Brianodins A−D, Briarane-Type Diterpenoids from Soft Coral *Pachyclavularia* sp.

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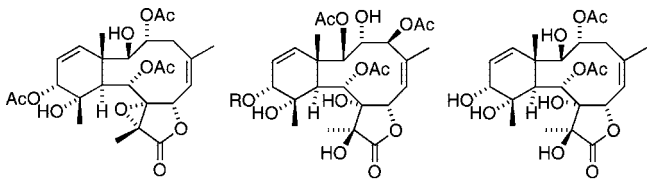
Four new briarane-type diterpenoids, brianodins A−D (**1**−**4**), were isolated from a soft coral, *Pachyclavularia* sp., and the structures and relative stereochemistry of **1**−**4** were elucidated on the basis of spectroscopic data. The absolute configurations of **3** and **4** were assigned by the MTPA method. Brianodin A (**1**) showed a modest cytotoxicity.

A characteristic feature of briarane-type diterpenoids is the presence of a highly substituted bicyclo[8.4.0]tetradecane skeleton, and most briarane diterpenoids possess a γ-lactone moiety.[1] More than 300 briarane diterpenoids have been isolated from soft corals so far,[2] and some of them show interesting biological properties such as cytotoxic,[3] anti-inflammatory,[4–6] antiviral,[6,7] insecticidal,[8] immunomodulation,[9] and multidrug resistance reversing activities.[10]

Chemical modifications of natural products such as taxane diterpenoids[11] have led to many unprecedented compounds useful for studies of structure–activity relationships. In order to obtain briarane diterpenoids for such a study, the terpenoid fractions of a soft coral *Pachyclavularia* sp. were purified. As a result, four new briarane-type diterpenoids, brianodins A−D (**1**−**4**), were isolated together with 10 known briarane diterpenoids. Herein, we describe the isolation and structure elucidation of **1**−**4**.



Results and Discussion

The soft coral *Pachyclavularia* sp. (SC-114) collected in Okinawa was extracted with MeOH, and the extract was partitioned between EtOAc and water. The EtOAc-soluble materials were subjected to passage over a silica gel column ($CHCl_3$/MeOH, 95:5, and then *n*-hexane/EtOAc, 1:3) followed by C_{18} HPLC (MeOH/H_2O, 40:60 → 70:30) to afford brianodins A−D (**1**−**4**) (**1**, 0.0032%, wet wt; **2**, 0.0006%; **3**, 0.0007%; **4**, 0.0013%) together with 10 known briarane-type diterpenoids, briarlides A,[12] G,[12] H,[12] and J[13] and violides B,[14] G,[15] J,[16] M,[16] O,[17] and P.[17]

Brianodin A (**1**) was obtained as a colorless solid, and the molecular formula, $C_{26}H_{34}O_{11}$, was established by HRFABMS (*m*/*z* 523.2178 $[M + H]^+$, Δ −0.1 mmu). The IR spectrum of **1** implied the presence of an ester (1740 cm^{-1}) functionality. The ^1H NMR spectrum of **1** revealed signals due to three acetyl methyls (δ_H 2.09, 2.14, and 2.21), an olefinic methyl (δ_H 1.94), and three tertiary methyls (δ_H 1.08, 1.24, and 1.72), and the ^{13}C NMR spectrum of **1** disclosed the presence of four carbonyl carbons (δ_C 168.4, 168.8, 169.3, and 170.1) and four olefinic carbons (δ_C 120.7, 121.1, 138.9, and 141.5) (Tables 1 and 2). The gross structure of **1** was elucidated by analysis of 2D NMR data ($^1H-^1H$ COSY, HMQC, and HMBC) (Figure 1). The presence of an 8,17-epoxide was indicated by the molecular formula and ^{13}C NMR chemical shifts of C-8 (δ_C 71.5) and C-17 (δ_C 64.8). Geometry of the trisubstituted olefin at C-5 and C-6 was assigned as *Z* from NOESY correlations of H_3-16 to H-6.

The relative stereochemistry of **1** was elucidated by ^1H coupling constants and NOESY correlations. NOESY correlations of H_3-20 to H-9 (δ_H 5.96, d, J = 3.9 Hz), H-12, and H_3-15, H-9 to H_3-18, and H_3-15 to H-3 indicated that H-3, H-12, Me-15, Me-18, and Me-20 had β-orientations and H-9 possessed an α-orientation. NOESY correlations of H-2 (δ_H 3.31, s) to H-10 and H_3-16, H_3-16 to H-4a and H-6, and H-4b to H-7 suggested that H-2, H-10, and 8,17-epoxide had α-orientations and H-7 and H-9 possessed β-orientations (Figure 2). Thus, the relative stereochemistry of brianodin A was elucidated to be **1**.

