American Journal of Plant Sciences, 2014, 5, 1370-1377
Published Online April 2014 in SciRes. http://www.scirp.org/journal/ajps
http://dx.doi.org/10.4236/ajps.2014.59151

Cembrane-Type Diterpenoids and a Phenolic Compound from the Leaves of a Thai Medicinal Plant, *Croton sublyratus* Kurz

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Received 19 February 2014; revised 28 March 2014; accepted 14 April 2014

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Abstract

From the leaves of a Thai medicinal plant, *Croton sublyratus*, collected in Thailand, two new cembrane-type diterpenoids, named sublylactones A and B, and a phenolic compound were isolated from the EtOAc-soluble fraction of a MeOH extract. Their structures were elucidated on the basis of spectroscopic evidence.

Keywords

Croton Sublyratus; Euphorbiaceae; Diterpene; Cembrane

1. Introduction

Croton sublyratus, belonging to the Euphorbiaceae family, is called “Plau-Noi” in Thai. An acyclic diterpene alcohol, plaunotol, was isolated from this plant [1], which is already on the market as an anti-ulcerative agent called Kelnac [2]. Diterpenelactones, plaunols A and B [3] [4], and *ent*-labdane and *ent*-kaurane [5] have also

How to cite this paper: Oka, Y., *et al.* (2014) Cembrane-Type Diterpenoids and a Phenolic Compound from the Leaves of a Thai Medicinal Plant, Croton sublyratus Kurz. *American Journal of Plant Sciences*, **5**, 1370-1377.
http://dx.doi.org/10.4236/ajps.2014.59151

been isolated from *C. sublyratus*. From this plant, isolation of a furanoid diterpene was also reported [6] [7]. Our reinvestigation of constituents of *C. sublyratus* resulted in the isolation of two cembrane-type diterpenoids, named sublylactones A (**1**) and B (**2**), and a phenolic compound (**3**) together with a known cembrane-type diterpenoid, laevigatlactone E (**4**), which has also been isolated from *Croton laevigatus* [8].

2. Results and Discussion

From the EtOAc-soluble fraction of a MeOH extract, two new cembrane-type diterpenes (**1** and **2**) and a phenolic compound (**3**) (**Figure 1**) were isolated by a combination of various types of chromatography. Their structures were elucidated from spectroscopic evidence.

Sublylactone A (**1**), $[\alpha]_D^{23}$ +3.90, was isolated as an amorphous powder and its elemental composition was determined to be $C_{20}H_{30}O_4$ by the observation of a quasi-molecular ion ($C_{20}H_{30}O_4Na$) on high-resolution (HR)-electrospray ionization (ESI)-mass spectroscopy (MS). The IR spectrum exhibited absorption bands for hydroxyl groups (3423 cm^{-1}), C-H (2968, 2929 and 2881 cm^{-1}), a lactone (1697 cm^{-1}), and double bonds (1631 cm^{-1}), and the UV spectrum indicated the presence of a conjugated system (234 nm). In the ^{1}H-NMR spectrum, signals assignable to two singlet methyls, two doublet methyls and five olefinic protons were observed (**Table 1**). The ^{13}C-NMR spectrum showed twenty signals that were assignable to four methyls, five methylenes, one methine, three oxygenated tertiary carbons, three double bonds and a carbonyl carbon (**Table 2**). Of the three double bonds, two were disubstituted ones and their geometry was determined to be *E* from the coupling constants of olefinic protons on them. ^{1}H-^{1}H correlation spectroscopy (COSY) established five partial structures, A: H-2 - H-3, B: H-5 - H-7, C: H-9 - H-11, D: H_2-13 - H_2-14 and E: H_3-16 - H-15 - H_3-17, and these partial structures were connected by heteronuclear multiple-bond correlation spectroscopy (HMBC) (**Figure 2**). Partial structures A and B were connected through an oxygenated tertiary carbon at δ_C 72.5 (C-4) by the following HMBC correlations: H_3-18 to C-3, C-4 and C-5, partial structures B and C through an oxygenated tertiary carbon at δ_C 72.9 (C-8) by the correlations: H_3-19 to C-7, C-8 and C-9, and partial structures C and D through C-12 including the position of the carbonyl group by the following correlations: H-11 to C-20, H-13 (δ_H 2.40) to C-20, H_2-10 to C-12, and H_2-14 to C-12. Finally, partial structures A and D were connected through the remaining oxygenated tertiary carbon at δ_C 87.4 by the following correlations: H-2 to C-1 and H_2-14 to C-1. The dimethyl group (partial structure E) was placed on C-1 by the HMBC correlations from H_3-16 and H_3-17 to C-1. Thus, a cyclic structure was proposed for sublylactone A (**1**), and the remaining one degree of unsaturation was expected to be compensated for by the formation of a lactone ring between the C-20 carboxylic acid and the hydroxy group at the C-1 position. Structurally related lactone cembranoids were isolated from *Croton laevigatus* as laevigatlac tones A-E and the relative structure of laevigatlactone A was determined by X-ray crystallographic analysis [8]. From the above evidence, the structure of sublylactone A (**1**) was expected to be that of a stereomeric isomer of laevigatlactone E (**4**), which was simultaneously isolated from this plant. On comparison of ^{13}C-NMR spectral data for sublylactone A (**1**) and laevigatlactone E (**4**) (**Table 2**), C-2 to C-7 showed some differences, C-2 by 2.1 ppm, C-4 by 1.6 ppm, C-6 by 0.7 and C-7 by 0.7 ppm. The most prominent difference was observed between the C-18 methyls, 6.2 ppm (**Table 2**). Therefore, the structure of sublylactone A (**1**) was elucidated to be 4-*epi*-laevigatlactone E, as shown in **Figure 1**.

