Nardosinane Sesquiterpenoids from the Formosan Soft Coral *Nephthea elongata*

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Seven new nardosinane sesquiterpenoids, elongatols A—G (1—7) were isolated from the methylene chloride solubles of the Formosan soft coral *Nephthea elongata*. Their structures were elucidated by extensive spectroscopic analysis and their cytotoxicity against selected cancer cells was measured *in vitro*.

Key words *Nephthea elongata*; nardosinane sesquiterpenoid; cytotoxicity

Soft corals of the genus *Nephthea* are rich in terpenoids and steroids.[1—14] As part of our search for bioactive substances from marine organisms, the Formosan soft coral *Nephthea elongata* KÜKENTHAL (Nephtheidae) was studied because the CH_2Cl_2 extracts showed significant cytotoxicity to P-388 (mouse lymphocytic leukemia) cell culture as determined by standard procedures.[15,16] Bioassay-guided fractionation resulted in the isolation and chraracterization of seven new sesquiterpenoids, elongatols A—G (**1**—**7**).

Elongatol A (**1**) gave a formula of $C_{15}H_{24}O_3$, from the interpretatoion of its HR-FAB-MS, ^{13}C-NMR, and DEPT spectroscopic data. Thus, four degrees of unsaturation were determined for **1**. The ^{13}C-NMR and DEPT spectra of **1** exhibited signals for three methyls, three sp^3 methylenes, six sp^3 methines, one sp^2 methine, one sp^3 quaternary carbon, and one sp^2 quaternary carbon. The presence of a secondary hydroxyl group in **1** was indicated from the IR (3460 cm^{-1}) and NMR data (δ_H 4.04 dt; δ_C 63.9 d) (Tables 1, 2). The presence of two sp^2 hybridized carbon atoms in the molecule, as deduced from the ^{13}C- and DEPT NMR spectra (Table 2), corresponding to one carbon–carbon double bond as the only multiple bond, indicated compound **1** to be tricyclic. The ^{1}H-NMR spectrum contained signals for three methyl groups, two doublets (δ_H 0.87, 1.21), and one singlet (δ_H 0.95). In addition, a signal at δ_H 5.00 was attributed to a proton on a carbon carrying two oxygens and confirmed by ^{13}C-NMR spectroscopy (δ_C 107.4 d). The presence of another carbon bearing oxygen (δ_C 78.3 d) was shown in the ^{13}C-NMR spectrum. The spectral data of **1** closely resembled those of armatin D isolated from the soft coral *Nephthea armata* except for the replacement of the methoxyl by a hydroxyl.[13] The α-configuration of hydroxy at C-2 was determined by comparison with $J_{1,2}$ of armatin D and its 2-epimeric analogues.[17] The α-configuration of hydroxy at C-12 was determined by comparison with $J_{11,12}$ of its 12-epimeric analogues.[17] The relative stereochemistry of **1** was deduced from a 2D NOESY experiment, which indicated that Me-13, Me-14, Me-15, H-6, H-7, and