Brianodin B (**2**) was revealed to have the molecular formula $C_{28}H_{38}O_{14}$ by HRFABMS (*m*/*z* 599.2336 $[M + H]^+$, Δ −0.3 mmu). The IR spectrum of **2** suggested the presence of an ester (1740 cm^{-1}) functionality. From the ^1H and ^{13}C NMR analyses, **2** was indicated to possess four acetoxy groups, a γ-lactone moiety [δ_H 2.10 (3H, s), 2.15 (3H, s), 2.15 (3H, s), 2.21 (3H, s), δ_C 169.9, 170.9, 171.3, 172.7, 176.4] and two olefins [δ_H 5.55 (1H, d, J = 4.5 Hz), 5.68 (1H, m), 5.75 (1H, br d, J = 10.0 Hz), δ_C 121.1, 126.5, 139.4, 141.7] (Tables 1 and 2). The gross structure of **2** was elucidated from $^1H-^1H$ COSY and HMBC correlations (Figure 3). The relative stereochemistry of **2** was assigned by ^1H coupling constants and NOESY correlations. NOESY correlations of H_3-20 to H_3-15, H-12 (δ_H 5.04, d, J = 3.3 Hz) and H-9 (δ_H 6.07, d, J = 4.8 Hz) indicated that H-12, Me-15, and Me-20 had β-orientations and H-9 possessed an α-orientation. NOESY correlations of H-2 (δ_H 4.66, br s) to H-10 (δ_H 2.96, d, J = 4.8 Hz) and H_3-16, H_3-16 to H-4 and H-6, and H-3 to H-7 suggested that H-2, H-4, and H-10 were α-orientated and H-3, H-7, and H-9 were β-orientated (Figure 4). The relative configuration at C-8 and C-17 was elucidated by comparison of ^{13}C NMR chemical shifts of brianodin B (**2**) with those of violide J,[16] whose structure was determined by X-ray analysis. Thus, the relative stereochemistry of brianodin B was elucidated to be **2**.

The molecular formula, $C_{26}H_{36}O_{13}$, of brianodin C (**3**) was established by HRFABMS (*m*/*z* 557.2247 $[M + H]^+$, Δ +1.3 mmu). The IR spectrum of **3** indicated the presence of ester (1730 cm^{-1}) and γ-lactone (1650 cm^{-1}) functionalities. The ^1H NMR spectrum of **3** was similar to that of brianodin B (**2**), except that H-12 (δ_H 3.71, d, J = 6.2 Hz) was shifted upfield by 1.33 ppm (Table 1) as compared with that of **2**, indicating that an acetyl group at C-12 in **2** was absent for **3**. The relative stereochemistry of **3** was elucidated by ^1H coupling constants and NOESY correlations. The relative configuration at C-8 and C-17 was elucidated by comparison of ^{13}C NMR chemical shifts of brianodin C (**3**) with those of violide J.[16] The absolute configuration of **3** was elucidated by a modified Mosher's method[18] for the 2-methoxy-2-trifluoromethylphenylacetic

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Table 1. ^{1}H NMR Data of Brianodins A−D (**1**−**4**) (*J* in Hz)

position	**1**[a]	**2**[a]	**3**[b]	**4**[b]
2	3.31 br s	4.66 br s	4.57 br s	3.26 br s
3	5.59 dd (12.2, 5.8)	5.07 d (11.2)	4.90 d (10.6)	5.61 dd (12.2, 5.7)
4a	2.11 m	4.86 br dd (11.0, 0.8)	5.17 d (11.3)	1.88 m
4b	3.04 br dd (13.8, 3.9)			2.92 br dd (13.8, 5.3)
6	5.46 br d (9.3)	5.75 br d (10.0)	5.72 br d (10.0)	5.45 br d (9.6)
7	5.70 d (9.6)	5.93 d (10.0)	6.04 d (9.9)	5.81 d (9.8)
9	5.96 d (3.9)[c]	6.07 d (4.8)	6.20 d (4.7)	6.07 d (4.3)
10	2.52 d (3.9)	2.96 d (4.8)	3.01 d (4.7)	2.67 d (4.3)
12	4.79 d (5.9)	5.04 d (3.3)	3.71 d (6.2)	3.58 d (6.0)
13	5.95 dd (10.3, 5,9)[c]	5.68 m	5.79 dd (10.4, 6.3)	5.65 br dd (10.3, 6.0)
14	6.05 d (10.3)	5.55 d (4.5)	5.56 d (10.6)	5.78 d (10.3)
15	1.08 s	1.29 s	1.32 s	0.92 s
16	1.94 s	2.13 br d (1.6)	2.17 br d (1.1)	1.78 br s
18	1.72 s	1.45 s	1.41 s	1.25 s
20	1.24 s	1.49 s	1.43 s	1.27 s
MeCO	2.09 (s), 2.14 (s), 2.21 (s)	2.10 (s), 2.15 (s), 2.15 (s), 2.21 (s)	2.14, 2.18, 2.19	1.85 (s), 2.00 (s)