Sublylactone B (**2**), $[M]_D$ –1.45, was isolated as an amorphous powder and its elemental composition was the same as that of **1**, NMR spectroscopic data also indicating that **2** possessed the same functionality as that of **1**. The geometry of two disubstituted double bonds (C-2=C-3 and C-6=C-7) was assigned as *E* from the coupling constants of their olefinic protons. The remaining double bond (C-11=C-12) was assigned to *Z* geometry from the significant evidence of the NOE correlation between the olefinic proton at H-11 (M_H 5.91) and H_2-13 (δ_H 2.48) in the phase-sensitive NOESY spectrum (**Figure 3**). The relative structures of the methyl groups at the 4- and 8-positions were estimated to be in a β orientation from the NOE correlation peaks between H_3-18 and H-7, H_3-19 and H-7, and H_3-19 and H-10 (δ_H 3.47) (**Figure 3**). Therefore, the relative structure was elucidated to be as shown in **Figure 1**.

Phenolic compound (**3**), $[\alpha]_D^{25}$ –0.47, was isolated as an amorphous powder and its elemental composition was determined to be $C_{19}H_{22}O_6$ by positive-ion HR-ESI-MS. The IR spectrum exhibited distinct absorptions assignable to hydroxy groups (3445 cm^{-1}) and an ester functional group (1701 cm^{-1}). The ^{1}H NMR together with the ^{13}C spectral data suggested the presence of monosubstituted and symmetrically tetrasubstituted aromatic rings as well as one methoxy signal (δ_H 3.87) for six protons, and one methoxy signal (δ_H 3.23) for three protons

