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Structures of new alkaloids sessilifoliamides A–D from *Stemona sessilifolia*

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Abstract—Four new *Stemona* alkaloids, sessilifoliamides A–D (**1**–**4**), were isolated from the roots of *Stemona sessilifolia*, along with five known alkaloids, stenine (**5**), 2-oxostenine (**6**), stemoninoamide (**7**), tuberostemonone (**8**), and neotuberostemonol (**9**). The structures and absolute configurations of the new alkaloids were determined by the spectral studies (HRMS, IR, ^{1}H, ^{13}C, and 2D NMR), single-crystal X-ray analyses, and chemical correlations. The absolute configuration of **7** was also determined by the modified Mosher's method.

1. Introduction

The genus *Stemona* plants (family Stemonaceae) have been used in China and Japan as insecticides and a cough remedy. A number of stemona alkaloids, reportedly having an insecticidal activity,[1–3] have been isolated from *S. japonica* Franch. & Sav. and *S. tuberosa* Lour.,[4] but only four alkaloids are so far reported in *Stemona sessilifolia* Franch. & Sav.[5–7] In the present study, from an alkaloidal fraction of *S. sessilifolia* we isolated four new alkaloids, sessilifoliamides A–D (**1**–**4**), along with five known alkaloids, stenine (**5**),[8] 2-oxostenine (**6**),[9,10] stemoninoamide (**7**),[11] tuberostemonone (**8**)[12] and neotuberostemonol (**9**)[13] and determined their structures (Fig. 1). In this paper, we describe their isolation and structural elucidation.

2. Results and discussion

2.1. Separation of alkaloids

From 15 kg of the roots of *S. sessilifolia*, 8 kg of a crude MeOH extract was obtained, from which 250 g of alkaloidal fraction was prepared. This crude alkaloidal fraction was subjected to Diaion HP-20 column chromatography to give MeOH and acetone eluates. The MeOH fraction (206 g) was further separated by alumina and silica gel chromatography, and reversed-phase HPLC to give four new alkaloids **1** (60 mg), **2** (100 mg), **3** (46 mg) and **4** (60 mg), and five known alkaloids, **5** (20 mg), **6** (50 mg), **7** (1.5 g), **8** (26 mg), and **9** (4.5 mg) (Fig. 1). Alkaloids **5**–**9**, identified as stenine, 2-oxostenine, stemoninoamide, tuberostemonone, and neotuberostemonol, respectively, by the comparison of their spectral data with those of the reported data, were isolated from this plant source for the first time in the present study.

2.2. Characterization of alkaloids 1–4

Alkaloid **1** (sessilifoliamide A) of the molecular formula $C_{17}H_{25}NO_4$ [HREIMS (*m*/*z* 307.1766 $[M]^+$, calcd 307.1784)] was obtained as colorless prisms. The IR absorptions at 1772 and 1687 cm^{-1} indicated that **1** had a lactone and a lactam ring. The ^{13}C NMR spectrum showed signals assignable to two methyls, seven methylenes, five methines, and three quaternary carbons, two of the quaternary carbon signals at δ 178.8 and 174.0 being assigned to carbonyl carbons. The ^{1}H NMR spectrum showed the presence of two methyl groups (δ 1.25, d and 1.01, t). The HMBC spectrum showed that C-11 (δ 114.6) was correlated with H-8 (δ 3.90, ddd), H-9 (δ 2.52, m), H-10 (δ 1.93, m), H_2-12 (δ 2.36, m and 1.97, m), H-13 (δ 2.93, m) and H_2-16 (δ 1.56, m), which suggested that **1** had a spiro structure at C-11 with two oxygen atoms connected to it. The ^{13}C NMR and ^{1}H NMR spectra of **1** were generally similar to those of **7**, but the C-12 and C-13 signals observed in **1** were of a methylene carbon (δ 38.9) and a methine carbon (δ 34.5), respectively (Tables 1 and 2).

In the NOESY spectrum, correlations were observed between H-9 and H_3-17, H-9a and H_3-17, and H-8 and H-10, suggesting that the relative stereochemistries of C-8, C-9, C-9a, and C-10 were the same as the corresponding ones of **7**. Thus, **1** was shown to be 12,13-dihydrostemoninoamide or its stereoisomer at C-11, which was verified by the production of **1** via catalytic hydrogenation

Keywords: sessilifoliamides A–D; *Stemona* alkaloids; pyrrolo[1,2-*a*]azepine; *Stemona sessilifolia*; Stemonaceae.
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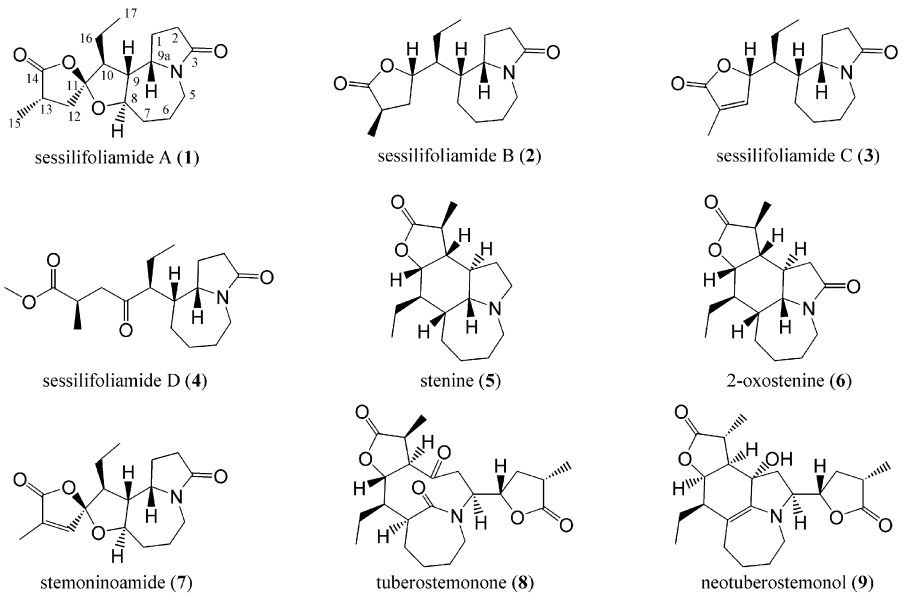


Figure 1.

of **7** with Pd/C (Scheme 1). Since no NOESY cross-peaks were observed for Me-13 to tell about the stereochemistry at C-13, an X-ray crystallographic analysis of **1** was performed. A single crystal for the analysis was prepared by slow evaporation of its EtOAc solution. A perspective view of the molecule is shown in Figure 2.

