Structures and Absolute Stereochemistry of Five New Secospatanes and a Spatane Isolated from the Brown Alga *Dilophus okamurai* Dawson

Hiroshi Yamase, Kimie Umemoto, Takashi Ooi, and Takenori Kusumi*

Faculty of Pharmaceutical Sciences, Tokushima University, Shomachi, Tokushima 770–8505, Japan.
Received January 11, 1999; accepted March 12, 1999

Five new secospatane diterpenoids, secospatacetal A, B, C, D, and E have been isolated from the brown alga *Dilophus okamurai* Dawson, and their structures as well as absolute configurations have been elucidated by means of NMR spectroscopy and chemical transformations. Also, the structure of a known spatane diterpene has been revised.

Key words *Dilophus okamurai*; secospatacetal; absolute configuration; marine natural product; chiral anisotropic reagent

An increasing number of unique natural products is being found from marine organisms,[1] and the marine products have been attracting the interest of organic chemists and biochemists because of their novel chemical structures and remarkable biological activities. Studies of marine natural products has also prompted the development of new methodology for spectroscopic elucidation of the complex chemical structures and absolute configurations of the intriguing secondary metabolites.[2]

The brown algae of Dictyotaceae are known to produce a variety of diterpenoids[3] which proved to have pharmaceutical activities[4] and to be antifeedants against mollusks and ichtyotoxins.[5] This report deals with the structures and absolute configurations of five new secospatane diterpenoids, secospatacetal A (**1**), B (**2**), C (**3**), D (**4**), and E (**5**), which were isolated from the brown alga *Dilophus okamurai* Dawson.

Results and Discussion

D. okamurai Dawson (Japanese name: Fukurin-amiji) was collected at Kikizu beach of Ehime Prefecture and immediately soaked in methanol. The methanol extract was condensed and the residue was partitioned between hexane and water. The hexane soluble material was repeatedly chromatographed to give five new diterpenoids.

Secospatacetal A (**1**) gave a molecular ion at *m/z* 436.2797 confirming the molecular formula to be $C_{25}H_{40}O_6$. The ^{1}H-NMR spectrum in C_6D_6 revealed the signals for three singlet methyls at δ 1.55 (H-20), 1.62 (H-14) and 1.66 (H-19), one doublet methyl at δ 1.06 (H-11) and two olefinic protons at δ 5.18 (H-17) and 5.23 (H-15). In addition, the ^{1}H-NMR spectrum showed the signals for three methoxyls at δ 3.15 (2-OMe), 3.33 (10-OMe) and 3.46 (12-OMe), an acetoxyl at δ 1.73 (5-OAc), a methine proton bearing the acetoxyl group at δ 5.69 (H-5), and two methines bearing a methoxyl group at δ 3.38 (H-2) and 4.88 (H-12). The remaining signals were due to three methylene protons at δ 2.00 and 2.06 (H-6), 2.01 and 2.19 (H-3) and 2.76 and 2.81 (H-16) and five methine protons at δ 2.31 (H-8), 2.43 (H-1), 2.63 (H-9), 2.78 (H-4) and 3.53 (H-7). The ^{13}C-NMR spectrum showed the signals of two acetal carbons at δ 101.9 (C-12) and 110.7 (C-10), together with an acetoxyl signal at δ 20.7 (q) and 169.3 (s).

The ^{1}H–^{1}H correlation spectroscopy (COSY) and heteronuclear single quantum coherence (HSQC) experiments allowed the complete assignment of the protons and carbons. The proton networks of the compound were easily deduced by the ^{1}H–^{1}H COSY spectrum, because the connectivity of the protons is only interrupted by the quaternary carbons at C-10, 13 and 18. The heteronuclear multiple bond correlation (HMBC) spectrum (see **1a**) allowed the complete connectivity of the carbons, which revealed the secospatane skeleton and the planar structure of **1**. The nuclear Overhauser enhancement and exchange spectroscopy (NOESY) cross-peaks depicted in **1b** allowed assignment of the relative stereochemistry of secospatacetal A (**1**).

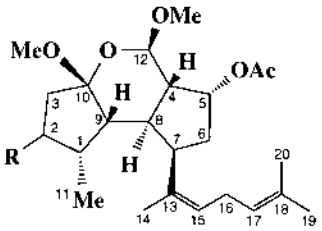
The absolute configuration of **1** was determined using the *OMe*-mandelate method.[6] Alkaline hydrolysis of **1** afforded the deacetyl product, and the hydroxy group of the product was esterified with (*R*)- and (*S*)-methoxyphenylacetic acids (MPA). The $\Delta\delta$ values ($\Delta\delta=\delta_R-\delta_S$) obtained for all the protons are indicated in **1c**. The systematic arrangement of the $\Delta\delta$ values enabled elucidation of the absolute configuration of **1** as shown in the structure.

The structures including the relative stereochemistry of secospatacetals B—E, **2**—**5**, were determined by the spectral analyses essentially similar to those described for **1**. The spectral data along with the assignment of protons and carbons are summarized in Experimental. We then focused on the absolute configuration of these four compounds.

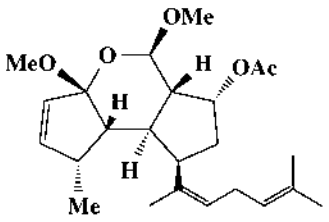
The two acetyl moieties of secospatacetal B (**2**) were removed by hydrolysis, and the resultant hydroxy groups were esterified with (*R*)- and (*S*)-MPA to give the diester. Usually, introduction of more than one anisotropic moiety in a small-sized molecule is unfavorable if the anisotropic effects from the multiple aromatic rings interfere with each other. In this case, however, based on the ideal conformation of the mandelates proposed by Trost and Curran,[6] the two phenyl rings of MPA in the diester may be oriented so that the anisotropic effects (upfield shift in this case) from the phenyl rings are in harmony with each other. Therefore, the signs of the $\Delta\delta$ values obtained for **2** must be systematically distributed and the values would be larger than those of **1**. As can be seen in **2a**, the speculation turned out to be correct: Arrangement of the positive and negative $\Delta\delta$ values is quite orderly and most of the values exceed those observed for **1**. From these data, the absolute configuration of **2** was determined to be 1*S*, 2*S*, 4*S*, 5*R*, 7*R*, 8*R*, 9*R*, 10*S*, 12*R*.

The yields of secospatacetals C (**3**) and D (**4**) were extremely poor, 0.8 mg and 0.6 mg, respectively. The problem of consuming the sample by derivatization into two diastere-

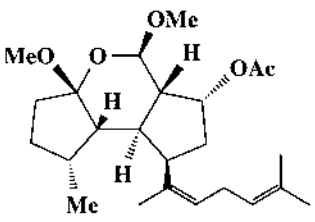
* To whom correspondence should be addressed.



