Pacovatinins A−C, New Labdane Diterpenoids from the Seeds of *Renealmia exaltata*

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Three new labdane diterpenoids, pacovatinins A−C (**1**−**3**), were isolated from seeds of the Brazilian medicinal plant *Renealmia exaltata* ("Pacová-catinga"), and their structures including absolute configurations were elucidated by spectroscopic data and a modified Mosher method.

Brazilian medicinal plants have proven to be a rich source of compounds that might be useful for the development of new pharmaceutical agents.[1] In our search for structurally unique compounds from Brazilian medicinal plants, chapecoderins A−C[2], labdane-derived diterpenoids, and echinophyllins A−F,[3,4] nitorogen-containing clerodane diterpenoids, have been isolated from the leaves of *Echinodorus macrophyllus*. Recent investigation on extracts from seeds of the Brazilian medicinal plant *Renealmia exaltata* led to the isolation of three new labdane diterpenoids, pacovatinins A−C (**1**−**3**). This plant is known in Brazil as "Pacová-catinga" and used as a stomachic and a vermifuge. In this paper we describe the isolation and structure elucidation of **1**−**3**.

Seeds of *Renealmia exaltata* L.f. (Zingiberaceae) were extracted with MeOH. The MeOH extracts were partitioned between hexane and 90% aqueous MeOH, and the aqueous MeOH layer was partitioned with EtOAc and H_2O. The EtOAc-soluble portions were subjected to a Si gel column ($CHCl_3$−MeOH, 98:2) followed by a reversed-phase C_{18} column (MeOH−H_2O, 80:20) and reversed-phase C_{18} HPLC (MeOH−H_2O, 50:50) to afford pacovatinins A (**1**, 0.0071%), B (**2**, 0.00095%), and C (**3**, 0.00026%).

The molecular formula, $C_{20}H_{30}O_3$, of pacovatinin A (**1**) was established by HRFABMS [*m*/*z* 319.2276 $(M + H)^+$, Δ +0.3 mmu]. The IR spectrum suggested the presence of hydroxy (3428 cm^{-1}) and unsaturated lactone carbonyl (1752 and 1675 cm^{-1}) groups, while the UV absorption at 226 nm also supported that **1** possessed an unsaturated lactone moiety. The gross structure of **1** was deduced from detailed analysis of the ^1H and ^{13}C NMR data (Table 1) aided with 2D NMR experiments ($^1H-^1H$ COSY, HMQC, and HMBC). The ^{13}C NMR data indicated that the molecule possessed one unsaturated ester carbonyl, one trisubstituted olefin, one exomethylene, two sp^3 quaternary carbons, seven methylenes (one of them bearing an oxygen atom), three methines (one of them bearing an oxygen atom), and three methyl groups. Since four of six unsaturations were thus accounted for, it was suggested that **1** contained two rings. The $^1H-^1H$ COSY spectrum revealed connectivities of C-1 to C-3, C-5 to C-7, C-9 to C-12, and C-14 to C-15. HMBC correlations (Figure 1) of H_3-18 and H_3-19 to C-3, C-4 (δ_C 34.4), and C-5 (δ_C 54.1) and H_3-20 to C-1, C-5, and C-10 (δ_C 40.1) suggested the presence of a cyclohexane ring (ring A) with Me-18 and Me-19 at C-4 and Me-20 at C-10, while those of H_2-17 to C-7 and C-9 (δ_C 55.7) and H_2-6 to C-8 (δ_C 151.6) indicated the presence of another cyclohexane ring (ring B) with an exomethylene (C-17) at C-8. A hydroxy group was connected to C-7, judging from the chemical shift (δ_C 74.2) of C-7. HMBC correlations of H_2-15 to C-13 (δ_C 126.7) and C-16 (δ_C 173.6), H-12 to C-14 and C-16, and H_2-11 to C-13 revealed the presence of a γ-lactone ring (C-13−C-15, C-16, and O-15) connected to C-12 (δ_C 142.6). Geometry of the trisubstituted olefin at C-12 was elucidated to be *E* from the NOESY correlation between H-11b and H_2-14 (Figure 2). Thus, the gross structure of pacovatinin A was elucidated to be **1**. NOESY correlations of H_3-20 to H-2a and H-6b, and H-5 to H-3a, indicated β-orientation of Me-20, α-orientation of H-5, and a *trans* relationship between Me-20 and H-5. Both α-orientations of H-7 and H-9 were deduced from NOESY correlations of H-5 to H-7, H-7 to H-9, and H_3-20 to H-11a. Chair conformations of rings A and B were also elucidated from other NOESY correlations, as shown in Figure 2. The absolute configuration at C-7 of **1** was determined by a modified Mosher method[5] as follows. Treatment of **1** with (*R*)-(−)- and (*S*)-(+)-2-methoxy-2-trifluoromethylphenylacetyl chloride (MTPACl) afforded the corresponding (*S*)-(−)- and (*R*)-(+)-MTPA esters (**4** and **5**, respectively). The values of $\Delta\delta$ [δ(*S*-MTPA ester) − δ(*R*-MTPA ester)] in the ^1H NMR (Figure 3) spectra suggested that the absolute configuration at C-7 of **1** was *S*. Thus, the structure of pacovatinin A was assigned as **1**.