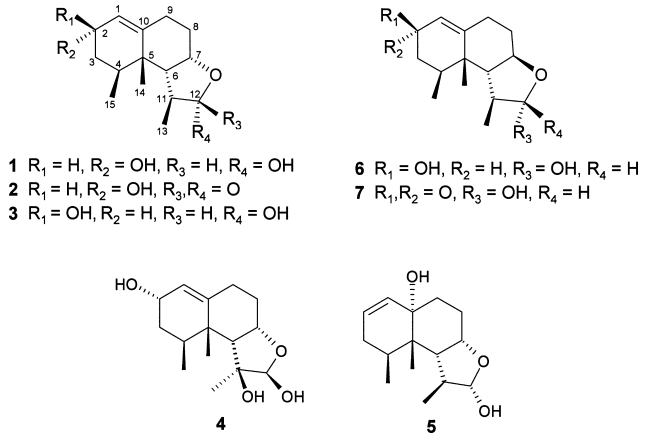

Fig. 1. Structures of Compounds **1**—**7**

Table 1. ^{1}H-NMR Data[a)] (300 MHz, in $CDCl_3$) of **1**—**7**

H	1	2	3	4	5	6	7
1	5.66 d (4.8)[b)]	5.75 d (4.5)	5.48 s	5.62 d (4.8)	5.44 d (9.6)	5.40 br s	5.82 s
2	4.04 dt (2.5, 4.8)	4.12 dt (2.5, 4.5)	4.22 m	4.14 m	5.71 ddd (9.6, 4.8, 1.8)	4.20 m	
3	1.57 m	1.62 m	1.24 m, 1.78 m	1.62 m	1.84 m, 1.97 m	1.43 m, 1.85 m	2.32 m
4	2.28 m	2.15 m	1.87 m	2.76 m	2.37 td (16.5, 6.9)	1.97 m	2.35 m
6	2.09 m	2.43 m	2.04 m	2.57 d (8.4)	1.98 m	1.57 m	1.78 m
7	4.30 dt (10.2, 5.4)	4.21 dt (9.5, 2.0)	4.30 dt (10.8, 6.6)	4.54 dt (9.6, 9.0)	4.58 t (4.2)	3.89 m	3.98 m
8	1.93 m	1.43 m, 2.23 m	1.87 m	1.65 m, 2.08 m	2.00 m, 2.33 m	1.56 m, 2.08 m	1.76 m, 2.17 m
9	2.18 m	2.20 m, 2.36 m	2.11 m, 2.23 m	2.20 m, 2.39 m	1.70 m, 2.30 m	2.03 m, 2.47 m	2.22 m, 2.70 m
11	2.02 m	2.42 m	1.96 m		2.56 q (6.9)	2.10 m	2.20 m
12	5.00 d (3.9)		5.02 d (4.5)	4.82 s	4.98 s	5.10 d (3.6)	5.13 d (3.9)
13	1.21 d (6.6)	1.39 d (7.0)	1.19 d (6.3)	1.52 s	0.96 d (6.9)	1.27 d (6.9)	1.31 d (6.9)
14	0.95 s	1.02 s	1.03 s	1.01 s	0.85 s	1.08 s	1.20 s
15	0.87 d (5.7)	0.93 d (6.5)	0.88 d (6.6)	1.02 d (6.0)	0.85 d (6.9)	1.01 d (6.6)	1.10 d (6.0)

a) Assigned by COSY, HSQC, and HMBC experiments. *b*) *J* values (in Hz) in parentheses.

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Table 2. ^{13}C-NMR Spectral Data[a] (75 MHz, in $CDCl_3$) of **1**—**7**

	1	2	3	4	5	6	7
1	124.3	125.8	127.8	122.6	130.3	125.8	125.5
2	63.9	63.6	67.5	64.1	128.3	67.2	198.8
3	35.6	35.5	36.9	35.7	31.6	39.1	43.5
4	28.7	29.1	33.3	27.5	30.8	31.8	33.2
5	41.0	40.8	40.9	39.6	38.2	40.1	40.9
6	54.8	51.8	54.9	51.1	46.4	59.9	59.4
7	78.3	75.7	78.6	75.0	77.2	76.7	75.8
8	30.7	29.5	31.1	30.5	31.1	30.1	29.4
9	29.7	28.5	29.7	28.9	25.4	27.3	28.5
10	145.3	143.4	141.9	145.9	78.4	148.8	172.6
11	42.0	36.2	41.9	78.3	39.0	44.0	44.0
12	107.4	179.8	107.5	108.7	102.0	106.9	106.7
13	19.3	17.7	19.2	23.2	15.6	18.5	18.1
14	20.0	19.2	21.2	21.4	14.4	21.2	19.6
15	16.0	15.8	16.1	16.8	13.1	18.7	18.7

a) Assigned by DEPT, COSY, HSQC, and HMBC experiments.