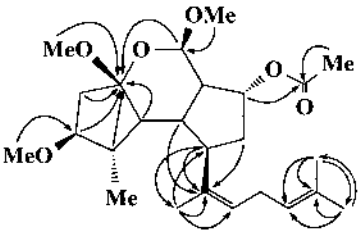
1: R = β-OMe (A)
2: R = β-OAc (B)
3: R = α-OMe (C)



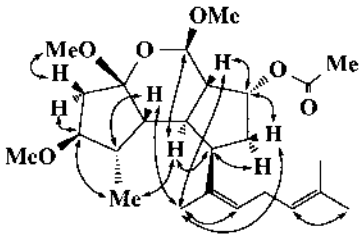
4 (D)



5 (E)



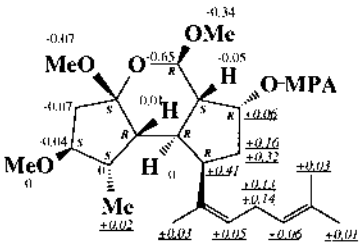
1a



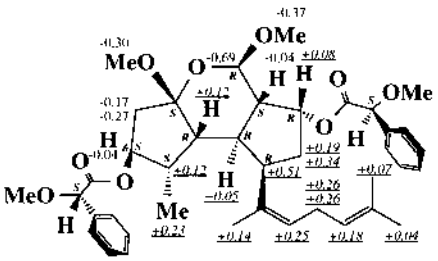
1b

HMBC cross peak

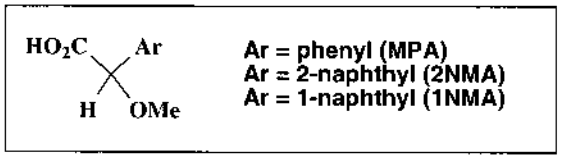
NOE cross peak



1c



2a



omers, (*R*)- and (*S*)-mandelates, can be greatly relieved if only one of the enantiomers of a certain chiral anisotropic reagent is effectively applied. Thus, methoxy(2-naphthyl)-acetic acid (2NMA),[7,8] having a stronger anisotropic effect than the mandelic acid, was adopted for determining the absolute configuration of these compounds (The ideal conformation[7] of an (*R*)-2NMA ester is shown in Fig. 1).

The hydrolytic products of compounds **3** and **4**, each 0.3 mg, were esterified with excess (*R*)-2NMA, and the chemical shifts of all the protons were assigned by means of ^{1}H–^{1}H COSY. We defined $\Delta\delta'$ value as $\Delta\delta' = \delta_{(\text{acetate})} - \delta_{(R\text{-2NMA ester})}$, and $\Delta\delta' = 0.1$ (ppm) as a threshold value. In structures **3a** and **4a**, the $\Delta\delta'$ values are assigned to the respective protons and the values above the threshold are underlined. It should be noted that, in each compound, introduction of the highly diamagnetic naphthalene moiety causes the upfield shift of the protons on both sides of the 2NMA plane. The protons with the $\Delta\delta'$ values larger than 0.1 ppm are located only on the left side of the 2NMA plane, thus leading to the *R*-configuration at C-5 of **3** and **4**.

We next turned our attention to methoxy(1-naphthyl)acetic acid (1NMA). Molecular models show that the anisotropy of the naphthalene ring is more conveniently used for a cyclic compound in a 1NMA ester (**A**) than in a 2NMA ester (**B**) (Fig. 2): The anisotropy of the two benzene rings of naphthalene is effectively given on the protons of the cyclic alcohol (L-menthol as an example) in 1NMA ester (**A**), whereas anisotropy of only one benzene ring is effective in 2NMA ester (**B**).

To confirm this assumption and compare the anisotropic effects between 1NMA and 2NMA, secospatacetal E (**5**), which was obtained in a very small quantity and whose relative stereochemistry was determined by spectroscopic analyses, was converted to 1NMA ester. The $\Delta\delta'$ values are as-

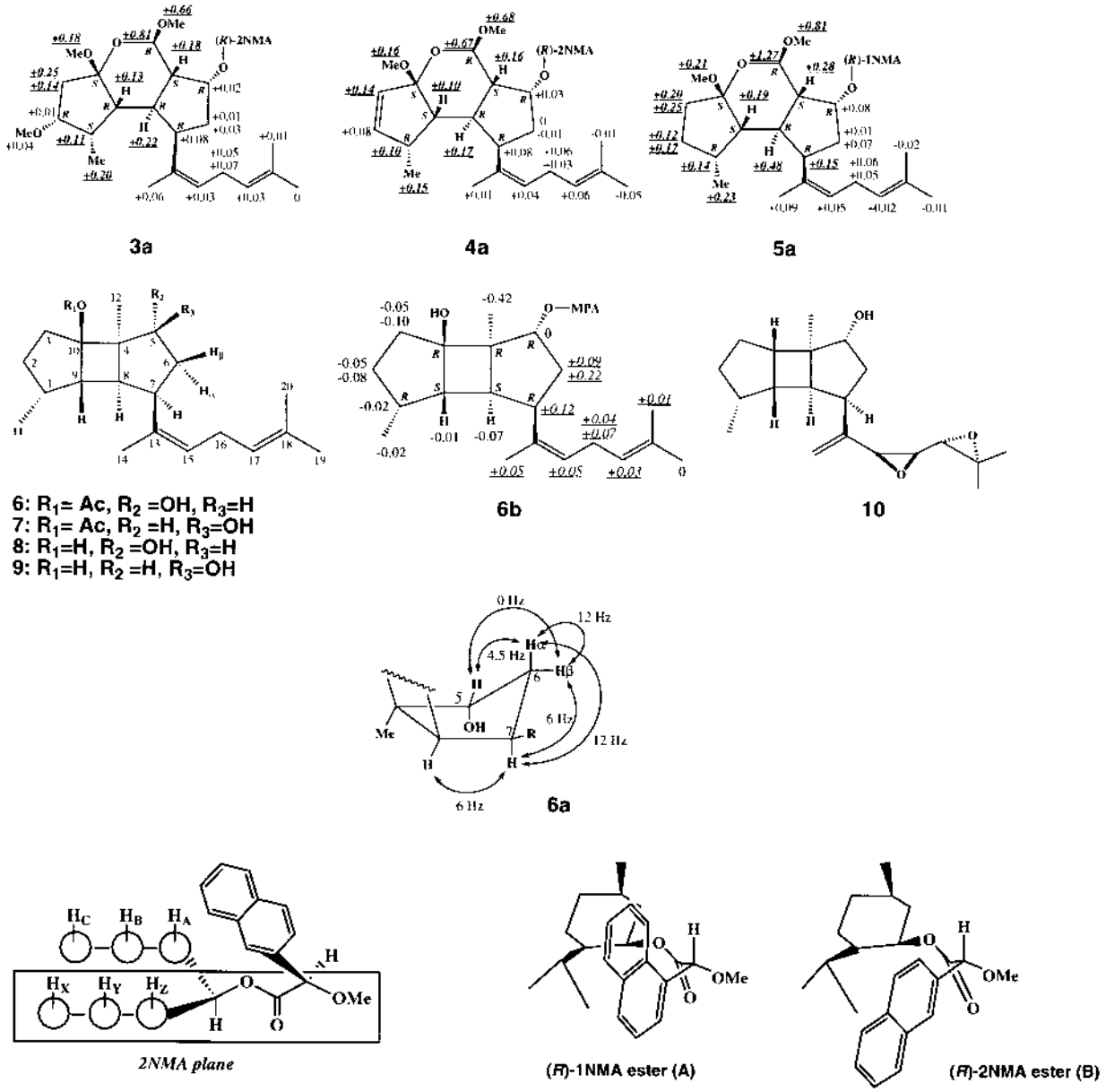


Fig. 1. An Ideal Conformation of a Methoxy-2-naphthylacetate (2NMA Ester)