The molecular formula, $C_{20}H_{30}O_4$, of pacovatinin B (**2**) was established by HRFABMS [*m*/*z* 335.2211 $(M + H)^+$, Δ −1.1 mmu], indicating that **2** was an oxygenated form of **1**. The ^{13}C NMR data indicated that **2** possessed one unsaturated ester carbonyl, one trisubstituted olefin, one exomethylene, two sp^3 quaternary carbons, six methylenes (one of them bearing an oxygen atom), four methines (two of them bearing an oxygen atom), and three methyl groups. ^1H and ^{13}C NMR data of **2** were similar to those of **1**. Comparison of the ^1H and ^{13}C NMR spectra of **2** with those of **1** revealed that a methylene (δ_H 1.43 and 1.21, H_2-3; δ_C 43.1, C-3) in **1** was replaced by an oxymethine (δ_H 3.28, H-3; δ_C 78.4, C-3) in **2**. The presence of a hydroxy group at C-3 was deduced from the $^1H-^1H$ COSY correlation of H_2-2 to H-3 and HMBC correlations (Figure 4) of H_3-18 and H_3-19 to C-3. HMBC correlations of H_2-15 to C-13 (δ_C 124.9) and C-16 (δ_C 170.8), H-12 to C-14 and C-16, and H_2-11 to C-13 revealed the presence of a γ-lactone ring (C-13−C-15, C-16, and O-15) connected to C-12 (δ_C 140.9). NOESY

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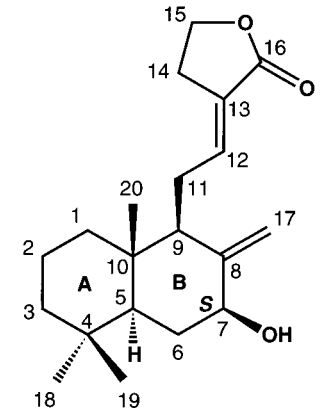

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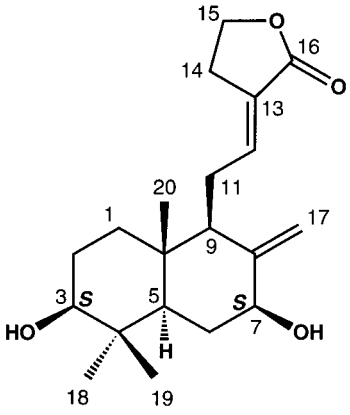