Alkaloid **2** (sessilifoliamide B) of the molecular formula $C_{17}H_{27}NO_3$ [HREIMS (*m/z* 293.2008 $[M]^+$, calcd 293.1991)] was obtained as a colorless oil. The IR absorptions at 1769 and 1682 cm^{-1} indicated that **2** possessed a lactone and a lactam ring. The ^{13}C NMR spectrum showed the signals of two methyls, eight methylenes, five methines and two quaternary carbons. The ^1H NMR spectrum showed the signals of two methyl groups (δ 1.30, d and 1.00, t). The HMBC spectrum showed that H-9 (δ 2.12, m) was correlated with C-8 (δ 24.5), C-9a (δ 61.2), C-11 (δ 79.6), and C-16 (δ 20.4), and H-10 (δ 1.51, m) was correlated with C-8, C-9 (δ 42.9), and C-9a, suggesting that a 1-(4-methyl-5-oxo-tetrahydrofuran-2-yl)-propyl moiety was attached to C-9 of the pyrrolo[1,2-*a*]azepine nucleus which was the basic skeleton of a majority of the *Stemona* alkaloids (Fig. 3).[4] The NOESY correlation observed between H-11 and Me-13 implied a *cis* relationship between H-11 and Me-13.

Table 1. ^{13}C NMR (125 MHz) spectral data for **1**–**4** in $CDCl_3$

Position	1	2	3	4
1	22.1	22.7	22.0	21.1
2	30.8	30.9	30.8	30.7
3	174.0	174.4	174.4	174.3
5	40.3	40.6	40.6	40.7
6	25.6	29.2	28.8	29.0
7	36.1	29.7	29.4	29.5
8	79.7	24.5	24.5	26.1
9	52.0	42.9	43.3	42.4
9a	56.4	61.2	60.8	59.4
10	49.4	46.1	44.2	55.0
11	114.6	79.6	82.1	211.1
12	38.9	34.5	148.3	47.2
13	34.5	34.5	130.4	34.2
14	178.8	180.0	174.3	176.1
15	15.2	16.6	10.7	17.1
16	21.2	20.4	19.1	22.8
17	12.9	13.6	13.3	11.0
OMe				51.9

Chemical shifts are reported in ppm relative to the solvent resonance at 77.0 ppm.

The stereochemistry of **2** was established by the correlation with **1**, as shown in Scheme 1. Thus, treatment of **1** with lithium borohydride gave an epimeric pair of triols **11a** and **11b**. Oxidation of **11a** and **11b** with 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (4-hydroxy-TEMPO) and chlorinated lime[14] yielded corresponding lactones, **12a** and **12b**, respectively, whose stereochemistry at C-11 was determined by the NOESY experiments. The NOESY correlation was observed between H-11 and Me-13 for **12a**, and between H-11 and H-13 for **12b**, showing that H-11 and Me-13 were *cis* in **12a** and *trans* in **12b**. Each of the lactones was treated with thiocarbonyldiimidazole (TCDI) to give corresponding thiocarbamates **13a** and **13b**, whose radical-induced reduction with tributhyltin hydride and triethylborane[15] yielded **14a** and **14b**, respectively. Neither of **14a** nor **14b**, whose H-11 and Me-13 relations were *cis* and *trans*, respectively, was identical to **2**. However, when **2** was epimerized at C-13 with sodium bis(trimethylsilyl)-amide, the product was found to be identical to **14b**. Thus, the configurations at C-9, C-9a, C-10, C-11 and C-13 of **2** were determined as shown in Figure 1.

Alkaloid **3** (sessilifoliamide C) of the molecular formula $C_{17}H_{25}NO_3$ [HREIMS (*m/z* 291.1829 $[M]^+$, calcd 291.1834)] was obtained as a colorless oil. The molecular formula showed that the molecular weight was smaller by two hydrogen atoms than that of **2**. The IR absorptions at 1751 and 1682 cm^{-1} showed that **3** had an unsaturated lactone and a lactam ring. Its ^{13}C and ^1H NMR spectra were very similar to those of **2**, excepting for the signals assignable to C-12 (δ_C 148.3 and δ_H 7.02, d), C-13 (δ_C 130.4) and C-15 (δ_C 10.7 and δ_H 1.94, d). The fact suggested

Table 2. ^{1}H NMR (500 MHz) spectral data for **1**–**4** in $CDCl_3$

Position	1	2	3	4
1	1.67 (m)	1.68 (m)	1.67 (m)	1.63 (m)
	1.98 (m)	1.93 (m)	1.95 (m)	1.91 (m)
2	2.37 (m)	2.36 (m)	2.38 (m)	2.35 (m)
	2.37 (m)	2.36 (m)	2.38 (m)	2.35 (m)
5	2.64 (brt, 12.4)	2.64 (brt, 12.4)	2.66 (brt, 12.3)	2.65 (dt, 1.5, 13.5)
	3.61 (brd, 14.0)	4.05 (brd, 14.0)	4.04 (brd, 13.9)	4.00 (brd, 14.0)
6	1.44 (m)	1.46 (m)	1.45 (m)	1.40 (m)
	1.69 (m)	1.75 (m)	1.72 (m)	1.69 (m)
7	1.53 (m)	1.25 (m)	1.34 (m)	1.25 (m)
	2.09 (m)	1.91 (m)	1.88 (m)	1.78 (m)
8	3.90 (ddd, 2.6, 9.9, 10.6)	1.38 (m)	1.35 (m)	1.13 (m)
		1.64 (m)	1.68 (m)	1.28 (m)
9	2.52 (m)	2.12 (m)	2.20 (m)	2.28 (m)
9a	4.00 (m)	3.82 (m)	3.93 (m)	3.85 (m)
10	1.93 (m)	1.51 (m)	1.67 (m)	2.48 (m)
11		4.69 (dt, 3.6, 7.6)	5.16 (brd, 1.9)	
12	1.97 (m)	1.96 (m)	7.02 (d, 1.4)	2.53 (dd, 5.3, 18)
	2.36 (m)	2.27 (m)		2.89 (dd, 7.9, 18)
13	2.93 (m)	2.70 (m)		2.96 (m)
14				
15	1.25 (d, 7.2)	1.30 (d, 7.5)	1.94 (d, 1.5)	1.18 (d, 7.1)
16	1.56 (m)	1.50 (m)	1.20 (m)	1.62 (m)
			1.36 (m)	
17	1.01 (t, 7.7)	1.00 (t, 7.3)	0.85 (t, 7.4)	0.83 (t, 7.5)
OMe				3.67 (s)

Chemical shifts are reported in ppm relative to residual $CHCl_3$ resonance at 7.26 ppm. Multiplicity and J values in Hz are given in parentheses.

that **3** was an analogue of **2** in which the α-methyl-γ-lactone ring of **2** was the α-methyl-α,β-unsaturated-γ-lactone ring in **3**. Catalytic hydrogenation of **3** using Pd/C gave **14b** (Scheme 1). Thus, structure of **3** was determined as shown in Figure 1.