Fig. 2. Stereoviews of (*R*)-1NMA (**A**) and (*R*)-2NMA (**B**) Esters of L-Menthol

The ideal conformations of the 1NMA and 2NMA esters are drawn. It is clear that, for the cyclic secondary alcohol L-menthol, 1NMA moiety is more effective than 2NMA, because two benzene rings of 1-naphthyl group are closer to the aliphatic ring protons than those of 2-naphthyl group.

signed in structure **5a**. They are clearly larger than those of 2NMA esters **3a** and **4a**. The distribution of the $\Delta\delta'$ values ($>$0.1 ppm) led to the *R*-configuration at C-5 of **5**.

This methodology, in which only one of the enantiomers of 1NMA or 2NMA (the former preferable for cyclic compounds) is used to determine the absolute configuration, seems to be valid in the series of the compounds described above. The authors, however, feel that it is somewhat risky to make it a general method at this stage. More examples to verify the method may be necessary, and the proper threshold of the $\Delta\delta'$ value, which is rather arbitrary in the present study, must be established. We recently reported a similar method using one enantiomer of (*R*)- and (*S*)-2NMA, which was applied to acyclic compounds.[9]

The spectral properties of compound **6** were identical with those reported by an Australian group.[10] In their report, structure **7** was proposed for this compound, and the relative and absolute stereochemistry was presumed by comparison of its spectral data with those of spatol (**10**), the absolute stereostructure of which had been determined by X-ray crystallography.[11]

By our extensive analyses of the NMR spectra, we came to the conclusion that the structure (**7**) must be corrected to **6** from the following points of view. (i) In the phase-sensitive NOESY experiments (400 MHz, $CDCl_3$) carried out for **6** and its hydrolytic product **8**, H-5 gives an intense cross peak to H-6β. This intensity was as large as the one between H-7 and H-6α. (ii) The coupling pattern of H-5 ($J_{5,6\alpha}$=0 Hz; $J_{5,6\beta}$=4.5 Hz) was similar to that reported for spatol. This coupling constant as well as other *J* values suggested that the conformation of the cyclopentane ring was as shown in **6a**, in which H-5 was oriented *anti* to H-7.

To obtain other evidence of the β-orientation of H-5,

chemical reactions were performed. Compound **6** was subjected to Swern oxidation, and the resulting ketone was reduced with $NaBH_4$ to give only one product. Consideration of the stereochemical pathway suggested that the hydride attacked from the convex side of the molecule, and, therefore, the H-5 of the product should have α-configuration. The spectral data (*e.g.*, NOESY: an intense cross peak between H-5 and H-6α) corroborated that the product was actually the 5-epimer of **8**. The coupling pattern of H-5 of the product ($J_{5,6\alpha}$=6.9 Hz; $J_{5,6\beta}$=10.0 Hz) was remarkably different from that of **8**. Thus, the structure of the product was established as **9**. Because the properties of **6** were identical with the reported ones, the present (and the Australian) diterpenoid must have structure **6**.

Finally, the absolute configuration of **6** was determined by *OMe*-mandelate method, and from the $\Delta\delta$ values denoted in structure **6b**, the 1*R*, 4*R*, 5*R*, 7*R*, 8*S*, 9*S*, 10*R* configuration was assigned to this spatane diterpenoid.

In conclusion, we have isolated five new diterpenoids, secospatacetal A—E, and determined their structures. The reported structure of a spatane was also revised by spectroscopic and chemical means. In the process of absolute configuration determination of these compounds, it was found that only one enantiomer of 1NMA and 2NMA was necessary to determine of the absolute configuration.

Experimental

^{1}H- and ^{13}C-NMR spectra were measured with a Bruker ARX-400 (^{1}H at 400 and ^{13}C at 100 MHz, respectively) spectrometer. HR-MS were taken under electron impact (EI) conditions using JEOL JMS-SX102A having a direct inlet system. Optical rotations were determined for solutions in methanol on a JASCO DIP-370 polarimeter. For column chromatography, Kieselgel 60 (Merck) was used. Preparative HPLC was performed on a JAI LC-908 instrument with LiChrosorb Si 60 columns (5 μm, 250×25 mm i.d. and 250×10 mm i.d., Merck).

Extraction and Isolation *Dilophus okamurai* Dawson (40 kg) was collected on Kikizu Beach, Ehime Prefecture, Japan in May 1995. The whole plant was extracted with MeOH at room temperature for 1 month. The MeOH extract was concentrated under a reduced pressure to give a residue, which was partitioned between hexane and H_2O. A part of the hexane-soluble portion (30 g) was subjected to silica gel chromatography eluting with hexane–AcOEt (4 : 1) to give five fractions (frs. 1—5). Fraction 3 was chromatographed on silica gel eluting with hexane–AcOEt (4 : 1) to give six fractions (frs. 3-1—6). Fraction 3-3 was subjected to silica gel chromatography eluting with hexane–AcOEt (8 : 1) to give seven fractions (frs. 3-3-1—7). Fraction 3-3-2 was purified by preparative HPLC [hexane–AcOEt (4 : 1)] to afford secospatacetal E (**5**, 1.9 mg). Fraction 3-3-6 was purified by preparative HPLC [hexane–AcOEt (2 : 1)] to afford secospatacetal C (**3**, 0.8 mg). Fraction 4 was chromatographed on silica gel eluting with hexane–AcOEt (4 : 1) to give ten fractions (frs. 4-1—10). Fraction 4-4 was subjected to chromatography on silica gel [hexane–AcOEt (6 : 1)] to give five fractions (frs. 4-4-1—5). Fraction 4-4-2 was purified by preparative HPLC [hexane–AcOEt (8 : 1)] to afford secospatacetal D (**4**, 0.6 mg). Fraction 4-4-4 was purified by preparative HPLC [hexane–AcOEt (6 : 1)] to afford secospatacetal B (**2**, 54.7 mg), a spatane (**6**, 60.6 mg) and a mixture of several compounds. The mixture was further separated by preparative HPLC [hexane–AcOEt (2 : 1)] to afford secospatacetal A (**1**, 21.0 mg).

