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Novel steroids from the soft coral *Nephthea chabrolii*

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Abstract—Three new metabolites including two new steroids, chabrolosteroids A and B (**1** and **2**), and a novel spirosteroid chabrolosteroid C (**3**), were isolated from the organic extract of a Taiwanese soft coral *Nephthea chabrolii*. The structures of these metabolites were elucidated by extensive spectroscopic analysis and by comparison of the spectral data with those of related steroids. This is the first report of a steroid with a spiro-ring A, B system in natural products.
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1. Introduction

Our previous study on the secondary metabolites of a Formosan soft coral *Nephthea chabrolii* Audouin (Alcyonacea, Nephthedae) has resulted in the isolation of a series of new meroditerpenoids, including naphthoquinone derivatives, tetraprenyltoluquinone-related metabolites, and tetraprenyltoluquinol-related metabolites.[1,2] Our continuing investigation on the chemical constituents of the EtOH extract of this soft coral again has afforded three new steroids. Among these metabolites **3** was found to possess a novel skeleton.

2. Results and discussion

A collection of *N. chabrolii* was homogenized with EtOH and filtered, and further extracted with EtOH. The combined extracts were concentrated and subsequently subjected to further purification to yield the new compounds **1–3** (Fig. 1).

Chabrolosteroid A (**1**) was isolated as a white powder. Its molecular formula $C_{28}H_{44}O_3$ was established by HRESIMS (*m/z* 451.3186, $[M+Na]^+$), implying seven degrees of unsaturation. The presence of hydroxy functionality was suggested by a strong absorption band at 3404 cm^{-1} in the IR spectrum. By the analysis of NMR (Table 1) and DEPT spectra of **1**, measured in $CDCl_3$, the carbon signals were assigned to five methyl, nine sp^3 methylenes (including one oxygenated δ 65.8), six sp^3 methines, three sp^2 methines, and five quaternary carbons. By comparison of some NMR data of **1**, δ 186.5 (C), 169.5 (C), 156.1 (CH), 127.4 (CH), and 123.7 (CH) with those of the previously reported steroids,[3,4] it was also found that the carbon signals appearing were similar to those of steroids with a cross-conjugated dienone structural unit in the ring A. The absorptions of the UV (248 nm) and IR (1658 cm^{-1}) spectra further confirmed

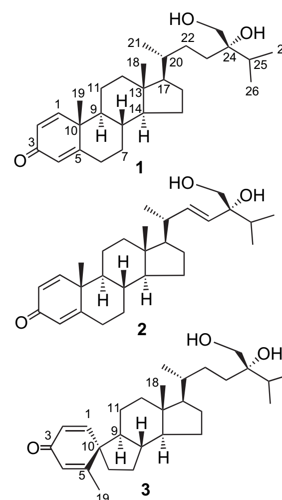

Figure 1. Structures of new metabolites **1–3**.

Keywords: Chabrolosteroids; Spirosteroid; *Nephthea chabrolii*.
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Table 1. ^{1}H and ^{13}C NMR chemical shifts of compounds **1–3**