Alkaloid **4** (sessilifoliamide D) of the molecular formula $C_{18}H_{29}NO_4$ [HREIMS (m/z 323.2098 $[M]^+$, calcd 323.2097)] was obtained as a colorless oil. IR absorptions at 1735, 1715 and 1682 cm^{-1} indicated that **4** had ester and ketone groups, and a lactam ring. The ^{13}C NMR spectrum showed the signals of three methyls, eight methylenes, four methines, and three carbonyl groups at δ 211.1, 176.1 and 174.3. The ^{1}H NMR spectrum showed the signals of two methyl groups (δ 1.18, d and 0.83, t) and one methoxyl group (δ 3.67, s). In the ^{1}H and ^{13}C NMR spectra, the chemical shifts of the resonances assignable to the protons and carbons of 1-9a of **4** were very similar to those of **2** and **3**, suggesting that **4** was also an octahydropyrrolo[1,2-*a*]-azepinone derivative with a different side chain at C-9. The positions of the ester and ketone carbonyl groups were determined to be at C-14 and C-11, respectively: the HMBC spectrum showed a correlation between C-14 and methoxyl protons (δ 3.67, s), and that C-11 was correlated with H-9 (δ 2.28, m), H-10 (δ 2.48, m), H-12 (δ 2.89, dd and 2.53, dd), H-13 (δ 2.96, m), and H_2-16 (δ 1.62, m). Reduction of **4** with lithium borohydride gave diols **15a** and **15b**, and **15a** was also obtained by reduction of **2**. Thus, the stereochemistry of C-9, C-9a, C-10 and C-13 for **4** were shown to be the same as those of **2** (Scheme 1).

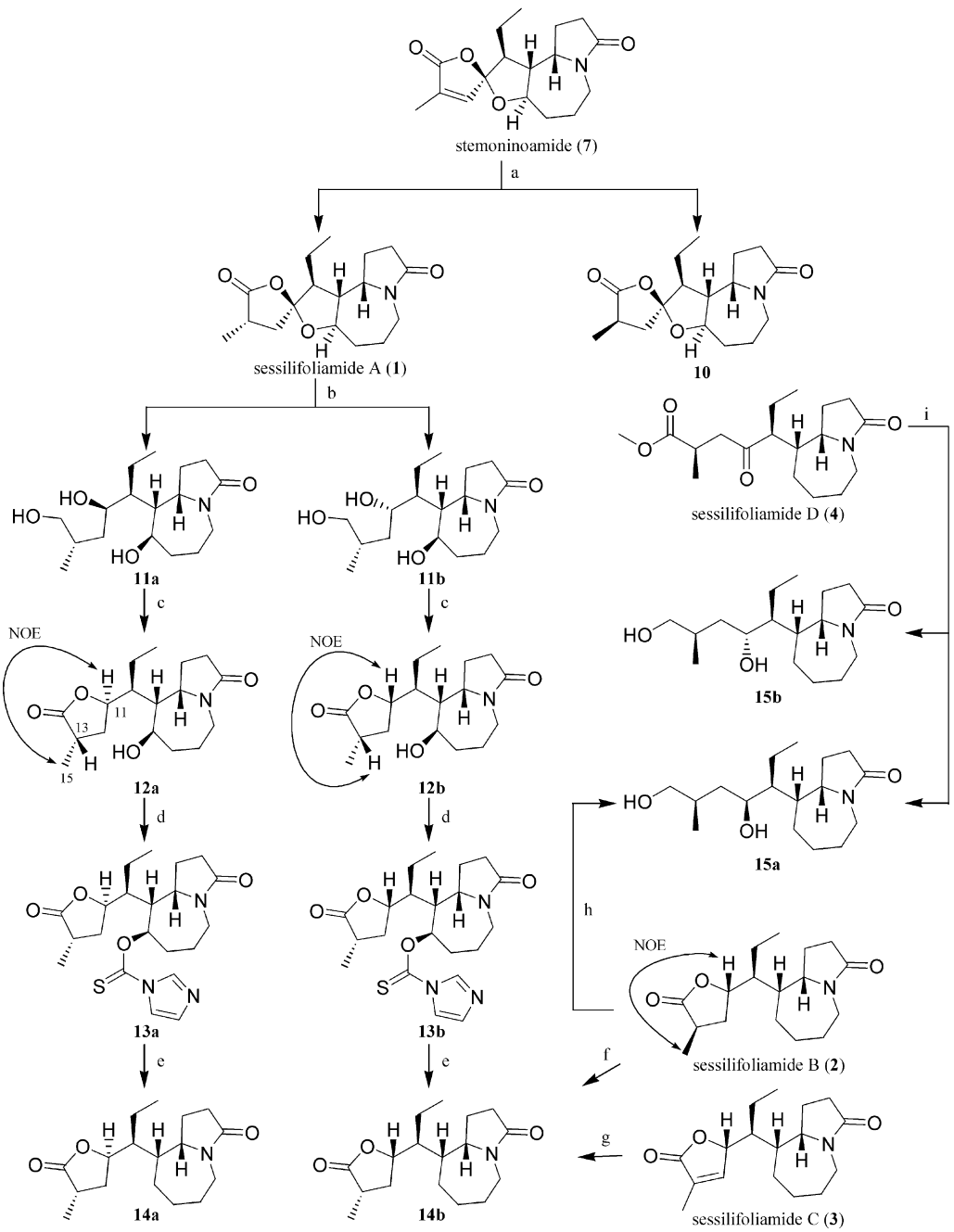
Since the absolute configuration of stemoninoamide (**7**) was unknown, the absolute configuration of alkaloids **1**–**4** could not be determined by their comparison with the derivatives of **7**. Therefore, the absolute configuration of the series of the alkaloids was determined by the modified Mosher's method,[16] by using **12a**. Treatment of **12a** with (*S*)- and (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA), 1,3-dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) in CH_2Cl_2 gave (*S*)- and (*R*)-MTPA esters of **12a**. The chemical shift differences between the (*S*)- and (*R*)-MTPA esters of **12a** ($\Delta\delta = \delta_S - \delta_R$) were positive for H_a-5, H_2-6 and H_2-7, zero for H_b-5 and negative for H_2-1, H_2-2, H-8, H-9, H-9a, H-10, H-11, H_2-12, H-13, H_3-15, H_2-16 and H_3-17, implying that the absolute configuration at C-8 of **12a** was *R* (Fig. 4). Once the absolute stereochemistry of **12a** was known, those of **1**–**4** and **7** were also determined, which are shown in Figure 1. Thus, the absolute configuration of the pyrrolo-[1,2-*a*]azepine nucleus of them were shown to be the same as that of stenine (**5**)[17] (Fig. 1).

Sesselifoliamide A (**1**) is a stemoamide-type alkaloid which is characterized by the tricyclic 2*H*-furo[3,2-*c*]pyrrolo[1,2-*a*]azepine, whereas sessilifoliamides B–D (**2**–**4**) are parvistemoline-type alkaloids[18,19] which are characterized by the pyrrolo[1,2-*a*]azepine with a side chain attached to the C-9 position. The latter type of alkaloids are not very usual, and only three have so far been reported.[4]

3. Experimental

3.1. General

Optical rotations were determined on a JASCO DIP-360 digital polarimeter, and IR spectra on a JASCO FT/IR 620 spectrophotometer. NMR spectra were obtained on Bruker DRX-500 and DPX-400 spectrometers at 300 K. In ^{1}H NMR spectra, the chemical shifts (δ) are given in ppm relative to the resonances of residual $CHCl_3$ at 7.26 ppm and CD_2HOD at 3.31 ppm. In ^{13}C NMR spectra the chemical shifts are given in ppm relative to the resonances at 77.0 ppm for $CDCl_3$ and at 49.0 ppm for CD_3OD. Mass



