2O and saturated aqueous NaCl solution, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with hexane–EtOAc=3:2) to give xeniaoxolane (**1**) (7.3 mg, 82 % yield) as a colorless oil: $[\alpha]_D^{25}=-140°$ (c 0.02, $CHCl_3$).

$NaBH_4$ reduction of xenialactol. To a cold (0°C) solution of xenialactol (**1**) (25.0 mg, 75 μmol) in MeOH (1.0 mL), $NaBH_4$ (28.0 mg, 737 μmol) was added. The mixture was stirred for 3 h and treated with saturated aqueous NaCl solution and stirred at rt for 10 min. The mixture was diluted with EtOAc, washed with H_2O and saturated aqueous NaCl solution, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with hexane–acetone=1:2) to give tetraol **4** (11.0 mg, 44% yield) as a colorless oil: $[\alpha]_D^{27}=-272°$ (c 1.03, MeOH).

Acknowledgements

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