No.	**1**		**2**		**3**	
	δ_H [a]	δ_C [b]	δ_H [a]	δ_C [b]	δ_H [a]	δ_C [b]
1	7.06 d (10.0) [c]	156.1 (CH) [d]	7.06 d (10.0)	156.0 (CH)	6.87 d (10.0)	154.8 (CH)
2	6.23 dd (10.0, 2.0)	127.4 (CH)	6.23 dd (10.0, 2.0)	127.5 (CH)	6.20 d (10.0)	126.6 (CH)
3		186.5 (C)		186.4 (C)		186.6 (C)
4	6.07 s	123.7 (CH)	6.07 s	123.8 (CH)	6.17 s	128.6 (CH)
5		169.5 (C)		169.4 (C)		163.2 (C)
6	2.35 dt (12.0, 2.5) 2.46 ddd (13.5, 12.0, 5.5)	32.9 (CH_2)	2.37 dt (12.0, 3.0) 2.46 ddd (13.5, 13.0, 5.5)	32.9 (CH_2)	1.76 m 1.99 m	34.9 (CH_2)
7	1.02 m; 1.94 m	33.7 (CH_2)	1.04 m; 1.94 m	33.6 (CH_2)	1.33 m; 1.98 m	30.6 (CH_2)
8	1.63 m	35.5 (CH)	1.61 m	35.5 (CH)	1.57 m	56.5 (CH)
9	1.04 m	52.3 (CH)	1.06 m	52.3 (CH)	1.77 m	42.5 (CH)
10		43.6 (C)		43.6 (C)		52.6 (C)
11	1.68 m	22.8 (CH_2)	1.68 m	22.8 (CH_2)	1.78 m	22.1 (CH_2)
12	1.16 m; 2.04 dt (12.5, 3.5)	39.4 (CH_2)	1.21 m; 2.02 dt (12.5, 3.5)	39.3 (CH_2)	1.95 m	39.3 (CH_2)
13		42.7 (C)		42.6 (C)		43.6 (C)
14	0.99 m	55.4 (CH)	1.03 m	55.4 (CH)	1.17 m	56.4 (CH)
15	1.12 m; 1.61 m	24.4 (CH_2)	1.57 m	24.4 (CH_2)	1.62 m	24.6 (CH_2)
16	1.30 m; 1.88 m	28.1 (CH_2)	1.67 m	28.7 (CH_2)	1.32 m; 1.91 m	28.5 (CH_2)
17	1.13 m	55.6 (CH)	1.20 m	55.5 (CH)	1.16 m	55.2 (CH)
18	0.74 s	12.0 (CH_3)	0.77 s	12.3 (CH_3)	0.66 s	12.2 (CH_3)
19	1.23 s	18.7 (CH_3)	1.23 s	18.7 (CH_3)	1.97 s	19.5 (CH_3)
20	1.40 m	36.1 (CH)	2.17 m	40.2 (CH)	1.39 m	36.0 (CH)
21	0.93 d (6.0)	18.6 (CH_3)	1.05 d (6.0)	20.7 (CH_3)	0.94 d (6.0)	18.7 (CH_3)
22	1.05 m; 1.40 m	28.8 (CH_2)	5.58 dd (15.5, 9.0)	138.5 (CH)	1.07 m; 1.36 m	29.0 (CH_2)
23	1.33 m; 1.64 m	30.3 (CH_2)	5.31 d (15.5)	127.8 (CH)	1.33 m; 1.64 m	30.3 (CH_2)
24		76.1 (C)		77.4 (C)		76.1 (C)
25	1.86 m	32.4 (CH)	1.81 m	34.0 (CH)	1.85 m	32.5 (CH)
26	0.93 d (7.0)	17.0 (CH_3)	0.88 d (7.0)	17.5 (CH_3)	0.93 d (7.5)	16.9 (CH_3)
27	0.91 d (7.0)	16.9 (CH_3)	0.90 d (7.0)	16.5 (CH_3)	0.92 d (7.5)	17.0 (CH_3)
28	3.45 d (11.0); 3.61 d (11.0)	65.8 (CH_2)	3.53 s	67.6 (CH_2)	3.46 d (10.0); 3.61 d (10.0)	65.9 (CH_2)

[a] Spectra recorded at 500 MHz in $CDCl_3$.
[b] Spectra recorded at 125 MHz in $CDCl_3$.
[c] *J* values (Hz) in parentheses.
[d] Attached protons determined by DEPT experiments.

the presence of this moiety as an important structural unit of **1**. Careful analysis of the ^{1}H–^{1}H COSY correlations observed for **1** has led to the establishment of five partial structures, as shown in Figure 2. The molecular framework of **1** was further established by an HMBC experiment (Fig. 2). The structures and connection among A, B, C, and D rings were elucidated on the basis of the following HMBC correlations: H-1 to C-3, C-5, and C-10; H-2 to C-1 and C-10; H-4 to C-2 and C-6; H_2-6 to C-5 and C-10; H-9 to C-14; H_2-12 to C-13; H_2-15 to C-13; H_2-16 to C-14; H-17 to C-13, C-20, and C-22; H_3-18 to C-12, C-13, C-14, and C-17; H_3-19 to C-1, C-5, C-9, and C-10. The planar structure of the side chain was elucidated mainly by the key HMBC correlations from H_2-28 to C-23, C-24, and C-25. On the basis of the above findings and HMBC correlations observed, the skeleton of **1** could be established unambiguously.

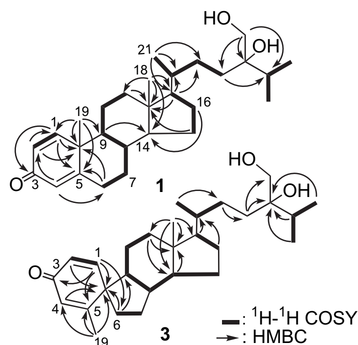


Figure 2. Selective ^{1}H–^{1}H COSY and HMBC correlations of **1** and **3**.