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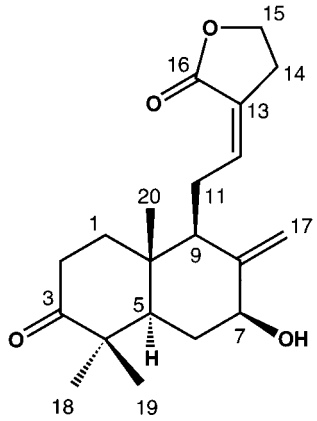

3

correlations (Figure 5) of H_3-20 to H-2a and H-6b, and H-5 to H-3a, indicated β-orientation of Me-20, α-orientation of H-5, and a *trans* relationship between Me-20 and H-5. The α-orientations of H-3, H-7, and H-9 were deduced from NOESY correlations of H-3 to H-5, H-5 to H-7, H-7 to H-9, and H_3-20 to H-11a. Geometry of the trisubstituted olefin at C-12 was elucidated to be *E* from the NOESY correlation between H-11b and H_2-14. Treatment of **2** with (*R*)-(−)- and (*S*)-(+)-MTPACl afforded the corresponding bis-(*S*)-(−)- and bis-(*R*)-(+)-MTPA esters (**6** and **7**, respectively). The values of $\Delta\delta$ [δ(*S*-MTPA ester) − δ(*R*-MTPA ester)] in the ^{1}H NMR (Figure 6) spectra suggested that the absolute configurations at C-3 and C-7 of **2** were both *S*. Thus, the structure of pacovatinin B was assigned as **2**.

Pacovatinin C (**3**) showed the pseudomolecular ion peak at *m/z* 333 $(M + H)^+$ in the FABMS. HRFABMS analysis revealed the molecular formula to be $C_{20}H_{28}O_4$ [*m/z* 355.1884 $(M + Na)^+$ Δ −0.2 mmu]. IR absorptions implied that **3** possessed hydroxyl (3430 cm^{-1}), unsaturated lactone (1742 and 1645 cm^{-1}), and ketone (1732 cm^{-1}) groups. Analysis of the ^{1}H and ^{13}C NMR data and the HMQC spectrum provided one unsaturated ester carbonyl, one ketone carbonyl, one trisubstituted olefin, one exomethylene, two sp^3 quaternary carbons, six methylenes (one of them bearing an oxygen atom), three methines (one of them bearing an oxygen atom), and three methyl groups. ^{1}H and ^{13}C NMR data of **3** were similar to those of **2** except for a functional group at C-3. Detailed analysis of the ^{1}H−^{1}H COSY spectrum (Figure 7) implied connectivities of C-1 to C-2, C-5 to C-7, C-9 to C-12, and C-14 to C-15. HMBC correlations (Figure 7) of H_3-18 and H_3-19 to C-4 and C-5 (δ_C 52.0), H_2-17 to C-7 and C-9, H_3-20 to C-1, C-5, C-9, and C-10 (δ_C 38.3) and the chemical shifts (δ_H 2.64 and 2.45, H_2-2; δ_C 33.2, C-2) indicated that **3** possessed a decaline skeleton with a ketone at C-3, Me-18 and Me-19 at C-4, a hydroxy group at C-7, an exomethylene at C-8, and Me-20 at C-10. HMBC correlations of H_2-15 to C-13 (δ_C 125.0) and C-16 (δ_C 169.9), H-12 to C-14 and C-16, and H_2-11 to C-13 revealed the presence of a γ-lactone ring (C-13−C-15, C-16, and O-15) connected to C-12 (δ_C 139.8). Geometry of the trisubstituted olefin at C-12 was elucidated to be *Z* from the NOESY correlation between H-12 and H_2-14 (Figure 8). The relative stereochemistry of **3** was deduced from NOESY correlations. Thus, the structure of pacovatinin C was elucidated to be **3**.