Esterification with Chiral Anisotropic Reagents Excess (>5 mole equivalent) amounts of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) and NEt_3 were added to a solution of a secondary alcohol and an excess of a chiral anisotropic reagent (MPA, 2NMA or 1NMA) and 4-dimethylaminopyridine (DMAP) in 1 ml of CH_2Cl_2. After the mixture was stirred for 48 h, 10 ml of CH_2Cl_2 was added, and the organic layer was washed with 10 ml of H_2O, 10 ml of 10% aqueous citric acid, 10 ml of 5% aqueous sodium hydrogen carbonate and 10 ml of brine, dried with Na_2SO_4 and concentrated *in vacuo* to yield a crude ester. The crude ester was purified by preparative HPLC.

Swern Oxidation of Compound 6 Followed by $NaBH_4$ Reduction Ten μl (140 μmol) of DMSO was added to a solution of 10 μl (115 μmol) of oxalyl chloride in CH_2Cl_2 cooled to −78 °C. After stirring for 10 min, 2 mg of compound **6** in CH_2Cl_2 was added. After stirring for 20 min at −78 °C and 1 h at −45 °C, 60 μl (430 μmol) of NEt_3 was added and the mixture was warmed slowly to 0 °C. Saturated aqueous NH_4Cl was added after stirring for 20 min and the aqueous layer was extracted with AcOEt. The organic layer was washed with H_2O and brine, dried with Na_2SO_4 and concentrated *in vacuo*. The oxidation product was dissolved in methanol (1 ml) and mixed with 10 mg of $NaBH_4$ and the reaction mixture was stirred at room temperature for 20 min. The mixture was extracted with ether, the ethereal layer dried with $MgSO_4$ and concentrated *in vacuo* to give compound **9** (1 mg).

Secospatacetal A (1) HR-MS *m/z*: 436.2797 (Calcd for $C_{25}H_{40}O_6$: 436.2825). $[\alpha]_D$ +85.6° (*c*=0.10, methanol). ^{1}H-NMR (C_6D_6) δ: 1.06 (3H, d, *J*=7.3 Hz, H-11), 1.55 (3H, s, H-20), 1.62 (3H, s, H-14), 1.66 (3H, s, H-19), 1.73 (3H, s, 5-OAc), 2.00 (1H, m, H-6α), 2.01 (1H, m, H-3β), 2.06 (1H, m, H-6β), 2.19 (1H, dd, *J*=13.2, 5.3 Hz, H-3α), 2.31 (1H, ddd, *J*=14.6, 10.6, 9.6 Hz, H-8), 2.43 (1H, m, H-1), 2.63 (1H, t, *J*=10.2 Hz, H-9), 2.76 (1H, m, H-16), 2.78 (1H, m, H-4), 2.81 (1H, m, H-16), 3.15 (3H, s, 2-OMe), 3.33 (3H, s, 10-OMe), 3.38 (1H, q, *J*=5.2 Hz, H-2), 3.46 (3H, s, 12-OMe), 3.53 (1H, dt, *J*=5.3, 9.1 Hz, H-7), 4.88 (1H, d, *J*=8.4 Hz, H-12), 5.18 (1H, t, *J*=7.1 Hz, H-17), 5.23 (1H, t, *J*=7.3 Hz, H-15), 5.69 (1H, t, *J*=4.6 Hz, H-5). ^{13}C-NMR (C_6D_6) δ: 14.2 (C-11), 17.7 (C-20), 20.7 (5-OAc), 21.8 (C-14), 25.7 (C-19), 27.3 (C-16), 37.89 (C-7), 37.91 (C-6), 38.7 (C-8), 39.3 (C-3), 40.2 (C-1), 47.0 (C-4), 47.5 (C-9), 50.4 (10-OMe), 55.6 (12-OMe), 56.4 (2-OMe), 74.8 (C-5), 86.4 (C-2), 101.9 (C-12), 110.7 (C-10), 123.8 (C-17), 127.7 (C-15), 131.3 (C-18), 135.3 (C-13), 169.3 (5-OAc).

Hydrolytic Product of Secospatacetal A ^{1}H-NMR (C_6D_6) δ: 0.82 (1H, br s, 5-OH), 1.06 (3H, d, *J*=7.3 Hz, H-11), 1.58 (3H, s, H-20), 1.66 (1H, dd, *J*=16.0, 9.9 Hz, H-6α), 1.68 (3H, s, H-19), 1.70 (3H, s, H-14), 1.93 (1H, dt, *J*=14.9, 5.3 Hz, H-6β), 2.03 (1H, dd, *J*=13.2, 5.2 Hz, H-3β), 2.21 (1H, dd, *J*=13.2, 5.3 Hz, H-3α), 2.35 (1H, ddd, *J*=14.4, 10.7, 9.7 Hz, H-8), 2.44 (1H, m, H-1), 2.60 (1H, ddd, *J*=14.5, 8.4, 4.6 Hz, H-4), 2.65 (1H, t, *J*=10.2 Hz, H-9), 2.80 (1H, m, H-16), 2.89 (1H, m, H-16), 3.16 (3H, s, 2-OMe), 3.36 (3H, s, 10-OMe), 3.40 (1H, q, *J*=5.2 Hz, H-2), 3.48 (3H, s, 12-OMe), 3.53 (1H, dt, *J*=5.2, 9.2 Hz, H-7), 4.28 (1H, t, *J*=4.3 Hz, H-5), 5.12 (1H, d, *J*=8.4 Hz, H-12), 5.23 (1H, t, *J*=7.2 Hz, H-17), 5.27 (1H, t, *J*=7.4 Hz, H-15). ^{13}C-NMR (C_6D_6) δ: 14.2 (C-11), 17.7 (C-20), 21.9 (C-14), 25.7 (C-19), 27.4 (C-16), 37.5 (C-8), 37.9 (C-7), 39.4 (C-3), 40.3 (C-1), 40.8 (C-6), 47.5 (C-9), 48.2 (C-4), 50.3 (10-OMe), 55.3 (12-OMe), 56.3 (2-OMe), 71.5 (C-5), 86.5 (C-2), 102.1 (C-12), 110.7 (C-10), 124.1 (C-17), 127.3 (C-15), 131.2 (C-18), 136.0 (C-13).

(*R*)-MPA Ester of Secospatacetal A ^{1}H-NMR (CD_3OD) δ: 0.92 (H-11), 1.66 (H-14), 1.68 (H-20), 1.73 (H-19), 1.96 (H-3), 1.98 (H-6α), 1.99 (H-8), 2.17 (H-6β), 2.20 (H-1), 2.22 (H-9), 2.32 (H-4), 2.75 (H-16), 2.77 (H-16), 3.04 (12-OMe), 3.17 (10-OMe), 3.30 (2-OMe), 3.40 (H-2), 3.44 (MPA), 3.47 (H-7), 3.90 (H-12), 4.94 (MPA), 5.09 (H-17), 5.25 (H-15), 5.36 (H-5), 7.42—7.50 (MPA). ^{13}C-NMR (CD_3OD) δ: 14.5, 17.9, 21.8, 25.8, 27.9, 38.0, 38.3, 38.8, 39.5, 40.6, 48.1, 48.2, 50.7, 55.7, 56.7, 57.5, 76.7, 83.5, 87.6, 101.9, 111.8, 124.3, 128.5, 128.8, 129.9, 130.0, 132.4, 136.0, 138.3, 171.7.