The stereochemistry regarding C-8, C-9, C-10, C-13, C-14, C-17, and C-20 in **1** was found to be the same by comparison of the NMR data (^{1}H and ^{13}C) with those of the related known compounds.[3,4] This was further established by a NOESY experiment, which showed the following key correlations: H-6β, H-7β, H_3-18, and H_3-19 with H-8; H-6β with H_3-19; H-6α and H-7α with H-9; H-11β with H_3-18; H_3-18 with H-20; H-11α and H-17 with H-14. The absolute configuration at C-24 was determined by comparison of the NMR data of **1** in CD_3OD with those of two related synthetic compounds, also measured in CD_3OD. The difference between the proton shifts of two protons at C-28, $\Delta\delta_H$=0.06 ppm, was found to be the same as those of 24*S*-24-hydroxymethyl-24-hydroxycholesterol **4** ($\Delta\delta_H$=0.06 ppm), while its 24*R*-epimer **5** showed the chemical shift difference of these two protons, $\Delta\delta_H$=0.04 ppm.[5] Also, the carbon shift of C-28 (δ=66.4) was found to be more closer to that of **4** (δ=66.3) relative to that of **5** (δ=66.0), too. Moreover, metabolite **1** has the nearly identical NMR shifts of H_2-28 and C-28 as those of a known compound certonardosterol B_4 (**6**)[6] (Fig. 3). Thus, it was suggested that the stereochemistry of **1** at C-24 should be 24*S*. The C-24 configuration of **1** was further confirmed by comparison of the ^{1}H NMR data of its (*R*)- and (*S*)-MTPA esters with those of **4** and **5**. It has been reported that the H_2-28 signals of the (*R*)-MTPA ester of **4** appeared at δ 4.33 and 4.21, and those of (*R*)-MTPA ester of **5** appeared at δ 4.37 and 4.17, while the H_2-28 signals

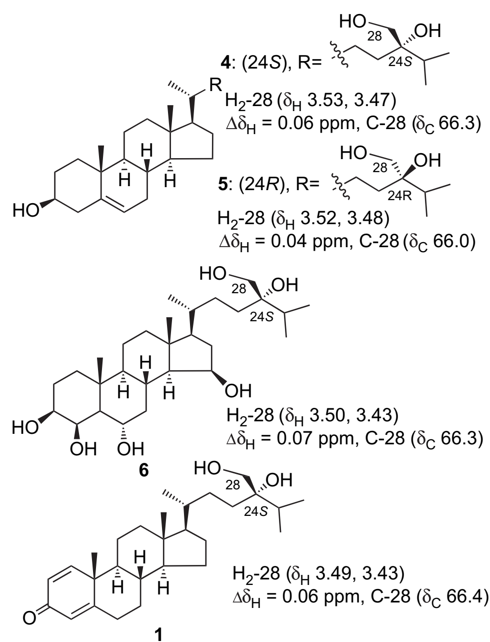


Figure 3. Selective ^{1}H and ^{13}C NMR data measured in CD_3OD for **1**, and **4–6** ($\Delta\delta_H=\delta_{H\text{-}28a}-\delta_{H\text{-}28b}$).

of the (*S*)-MTPA ester of **4** appeared at δ 4.41 and 4.14 and those of the (*S*)-MTPA ester of **5** appeared at δ 4.30 and 4.23.[5] We found that the H_2-28 signals of the (*S*)-MTPA ester of **1** appeared as two well-separated doublets at δ 4.40 and 4.13 (δ_H=0.27 ppm), while those of the (*R*)-MTPA ester appeared as two closely spaced doublets at δ 4.32 and 4.20 (δ_H=0.12 ppm). Thus, **1** should possess 24*S* configuration, the same as that of **4**. On the basis of the above analysis, the structure of **1** was established.