Pacovatinins A−C (**1**−**3**) are the first labdane diterpenoids possessing a γ-lactone conjugated with an *exo*-olefin group from *Renealmia exaltata*, although some labdane diterpenoids have been reported from other species of the genus *Renealmia*.[6,7] It is noted that the double bonds at C-12 in **1** and **2** are both *E*, while that of **3** is *Z*. Pacovatinins A (**1**) and C (**3**) exhibited cytotoxicity[8] against murine lymphoma L1210 cells with IC_{50} values of 3.2 and 4.7 μg/mL, respectively, and human epidermoid carcinoma KB cells with IC_{50} values of 9.8 and 7.3 μg/mL, respectively, while pacovatinin B (**2**) showed no cytotoxicity (IC_{50} >10 μg/mL).

Experimental Section

General Experimental Procedures. Optical rotations were determined on a JASCO P-1030 polarimeter. UV and IR spectra were obtained on JASCO Ubest-35 and JASCO FT/IR-230 spectrometers, respectively. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX-500 spectrometer. The 3.35 and 49.8 ppm resonances of residual CD_3OD and the 7.26 and 77.0 ppm resonances of residual $CDCl_3$ were used as internal references for ^{1}H and ^{13}C NMR spectra, respectively. FAB mass spectra were measured on a JEOL HX-110 spectrometer using a glycerol matrix.

Plant Material. Seeds of *Renealmia exaltata* ("Pacová-catinga") were purchased in São Paulo, Brazil, in March 2000. The plant was identified by Dr. G. Hashimoto (Centro de Pesquisas de História Natural, São Paulo, Brazil), and a voucher specimen has been deposited at the Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University.

Extraction and Separation. Seeds (420 g) were extracted with MeOH (500 mL × 3), and the extracts partitioned between hexane (500 mL × 3) and 90%MeOH (500 mL). The MeOH layer was partitioned with EtOAc (500 mL × 3) and H_2O (50 mL). The EtOAc-soluble portions (4.2 g) were subjected to Si gel column chromatography ($CHCl_3$−MeOH, 98:2) to afford fraction I (1.7 g). This fraction was purified by a

Table 1. ^{1}H and ^{13}C NMR Data of Pacovatinins A (**1**), B (**2**), and C (**3**)

	1[a]		**2**[b]		**3**[b]	
position	^{1}H[c]	^{13}C[c]	^{1}H[c]	^{13}C[c]	^{1}H[c]	^{13}C[c]
1 (a)	1.74 (m)	40.2	1.73 (m)	36.8	1.99 (m)	36.5
1 (b)	1.13 (dt, 3.7 12.8)		1.18 (m)		1.60 (m)	
2 (a)	1.65 (m)	20.4	1.57 (m)	27.4	2.64 (m)	33.2
2 (b)	1.53 (m)		1.15 (m)		2.45 (m)	
3 (a)	1.43 (m)	43.1	3.28 (dd, 12.0 4.3)	78.4		213.0
3 (b)	1.21 (m)					
4		34.4		38.8		38.8
5	1.23 (m)	54.1	1.16 (m)	51.7	1.71 (m)	52.0
6 (a)	2.04 (m)	34.5	2.13 (ddd, 9.5 5.4 2.4)	32.7	2.06 (ddd, 9.5 5.4 2.4)	33.7
6 (b)	1.26 (m)		1.37 (m)		1.47 (m)	
7	3.94 (m)	74.2	4.02 (dd, 11.3 5.5)	73.2	4.04 (m)	72.2
8		151.6		149.5		148.1
9	1.86 (m)	55.7	1.79 (m)	53.7	1.88 (m)	52.9
10		40.1		39.1		38.3
11 (a)	2.45 (m)	26.2	2.36 (m)	24.9	2.38 (m)	25.3
11 (b)	2.37 (m)		2.36 (m)		2.38 (m)	
12	6.61 (m)	142.6	6.64 (dt, 9.2 6.0)	140.9	6.65 (m)	139.8
13		126.7		124.9		125.0
14	2.93 (m)	26.1	2.87 (m)	25.3	2.88 (m)	26.1
15	4.38 (t, 7.4)	67.3	4.38 (t, 7.2)	65.1	4.39 (t, 7.2)	63.8
16		173.6		170.8		169.9
17 (a)	5.23 (s)	105.0	5.22 (s)	104.4	5.30 (s)	105.0
17 (b)	4.60 (s)		4.60 (s)		4.66 (s)	
18	0.92 (s)	34.0	1.05 (s)	28.2	1.14 (s)	25.5
19	0.85 (s)	22.2	0.80 (s)	15.3	1.05 (s)	20.9
20	0.75 (s)	14.9	0.73 (s)	14.4	0.91 (s)	13.7

[a] In CD_3OD. [b] In $CDCl_3$. [c] δ in ppm.