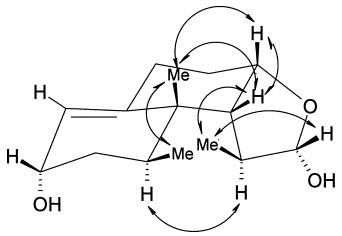


Fig. 2. Selected NOESY Correlations of **1**

H-12 are on one side of the molecule, while H-4, and H-11 are on the opposite side of the molecule (Fig. 2). From the aforementioned data, elongatol A can be formulated as lemnal-1(10)-ene-2α,12α-diol.

HR-EI-MS and NMR spectroscopic data revealed elongatol B (**2**) to have a molecular formula of $C_{15}H_{22}O_3$. The IR spectrum showed the presence of a lactone (1742 cm^{-1}) and a secondary hydroxyl group (3530 cm^{-1}). The ^{13}C-NMR features (Table 2) of **2** closely resembled those of **1** except that the resonances for the hemiacetal in **1** were replaced by those of a γ-lactone in **2**. HMBC correlations from H-13 to C-6/C-11/C-12; from H-6 to C-5/C-7/C-8/C-13/C-14; from H-7 to C-5/C-6/C-8/C-9/C-11; and from H-11 to C-5/C-6/C-13 confirmed the position of the γ-lactone in **2**. The relative stereochemistry of **2** was deduced from a 2D NOESY experiment, which indicated that Me-13, Me-14, Me-15, H-7, and H-6 are on one side of the molecule, while H-4, and H-11 are on the opposite side of the molecule. Therefore, elongatol B was assigned as 2α-hydroxy-lemnal-1(10)-en-12-one on the basis of the above results.

Elongatol C (**3**) was assigned a molecular formula of $C_{15}H_{24}O_3$, as indicated by HR-FAB-MS and ^{13}C-NMR (Table 2). The spectroscopic data of **3** were very similar to those of **1** with the exception for the resonances and splitting pattern for the secondary hydroxyl methine at C-2. The β-configuration of hydroxy at C-2 was determined by comparison with $J_{1,2}$ of lemnacarol ($J_{1,2}$=6 Hz) and its 2-epimeric analogues ($J_{1,2}$=0 Hz).[17] The α-configuration of hydroxy at C-12 was determined by comparison with $J_{11,12}$ of its 12-epimeric analogues.[17] The relative stereochemistry of **3** was deduced from a 2D NOESY experiment, which showed similar results as described for **1**. The structure of elongatol C (**3**) was thus

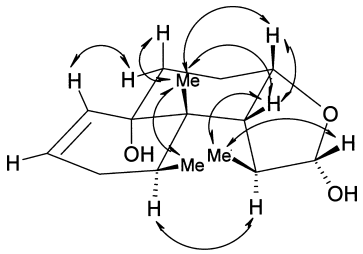


Fig. 3. Selected NOESY Correlations of **5**

determined as lemnal-1(10)-en-2β,12α-diol.

Elongatol D (**4**) was shown to have a molecular formula of $C_{15}H_{24}O_4$ from its HR-FAB-MS and NMR spectroscopic data. The NMR features of **4** closely resembled those of **1** except that the resonances for the secondary Me-13 in **1** were replaced by those of a tertiary methyl adjacent to a tertiary hydroxyl in **4**. HMBC correlations from H-13 to C-6/C-11/C-12; from H-6 to C-5/ C-13/C-14; and from H-11 to C-5/C-6/C-13 helped ascertain the position of the tertiary hydroxyl at C-12 in **4**. The α-configuration of hydroxy at C-2 was determined by comparison with $J_{1,2}$ of lemnacarol and its 2-epimeric analogues.[17] The relative stereochemistry of **4** was deduced from a 2D NOESY experiment, which indicated that Me-14, Me-15, H-7, and H-6 are on one side of the molecule, while H-4, and Me-13 are on the opposite side of the molecule. From the these data, elongatol D (**4**) was formulated as lemnal-1(10)-en-2α,11β,12β-triol.