[a] In $CDCl_3$. [b] In CD_3OD. [c] Overlapping with other signals in the same column.

Table 2. ^{13}C NMR Data of Brianodins A−D (**1**−**4**)

position	**1**[a]	**2**[a]	**3**[b]	**4**[b]
1	48.0	47.0	49.0	49.9
2	77.7	78.4	79.8	79.6
3	71.7	70.8	72.8	75.0
4	33.9	77.1	80.5	35.6
5	138.9	139.4	141.8	139.8
6	120.7	126.5	128.2	124.9[c]
7	74.0	79.3[d]	80.1	81.8
8	71.5	79.3[d]	81.2	81.7[d]
9	65.0	65.6	68.4	68.8
10	44.1	39.6	40.8	41.4
11	72.0	75.8	77.1	77.0
12	73.0	72.2	72.3	73.2
13	121.1	121.1	126.4	124.6[c]
14	141.5	141.7	140.9	142.7
15	13.4	16.8	17.1	15.8
16	27.4	25.9	26.9	35.6
17	64.8	80.2	81.7	81.7[d]
18	9.5	15.6	16.8	17.0
19	170.1	176.4	179.4	179.6
20	21.0	23.6	23.8	23.6
MeCO	20.6, 20.8, 20.8	21.0, 21.2, 21.4, 22.3	21.5, 21.8, 23.1	23.1, 22.0
MeCO	168.4, 168.8, 169.3	169.9, 170.9, 171.3, 172.7	173.1, 173.1, 173.4	173.0, 173.5

[a] In $CDCl_3$. [b] In CD_3OD. [c] Data interchangeable. [d] Overlapping with other signals in the same column.

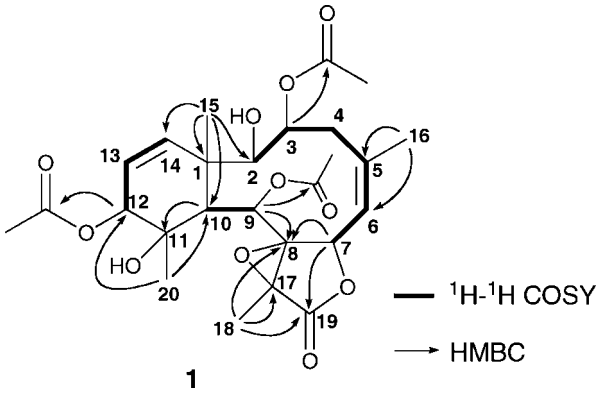

Figure 1. Selected 2D NMR correlations for brianodin A (**1**).

acid (MTPA) esters at C-12 of **3**, due to steric hindrance at C-2. The values of $\Delta\delta$ [δ(*S*-MTPA ester) − δ(*R*-MTPA ester)] for H-2, H-3, H-4, H-13, and H-14 were positive, while the values of $\Delta\delta$ for H-6, H-7, H-9, and H-10 were negative, suggesting that the absolute configuration at C-12 was *R*. Thus, the absolute configuration of **3** was assigned as shown in Figure 5.

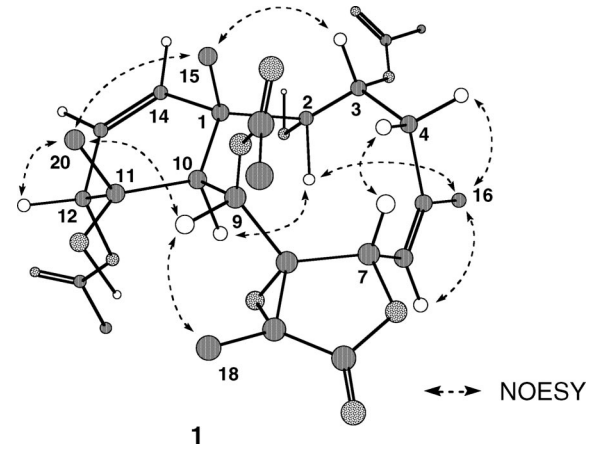

Figure 2. Selected NOESY correlations for brianodin A (**1**).