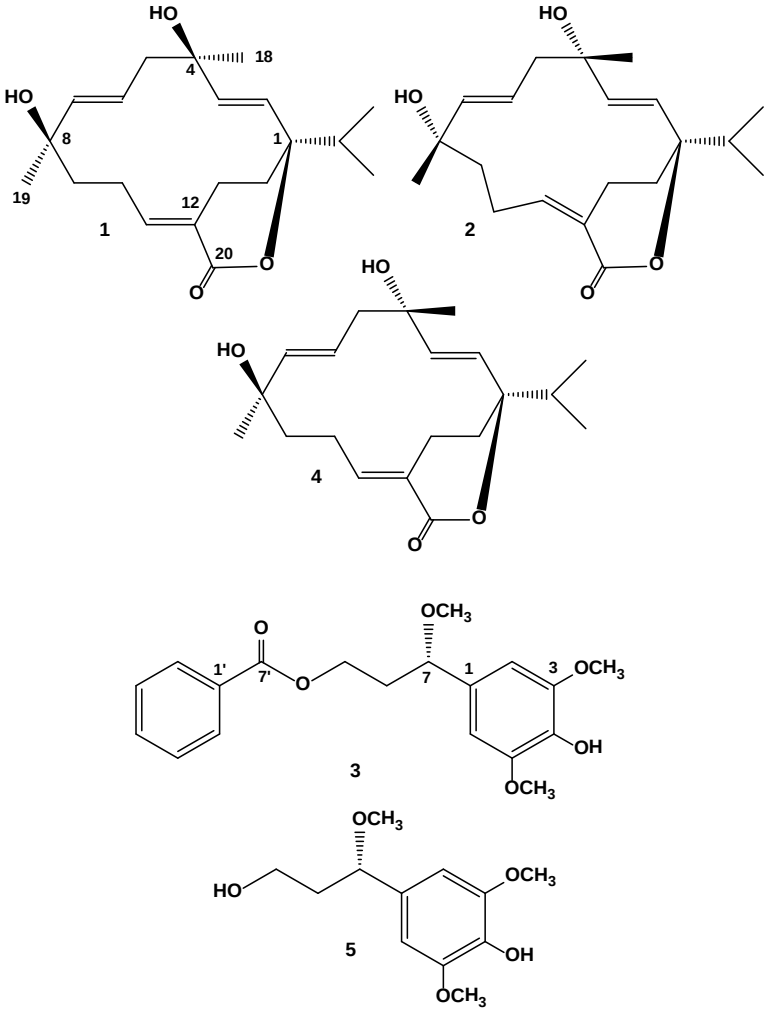

Figure 1. Structures of compounds isolated.

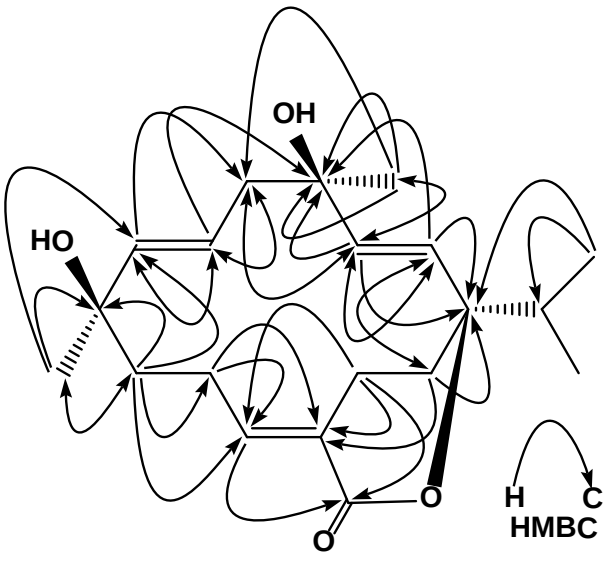

Figure 2. HMBC correlations of 1.

Table 1. ^{1}H-NMR spectral data for sublylactones A (1) and B (2), and 4 ($CDCl_3$, 600 MHz).

H	1		2	3
2	5.41 (d, 16)	[5.48] (d, 16)	5.60 (d, 16)	[5.54] (d, 16)
3	5.45 (d, 16)	[5.36] (d, 16)	5.48 (d, 16)	[5.23] (d, 16)
5	2.34 (2H, d, 7)	[2.31] (2H, m)	2.09 (dd, 13, 12)	[2.18] (m)
			2.45 (ddd, 13,2,2)	[2.32] (ddd, 15, 3, 3)
6	5.45 (d, 16)	[5.38] (br d,16)	5.63 (ddd, 15, 12, 3)	[5.64] (ddd, 16, 11, 3)
7	5.49 (d, 16)	[5.41] (dd,16, 2)	5.35 (dd, 15, 2)	[5.34] (dd, 16,2)
9	1.87 (m)	[1.84] (2H, m)	1.66 (dd, 14, 14)	[1.85 (2H, m)
	1.90 (m)		1.89 (m)	
10	2.16 (2H, m)	[2.18] (2H, m)	2.20 (m)	[2.15 (dd, 12, 3)
			3.47 (m)	[2.24] (m)
11	6.95 (m)	[6.89] (ddd, 11, 2, 2)	5.91 (ddd, 11, 2, 2)	[6.83] (ddd, 11, 2, 2)
13	2.35 (2H, dd, 14, 6)	[2.22] (m)	2.48 (2H, m)	[2.24] (m)
		[2.40] (ddd, 17, 2, 2)		[2.44] (ddd, 17, 6, 5, 2)
14	1.79 (ddd, 14, 14, 6)	[1.76] (ddd, 14, 14, 6)	1.79 (m)	[1.75] (ddd, 14, 14, 6)
	1.95 (dd, 14, 6)	[2.04] (dd, 14, 6)	1.88 (m)	[2.01] (dd, 14, 6)
15	1.88 (m)	[1.86] (m)	1.84 (m)	[1.84] (m)
16	0.98 (3H, d, 7)	[0.98] (3H, d, 7)	0.95 (3H, d, 7)	[0.97] (3H, d, 7)
17	0.96 (3H, d, 7)	[0.99] (3H, d, 7)	0.96 (3H, d, 7)	[0.97] (3H, d, 7)
18	1.40 (3H, s)	[1.39] (3H, s)	1.39 (3H, s)	[1.28] (3H, s)
19	1.29 (3H, s)	[1.28] (3H, s)	1.21 (3H, s)	[1.31] (3H, s)