Elongatol E (**5**) analyzed for $C_{15}H_{24}O_3$ from HR-FAB-MS and ^{13}C-NMR spectroscopic data. The spectroscopic data of **5** were analogous to those of **1** with the exception that the resonance for the secondary hydroxyl and the trisubstituted olefin in **1** were replaced by those of a tertiary hydroxyl and a disubstituted olefin in **5**. COSY correlation from H-1 to H-2 and HMBC correlations from H-1 to C-5/C-9/C-10; from H-3 to C-2/C-1; and from H-14 to C-5/C-10 helped ascertain the position of the tertiary hydroxyl and the disubstituted olefin. The relative stereochemistry of **5** was deduced from a 2D NOESY experiment, which indicated that Me-13, Me-14, Me-15, H-12, H-6, and H-7 are on one side of the molecule, while H-4, H-11, and OH-10 are on the opposite side of the molecule (Fig. 3). The structure of elongatol E (**5**) was thus formulated as lemnal-1(2)-en-12β,10α-diol.

Elongatol F (**6**) was assigned to have a molecular formula of $C_{15}H_{24}O_3$, as shown by its HR-FAB-MS, ^{13}C-NMR, and DEPT spectroscopic data. Thus, four degrees of unsaturation were determined for **6**. The ^{1}H- and ^{13}C-NMR spectral data of **6** closely resembled those of armatin A isolated from the soft coral *Nephthea armata* except for the chemical shifts and coupling constants of H-1/H-2 and C-1/C-2.[13] The β-configuration of hydroxy at C-2 was determined by comparison with $J_{1,2}$ of armatin A and its 2-epimeric analogues.[17] The relative stereochemistry of **6** was deduced from a 2D NOESY experiment, which indicated that Me-13, Me-14, Me-15, H-6, and H-12 are on one side of the molecule, while H-4, H-7, and H-11 are on the opposite side of the molecule (Fig. 4). From these results, elongatol F can be formulated as (7αH)-lemnal-1(10)-ene-2β,12α-diol.

The molecular formula of elongatol G (**7**) was obtained from HR-FAB-MS and ^{13}C-NMR (Table 2) spectroscopic data. The spectroscopic data of **7** were analogous to those of

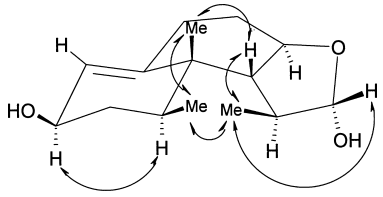
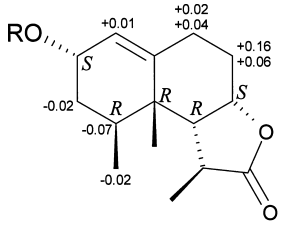


Fig. 4. Selected NOESY Correlations of **6**



2a R = (*S*)-MTPA
2b R = (*R*)-MTPA

$\Delta\delta = \delta(S)\text{-MTPA} - \delta(R)\text{-MTPA}$ (ppm)

Fig. 5. ^{1}H-NMR Chemical Shift Differences [δ(*S*)MTPA−δ(*R*)-MTPA] of the MTPA Esters

6 with the exception that the resonance for the secondary hydroxyl in **6** was replaced by that of a ketone in **7**. HMBC correlations from H-1 to C-2/C-3/C-9; from H-3 to C-2/C-1; and from H-4 to C-2/C-3/C-6 helped ascertain the position of the α,β-unsaturated ketone group. The relative stereochemistry of **7** was deduced from a 2D NOESY experiment, which showed similar results as described for **6**. The structure of elongatol G was thus assigned as 12α-hydroxy-(7αH)-lemnal-1(10)-en-2-one.

Using Mosher's method,[18] the absolute stereochemistry of **2** was readily defined by analysis of NMR shift data from the corresponding C-2 (*R*)- and (*S*)-MTPA esters. The significant proton chemical shift differences between the (*S*)- and (*R*)-MTPA esters **2a** and **2b** demonstrated that C-2 possessed the *S*-configuration (Fig. 5). This analysis required that **2** possessed 2*S*, 4*R*, 5*R*, 6*R*, 7*S*, and 11*S* absolute configuration.

Compounds **1** and **5** exhibited cytotoxicity against P-388 cell line with ED_{50} of 3.8 and 3.6 μg/ml, respectively. The other compounds were not cytotoxic to P-388 line.