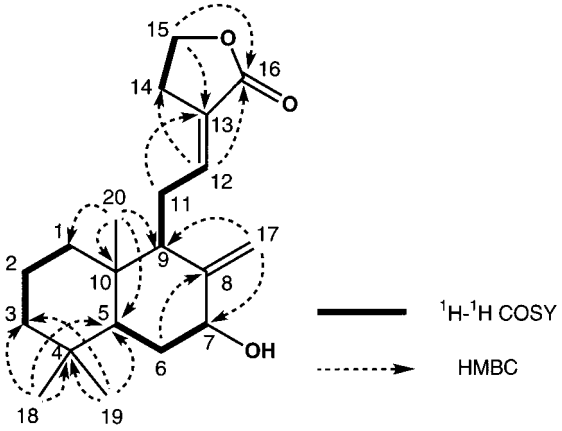

Figure 1. Selected 2D NMR data of pacovatinin A (**1**).

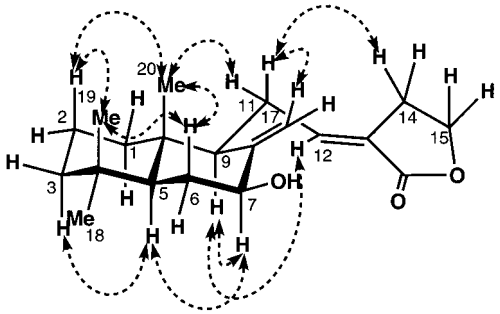

Figure 2. Relative stereochemistry of pacovatinin A (**1**). Dotted arrows denote NOESY correlations.

C_{18} columun (Cosmosil ODS, MeOH−H_2O, 80:20) to give pacovatinin A (30 mg) and fraction II (137 mg). This fraction was subjected to a Si gel column (hexane−acetone, 2:1) to give fraction III, which was purified by reversed-phase HPLC [Develosil ODS HG-5, Nomura Chemical, 1 × 25 cm, flow rate 2.5 mL/min; MeOH−H_2O (1:1) to give pacovatinins B (**2**, t_R 21.6 min, 4.0 mg) and C (**3**, t_R 16.0 min, 1.1 mg).

Pacovatinin A (1): a colorless amorphous solid; $[\alpha]^{23}_D$ +10.0° (*c* 1.00, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 226 (4.00) and 205 (3.91) nm; IR (KBr) ν_{max} 3428, 1752, and 1675 cm^{-1}; ^{1}H and ^{13}C NMR (Table 1); FABMS *m*/*z* 319 (M + H)$^+$; HRFABMS *m*/*z* 319.2276 (M + H)$^+$ (calcd for $C_{20}H_{31}O_3$, 319.2273).

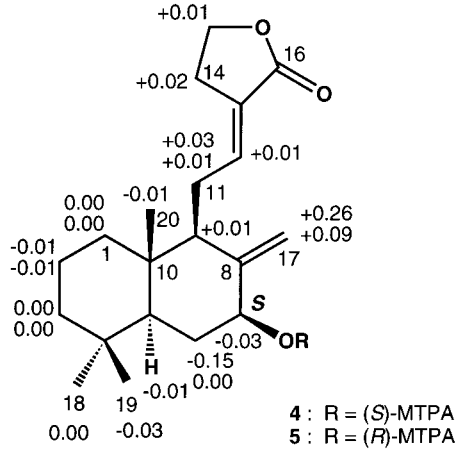

Figure 3. ^{1}H NMR chemical shift differences ($\Delta\delta$) for MTPA esters of pacovatinin A (**1**); $\Delta\delta$ (ppm) = δ[(*S*)-MTPA ester (**4**)] − δ[(*R*)-MTPA ester (**5**)].