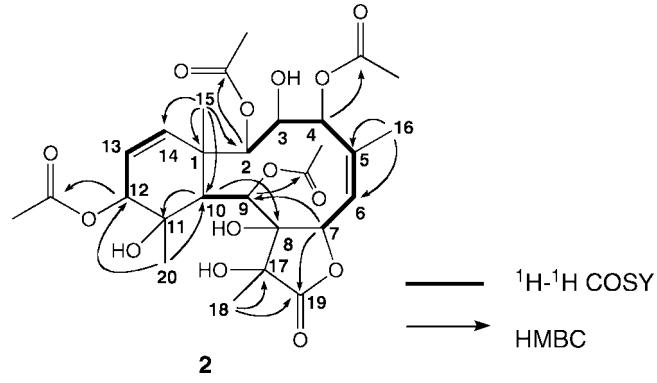

Figure 3. Selected 2D NMR correlations for brianodin B (**2**).

Brianodin D (**4**) had the molecular formula $C_{24}H_{34}O_{11}$ by HRFABMS (*m*/*z* 499.2187 [M + H]$^+$, Δ +0.6 mmu). The IR spectrum of **4** suggested the presence of an ester (1730 cm^{-1}) functionality. The ^{1}H NMR spectrum of **4** showed signals due to two acetyl methyls (δ_H 1.85, 2.00), an olefinic methyl (δ_H 1.78), and three tertiary methyls (δ_H 0.92, 1.25, and 1.27). The ^{13}C NMR spectrum of **4** indicated the presence of three carbonyl carbons (δ_C 173.0, 173.5, and 179.6) and four olefinic carbons (δ_C 124.6, 124.9, 139.8, and 142.7) (Table 2). The gross structure of **4** was elucidated from ^{1}H−^{1}H COSY and HMBC correlations (Figure 6). The relative stereochemistry of **4** was elucidated by ^{1}H coupling constants and NOESY correlations. NOESY correlations from H_3-20 to H_3-15, H-12 (δ_H 3.58, d, J = 6.0 Hz) and H-9 (δ_H 6.07, d, J = 4.3 Hz) indicated β-orientations for H-12, Me-15, and Me-20 and an α-orientation for H-9. NOESY correlations of H-2 (δ_H 3.26, s) to

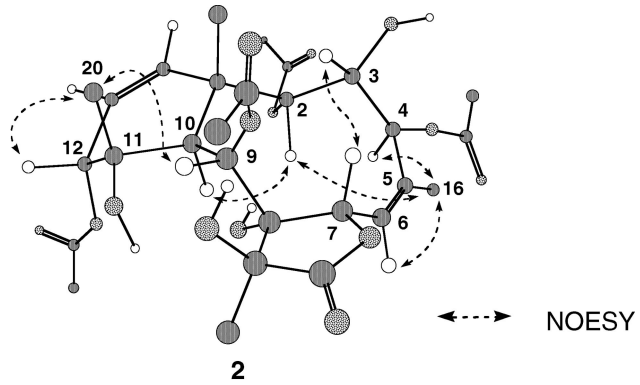

Figure 4. Selected NOESY correlations for brianodin B (**2**).

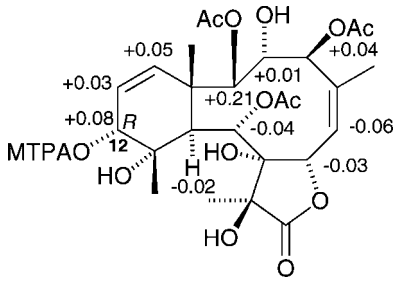

Figure 5. $\Delta\delta$ values [$\Delta\delta$ (in ppm) = $\delta_S - \delta_R$] obtained for (*S*)- and (*R*)-MTPA esters at C-12 of brianodin C (**3**).

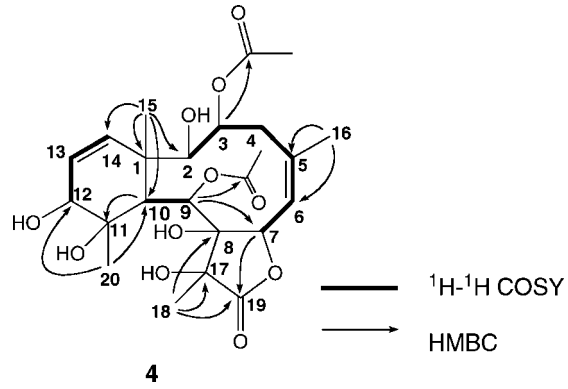

Figure 6. Selected 2D NMR correlations for brianodin D (**4**).