Experimental

General Experimental Procedures Optical rotations were determined on a JASCO DIP-181 polarimeter. IR spectra were recorded on a Hitachi 26-30 spectrophotometer. The NMR spectra were recorded on Bruker Avance 300 NMR spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C, respectively, using TMS as internal standard. HR-MS were obtained with a JEOL JMS-SX/SX 102A mass spectrometer at 70 eV. Silica gel 60 (Merck, 230—400 mesh) was used for column chromatography; precoated silica gel plates (Merck, Kieselgel 60 F_{254}, 0.25 mm) were used for TLC analysis.

Animal Material The soft coral *N. elongata* was collected at Green Island, off Taiwan, in September 2004, at a depth of 3 m and was stored for 2 weeks in a freezer until extraction. A voucher specimen, NSUGN-071, was deposited in the Department of Marine Biotechnology and Resources, National Sun Yat-sen University, Taiwan.

Extraction and Isolation The bodies of the soft coral *N. elongata* were freeze dried to give 1.2 kg of a solid, which was extracted with CH_2Cl_2 (2 l×3, overnight for each cycle) at room temperature. After removal of solvent *in vacuo*, the residue (40 g) was chromatographed over a column containing silica gel 60 using *n*-hexane–EtOAc and MeOH–EtOAc mixtures as eluting solvents. Elution by *n*-hexane–EtOAc (60 : 40) afforded fractions containing **2** and **3**. Elution by *n*-hexane–EtOAc (55 : 45) afforded fractions containing **1** and **5**. Elution by *n*-hexane–EtOAc (30 : 70) afforded fractions containing **4**. Elution by EtOAc afforded fractions containing **6** and **7**. Compound **1** (10 mg) was further purified by silica gel column chromatography, eluting with MeOH–CH_2Cl_2 (95 : 5). Compound **2** (5 mg) was further purified by silica gel column chromatography, eluting with *n*-hexane–acetone (85 : 15). Compound **3** (12 mg) was further purified by HPLC (LiChrosorb Si 60, 7 μ, 25×250 mm), eluting with *n*-hexane–acetone (85 : 15). Compound **4** (2 mg) was further purified by silica gel column chromatography, eluting with MeOH–CH_2Cl_2 (90 : 10). Compound **5** (8 mg) was further purified by silica gel column chromatography, eluting with MeOH–CH_2Cl_2 (99 : 1). Compound **6** (2 mg) was further purified by HPLC (LiChrosorb RP-18, 7 μ, 25×250 mm), by eluting with MeOH–H_2O (52 : 48). Compound **7** (1 mg) was further purified by HPLC (LiChrosorb RP-18, 7 μ, 25×250 mm), by eluting with MeOH–H_2O (55 : 45).

Elongatol A (**1**): $[\alpha]_D^{25}$ −42° (*c*=0.3, $CHCl_3$). IR (neat) cm^{-1}: 3460. ^{1}H-NMR: see Table 1. ^{13}C-NMR: see Table 2. HR-FAB-MS *m/z*: 275.1626 (Calcd for $C_{15}H_{24}O_3Na$: 275.1623).

Elongatol B (**2**): $[\alpha]_D^{25}$ −90° (*c*=0.2, $CHCl_3$). IR (neat) cm^{-1}: 3530, 1742. ^{1}H-NMR: see Table 1. ^{13}C-NMR: see Table 2. HR-EI-MS *m/z*: 250.1566 (Calcd for $C_{15}H_{22}O_3$: 250.1569).

Elongatol C (**3**): $[\alpha]_D^{25}$ +23° (*c*=0.2, $CHCl_3$). IR (neat) cm^{-1}: 3456. ^{1}H-NMR: see Table 1. ^{13}C-NMR: see Table 2. HR-FAB-MS *m/z*: 275.1628 (Calcd for $C_{15}H_{24}O_3Na$: 275.1623).