Chabrolosteroid B (**2**) was obtained as a white powder, which exhibited a pseudomolecular ion peak $[M+Na]^+$ at *m/z* 449.3029 in the HRESIMS. The ^{1}H and ^{13}C NMR spectra (Table 1) for the tetracyclic moiety of **2** were similar to those of **1**. However, the NMR data of the side chain of **2** showed the presence of an additional double bond [δ 5.58 (1H, dd, *J*=15.5, 9.0 Hz, H-22), 5.31 (1H, d, *J*=15.5 Hz, H-23), 138.5 (CH, C-22), 127.8 (CH, C-23)] by comparison of those of **1**. The HMBC correlations between methyl protons at δ 1.05 (3H, d, *J*=6.0 Hz, H-21) and C-20 (δ 40.2, CH), C-22, and C-17 (δ 55.5, CH), further assigned the position of the double bond at C-22 and C-23. The coupling constant (15.5 Hz) between two olefinic protons confirmed the *E*-geometry of 22,23-double bond. Although it was found that the stereochemistry at C-24 could not be firmly established by the NOESY experiment, which showed the following NOE interactions for protons near C-24: H-22/H-17, H-22/H_3-21, H-23/H-20, H-23/H-25, H-23/H_3-26, H-23/H_2-28, H_2-28/H-25, and H_2-28/H_3-27, as these NOEs could appear in both 24*R* and 24*S* configurations, however, based on the well established 24*S* configuration of **1** and by the fact that both **1** and **2** could be the precursors of each other by dehydrogenation and hydrogenation, respectively, the structure of **2** was then established as shown.

The HRESIMS of chabrolosteroid (**3**) exhibited a pseudomolecular ion peak at *m/z* 451.3186 $[M+Na]^+$. This information along with the ^{13}C NMR (Table 1) and the DEPT spectra, which assigned the 28 carbons into five methyls, nine methylenes, nine methines, and five quaternary carbons, allowed the determination of the molecular formula as $C_{28}H_{44}O_3$. The ^{1}H NMR spectrum of **3** exhibited three doublet methyl signals at δ 0.92, 0.93, and 0.94, two singlet methyl signals at δ 0.66 and 1.97, an oxygenated methylene group at δ 3.46 and 3.61 (each d, *J*=10.0 Hz), and three olefinic protons at δ 6.17 (s), 6.20 (d, *J*=10.0 Hz), and 6.87 ppm (d, *J*=10.0 Hz). The planar structure of **3** was further established by the 2D NMR studies, particularly in ^{1}H–^{1}H COSY, HMQC, and HMBC experiments (Fig. 2). The proton sequence from H-1 (δ 6.87, 1H) to H-2 (δ 6.20, 1H) and the HMBC correlations from H-1 to C-3 (δ 186.6, C), C-5 (δ 163.2, C), C-10 (δ 52.6, C), both H-2 and H-4 (δ 6.17, 1H) to C-10, and H_3-19 (δ 1.97, 3H, s) to C-4 (δ 128.6, CH), C-5, and C-10, suggested a dienone moiety in **3**. The above information, together with the HMBC information from H-1 to C-6 and H-6 to C-9 and C-10, established a spiro[4,5]decane with the 3-oxo-1,4-diene substructure in the A ring of **3**. It was found that the remaining structure, including rings C and D, and the side chain of **3**, is identical to that of **1** by comparison of the related 1D (^{1}H and ^{13}C) and 2D NMR data, particularly in ^{1}H–^{1}H COSY and HMBC correlations. The stereochemistry of compound **3** was determined by the NOESY spectrum (Fig. 4), which exhibited NOE correlations between H-1 and H-6α (δ 1.76), and H-8 and H_3-19, and established the β-orientation of C-5, and the α-orientation of C-1. The configurations of other chiral centers were confirmed by other key NOE correlations and by comparison of the NMR spectral data of side-chain protons and carbons with those of **1**. All of these findings were found to be in full agreement with the *R* and *S* configurations at C-10 and C-24, respectively. Therefore, the structure of steroid **3**, with a spiro-ring A, B system, was established. Compound **3** is the first natural product possessing this molecular skeleton.

The biosynthetic pathway of the novel spirosteroid **3** was proposed as shown in Scheme 1. The cross-conjugated dienone moiety of **1** was protonated at the carbonyl oxygen

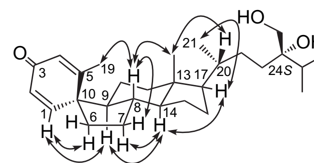
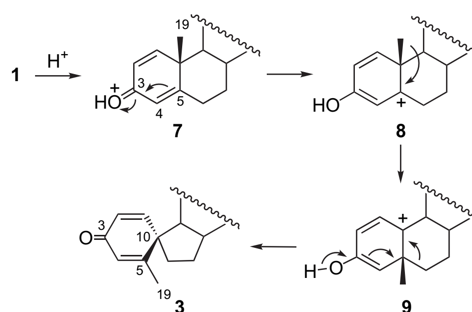


Figure 4. Selective NOESY correlations of **3**.