(*S*)-MPA Ester of Secospatacetal A ^{1}H-NMR (CD_3OD) δ: 0.90 (H-11), 1.63 (H-14), 1.65 (H-20), 1.66 (H-6α), 1.72 (H-19), 1.99 (H-8), 2.01 (H-6β), 2.03 (H-3), 2.21 (H-1), 2.23 (H-9), 2.38 (H-4), 2.62 (H-16), 2.63 (H-16), 3.06 (H-7), 3.24 (10-OMe), 3.30 (2-OMe), 3.38 (12-OMe), 3.44 (H-2), 3.46 (MPA), 4.55 (H-12), 4.95 (MPA), 5.04 (H-17), 5.20 (H-15), 5.30 (H-5), 7.40—7.49 (MPA). ^{13}C-NMR (CD_3OD) δ: 14.5, 17.9, 21.7, 25.8, 27.8, 37.5, 37.8, 38.7, 39.5, 40.6, 48.0, 48.3, 50.8, 55.9, 56.7, 57.6, 77.1, 83.6, 87.6, 102.2, 112.0, 124.2, 128.3, 128.7, 129.7, 129.9, 132.1, 135.7, 138.1, 171.8.

Secospatacetal B (2) HR-MS *m/z*: 464.2722 (Calcd for $C_{26}H_{40}O_7$: 464.2774). $[\alpha]_D$ +56.1° (*c*=0.28, methanol). ^{1}H-NMR (C_6D_6) δ: 0.98 (3H, d, *J*=7.4 Hz, H-11), 1.55 (3H, s, H-20), 1.61 (3H, s, H-14), 1.69 (3H, s, H-19), 1.71 (3H, s, 2-OAc), 1.73 (3H, s, 5-OAc), 2.00 (1H, dd, *J*=14.1, 9.0 Hz, H-6α), 2.06 (1H, dt, *J*=14.2, 4.7 Hz, H-6β), 2.08 (1H, dd, *J*=13.4, 4.8 Hz, H-3β), 2.24 (1H, m, H-8), 2.34 (1H, dd, *J*=13.8, 5.6 Hz, H-3α), 2.42 (1H, m, H-1), 2.61 (1H, t, *J*=10.5 Hz, H-9), 2.72 (1H, m, H-4), 2.73 (2H, m, H-16), 3.28 (3H, s, 10-OMe), 3.42 (3H, s, 12-OMe), 3.48 (1H, m, H-7), 4.84 (1H, d, *J*=8.4 Hz, H-12), 5.04 (1H, q, *J*=5.0 Hz, H-2), 5.17 (1H, t, *J*=7.0 Hz, H-17), 5.24 (1H, t, *J*=6.5 Hz, H-15), 5.67 (1H, t, *J*=5.0 Hz, H-5). ^{13}C-NMR (C_6D_6) δ: 13.8 (C-11), 17.7 (C-20), 20.7 (2-OAc), 20.8 (5-OAc), 21.8 (C-14), 25.7 (C-19), 27.3 (C-16), 37.85 (C-7), 37.90 (C-6), 38.6 (C-8), 40.1 (C-3), 40.6 (C-1), 46.9 (C-4), 47.8 (C-9), 50.5 (10-OMe), 55.7 (12-OMe), 74.6 (C-5), 79.6 (C-2), 101.8 (C-12), 110.5 (C-10), 123.6 (C-17), 127.9 (C-15), 131.5 (C-18), 135.2 (C-13), 169.3 (5-OAc), 170.0 (2-OAc).

Hydrolytic Product of Secospatacetal B ^{1}H-NMR (C_6D_6) δ: 0.96 (3H, d, J=7.3 Hz, H-11), 1.59 (3H, s, H-20), 1.69 (1H, m, H-6α), 1.70 (3H, s, H-19), 1.71 (3H, s, H-14), 1.91 (1H, m, H-3β), 1.93 (1H, m, H-6β), 2.13 (1H, dd, J=13.2, 5.2 Hz, H-3α), 2.21 (1H, m, H-1), 2.30 (1H, ddd, J=14.3, 11.1, 9.4 Hz, H-8), 2.51 (1H, ddd, J=13.0, 8.3, 4.7 Hz, H-4), 2.62 (1H, dd, J=11.1, 9.6 Hz, H-9), 2.78 (1H, m, H-16), 2.91 (1H, m, H-16), 3.30 (3H, s, 10-OMe), 3.45 (3H, s, 12-OMe), 3.53 (1H, dt, J=5.3, 9.1 Hz, H-7), 3.78 (1H, q, J=5.1 Hz, H-2), 4.29 (1H, t, J=4.8 Hz, H-5), 5.10 (1H, d, J=8.3 Hz, H-12), 5.24 (1H, t, J=7.1 Hz, H-17), 5.28 (1H, t, J=7.3 Hz, H-15). ^{13}C-NMR (C_6D_6) δ: 14.1 (C-11), 17.8 (C-20), 22.0 (C-14), 25.7 (C-19), 27.4 (C-16), 37.7 (C-8), 37.8 (C-7), 40 8 (C-6), 42.7 (C-3), 43.6 (C-1), 48.1 (C-9), 48.5 (C-4), 50.3 (10-OMe), 55.4 (12-OMe), 71.5 (C-5), 77.4 (C-2), 102.1 (C-12), 110.6 (C-10), 124.0 (C-17), 127.4 (C-15), 131.3 (C-18), 135.8 (C-13).

(*R*)-MPA Ester of Secospatacetal B ^{1}H-NMR (CD_3OD) δ: 0.91 (H-11), 1.67 (H-14 and H-20), 1.73 (H-19), 1.91 (H-3), 1.94 (H-8), 1.98 (H-6α), 2.16 (H-6β), 2.22 (H-4), 2.23 (H-9), 2.24 (H-1), 2.70 (H-16), 2.74 (H-16), 2.92 (10-OMe), 3.01 (12-OMe), 3.42 (MPA), 3.43 (MPA), 3.44 (H-7), 3.84 (H-12), 4.81 (H-2), 4.83 (MPA), 4.93 (MPA), 5.05 (H-17), 5.24 (H-15), 5.36 (H-5), 7.37—7.47 (MPA). ^{13}C-NMR (CD_3OD) δ: 14.0, 17.9, 21.8, 25.8, 27.8, 37.9, 38.1, 38.6, 39.4, 41.6, 48.1, 48.6, 50.6, 55.7, 76.7, 81.9, 83.5, 83.7, 101.9, 111.5, 124.2, 128.3, 128.4, 128.8, 129.6, 129.7, 129.9, 130.0, 132.5, 135.9, 137.8, 138.3, 171.8, 172.2.