Scheme 1. *Reagents and conditions*: (a) H_2, Pd/C, EtOH, 3 h, 53% (**1**) and 10% (**10**); (b) $LiBH_4$, THF, 2 h, 49% (**11a**) and 16% (**11b**); (c) 4-hydroxy-TEMPO, $Ca(OCl)_2$, acetone, 48 h, 52% for **12a**, 27% for **12b**; (d) TCDI, dichloroethane, 48 h, 65% for **13a**, 70% for **13b**; (e) $^nBu_3SnH$, Et_3B, toluene, 5 h, 59% for **14a**, 65% for **14b**; (f) $NaN[Si(CH_3)_3]_2$, THF, 3 h, then NH_4Cl, 56% (**14b**) and 6% (**2**); (g) H_2, Pd/C EtOH, 3 h, 68%; (h) $LiBH_4$, THF, 2 h, 65%; (i) $LiBH_4$, THF, 2 h, 32% (**15a**) and 5% (**15b**).

spectra were obtained with VG AutoSpec E and Micromass LCT spectrometers. Preparative HPLC was carried out on a Shimadzu LC-6AD system equipped with a SPD-10A UV detector (220 nm) and an Inertsil PREP-ODS column (10 μm, 20×250 mm), by using a mixed solvent of MeOH/H_2O or MeCN/H_2O at a flow rate of 10 mL/min. X-Ray single-crystal analysis was performed on a Mac Science DIP diffractometer with Mo Kα radiation (λ=0.71073 Å).

3.2. Plant material

Stemona sessilifolia Franch. & Sav. was cultivated and harvested in Shandong Province, China in 2000. The species of the plant was identified by Professor Z. W. Xie of the China Academy of Traditional Chinese Medicine.

3.3. Extraction and isolation

The air-dried roots (15 kg) were extracted with hot MeOH (3×35 L). The solvent was removed to give a crude MeOH extract (8 kg), which was after acidifications with 3% aqueous tartaric acid (8 L), washed with EtOAc (3×8 L). The aqueous layer was then adjusted to pH 9 with solid Na_2CO_3 and extracted with $CHCl_3$ (3×8 L). The combined $CHCl_3$ extracts were evaporated in vacuo to give a residue

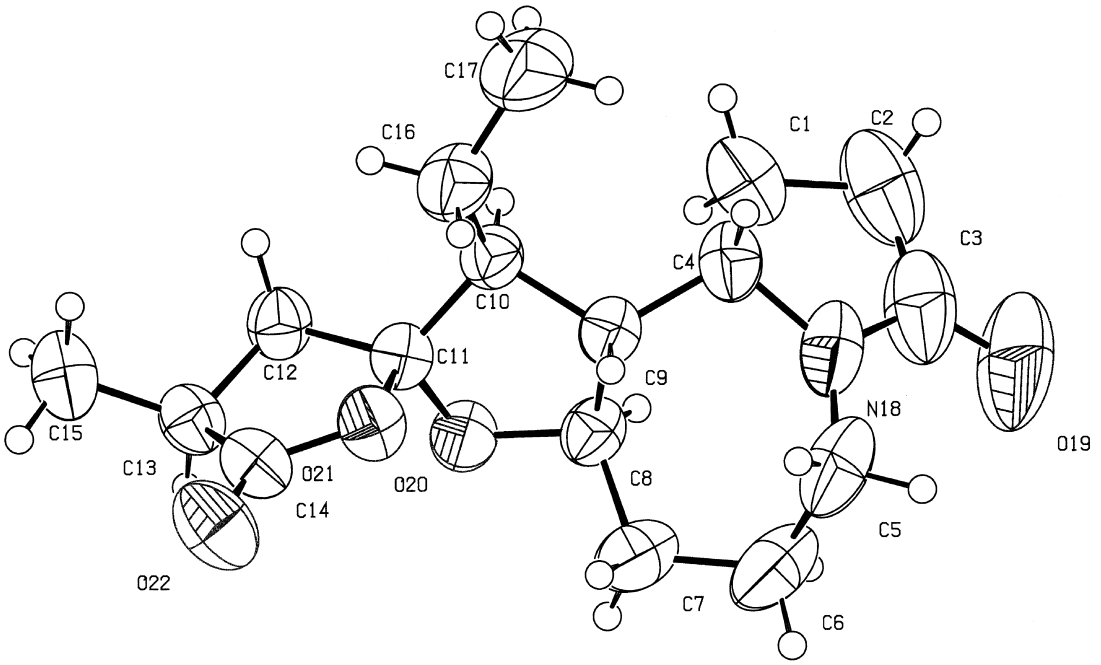


Figure 2. Molecular structure of sessilifoliamide A (**1**) as determined by single-crystal X-ray analysis.

(250 g), which was subjected to HP-20 (DIAION, 1250 g) column chromatography eluting with MeOH (10 L), then with acetone (3 L). The residue of the MeOH fraction (206 g) was placed on an alumina column (Merck Aluminiumoxid 90, 2 kg) and eluted sequentially with $CHCl_3$ (4 L), $CHCl_3$/MeOH (5:1, 2 L), and MeOH (2 L). The residue of the $CHCl_3$ fraction (150 g) was placed on a silica gel column (Merck Kieselgel 60, 70–230 mesh, 900 g) and eluted with petrol ether containing an increasing amount of EtOAc (4:1–0:1, 22 L), and then with $CHCl_3$/MeOH (10:1, 4.5 L). The $CHCl_3$/MeOH (10:1) fraction (13.5 g) was further subjected to silica gel column chromatography eluting sequentially with petrol ether/acetone (1:1, 4 L), acetone (1 L), and MeOH (1 L) to give four fractions, F-1 (2.99 g, first petrol ether/acetone (1:1) eluate), F-2 (2.81 g, second petrol ether/acetone (1:1) eluate), F-3 (4.42 g, acetone eluate) and F-4 (1.79 g, MeOH eluate). F-1 was further separated by ODS HPLC eluting with MeOH/0.1 M aqueous $(NH_4)_2CO_3$ (55:45) to give alkaloid **9** (4.5 mg). F-2 gave, by ODS HPLC eluting with MeOH/0.1 M aqueous $(NH_4)_2CO_3$ (4:6), alkaloids **2** (100 mg), **3** (46 mg), **4** (60 mg) and **6** (50 mg). F-3 gave, by ODS HPLC eluting with MeOH/0.1 M aqueous NH_4OAc (35:65), alkaloids **7** (2.0 g) and **8** (26 mg). This alkaloid **7** was not pure and recrystallized from Et_2O/acetone (1:1) to give pure **7** (1.5 g), and the mother liquor, when concentrated and applied to ODS HPLC eluting with MeOH/0.1 M aqueous NH_4OAc (35:65) gave alkaloid **1** (60 mg). From F-4, alkaloid **5** (20 mg) was obtained by preparative TLC (Merck Silica gel 1.05744) using $CHCl_3$/MeOH (20:1).

3.4. Characteristics of each alkaloid

3.4.1. Sessilifoliamide A (1). Colorless prisms (EtOAc); mp 166–168°C; $[\alpha]_D^{27}=-128°$ (*c* 0.35, $CHCl_3$); IR ν_{max} (film) 1772 (γ-lactone) and 1687 (γ-lactam) cm^{-1}; ^1H and ^{13}C NMR data, given in Tables 1 and 2; EIMS *m/z* (%): 307 (M^+, 100), 263 (24) and 193 (7); HREIMS *m/z* 307.1766 (M^+, calcd for $C_{17}H_{25}NO_4$, 307.1784).