Scheme 1. Proposed biosynthetic pathways of **3**.

to form the intermediate **7**, which could appear as an enol allylic carbonium ion **8** via resonance. The following 1,2-shift of the methyl substitution at C-10 afforded a carbonium ion **9**, which has a positive charge at C-10. The subsequent 1,2-shift of C-6 from C-5 to C-10 and the following deprotonation, would complete the biosynthesis of **3**.

The cytotoxicity of compounds **1**–**3** against the proliferation of a limited cancer cell lines, including human hepatocellular carcinomas (Hep G2 and Hep 3B), human breast carcinomas (MCF-7 and MDA-MB-231), and human lung carcinoma (A-549) was studied. It was found that **1** and **3** are not cytotoxic toward the above cancer cells. Metabolite **2** has been shown to exhibit a weak cytotoxicity toward Hep 3B (IC_{50} 19.9 μg/mL) cancer cell line, but is not active against the growth of other cancer cells.

3. Experimental

3.1. General experimental procedures

Melting points were determined using a Fisher–Johns melting point apparatus. Optical rotations were measured on a Jasco DIP-1000 digital polarimeter. IR spectra were recorded on a Hitachi I-2001 infrared spectrophotometer. Ultraviolet spectra were recorded on a Hitachi U-3210 UV spectrophotometer. NMR spectra were recorded on a Bruker AVANCE DPX300 FT-NMR at 300 MHz for ^{1}H and 75 MHz for ^{13}C or on a Varian Unity INOVA 500 FT-NMR at 500 MHz for ^{1}H and 125 MHz for ^{13}C. Low-resolution MS data were obtained by ESI on a Bruker APEX II mass spectrometer. HRMS were recorded on ESI on a Bruker APEX II mass spectrometer. Silica gel (Merck, 230–400 mesh) was used for column chromatography. Precoated silica gel plates (Merck, Kieselgel 60 F-254, 0.2 mm) were used for analytical TLC. Isolation by HPLC was performed by Shimadzu SPD-10A instrument equipped with a normal phase column (Lichrosorb Si-60, 7 μm, 250×25 mm).

3.2. Organism

The soft coral *N. chabrolii* was collected by hand using SCUBA off the coast of Pingtung county, southern Taiwan, in July 2001, at depths of 15–20 m, and stored in a freezer until extraction. A voucher sample was deposited at the Department of Marine Biotechnology and Resources, National Sun Yat-sen University.

3.3. Extraction and separation

The sliced bodies of *N. chabrolii* (1.8 kg, wet wt) were exhaustively homogenized with EtOH and filtered. The ground organism was repeatedly extracted with EtOH. The combined EtOH extract was concentrated under vacuum to afford a dark brown viscous residue (20.8 g). The residue was triturated with *n*-hexane to afford an *n*-hexane soluble fraction, and then with EtOAc. The combined EtOAc soluble fraction was evaporated under vacuum to yield an oily residue (15.8 g), which was subjected to column chromatography on Si gel, using *n*-hexane, *n*-hexane and EtOAc mixtures of increasing polarity, and finally pure EtOAc, to yield 28 fractions. Fraction 20 eluted with *n*-hexane–EtOAc (1:1), was further purified by normal phase HPLC using MeOH–CH_2Cl_2 (1:100) to afford **1** (4.0 mg), **2** (1.8 mg), and **3** (0.8 mg).