(*S*)-MPA Ester of Secospatacetal B ^{1}H-NMR (CD_3OD) δ: 0.78 (H-11), 1.53 (H-14), 1.59 (H-20), 1.64 (H-6α), 1.69 (H-19), 1.89 (H-8), 1.97 (H-6β), 2.01 (H-1), 2.08 (H-3β), 2.11 (H-9), 2.18 (H-3α), 2.33 (H-4), 2.44 (H-16), 2.48 (H-16), 2.93 (H-7), 3.23 (10-OMe), 3.38 (12-OMe), 3.41 (MPA), 3.45 (MPA), 4.53 (H-12), 4.83 (MPA), 4.85 (H-2), 4.86 (H-17), 4.94 (MPA), 4.99 (H-15), 5.28 (H-5), 7.36—7.45 (MPA). ^{13}C-NMR (CD_3OD) δ: 14.0, 17.9, 21.7, 25.8, 27.6, 37.3, 37.5, 38.6, 39.7, 41.6, 48.0, 48.6, 50.9, 56.0, 77.0, 81.7, 83.6 (x2), 102.2, 111.9, 124.1, 128.2, 128.3, 128.7, 129.68, 129.73, 129.8, 129.9, 132.3, 135.2, 137.9, 138.1, 171.7, 172.2.

Secospatacetal C (3) HR-MS m/z: 436.2813 (Calcd for $C_{25}H_{40}O_6$: 436.2825). ^{1}H-NMR (C_6D_6) δ: 1.10 (3H, d, J=7.3 Hz, H-11), 1.55 (3H, s, H-20), 1.63 (3H, s, H-14), 1.67 (3H, s, H-19), 1.72 (3H, s, 5-OAc), 1.997 (1H, m, H-3α), 2.002 (1H, m, H-6α), 2.10 (1H, dt, J=15.5, 5.4 Hz, H-6β), 2.24 (1H, dd, J=11.2, 7.2 Hz, H-9), 2.42 (1H, m, H-8), 2.47 (1H, m, H-3β), 2.51 (1H, m, H-1), 2.68 (1H, ddd, J=14.5, 8.3, 4.8 Hz, H-4), 2.77 (1H, m, H-16), 2.79 (1H, m, H-16), 3.13 (3H, s, 2-OMe), 3.30 (3H, s, 10-OMe), 3.43 (3H, s, 12-OMe), 3.53 (1H, dt, J=5.6, 9.2 Hz, H-7), 3.67 (1H, dt, J=11.3, 6.3 Hz, H-2), 4.89 (1H, d, J=8.3 Hz, H-12), 5.19 (1H, t, J=7.0 Hz, H-17), 5.27 (1H, t, J=7.2 Hz, H-15), 5.71 (1H, t, J=4.9 Hz, H-5). ^{13}C-NMR (C_6D_6) δ: 8.9 (C-11), 17.7 (C-20), 20.7 (5-OAc), 21.9 (C-14), 25.7 (C-19), 27.3 (C-16), 36.4 (C-1), 37.49 (C-3), 37.50 (C-7), 37.6 (C-6), 38.4 (C-8), 47.2 (C-4), 49.2 (C-9), 50.1 (10-OMe), 55.7 (12-OMe), 56.5 (2-OMe), 75.0 (C-5), 80.5 (C-2), 102.1 (C-12), 108.7 (C-10), 123.8 (C-17), 127.7 (C-15), 131.3 (C-18), 135.3 (C-13), 169.3 (5-OAc).

(*R*)-2NMA Ester of Secospatacetal C ^{1}H-NMR (CD_3OD) δ: 0.66 (H-11), 1.39 (H-3), 1.63 (H-14), 1.66 (H-20), 1.72 (H-19), 1.82 (H-9), 1.98 (H-6 and H-8), 2.17 (H-6), 2.18 (H-4), 2.23 (H-3), 2.26 (H-1), 2.70 (H-16), 2.80 (12-OMe), 3.07 (10-OMe), 3.30 (2-OMe), 3.42 (H-7), 3.50 (2NMA), 3.57 (H-2), 3.83 (H-12), 5.07 (H-17), 5.13 (2NMA), 5.23 (H-15), 5.35 (H-5), 7.91—8.00 (2NMA).

Secospatacetal D (4) HR-MS Found 404.2557 (Calcd for $C_{24}H_{36}O_5$: 404.2563). ^{1}H-NMR (C_6D_6) δ: 1.01 (3H, d, J=7.3 Hz, H-11), 1.55 (3H, s, H-20), 1.62 (3H, s, H-14), 1.67 (3H, s, H-19), 1.71 (3H, s, 5-OAc), 2.01 (1H, dd, J=15.6, 9.1 Hz, H-6α), 2.13 (1H, dt, J=15.5, 5.4 Hz, H-6β), 2.37 (1H, ddd, J=14.5, 11.0, 9.5 Hz, H-8), 2.54 (1H, dd, J=11.1, 8.5 Hz, H-9), 2.70 (1H, m, H-16), 2.80 (1H, m, H-16), 2.81 (1H, m, H-1), 2.82 (1H, m, H-4), 3.42 (3H, s, 10-OMe), 3.48 (3H, s, 12-OMe), 3.54 (1H, dt, J=5.0, 9.3 Hz, H-7), 4.94 (1H, d, J=8.3 Hz, H-12), 5.16 (1H, t, J=7.0 Hz, H-17), 5.23 (1H, t, J=6.7 Hz, H-15), 5.73 (1H, t, J=4.9 Hz, H-5), 5.81 (1H, dd, J=5.9, 2.6 Hz, H-2), 6.05 (1H, dd, J=5.9, 1.6 Hz, H-3). ^{13}C-NMR (C_6D_6) δ: 17.6 (C-11), 17.7 (C-20), 20.6 (5-OAc), 21.8 (C-14), 25.7 (C-19), 27.2 (C-16), 37.5 (C-6), 37.9 (C-7), 38.8 (C-8), 40.6 (C-1), 47.3 (C-4), 47.5 (C-9), 50.7 (10-OMe), 55.7 (12-OMe), 74.9 (C-5), 101.9 (C-12), 114.0 (C-10), 123.8 (C-17), 127.3 (C-3), 128.0 (C-15), 131.3 (C-18), 135.4 (C-13), 141.5 (C-2), 169.3 (5-OAc).