Pacovatinin B (2): a colorless amorphous solid; $[\alpha]^{23}_D$ +5.9° (*c* 1.00, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 229 (4.03) and 209 (3.84) nm; IR (KBr) ν_{max} 3429, 1744, and 1645 cm^{-1}; ^{1}H and ^{13}C NMR (Table 1); FABMS *m*/*z* 335 (M + H)$^+$; HRFABMS *m*/*z* 335.2211 (M + H)$^+$ (calcd for $C_{20}H_{31}O_4$, 335.2222).

Pacovatinin C (3): a colorless amorphous solid; $[\alpha]^{23}_D$ +8.9° (*c* 0.50, MeOH); UV (MeOH) λ_{max} (log ϵ) 227 (4.02) and 208 (3.88) nm; IR (KBr) ν_{max} 3430, 1742, 1732, and 1645 cm^{-1}; ^{1}H and ^{13}C NMR (Table 1); FABMS *m*/*z* 355 (M + Na)$^+$; HR-FABMS *m*/*z* 355.1884 (M + Na)$^+$ (calcd for $C_{20}H_{28}O_4Na$, 355.1886).

(*S*)- and (*R*)-MTPA Esters (4 and 5) of Pacovatinin A (1). Two aliquots of pacovatinin A (**1**) (each 0.5 mg) were separately esterified with (*R*)-(−)- and (*S*)-(+)-MTPACl (each 0.9 μL), DMAP (0.01 mg), and Et_3N (0.7 μL) in CH_2Cl_2 (50 μL) at room temperature for 3.5 h, and then *N*,*N*-dimethyl-1,3-propanediamine (2 μL) was added to the reaction mixture and stirring was continued for 10 min. The reaction mixture was

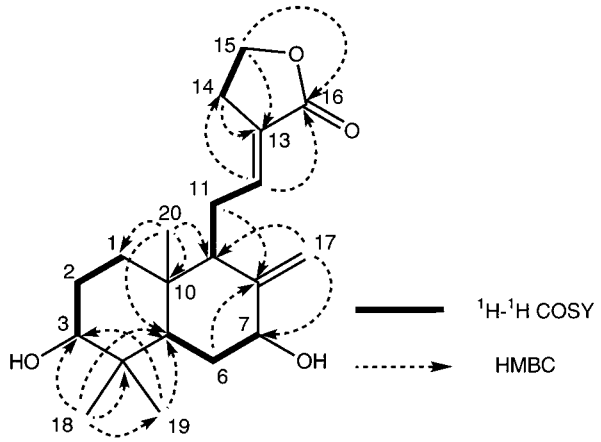

Figure 4. Selected 2D NMR data of pacovatinin B (**2**).

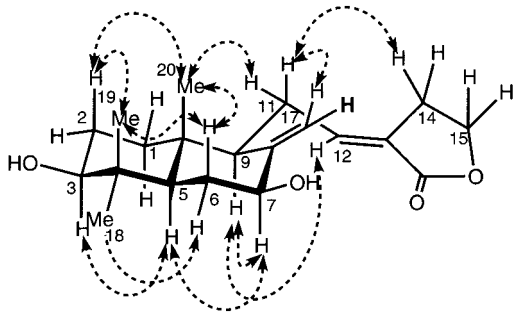

Figure 5. Relative stereochemistry of pacovatinin B (**2**). Dotted arrows denote NOESY correlations.