Elongatol D (**4**): $[\alpha]_D^{25}$ −38° (*c*=0.1, $CHCl_3$). IR (neat) cm^{-1}: 3515. ^{1}H-NMR: see Table 1. ^{13}C-NMR: see Table 2. HR-FAB-MS *m/z*: 291.1576 (Calcd for $C_{15}H_{24}O_4Na$: 291.1572).

Elongatol E (**5**): $[\alpha]_D^{25}$ −25° (*c*=0.2, $CHCl_3$). IR (neat) cm^{-1}: 3520. ^{1}H-NMR: see Table 1. ^{13}C-NMR: see Table 2. HR-FAB-MS *m/z:* 275.1626 (Calcd for $C_{15}H_{24}O_3Na$: 275.1623).

Elongatol F (**6**): $[\alpha]_D^{25}$ +108° (*c*=0.1, $CHCl_3$). IR (neat) cm^{-1}: 3450. ^{1}H-NMR: see Table 1. ^{13}C-NMR: see Table 2. HR-FAB-MS *m/z*: 275.1622 (Calcd for $C_{15}H_{24}O_3Na$: 275.1623).

Elongatol G (**7**): $[\alpha]_D^{25}$ −163° (*c*=0.1, $CHCl_3$); IR (neat) cm^{-1}: 3480, 1710. UV λ_{max} (MeOH) nm (log ε): 236 (3.68). ^{1}H-NMR: see Table 1. ^{13}C-NMR: see Table 2. HR-FAB-MS *m/z*: 275.1620 (Calcd for $C_{15}H_{22}O_3Na$: 273.1467).

Preparation of (*R*)- and (*S*)-MTPA Esters (2a, 2b) of 2 To a solution of compound **2** (1.4 mg, 5.6 μmol) in pyridine (0.5 ml) at RT was added (*R*)-MTPA-Cl (2.0 μl, 10.6 μmol) and the resultant mixture was stirred for 24 h at room temperature. The reaction mixture was worked up by adding 2 ml of H_2O to give the corresponding (*S*)-MTPA ester **2a** (0.4 mg): ^{1}H-NMR ($CDCl_3$, 300 MHz), δ: 7.40—7.66 (5H, aromatic H), 5.82 (1H, d, *J*=5.1 Hz, H-1), 5.34 (1H, m, H-2), 4.70 (1H, m, H-7), 3.53 (3H, s, OMe), 2.35 (1H, m, H-6), 2.36 (1H, m, H-8β), 2.35 (1H, m, H-9β), 2.21 (1H, m, H-9α), 1.93 (1H, m, H-4), 1.66 (2H, m, H-3), 1.33 (1H, m, H-8α), 1.16 (3H, d, d, *J*=6.6 Hz, H_3-13), 1.02 (3H, m, H_3-14), 0.85 (3H, d, *J*=6.6 Hz, H_3-15). Treatment of **2** (1.1 mg) in the same manner with (*S*)-MTPA chloride in pyridine gave the corresponding (*R*)-MTPA ester **2b** (0.5 mg): ^{1}H-NMR ($CDCl_3$, 300 MHz), δ: 7.41—7.65 (5H, aromatic H), 5.81 (1H, d, *J*=5.1 Hz, H-1), 5.28 (1H, m, H-2), 4.66 (1H, m, H-7), 3.55 (3H, s, OMe), 2.34 (1H, m, H-6), 2.20 (1H, m, H-8β), 2.31 (1H, m, H-9β), 2.19 (1H, m, H-9α), 2.00 (1H, m, H-4), 1.68 (1H, m, H-3), 1.27 (1H, m, H-8α), 1.15 (3H, d, *J*=6.6 Hz, H_3-13), 1.01 (3H, m, H_3-14), 0.87 (3H, d, *J*=6.6 Hz, H_3-15).

Cytotoxicity Testing P-388 cells were kindly supplied by Dr. J. M. Pezzuto, formerly of the Department of Medicinal Chemistry and Pharmacognosy, University of Illinois at Chicago; Cytotoxic assays were carried out according to the procedure described previously.[16] Three concentrations (50, 5, 0.5 μg/ml) of the tested compounds were used in the cytotoxicity assays.

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