Hydrolytic Product of Secospatacetal D ^{1}H-NMR (C_6D_6) δ: 1.01 (3H, d, J=7.3 Hz, H-11), 1.58 (3H, s, H-20), 1.66 (1H, dd, J=14.9, 9.1 Hz, H-6α), 1.69 (3H, s, H-19), 1.71 (3H, s, H-14), 1.97 (1H, dt, J=14.9, 5.3 Hz, H-6α), 2.44 (1H, ddd, J=14.2, 11.0, 9.3 Hz, H-8), 2.55 (1H, dd, J=11.1, 8.4 Hz, H-9), 2.66 (1H, ddd, J=14.3, 8.4, 4.6 Hz, H-4), 2.76 (1H, m, H-16), 2.84 (1H, m, H-1), 2.87 (1H, m, H-16), 3.44 (3H, s, 10-OMe), 3.49 (3H, s, 12-OMe), 3.54 (1H, dt, J=5.1, 9.2 Hz, H-7), 4.32 (1H, t, J=5.0 Hz, H-5), 5.17 (1H, d, J=8.3 Hz, H-12), 5.21 (1H, t, J=7.0 Hz, H-17), 5.27 (1H, t, J=6.7 Hz, H-15), 5.83 (1H, dd, J=5.9, 2.6 Hz, H-2), 6.07 (1H, dd, J=6.0, 1.6 Hz, H-3). ^{13}C-NMR (C_6D_6) δ: 17.6 (C-11), 17.7 (C-20), 22.0 (C-14), 25.7 (C-19), 27.3 (C-16), 37.6 (C-8), 37.9 (C-7), 40.3 (C-6), 40.7 (C-1), 47.5 (C-9), 48.5 (C-4), 50.6 (10-OMe), 55.4 (12-OMe), 71.7 (C-5), 102.2 (C-12), 114.0 (C-10), 124.0 (C-17), 127.3 (C-3), 127.4 (C-15), 129.0 (C-18), 135.9 (C-13), 141.4 (C-2).

(R)-2NMA Ester of Secospatacetal D ^{1}H-NMR (CD_3OD) δ: 0.88 (H-11), 1.65 (H-14 and H-20), 1.72 (H-19), 2.00 (H-6), 2.03 (H-8), 2.13 (H-9), 2.21 (H-6), 2.38 (H-4), 2.67 (H-16), 2.73 (H-1), 2.78 (H-16), 2.80 (12-OMe), 3.19 (10-OMe), 3.47 (H-7), 3.49 (2NMA), 4.01 (H-12), 5.06 (H-17), 5.11 (2NMA), 5.25 (H-15), 5.36 (H-5), 5.86 (H-3), 5.97 (H-2), 7.53—8.01 (2NMA).

Secospatacetal E (5) HR-MS Found 406.2690 (Calcd for $C_{24}H_{38}O_5$: 406.2719). $[\alpha]_D$ +59.4° (c=0.13, methanol). ^{1}H-NMR (C_6D_6) δ: 1.00 (3H, d, J=6.5 Hz, H-11), 1.38 (1H, m, H-2α), 1.56 (3H, s, H-20), 1.64 (3H, s, H-14), 1.68 (3H, s, H-19), 1.68 (1H, m, H-2β), 1.71 (3H, s, 5-OAc), 1.91 (2H, dd, J=7.9, 6.1 Hz, H-3), 2.01 (1H, dd, J=15.5, 9.0 Hz, H-6α), 2.09 (1H, dt, J=15.6, 5.5 Hz, H-6β), 2.27 (1H, m, H-1), 2.28 (1H, m, H-8), 2.30 (1H, m, H-9), 2.73 (1H, m, H-4), 2.76 (1H, m, H-16), 2.84 (1H, m, H-16), 3.33 (3H, s, 10-OMe), 3.46 (3H, s, 12-OMe), 3.54 (1H, dt, J=5.3, 8.7 Hz, H-7), 4.91 (1H, d, J=8.3 Hz, H-12), 5.20 (1H, t, J=7.0 Hz, H-17), 5.25 (1H, t, J=7.2 Hz, H-15), 5.72 (1H, t, J=4.9 Hz, H-5). ^{13}C-NMR (C_6D_6) δ: 15.9 (C-11), 17.7 (C-20), 20.7 (5-OAc), 21.9 (C-14), 25.7 (C-19), 27.3 (C-16), 31.8 (C-2), 33.9 (C-3), 35.0 (C-1), 37.86 (C-7), 37.88 (C-6), 39.0 (C-8), 47.3 (C-4), 50.1 (10-OMe), 50.3 (C-9), 55.6 (12-OMe), 74.9 (C-5), 101.9 (C-12), 112.7 (C-10), 123.8 (C-17), 127.6 (C-15), 131.3 (C-18), 135.5 (C-13), 169.3 (5-OAc).

(*R*)-1NMA Ester of Secospatacetal E ^{1}H-NMR (CD_3OD) δ: 0.73 (H-11), 1.21 (H-2α), 1.52 (H-3α), 1.56 (H-2β), 1.59 (H-8), 1.61 (H-14), 1.68 (H-20), 1.73 (H-19), 1.74 (H-3β), 1.83 (H-9), 1.97 (H-6α), 2.06 (H-1), 2.10 (H-4), 2.11 (H-6β), 2.66 (12-OMe), 2.67 (H-16), 2.75 (H-16), 3.04 (10-OMe), 3.36 (H-12), 3.35 (H-7), 3.49 (1NMA), 5.06 (H-17), 5.18 (H-15), 5.30 (H-5), 5.63 (1NMA), 7.53-8.41 (1NMA).

Spatane Diterpenoid (6) ^{1}H-NMR ($CDCl_3$) δ: 0.80 (3H, d, J=6.7 Hz, H-11), 1.14 (3H, s, H-12), 1.28 (1H, m, H-2), 1.52 (1H, dt, J=7.1, 13.3 Hz, H-3), 1.61 (3H, s, H-20), 1.67 (3H, s, H-19), 1.75 (3H, s, H-14), 1.78 (1H, m, H-2), 1.83 (1H, m, H-6α), 1.84 (1H, m, H-8), 2.00 (3H, s, 10-OAc), 2.11 (1H, m, H-1), 2.25 (1H, m, H-6β), 2.38 (1H, t, J=5.8 Hz, H-9), 2.53 (1H, dd, J=9.9, 6.3 Hz, H-3), 2.65 (1H, m, H-16), 2.70 (1H, m, H-16), 3.29 (1H, dt, J=12.5, 6.2 Hz, H-7), 3.94 (1H, d, J=4.5 Hz, H-5), 5.07 (1H, t, J=7.2 Hz, H-17), 5.19 (1H, t, J=7.2 Hz). ^{13}C-NMR ($CDCl_3$) δ: 13.5 (C-12), 13.6 (C-11), 17.6 (C-20), 21.1 (10-OAc), 23.7 (C-14), 25.6 (C-19), 26.8 (C-16), 33.1 (C-2), 34.5 (C-1), 34.9 (C-3), 37.6 (C-6), 40.5 (C-7), 42.9 (C-8), 46.2 (C-9), 51.7 (C-4), 75.5 (C-5), 88.7 (C-10), 123.2 (C-17), 126.4 (C-15), 131.2 (C-18), 133.6 (C-13), 170.5 (10-OAc).