Data in brackets are for CD_3OD. In parentheses, number of hydrogen are specified, when they are not 1H. Letters and figures are multiplicities and *J* in Hz).

Table 2. ^{13}C-NMR spectral data for sublylac- tones A (1) and B (2), and laevigatlactone E (4) ($CDCl_3$, 150 MHz).

C	1		2	4	
1	85.5	(87.4)	86.7	85.7	(87.7)
2	127.2	(128.4)	124.6	125.2	(126.3)
3	138.5	(140.0)	139.1	138.8	(140.3)
4	72.5	(73.0)	73.6	73.7	(74.1)
5	46.6	(48.4)	49.1	46.2	(47.6)
6	123.9	(125.0)	122.8	124.3	(125.7)
7	138.0	(139.1)	140.4	137.7	(138.4)
8	72.4	(72.9)	72.0	72.4	(73.0)
9	41.0	(42.4)	42.2	41.4	(42.5)
10	25.6	(25.9)	25.1	25.0	(25.9)
11	145.9	(148.5)	150.4	146.1	(148.4)
12	124.3	(125.5)	123.2	124.4	(125.6)
13	21.0	(21.9)	24.9	21.1	(22.0)
14	26.8	(28.2)	28.2	27.8	(28.9)
15	37.1	(38.3)	36.9	37.0	(38.1)
16	17.2	(17.7)	17.3	17.4	(17.7)
17	16.8	(16.9)	16.6	16.5	(16.8)
18	25.1	(24.7)	28.3	31.1	(30.9)
19	26.5	(25.8)	31.4	24.7	(24.7)
20	167.7	(170.6)	167.4	169.0	(170.7)

Data in parentheses are for CD_3OD.

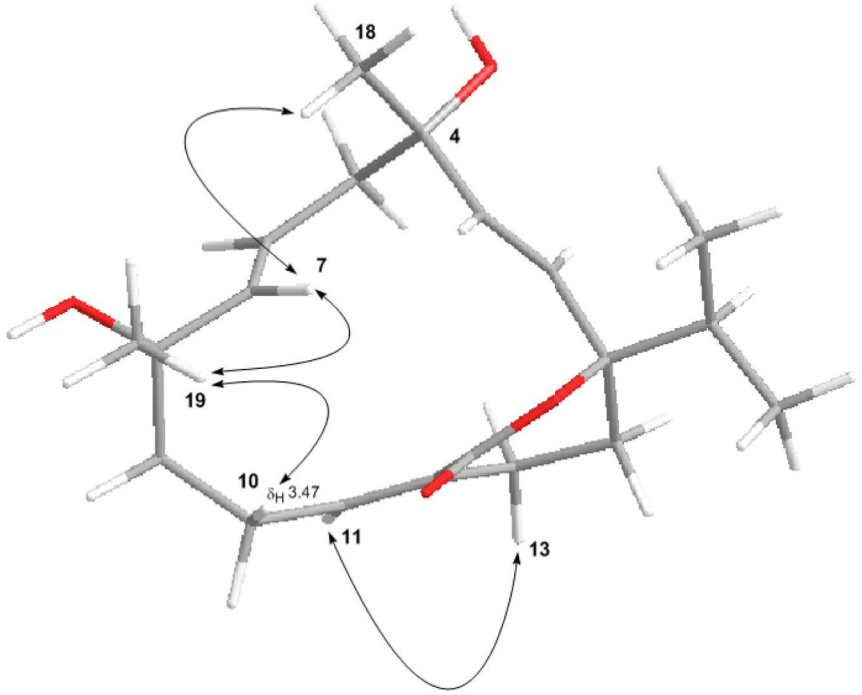

Figure 3. NOESY correlations of 1.