3.3.1. Chabrolosteroid A (1). White powder; mp 183–185 °C; $[\alpha]_D^{25}$ −23 (*c* 1.04, $CHCl_3$); UV (MeOH) λ_{max} 248 nm; IR (neat) ν_{max} 3404, 1658 cm^{-1}; ^{1}H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR, see Table 1; ^{1}H NMR (500 MHz, CD_3OD) δ_H: 7.29 (1H, d, J=10.0 Hz, H-1), 6.21 (1H, dd, J=10.0, 1.5 Hz, H-2), 6.06 (1H, s, H-4), 3.49 (1H, d, J=11.0 Hz, H-28), 3.43 (1H, d, J=11.0 Hz, H-28), 2.57 (1H, ddd, J=13.0, 8.0, 5.0 Hz, H-6β), 2.40 (1H, dt, J=13.0, 2.5 Hz, H-6α), 2.08 (1H, dt, J=12.5, 3.0 Hz, H-12β), 1.99 (1H, m, H-7α), 1.91 (1H, m, H-16), 1.82 (1H, m, H-25), 1.74 (1H, m, H-11), 1.72 (1H, m, H-8), 1.66 (1H, m, H-23), 1.62 (1H, m, H-15), 1.46 (1H, m, H-22), 1.39 (1H, m, H-20), 1.32 (1H, m, H-23), 1.28 (3H, s, H_3-19), 1.18 (1H, m, H-12α), 1.16 (1H, m, H-17), 1.08 (1H, m, H-22), 1.04 (1H, m, H-14), 1.03 (1H, m, H-7β), 1.02 (1H, m, H-9), 0.96 (3H, d, J=6.0 Hz, H_3-19), 0.92 (3H, d, J=6.5 Hz, H_3-27), 0.90 (3H, d, J=7.0 Hz, H_3-26), 0.80 (3H, s, H_3-18). ^{13}C NMR (125 MHz, CD_3OD) δ_C: 188.9 (C, C-3), 174.1 (C, C-5), 159.9 (CH, C-1), 127.7 (CH, C-2), 124.0 (CH, C-4), 77.2 (C, C-24), 66.4 (CH_2, C-28), 57.4 (CH, C-17), 57.0 (CH, C-14), 54.4 (CH, C-9), 45.6 (C, C-10), 44.0 (C, C-13), 41.1 (CH_2, C-12), 37.8 (CH, C-20), 36.9 (CH, C-8), 35.3 (CH_2, C-7), 34.1 (CH_2, C-6), 33.8 (CH, C-25), 31.8 (CH_2, C-23), 30.1 (CH_2, C-22), 29.4 (CH_2, C-16), 25.5 (CH_2, C-15), 24.2 (CH_2, C-11), 19.3 (CH_3, C-19), 19.2 (CH_3, C-21), 17.6 (CH_3, C-27), 17.5 (CH_3, C-26), 12.6 (CH_3, C-18). ESIMS m/z 451 $[M+Na]^+$; HRESIMS m/z 451.3186 (calcd for $C_{28}H_{44}O_3Na$, 451.3190).

3.3.2. Chabrolosteroid B (2). White powder; mp 189–192 °C; $[\alpha]_D^{25}$ −34 (*c* 0.72, $CHCl_3$); UV (MeOH) λ_{max} 248 nm; IR (neat) ν_{max} 3422, 1660 cm^{-1}; ^{1}H and ^{13}C NMR, see Table 1; ESIMS m/z 449 $[M+Na]^+$; HRESIMS m/z 449.3029 (calcd for $C_{28}H_{42}O_3Na$, 449.3034).

3.3.3. Chabrolosteroid C (3). White powder; mp 149–152 °C; $[\alpha]_D^{25}$ −159 (*c* 0.16, $CHCl_3$); UV (MeOH) λ_{max} 246 nm; IR (neat) ν_{max} 3356, 1655 cm^{-1}; ^{1}H and ^{13}C NMR, see Table 1; ESIMS m/z 451 $[M+Na]^+$; HRESIMS m/z 451.3186 (calcd for $C_{28}H_{44}O_3Na$, 451.3190).

3.3.4. Preparation of (*S*)- and (*R*)-MTPA esters of 1. To a solution of **1** (1.0 mg) in pyridine (50 μL) was added (−)-MTPA chloride (5 μL), and the solution was allowed to stand overnight at room temperature. The reaction mixture was added with 1 mL of water, followed by extraction with CH_2Cl_2 (1 mL×3). The CH_2Cl_2 soluble layers were combined, dried over anhydrous $MgSO_4$, and evaporated. The residue was subjected to short Si gel column chromatography using EtOAc–*n*-hexane (1:2) to yield the (*S*)-MTPA ester of **1** (0.5 mg, 34%). The same procedure was applied to obtain the (*R*)-MTPA ester of **1** (0.5 mg, 34%) from the reaction of (+)-MTPA chloride with **1** in pyridine.

3.4. Cytotoxicity testing

Cell lines were purchased from the American Type Culture Collection (ATCC). Cytotoxicity assays of the test

compounds **1–3** were performed using MTT [3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyltetrazolium bromide] colorimetric method.[7,8]

Acknowledgements

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