3.4.2. Sessilifoliamide B (2). Colorless oil; $[\alpha]_D^{24}=-43°$ (*c* 0.10, $CHCl_3$); IR ν_{max} (film) 1769 (γ-lactone) and 1682 (γ-lactam) cm^{-1}; ^1H and ^{13}C NMR data, given in Tables 1 and 2; EIMS *m/z* (%): 293 (M^+, 100), 246 (24), 194 (53), 110 (46), 97 (69) and 41 (70); HREIMS *m/z* 293.2008 (M^+, calcd for $C_{17}H_{27}NO_3$, 293.1991).

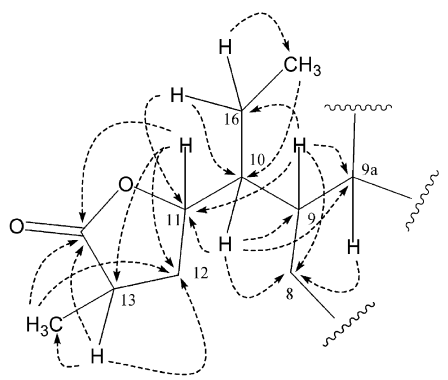


Figure 3. Significant HMBC correlations for sessilifoliamide B (**2**).

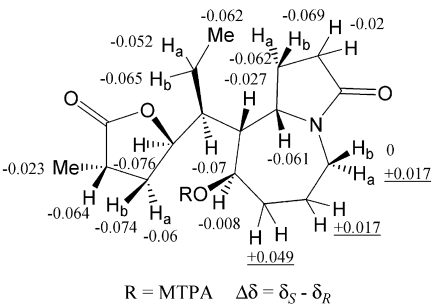


Figure 4. Modified Mosher's method using MTPA ester derivarives of **12a**.

3.4.3. Sessilifoliamide C (3). Colorless oil; $[\alpha]_D^{26}=-140°$ (*c* 0.17, $CHCl_3$); IR ν_{max} (film) 1751 (unsaturated γ-lactone) and 1682 (γ-lactam) cm^{-1}; ^1H and ^{13}C NMR data, given in Tables 1 and 2; EIMS *m/z* (%): 291 (M^+, 100), 262 (5), 194 (66) and 151 (7); HREIMS *m/z* 291.1829 (M^+, calcd for $C_{17}H_{25}NO_3$, 291.1834).

3.4.4. Sessilifoliamide D (4). Colorless oil; $[\alpha]_D^{26}=-94°$ (*c* 0.16, $CHCl_3$); IR ν_{max} (film) 1735 (ester), 1715 (ketone) and 1682 (γ-lactam) cm^{-1}; ^1H and ^{13}C NMR data, given in Tables 1 and 2; EIMS *m/z* (%): 323 (M^+, 100), 291 (12), 129 (29) and 40 (28); HREIMS *m/z* 323.2098 (M^+, calcd for $C_{18}H_{29}NO_4$, 323.2097).

3.5. Identification of structual relations between the alkaloids from *S. sessilifolia* by synthetic procedures (Scheme 1)

3.5.1. Catalytic hydrogenation of 7 to 1. A solution of **7** (30 mg, 0.098 mmol) in EtOH (4 mL) was stirred at room temperature under a hydrogen atmosphere for 3 h in the presence of 10% Pd/C (60 mg). After filtration, the reaction mixture was evaporated, and the residue was separated by ODS HPLC with MeOH/H_2O (35:65) to give two products. By the comparisons of their ^1H NMR spectra, t_R of HPLC analysis and optical rotations, the major product [16 mg, 53%, $[\alpha]_D^{30}=-130°$ (*c* 0.32, $CHCl_3$)] was shown to be identical to **1**. The minor product was shown to be **10** (3 mg, 10%): colorless oil; IR ν_{max} (film) 1772 (γ-lactone) and 1687 (γ-lactam) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (t, 3H, *J*=7.5 Hz), 1.37 (d, 3H, *J*=7.4 Hz), 1.45–1.50 (m, 2H), 1.51 (m, 1H), 1.65 (m, 1H), 1.69 (m, 1H), 1.75 (m, 1H), 1.97 (m, 1H), 2.00 (m, 1H), 2.14 (m, 1H), 2.35 (m, 1H), 2.40 (m, 2H), 2.55 (m, 1H), 2.56 (dd, 1H, *J*=10, 13.4 Hz), 2.66 (brt, 1H, *J*=12.5 Hz), 2.72 (m, 1H), 3.90 (m, 1H), 4.00 (m, 1H) and 4.06 (brd, 1H, *J*=14 Hz); EIMS *m/z* 307 (M^+); HRESIMS *m/z* 308.1857 ($[M+H]^+$, calcd for $C_{17}H_{26}NO_4$, 308.1862).

3.5.2. Preparation of triols 11a and 11b. A $LiBH_4$ solution (2 M in THF, 1 mL) was added dropwise to a solution of **1** (30 mg, 0.098 mmol) in THF (0.5 mL) at 0°C, and the mixture was stirred at room temperature under an argon atmosphere for 2 h. The mixture was quenched with saturated aqueous NH_4Cl (1 mL) at 0°C and extracted with $CHCl_3$ (3×10 mL). The combined extracts were washed with brine (2 mL), dried over Na_2SO_4, and concentrated in vacuo to give a residue, which was separated by ODS HPLC with MeOH/H_2O (23:77) to give **11a** (15 mg, 49%) and **11b** (5 mg, 16%).

Compound **11a**. Colorless oil; $[\alpha]_D^{27}=-80°$ (*c* 0.26, $CHCl_3$); IR ν_{max} (film) 3364 (hydroxyl) and 1684 (γ-lactam) cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 0.96 (t, 3H, *J*=7 Hz), 0.98 (d, 3H, *J*=6.8 Hz), 1.36 (m, 1H), 1.43 (m, 1H), 1.55 (m, 1H), 1.56 (m, 1H), 1.66 (m, 1H), 1.69 (m, 1H), 1.78 (m, 1H), 1.79 (m, 1H), 1.83 (m, 1H), 1.84 (m, 1H), 1.92 (m, 1H), 2.16 (m, 1H), 2.29 (dd, 1H, *J*=1.3, 9.5 Hz), 2.34 (m, 1H), 2.35 (m, 1H), 2.95 (ddd, 1H, *J*=4, 9.5, 13.5 Hz), 3.45 (dd, 2H, *J*=1, 5.5 Hz), 3.76 (m, 1H), 3.79 (m, 1H), 3.89 (m, 1H) and 4.26 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 14.3, 18.0, 22.1, 23.8, 25.3, 32.1, 34.0, 37.8, 40.0, 40.4, 45.8, 45.9, 60.3, 67.9, 68.0, 68.8 and 177.1; HRESIMS *m/z* 336.2129 ($[M+Na]^+$, calcd for $C_{17}H_{31}NO_4Na$, 336.2151).