(**Table 3**). From their chemical shifts, the former were expected to be on the aromatic carbons and the latter on the aliphatic carbon. The remaining signals comprised those of one methylene, one oxygenated methylene, one oxygenated methine and a carbonyl carbon. In the ^{1}H-^{1}H COSY spectrum, two proton chains were observed, these are oxymethylene (H_2-9)-methylene (H_2-8)-oxymethine (H-7) and H-2' through H-4'. In the HMBC spectrum, oxymethylene protons (δ_H 4.36 and 4.41) showed significant correlation cross peaks with the carbonyl carbon (δ_C 166.5), to which the aromatic protons of H-2' and 6' [δ_H 8.02 (2H, dd, J = 8, 1 Hz)] were also correlated. The oxymethylene protons further correlated with C-7 (δ_C 81.2) and methylene protons (δ_H 2.08 and 2.25) with C-1 (δ_C 132.9). The positions of the methoxy groups were assigned as on C-3 and 5, and C-7 by the HMBC correlation shown in **Figure 4**. Therefore, the structure of **3** was elucidated to be 7-methoxydihydrosynapyl alcohol 9-*O*-benzoyl ester, as shown in **Figure 1**. Due to the very small optical rotation value, it is uncertain whether **3** is a racemic, partially racemic or chiral compound. A related compound, (7*S*)-7-methoxydihydrosynapyl alcohol (**5**) was isolated from *Acer truncatum* [9]. The optical rotation value of **5** was reported to be –6.8 in $CHCl_3$ ($[M]_D$ –16.4, where molecular rotation is calculated as $[M]_D=[\alpha]_D \times$ MW./100). Thus, **3** ($[M]_D$ –5.0) was estimated to be nearly a racemic compound in which an *S*-form is slightly dominant.

3. Material and Method

3.1. Plant Material

Leaves of *C. sublyratus* were collected in the Botanical Garden of the Faculty of Pharmacy, Chiang Mai University, Thailand in July 2008. A voucher specimen was deposited in the Herbarium of the Faculty of Pharmacy, Chiang Mai University（CS-CMU-July-2008).

3.2. General Experimental Proceddures

Optical rotations were measured on a JASCO P-1030 digital polarimeter. IR and UV spectra were measured on Horiba FT-710 and JASCO V-520 UV/Vis spectrophotometers, respectively. ^{1}H- and ^{13}C-NMR spectra were taken on a JEOL ECA-600 at 600 MHz and 150 MHz with tetramethylsilane as an internal standard. Positive-ion HR-ESI-MS was performed with an Applied Biosystems QSTAR XL NanoSprayTM System. Silica gel CC was performed on silica gel 60 (E. Merck, Darmstadt, Germany).

Table 3. NMR spectroscopic data for compound 1 (3) ($CDCl_3$, ^{13}C: 100 MHz, ^{1}H: 400 MHz).

	C	H
1	132.9	-
2, 6	103.3	6.55 (2H, s)
3, 5	147.3	-
4	134.3	-
7	81.2	4.22 (1H, dd, 8, 6)
8	37.4	2.08 (1H, m)
		2.25 (1H, m)
9	62.4	
		4.41 (1H, m)
1’	130.4	-
2’, 6’	129.5	8.02 (2H, dd, 8, 1)
3’, 5’	128.4	7.44 (2H, dd, 8, 8)
4’	132.9	7.56 (1H, tt, 8, 1)
7’	166.5	-
4’-OH		5.49 (1H, s)
3, 5-OMe	56.4	3.87 (6H, s)
7Me	56.6	3.23 (3H, s)

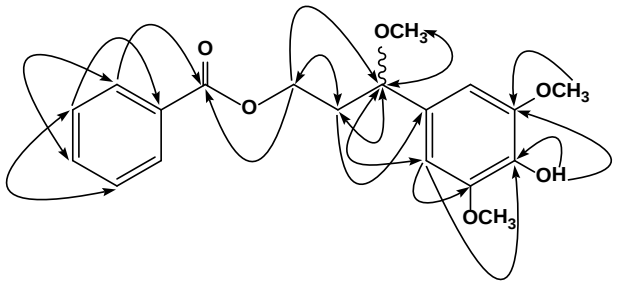

Figure 4. HMBC correlations of compound 1 (3).