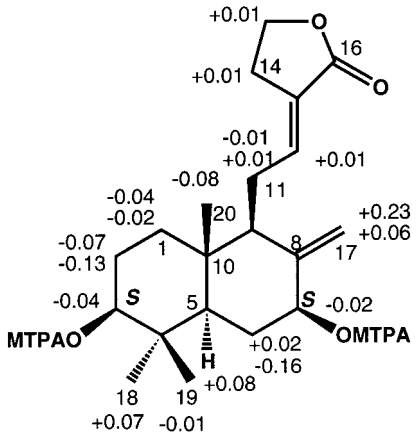

Figure 6. ^{1}H NMR chemical shift differences ($\Delta\delta$) for MTPA esters of pacovatinin B (**2**); $\Delta\delta$ (ppm) = δ[(*S*)-MTPA ester (**6**)] − δ[(*R*)-MTPA ester (**7**)].

partitioned with $CHCl_3$ (100 μL × 3) and H_2O (100 μL), and the $CHCl_3$ layer was evaporated. The residue was purified by a silica gel column (hexane−acetone, 4:1) to give the (*S*)- and (*R*)-MTPA esters (**4**, 0.5 mg, and **5**, 0.8 mg, respectively) of **1**.

Compound 4: ^{1}H NMR ($CDCl_3$) δ 1.70 (1H, m, H-1a), 1.07 (1H, m, H-1b), 1.58 (2H, m, H-2), 1.46 (1H, m, H-3a), 1.22 (1H, m, H-3b), 1.24 (1H, m, H-5), 2.15 (1H, m, H-6a), 1.34 (1H, m, H-6b), 5.35 (1H, m, H-7), 1.88 (1H, m, H-9), 2.42 (1H, m, H-11a), 2.28 (1H, m, H-11b), 6.68 (1H, m, H-12), 2.87 (2H, m, H-14), 4.39 (2H, m, H-15), 5.08 (1H, s, H-17a), 4.55 (1H, s, H-17b), 0.92 (3H, s, H-18), 0.80 (3H, s, H-19), and 0.72 (3H, s, H-20); FABMS *m*/*z* 557 (M + Na)$^+$; HRFABMS *m*/*z* 557.2538 (M + Na)$^+$ (calcd for $C_{30}H_{37}O_5F_3Na$, 557.2491).

Compound 5: ^{1}H NMR ($CDCl_3$) δ 1.70 (1H, m, H-1a), 1.07 (1H, m, H-1b), 1.59 (2H, m, H-2), 1.46 (1H, m, H-3a), 1.22 (1H, m, H-3b), 1.25 (1H, m, H-5), 2.15 (1H, m, H-6a), 1.49 (1H, m, H-6b), 5.38 (1H, m, H-7), 1.87 (1H, m, H-9), 2.41 (1H, m, H-11a), 2.25 (1H, m, H-11b), 6.67 (1H, m, H-12), 2.85 (2H, m, H-14), 4.38 (2H, m, H-15), 4.82 (1H, s, H-17a), 4.46 (1H, s, H-17b), 0.92 (3H, s, H-18), 0.83 (3H, s, H-19), and 0.73 (3H, s, H-20); FABMS *m*/*z* 557 (M + Na)$^+$; HRFABMS *m*/*z* 557.2464 (M + Na)$^+$ (calcd for $C_{30}H_{37}O_5F_3Na$, 557.2491).

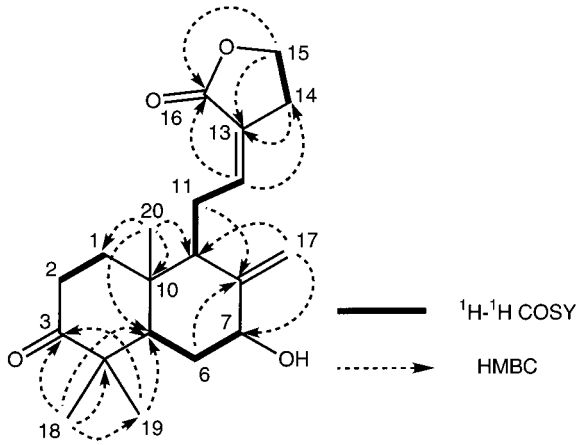

Figure 7. Selected 2D NMR data of pacovatinin C (**3**).