Compound **11b**. Colorless oil; $[\alpha]_D^{20}=-96°$ (*c* 0.25, $CHCl_3$); IR ν_{max} (film) 3351 (hydroxyl) and 1662 (γ-lactam) cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 0.92 (d, 3H, *J*=6.6 Hz), 1.03 (t, 3H, *J*=7.4 Hz), 1.07 (m, 1H), 1.44 (m, 1H), 1.47 (m, 1H), 1.61 (m, 2H), 1.76 (m, 1H), 1.78 (m, 1H), 1.82 (m, 1H), 1.83 (m, 1H), 1.96 (m, 1H), 1.97 (m, 1H), 2.07 (m, 1H), 2.21 (m, 1H), 2.39 (t, 2H, *J*=8.6 Hz), 3.20 (ddd, 1H, *J*=2.9, 6.5, 13.6 Hz), 3.39 (d, 2H, *J*=6 Hz), 3.55 (m, 1H), 3.87 (brd, 1H, *J*=10 Hz), 4.14 (dt, 1H, *J*=2, 5.4 Hz) and 4.23 (dt, 1H, *J*=3.5, 7 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 14.0, 17.0, 21.8, 21.9, 24.5, 32.1, 33.0, 36.4, 42.2, 43.2, 47.1, 50.4, 59.6, 68.6, 69.2, 69.9 and 177.3; HRESIMS *m/z* 336.2143 ($[M+Na]^+$, calcd for $C_{17}H_{31}NO_4Na$, 336.2151).

3.5.3. Preparation of lactone 12a. 4-Hydroxy-TEMPO (19 mg, 0.108 mmol) and $Ca(OCl)_2$ (13 mg, 0.135 mmol) were added to a solution of **11a** (8.5 mg, 0.027 mmol) in acetone (0.5 mL) at 0°C, and the mixture was stirred at room temperature for 48 h. Saturated aqueous $NaHCO_3$ (3 mL) was added to the solution, and the mixture was extracted with $CHCl_3$ (3×5 mL). The combined extracts were dried over Na_2SO_4, and concentrated in vacuo. The residue was separated by ODS HPLC with MeOH/H_2O (35:65) to give **12a** (4.3 mg, 52%) as an amorphous solid; $[\alpha]_D^{21}=-85°$ (*c* 0.27, $CHCl_3$); IR ν_{max} (film) 3396 (hydroxyl), 1772 (γ-lactone) and 1684 (γ-lactam) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.03 (t, 3H, *J*=7.4 Hz), 1.21 (m, 1H), 1.31 (d, 3H, *J*=7.5 Hz), 1.62 (m, 1H), 1.67 (m, 1H), 1.68 (m, 1H), 1.80 (m, 1H), 1.90 (m, 1H), 1.91 (m, 1H), 1.97 (m, 1H), 1.98 (m, 1H), 2.07 (m, 1H), 2.28 (m, 1H), 2.35 (m, 2H), 2.42 (m, 1H), 2.72 (m, 1H), 2.82 (m, 1H), 3.93 (m, 1H), 3.99 (m, 1H), 4.00 (m, 1H) and 4.56 (dt, 1H, *J*=6.9, 9.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 16.1, 22.5, 22.9, 24.4, 31.2, 34.6, 35.3, 37.8, 38.7, 44.9, 45.6, 56.6, 68.1, 79.6, 174.3 and 179.6; HRESIMS *m/z* 332.1816 ($[M+Na]^+$, calcd for $C_{17}H_{27}NO_4Na$, 332.1838).

3.5.4. Preparation of lactone 12b. This lactone (**12b**) was obtained from **11b** in the same manner as described for **12a** in 27% yield. Amorphous solid; $[\alpha]_D^{22}=-2.7°$ (*c* 0.26, $CHCl_3$); IR ν_{max} (film) 3392 (hydroxyl), 1767 (γ-lactone) and 1682 (γ-lactam) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.03 (t, 3H, *J*=7.4 Hz), 1.26 (d, 3H, *J*=7.1 Hz), 1.46 (m, 2H), 1.65 (m, 1H), 1.66 (m, 1H), 1.68 (m, 1H), 1.74 (m, 1H), 1.92 (m, 1H), 1.93 (m, 1H), 2.00 (m, 1H), 2.02 (m, 1H), 2.28 (m, 1H), 2.36 (m, 1H), 2.39 (brd, 2H, *J*=7.1 Hz), 2.63 (m, 1H), 3.24 (td, 1H, *J*=4.7, 14.2 Hz), 3.49 (m, 1H), 4.14 (brd, 1H, *J*=2.5 Hz), 4.28 (m, 1H) and 4.41 (ddd, 1H, *J*=2.1, 5.8, 10.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 14.9, 19.7, 19.9, 23.6, 31.2, 35.4, 35.7, 36.2, 42.6, 43.1, 49.8, 55.8, 67.0, 78.2, 174.8 and 179.3; HRESIMS *m/z* 332.1816 ($[M+Na]^+$, calcd for $C_{17}H_{27}NO_4Na$, 332.1838).

3.5.5. Preparation of thiocarbamate 13a. TCDI (20 mg, 0.11 mmol) was added to a solution of **12a** (7.0 mg, 0.023 mmol) in dichloroethane (0.5 mL), and the mixture was stirred at room temperature for 48 h. Brine (2 mL) was added to the mixture, and the whole was extracted with $CHCl_3$ (3×5 mL). The combined extracts were dried over Na_2SO_4, and concentrated in vacuo. The residue was separated by ODS HPLC with MeOH/H_2O (50:50) to give **13a** (6.3 mg, 65%) as an amorphous solid; $[\alpha]_D^{21}=-58°$ (*c* 0.36, $CHCl_3$); IR ν_{max} (film) 1772 (γ-lactone) and 1684

(γ-lactam) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.80 (t, 3H, J=7.5 Hz), 1.21 (m, 1H), 1.32 (d, 3H, J=7.5 Hz), 1.50 (m, 1H), 1.72 (m, 1H), 1.81 (m, 1H), 1.86 (m, 1H), 1.87 (m, 1H), 1.95 (m, 1H), 2.03 (m, 1H), 2.05 (m, 1H), 2.07 (m, 1H), 2.20 (m, 1H), 2.42 (m, 2H), 2.74 (m, 1H), 2.95 (m, 1H), 2.97 (m, 1H), 4.05 (m, 1H), 4.07 (m, 1H), 4.44 (dt, 1H, J=7.7, 9.6 Hz), 5.89 (dt, 1H, J=3.8, 12.2 Hz), 7.07 (s, 1H), 7.62 (s, 1H) and 8.35 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 16.1, 21.7, 23.2, 24.7, 31.0, 32.9, 34.7, 35.7, 38.9, 44.5, 45.4, 57.6, 79.0, 81.3, 117.7, 131.3, 136.8, 174.1, 179.0 and 182.6; HRESIMS m/z 420.1941 ($[M+H]^+$, calcd for $C_{21}H_{30}N_3O_4S$, 420.1957).