3.3. Extraction and Isolation

Powdered and air-dried leaves of *C. sublyratus* (450 g) were extracted with MeOH (2 L × 3) and the total extracts were concentrated to 1 L. The concentrated MeOH extract was washed with *n*-hexane (1 L, 7.35 g) and then the remaining MeOH layer was concentrated to a viscous gum. The viscous gum was suspended in H_2O (1 L), and then partitioned successively with EtOAc (1 L) and 1-BuOH (1 L) to give EtOAc-soluble (24.0 g) and 1-BuOH-soluble (7.88 g) fractions, respectively. The H_2O layer was evaporated to leave 16.3 g of a residue.

The residue (24.0 g) of the EtOAc-soluble fraction was subjected to silica gel (500 g) CC with a solvent system consisting of *n*-hexane (3 L), *n*-hexane-EtOAc [9:1 (3 L), 4:1 (3 L), 7:3 (3 L), 3:2 (3 L), 1:1 (3 L), and 3:7 (3 L)], EtOAc (3 L), and MeOH (3 L), 1 L fractions being collected. The residue (3.51 g) in fractions 6 - 8 was fractionated by ODS CC (Cosmosil 75 C_{18}OPN) (Φ = 40 mm, L = 250 mm), by elution with H_2O-MeOH [(3:7, 800 mL), (1:3, 800 mL), (1:4, 800 mL), (3:17, 800 mL), (1:9, 800 mL), and (1:19, 800 mL)], MeOH (800 mL), $(CH_3)_2CO$ (800 mL), and EtOAc (800 mL), 800 mL fractions being collected. The residue (745 mg) in fraction 1 was further separated by ODS CC (Cosmosil 75 C_{18}OPN) (Φ = 40 mm, L = 250 mm) using H_2O-MeOH [(7:3, 800 mL), (3:2, 800 mL), (1:1, 800 mL), (2:3, 800 mL), (7:13, 800 mL), and (3:7. 800 mL)], and MeOH (800 mL), 800 mL-fractions being collected. The residue (108 mg) in fraction 4 was again purified by silica gel CC (Φ = 10 mm, L = 30 cm) with a linear gradient solvent system from *n*-hexane (250 mL) to *n*-hexane-EtOAc (1:1, 250 mL), 4-gram fractions being collected. From fractions 109–120, 5.6 mg of **2** was obtained.

The residue (869 mg) in fractions 11 - 12 obtained on the first silica gel CC was separated by ODS CC with H_2O-MeOH [(7:3, 800 mL), (3:2, 800 mL), (1:1, 800 mL), (2:3, 800 mL), (7:13, 800 mL), (3:7. 800 mL), (1:3, 800 mL), (1:4, 800 mL), (3:17, 800 mL), (1:9, 800 mL), and (1:19, 800 mL)], MeOH (800 mL), $(CH_3)_2CO$ (800

mL), and EtOAc (800 mL), 800 mL fractions being collected. The residue (203 mg) in fraction 3 was purified by silica gel CC (Φ = 10 mm, L = 40 cm) with a linear gradient solvent system from *n*-hexane (250 mL) to *n*-hexane-EtOAc (1:1, 250 mL), 4-gram fractions being collected. Further amounts of *n*-hexane-EtOAc (1:1, 750 mL) and MeOH (250 mL) were eluted and 250 mL-fractions were collected. From the third *n*-hexane-EtOAc (1:1, 250 mL) fraction, 11.0 mg of **4** was obtained. The residue (276 mg) in fraction 4 was separated by silica gel CC (Φ = 10 mm, L = 40 cm) with a linear gradient solvent system from *n*-hexane (250 mL) to *n*-hexane-EtOAc (1:1, 250 mL), 4-gram fractions being collected. From fractions 67 - 74, 20.0 mg of **3** was obtained.