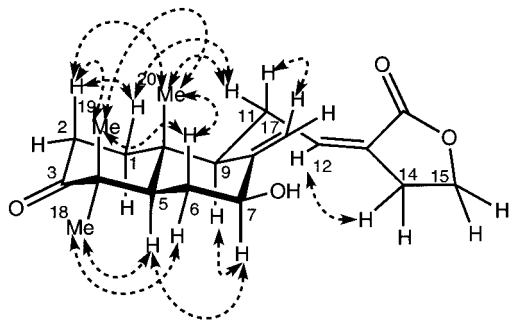

Figure 8. Relative stereochemistry of pacovatinin C (**3**). Dotted arrows denote NOESY correlations.

Bis-(*S*)- and Bis-(*R*)-MTPA Esters (6 and 7) of Pacovatinin B (2). Two aliquots of pacovatinin B (**2**) (each 0.5 mg) were separately esterified with (*R*)-(−)- and (*S*)-(+)-MTPACl (each 1.2 μL), DMAP (0.01 mg), and Et_3N (0.7 μL) in CH_2Cl_2 (50 μL) at room temperature for 3.5 h, and then *N*,*N*-dimethyl-1,3-propanediamine (2 μL) was added to the reaction mixture and stirring was continued for 10 min. The reaction mixture was partitioned with $CHCl_3$ (100 μL × 3) and H_2O (100 μL), and then the $CHCl_3$ layer was evaporated. The residue was purified by a silica gel column (hexane−acetone, 4:1) to give the bis-(*S*)- and bis-(*R*)-MTPA esters (**6**, 0.8 mg, and **7**, 0.8 mg, respectively) of **2**.

Compound 6: ^{1}H NMR ($CDCl_3$) δ 1.77 (1H, m, H-1a), 1.33 (1H, m, H-1b), 1.90 (1H, m, H-2a), 1.64 (1H, m, H-2b), 4.72 (1H, m, H-3), 1.44 (1H, m, H-5), 2.14 (1H, m, H-6a), 1.38 (1H, m, H-6b), 5.35 (1H, m, H-7), 1.87 (1H, m, H-9), 2.37 (1H, m, H-11a), 2.28 (1H, m, H-11b), 6.66 (1H, m, H-12), 2.87 (2H, m, H-14), 4.40 (2H, m, H-15), 5.11 (1H, s, H-17a), 4.56 (1H, s, H-17b), 0.93 (3H, s, H-18), 0.78 (3H, s, H-19), and 0.74 (3H, s, H-20); FABMS *m*/*z* 789 (M + Na)$^+$; HRFABMS *m*/*z* 789.2806 (M + Na)$^+$ (calcd for $C_{40}H_{44}O_8F_6Na$, 789.2838).

Compound 7: ^{1}H NMR ($CDCl_3$) δ 1.81 (1H, m, H-1a), 1.35 (1H, m, H-1b), 1.97 (1H, m, H-2a), 1.77 (1H, m, H-2b), 4.76 (1H, m, H-3), 1.36 (1H, m, H-5), 2.12 (1H, m, H-6a), 1.54 (1H, m, H-6b), 5.37 (1H, m, H-7), 1.87 (1H, m, H-9), 2.38 (1H, m, H-11a), 2.27 (1H, m, H-11b), 6.65 (1H, m, H-12), 2.86 (2H, m, H-14), 4.39 (2H, m, H-15), 4.88 (1H, s, H-17a), 4.50 (1H, s, H-17b), 0.86 (3H, s, H-18), 0.79 (3H, s, H-19), and 0.82 (3H, s, H-20); FABMS *m*/*z* 789 (M + Na)$^+$; HRFABMS *m*/*z* 789.2832 (M + Na)$^+$ (calcd for $C_{40}H_{44}O_8F_6Na$, 789.2838).

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