3.5.6. Preparation of thiocarbamate 13b. This thiocarbamate (**13b**) was obtained from **12b** in the same manner as described for **13a** in 70% yield. Colorless oil; IR ν_{max} (film) 1772 (γ-lactone) and 1684 (γ-lactam) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, 3H, J=7.5 Hz), 1.27 (d, 3H, J=7.5 Hz), 1.47 (m, 1H), 1.55 (m, 1H), 1.66 (m, 1H), 1.67 (m, 1H), 1.72 (m, 1H), 1.75 (m, 1H), 1.99 (m, 1H), 2.08 (m, 1H), 2.22 (m, 1H), 2.37 (m, 1H), 2.41 (m, 2H), 2.41 (m, 1H), 2.64 (m, 1H), 3.33 (m, 1H), 3.45 (m, 1H), 3.46 (m, 1H), 4.27 (m, 1H), 4.37 (m, 1H), 5.64 (brs, 1H), 7.07 (s, 1H), 7.63 (s, 1H) and 8.34 (s, 1H); EIMS m/z 420 (M^+); HRESIMS m/z 420.1962 ($[M+H]^+$, calcd for $C_{21}H_{30}N_3O_4S$, 420.1957).

3.5.7. Preparation of lactone 14a. $^nBu_3SnH$ (35 μL, 0.12 mmol) and Et_3B (35 μL, 0.24 mmol) were added dropwise to a solution of **13a** (7.0 mg, 0.017 mmol) in toluene (0.5 mL), and the mixture was stirred at room temperature under an argon atmosphere for 5 h. Brine (2 mL) was added to the mixture, and the whole was extracted with $CHCl_3$ (3×5 mL). The combined extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was separated by ODS HPLC with MeOH/H_2O (50:50) to give **14a** (3.1 mg, 59%) as an amorphous solid; $[\alpha]_D^{22}=-29°$ (c 0.10, $CHCl_3$); IR ν_{max} (film) 1772 (γ-lactone) and 1684 (γ-lactam) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.00 (t, 3H, J=7.5 Hz), 1.27 (m, 1H), 1.28 (m, 1H), 1.32 (d, 3H, J=7.5 Hz), 1.43 (m, 1H), 1.45 (m, 1H), 1.52 (m, 1H), 1.68 (m, 1H), 1.69 (m, 1H), 1.72 (m, 1H), 1.80 (m, 1H), 1.87 (m, 1H), 1.88 (m, 1H), 2.01 (m, 1H), 2.24 (m, 1H), 2.26 (m, 1H), 2.34 (dd, 2H, J=4.7, 10.6 Hz), 2.66 (brt, 1H, 12.6 Hz), 2.73 (m, 1H), 3.90 (m, 1H), 4.05 (brd, 1H, J=14 Hz) and 4.56 (q, 1H, J=7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 16.3, 21.4, 23.3, 25.5, 29.3, 29.8, 31.1, 34.6, 34.6, 40.4, 42.7, 47.3, 60.6, 79.8, 174.4 and 179.6; HRESIMS m/z 316.1875 ($[M+Na]^+$, calcd for $C_{17}H_{27}NO_3Na$, 316.1889).

3.5.8. Preparation of lactone 14b from 13b. This lactone (**14b**) was obtained from **13b** in the same manner as described for **14a** in 65% yield. Amorphous solid; $[\alpha]_D^{22}=-56°$ (c 0.25, $CHCl_3$); IR ν_{max} (film) 1772 (γ-lactone) and 1684 (γ-lactam) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.00 (t, 3H, J=7.2 Hz), 1.26 (m, 1H), 1.28 (d, 3H, J=7.2 Hz), 1.35 (m, 1H), 1.44 (m, 1H), 1.49 (m, 2H), 1.51 (m, 1H), 1.65 (m, 1H), 1.67 (m, 1H), 1.69 (m, 1H), 1.71 (m, 1H), 1.90 (m, 1H), 1.92 (m, 1H), 2.10 (m, 1H), 2.35 (m, 2H), 2.40 (m, 1H), 2.64 (dt, 1H, J=1.3, 14 Hz), 2.67 (m, 1H), 3.82 (m, 1H), 4.04 (brd, 1H, J=14 Hz) and 4.50 (ddd, 1H, J=3.2, 5.5, 11 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 15.0, 20.8, 22.6, 24.3, 29.2, 29.7, 30.9, 35.6, 35.9, 40.6, 42.9, 45.4, 61.3, 79.5, 174.3 and 179.2; HRESIMS m/z 316.1916 ($[M+Na]^+$, calcd for $C_{17}H_{27}NO_3Na$, 316.1889).

3.5.9. Preparation of 14b by epimerization of 2. A sodium bis(trimethylsilyl) amide solution (1 M in THF, 0.05 mL) was added dropwise to a solution of **2** (8.0 mg, 0.027 mmol) in THF (2 mL), and the mixture was stirred at room temperature under an argon atmosphere for 3 h. After quenching with dropwise addition of saturated aqueous NH_4Cl (1 mL) at 0°C, the mixture was extracted with $CHCl_3$ (3×5 mL). The combined extracts were washed with brine (3 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was separated by ODS HPLC with MeOH/H_2O (40:60) to give **2** (0.5 mg, 6%) and another compound (4.5 mg, 56%); $[\alpha]_D^{24}=-57°$ (c 0.26, $CHCl_3$), the latter shown to be identical to **14b** obtained from **13b** by the comparison of their ^1H NMR spectra, t_R of HPLC analysis and optical rotations.

3.5.10. Preparation of 14b by catalytic hydrogenation of 3. A solution of **3** (12 mg, 0.041 mmol) in EtOH (3 mL) was stirred at room temperature under a hydrogen atmosphere for 3 h, in the presence of 10% Pd/C (25 mg). The mixture was filtered and evaporated, and the residue was separated by ODS HPLC with MeOH/H_2O (40:60) to give a reduction product (8.1 mg, 68%); $[\alpha]_D^{24}=-57°$ (c 0.19, $CHCl_3$). By the comparison of the ^1H NMR spectra, t_R of HPLC analysis and optical rotations, this product was shown to be identical to **14b** from **13b**.

3.5.11. Preparation of diol 15a. A $LiBH_4$ solution (2 M in THF, 0.3 mL) was added dropwise to a solution of **2** (10 mg, 0.034 mmol) in THF (1 mL), and the mixture was stirred at room temperature under an argon atmosphere for 2 h. After quenching by the addition of 10% aqueous HCl (10 drops) at 0°C, the mixture was extracted with $CHCl_3$ (3×10 mL), and the combined extracts were washed with brine (2 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was separated by ODS HPLC with MeOH/H_2O (30:70) to give **15a** (6.5 mg, 65%). **15a**: colorless oil; $[\alpha]_D^{22}=-103°$ (c 0.12, $CHCl_3$); IR ν_{max} (film) 3396 (hydroxyl), 1772 (γ-lactone) and 1684 (γ-lactam) cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 0.98 (d, 3H, J=6.8 Hz), 1.01 (t, 3H, J=7.4 Hz), 1.26 (m, 1H), 1.29 (m, 1H), 1.37 (m, 1H), 1.39 (m, 1H), 1.42 (m, 1H), 1.47 (m, 2H), 1.58 (m, 1H), 1.72 (m, 1H), 1.76 (m, 1H), 1.79 (m, 1H), 1.86 (m, 1H), 1.88 (m, 1H), 2.00 (m, 1H), 2.14 (m, 1H), 2.28 (m, 1H), 2.39 (m, 1H), 2.80 (brt, 1H, J=12.8 Hz), 3.44 (dt, 2H, J=5.9, 16 Hz), 3.90 (brd, 1H, J=13 Hz), 3.95 (td, 1H, J=3.6, 9.1 Hz) and 4.01 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 14.3, 18.4, 21.4, 23.2, 25.3, 30.3, 30.7, 31.9, 34.0, 40.5, 41.8, 44.1, 47.9, 63.2, 67.7, 71.3 and 177.3; EIMS m/z 297 (M^+); HRESIMS m/z 320.2221 ($[M+Na]^+$, calcd for $C_{17}H_{31}NO_3Na$, 320.2202).