The residue (1.17 g) in fractions 13 - 14 obtained on the first silica gel CC was separated by ODS CC with H_2O-MeOH [(7:3, 800 mL), (3:2, 800 mL), (1:1, 800 mL), (2:3, 800 mL), (7:13, 800 mL), (3:7. 800 mL), (1:3, 800 mL), (1:4, 800 mL), (3:17, 800 mL), (1:9, 800 mL), and (1:19, 800 mL)], MeOH (800 mL), $(CH_3)_2CO$ (800 mL), and EtOAc (800 mL), 800 mL fractions being collected. The residue (121 mg) in fraction 3 was purified by silica gel CC (Φ = 10 mm, L = 34 cm) with a linear gradient solvent system from *n*-hexane (250 mL) to *n*-hexane-EtOAc (1:1, 250 mL), and *n*-hexane-EtOAc (1:1, 700 mL). Further amounts of *n*-hexane-EtOAc (1:1, 250 mL) and MeOH (250 mL) were eluted. From the final 250 mL *n*-hexane-EtOAc fraction, 8.2 mg of **1** was obtained.

The residue (779 mg) in fractions 17 - 18 obtained on the first silica gel CC was separated by ODS CC with H_2O-MeOH [(7:3, 800 mL), (3:2, 800 mL), (1:1, 800 mL), (2:3, 800 mL), (7:13, 800 mL), (3:7. 800 mL), (1:3, 800 mL), (1:4, 800 mL), (3:17, 800 mL), (1:9, 800 mL), and (1:19, 800 mL)], MeOH (800 mL), $(CH_3)_2CO$ (800 mL), and EtOAc (800 mL), 800 mL fractions being collected. The residue (74.2 mg) in fraction 3 was purified by silica gel CC (Φ = 10 mm, L = 28 cm) with a linear gradient solvent system from *n*-hexane (250 mL) to *n*-hexane-EtOAc (1:1, 250 mL), 4-gram fractions being collected. From fractions 101 - 124, a further amount of **2** (17.2 mg) was obtained.

3.4. Sublylactone A (1)

Amorphous powder, $[\alpha]_D^{23}$ +3.90 (*c* 0.28, $CHCl_3$); IR ν_{max} (film) cm^{-1}: 3423, 2968, 2929, 2881, 1697, 1631, 1469, 1371, 1320, 1267, 1094, 977; UV λ_{max} (MeOH) nm (log ε): 234 (3.56); ^{1}H-NMR ($CDCl_3$ and CD_3OD, 600 MHz): **Table 1**; ^{13}C-NMR ($CDCl_3$ and CD_3OD, 150 MHz): **Table 2**; HR-ESI-MS (positive-ion mode): 357.2036 $[M + Na]^+$ (Calcd for $C_{20}H_{30}O_4Na$: 357.2036).

3.5. Sublylactone B (2)

Amorphous powder, $[\alpha]_D^{25}$ –1.45 (*c* 0.46, CD_3OD); IR ν_{max} (film) cm^{-1}: 3445, 2967, 2929, 2881, 1693, 1630, 1455, 1381, 1320, 1244, 1118, 978; UV λ_{max} (MeOH) nm (log ε): 233 (3.76); ^{1}H-NMR ($CDCl_3$, 600 MHz): **Table 1**; ^{13}C-NMR ($CDCl_3$, 150 MHz): **Table 1**; HR-ESI-MS (positive-ion mode): 357.2031 $[M + Na]^+$ (Calcd for $C_{20}H_{30}O_4Na$: 357.2036).

3.6. Compound 1 (3)

Amorphous powder, $[\alpha]_D^{25}$ –0.47 (*c* 0.54, $CHCl_3$); IR ν_{max} (film) cm^{-1}: 3445, 2962, 2934, 2841, 1701, 1274; UV λ_{max} (MeOH) nm (log ε): 212 (4.20), 227 (4.14); ^{1}H-NMR ($CDCl_3$, 600 MHz): **Table 3**; ^{13}C-NMR ($CDCl_3$, 150 MHz): **Table 3**; HR-ESI-MS (positive-ion mode): 369.1311 $[M + Na]^+$ (Calcd for $C_{19}H_{22}O_6Na$: 369.1308).

Acknowledgements

The authors are grateful for access to the superconducting NMR instrument (JEOL JNM α-400) and an Applied Biosystem QSTAR XL system ESI (Nano Spray)-MS at the Analysis Center of Life Science of the Graduate School of Biomedical Sciences, Hiroshima University. This work was supported in part by Grants-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and the Japan Society for the Promotion of Science. Thanks are also due to the Research Foundation for Pharmaceutical Sciences and the Takeda Science Foundation for the financial support.

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