Compound 8 ^{1}H-NMR ($CDCl_3$) δ: 0.80 (3H, d, J=6.1 Hz, H-11), 1.03 (3H, s, H-12), 1.26 (1H, m, H-2), 1.43 (1H, dt, J=6.7, 13.0 Hz, H-3), 1.61 (3H, s, H-20), 1.67 (3H, s, H-19), 1.76 (3H, s, H-14), 1.78 (1H, m, H-2), 1.80 (1H, m, H-8), 1.84 (1H, dd, J=12.0, 6.0 Hz, H-6α), 2.11 (1H, m, H-1), 2.12 (1H, m, H-9), 2.13 (m, H-3), 2.36 (1H, dt, J=4.5, 12.0 Hz, H-6β), 2.66 (1H, m, H-16), 2.73 (1H, m, H-16), 3.26 (1H, dt, J=12.0, 6.3 Hz, H-7), 4.39 (1H, d, J=4.5 Hz, H-5), 5.08 (1H, t, J=7.2 Hz, H-17), 5.18 (1H, t, J=7.1 Hz, H-15). ^{13}C-NMR ($CDCl_3$) δ: 12.9 (C-12), 13.9 (C-11), 17.6 (C-20), 23.9 (C-14), 25.6 (C-19), 26.8 (C-16), 33.3 (C-2), 35.3 (C-1), 38.3 (C-6), 38.4 (C-3), 40.7 (C-7), 42.3 (C-8), 49.0 (C-9), 51.5 (C-4), 74.9 (C-5), 82.1 (C-10), 123.4 (C-17), 126.2 (C-15), 131.1 (C-18), 133.9 (C-13).

Compound 9 ^{1}H-NMR ($CDCl_3$) δ: 0.79 (3H, d, J=6.7 Hz, H-11), 1.10 (3H, s, H-12), 1.17 (1H, m, H-2), 1.61 (3H, s, H-20), 1.65 (1H, m, H-3), 1.68 (3H, s, H-19), 1.74 (3H, s, H-14), 1.75 (1H, m, H-8), 1.76 (1H, m, H-2), 1.96 (dd, J=13.3, 6.3 Hz, H-3), 2.05 (1H, dt, J=10.2, 12.8 Hz, H-6β), 2.17 (1H, m, H-1), 2.26 (1H, dt, J=12.4, 6.2 Hz, H-6α), 2.35 (1H, t, J=5.5 Hz, H-9), 2.62 (1H, m, H-16), 2.66 (1H, m, H-16), 2.94 (1H, dt, J=12.5, 6.1 Hz, H-7), 4.21 (1H, dd, J=10.0, 6.9 Hz, H-5), 5.05 (1H, t, J=7.1 Hz, H-17), 5.18 (1H, t, J=7.2 Hz, H-15).

(*R*)-MPA Ester of Compound 8 ^{1}H-NMR ($CDCl_3$) δ: 0.46 (H-12), 0.76 (H-11), 1.15 (H-2), 1.39 (H-3), 1.65 (H-20), 1.70 (H-8), 1.71 (H-19), 1.72 (H-2), 1.73 (H-14), 1.84 (H-6), 1.97 (H-3), 2.07 (H-1), 2.10 (H-9), 2.40 (H-6), 2.61 (H-16), 2.73 (H-16), 3.11 (H-7), 3.40 (MPA), 4.72 (MPA), 5.10 (H-17), 5.20 (H-15), 5.51 (H-5), 7.28—7.43 (MPA).

(S)-MPA Ester of Compound 8 ^{1}H-NMR ($CDCl_3$) δ: 0.78 (H-11), 0.88 (H-12), 1.23 (H-2), 1.45 (H-3), 1.61 (H-6), 1.64 (H-20), 1.68 (H-14), 1.70 (H-19), 1.76 (H-2), 1.77 (H-8), 2.07 (H-3), 2.09 (H-1), 2.10 (H-9), 2.32 (H-6), 2.57 (H-16), 2.66 (H-16), 2.99 (H-7), 3.42 (MPA), 4.75 (MPA), 5.07 (H-

17), 5.15 (H-15), 5.51 (H-5), 7.29—7.43 (MPA).

References

1) Faulkner D. J., *Nat. Prod. Rep.*, **14**, 259—302 (1997).
2) Ohtani I., Kusumi T., Kashman Y., Kakisawa H., *J. Am. Chem. Soc.*, **113**, 4092—4096 (1991).
3) Faulkner D. J., *Nat. Prod. Rep.*, **13**, 75—125 (1996).
4) *a*) Finer J., Clardy J., Fenical W., Minale L., Riccio R., Battaile J., Kirkup M., Moore R. E., *J. Org. Chem.*, **44**, 2044—2047 (1979); *b*) Ishitsuka M., Kusumi T., Kakisawa H., *Tetrahedron Lett.*, **23**, 3179—3180 (1982); *c*) Ishitsuka M., Kusumi T., Kakisawa H., Kawakami Y., Nagai Y., Sato T., *J. Org. Chem.*, **48**, 1937—1938 (1983); *d*) Ishitsuka M., Kusumi T., Kakisawa H., *ibid.*, **53**, 5010—5013 (1988).
5) *a*) Tanaka J., Higa T., *Chemistry Lett.*, **1984**, 231—232; *b*) Ukongolo D. M., Kusumi T., Ishitsuka M., Kakisawa H., *Heterocycles*, **22**, 2301—2307 (1984).
6) *a*) Trost B. M., Curran D. P., *Tetrahedron Lett.*, **22**, 4929—4932 (1981); *b*) Trost B. M., Belletire J. L., Godleski S., McDougal P. G., Balkovec J. M., *J. Org. Chem.*, **51**, 2370—2374 (1986).
7) *a*) Kusumi T., Takahashi H., Xu P., Fukushima T., *Tetrahedron Lett.*, **35**, 4397—4400 (1994); *b*) Kusumi T., Takahashi H., Hashimoto T., Asakawa Y., *Chemistry Lett.*, **1994**, 1093—1094; *c*) Hashimoto T., Kusumi T., Takahashi H., Asakawa Y., *Chem. Pharm. Bull.*, **42**, 1531—1533 (1994); *d*) Takahashi H., Kusumi T., Kan Y., Satake M., Yasumoto T., *Tetrahedron Lett.*, **37**, 7087—7090 (1996); *e*) Ichikawa A., Takahashi H., Ooi T., Kusumi T., *Biosci. Biotech. Biochem.*, **61**, 881—883 (1997).
8) *a*) Seco J. M., Latypov Sh. K., Quinoa E., Riguera R., *Tetrahedron Lett.*, **35**, 2921—2924 (1994); *b*) Latypov Sh. K., Seco J. M., Quinoa E., Riguera R., *J. Org. Chem.*, **60**, 504—515 (1995).
9) Yamase H., Ooi T., Kusumi T. *Tetrahedron Lett.*, **39**, 8113—8116 (1998).
10) Ravi B. M., Wells R. J., *Aust. J. Chem.*, **35**, 129—144 (1982).
11) *a*) Gerwick W. H., Fenical W., Engen D. V., Clardy J., *J. Am. Chem. Soc.*, **102**, 7993—7994 (1980); *b*) Gerwick W. H., Fenical W., *J. Org. Chem.*, **48**, 3325—3329 (1983).