3.5.12. Reduction of 4. A $LiBH_4$ solution (2 M in THF, 0.3 mL) was added dropwise to a solution of **4** (10 mg, 0.031 mmol) in THF (1 mL), and the mixture was stirred at room temperature under an argon atmosphere for 2 h. After addition of 10% aqueous HCl (10 drops) at 0°C, the mixture was extracted with $CHCl_3$ (3×10 mL), and the combined extracts were washed with brine (2 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was separated by

ODS HPLC with MeOH/H_2O (30:70) to give two products. By the comparisons of the ^1H NMR spectra, t_R of HPLC analysis and optical rotations, the major product [3.0 mg, 32%, $[\alpha]_D^{22}=-100°$ (*c* 0.30, $CHCl_3$)] was shown to be identical to **15a** from **2**. The minor one was shown to be **15b** (0.5 mg, 5%): colorless oil; IR ν_{max} (film) 3396 (hydroxyl), 1772 (γ-lactone) and 1684 (γ-lactam) cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 0.95 (d, 3H, *J*=6.8 Hz), 0.98 (t, 3H, *J*=7.4 Hz), 1.26 (m, 1H), 1.29 (m, 1H), 1.37 (m, 1H), 1.39 (m, 1H), 1.42 (m, 1H), 1.43 (m, 1H), 1.46 (m, 1H), 1.48 (m, 1H), 1.62 (m, 1H), 1.74 (m, 1H), 1.78 (m, 1H), 1.85 (m, 1H), 1.86 (m, 1H), 2.05 (m, 1H), 2.23 (m, 1H), 2.25 (m, 1H), 2.35 (m, 1H), 2.79 (brt, 1H, *J*=12.8 Hz), 3.43 (d, 2H, *J*=6.2 Hz), 3.84 (td, 1H, *J*=2.3, 8.3 Hz), 3.90 (brd, 1H, *J*=13.3 Hz) and 4.10 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 15.0, 17.0, 21.7, 24.3, 27.7, 30.4, 30.8, 32.1, 34.4, 39.9, 41.6, 43.2, 51.8, 62.6, 69.3, 70.7 and 177.3; EIMS *m/z* 297 (M^+); HRESIMS *m/z* 320.2196 ($[M+Na]^+$, calcd for $C_{17}H_{31}NO_3Na$, 320.2202).

3.5.13. Preparation of MTPA esters of 12a. A solution of **12a** (4.5 mg, 0.015 mmol) in CH_2Cl_2 (0.5 mL) was treated with DCC (9.0 mg, 0.049 mmol), DMAP (6.0 mg, 0.045 mmol) and (*S*)-MTPA (11 mg, 0.047 mmol) at room temperature for 22 h. The mixture was filtered and the filtrate was separated by ODS HPLC with MeOH/H_2O (60:40) to give (*S*)-MTPA ester of **12a** (1.7 mg, 20%). In the same manner, from **12a** and (*R*)-MTPA, (*R*)-MTPA ester of **12a** was prepared in 38% yield.

(*S*)-*MTPA ester*. ^1H NMR (500 MHz, $CDCl_3$) δ 0.836 (t, 3H, *J*=7.5 Hz, H-17), 1.19 (m, 1H, H_a-16), 1.271 (d, 3H, *J*=7.5 Hz, H-15), 1.42 (m, 1H, H_b-16), 1.544 (m, 1H, H-10), 1.746 (m, 2H, H-6), 1.829 (m, 1H, H_a-1), 1.857 (m, 2H, H-7), 1.893 (m, 1H, H_b-12), 1.986 (m, 1H, H_b-1), 2.06 (ddd, 1H, *J*=6.9, 9.1, 13 Hz, H_a-12), 2.363 (m, 2H, H-2), 2.433 (m, 1H, H-9), 2.571 (m, 1H, H-13), 3.093 (m, 1H, H_b-5), 3.446 (s, 3H, OMe), 3.829 (m, 1H, H_a-5), 3.921 (m, 1H, H-9a), 4.324 (q, 1H, *J*=7 Hz, H-11), 5.386 (m, 1H, H-8) and 7.39–7.54 (m, 5H, Ph); HRESIMS *m/z* 526.2428 ($[M+H]^+$, calcd for $C_{27}H_{35}F_3NO_6$, 526.2416).

(*R*)-*MTPA ester*. ^1H NMR (500 MHz, $CDCl_3$) δ 0.898 (t, 3H, *J*=7.5 Hz, H-17), 1.242 (m, 1H, H_a-16), 1.294 (d, 3H, *J*=7.5 Hz, H-15), 1.485 (m, 1H, H_b-16), 1.614 (m, 1H, H-10), 1.729 (m, 2H, H-6), 1.808 (m, 2H, H-7), 1.843 (m, 1H, H_a-1), 1.967 (ddd, 1H, *J*=5, 6.9, 12 Hz, H_b-12), 2.055 (m, 1H, H_b-1), 2.12 (ddd, 1H, *J*=7.3, 9.1, 13 Hz, H_a-12), 2.383 (m, 2H, H-2), 2.46 (m, 1H, H-9), 2.635 (m, 1H, H-13), 3.034 (s, 3H, OMe), 3.093 (m, 1H, H_b-5), 3.812 (m, 1H, H_a-5), 3.982 (m, 1H, H-9a), 4.40 (q, 1H, *J*=7.2 Hz, H-11), 5.394 (m, 1H, H-8) and 7.42–7.52 (m, 5H, Ph); HRESIMS *m/z* 526.2409 ($[M+H]^+$, calcd for $C_{27}H_{35}F_3NO_6$, 526.2416).

3.6. X-Ray crystallographic studies of 1

$C_{17}H_{25}NO_4$, *M*=307.39, 0.60×0.45×0.40 mm^3, orthorhombic, $P2_12_12_1$, *a*=9.5740(4) Å, *b*=10.7610(2) Å, *c*=16.3680(6) Å, *V*=1686.33(10) $Å^3$, *Z*=4, D_x=1.211 mg m^{-3}, μ (Mo Kα)=0.086 mm^{-1}, 2144 reflection measured, 2105 unique reflections, *R*=0.039, R_w=0.113. The structure was determined by the direct method using the maXus crystallographic software package[20] and the refinement was carried out by the program SHELXL-97.[21]

Crystallographic data for **1** have been deposited at the Cambridge Crystallographic Data Centre, under the reference number CCDC Ref. No. 209255. These data can be obtained, free of charge, on application to the CCDC, via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).

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