H-10 and H_3-16, H_3-16 to H-6, and H-4a to H-3 and H-7 suggested that H-2 and H-10 were α-orientated and H-3, H-7 and H-9 were β-orientated (Figure 7). The relative configuration at C-8 and C-17 was elucidated by comparison of ^{13}C NMR chemical shifts of brianodin D (**4**) with those of violide J.[16] Thus, the relative stereochemistry of brianodin D was elucidated to be **4**. The absolute stereochemistry of **4** was assigned as follows. Compound **4** was converted into its (*S*)- and (*R*)-MTPA esters of a hydroxy group at C-12, due to steric hindrance at C-2. The $\Delta\delta$ [δ(*S*-MTPA ester) − δ(*R*-MTPA ester)] values obtained from the ^{1}H NMR spectra of the MTPA esters suggested that the absolute configuration at C-12 in **4** was *R* (Figure 8).

In this study, four new briarane diterpenoids, brianodins A−D (**1**−**4**), were isolated from a soft coral *Pachyclavularia* sp., in which compounds **2**−**4** are rare examples[16] of briarane diterpenoids with a 1,2-diol moiety at C-8 and C-17. The absolute configurations for brianodins C (**3**) and D (**4**) were assigned, although absolute configurations of many briarane diterpenoids remain to be defined. Brianodin A (**1**) showed cytotoxicity[19] against L1210 murine leukemia (IC_{50}, 1.8 μg/mL) and KB human epidermoid carcinoma cells (IC_{50}, 4.3 μg/mL) *in vitro*, while brianodins B−D (**2**−**4**) did not show such activity (IC_{50}, >10 μg/mL). Chemical modifications of briarane diterpenoids and SAR studies[5] are currently underway.

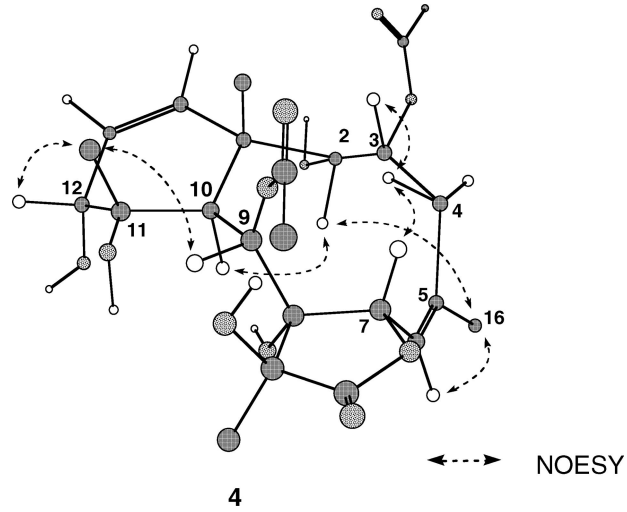

Figure 7. Selected NOESY correlations for brianodin D (**4**).

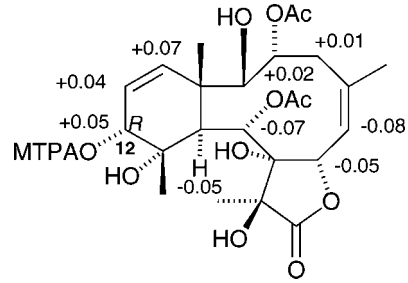

Figure 8. $\Delta\delta$ values [$\Delta\delta$ (in ppm) = $\delta_S - \delta_R$] obtained for (*S*)- and (*R*)-MTPA esters at C-12 of brianodin D (**4**).

Experimental Section

General Experimental Procedures. Optical rotations were recorded on a JASCO DIP-1000 polarimeter. IR spectra were taken on a JASCO FT/IR-5300 IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX-600 NMR spectrometer and a JEOL ECA500 NMR spectorometer. 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, while the 3.35 and 49.8 ppm resonances of residual MeOH-d_4 were used as internal references for ^{1}H and ^{13}C NMR spectra, respectively. FAB mass spectra were obtained on a JEOL HX110 spectrometer. ESI mass spectra were obtained on a JEOL JMS-T100LP spectrometer.

Animal Material. The soft coral *Pachyclavularia* sp. (SC-114) was collected from Okinawa, Japan, and kept frozen until used. A voucher specimen was deposited at the Graduate School of Pharmaceutical Sciences, Hokkaido University.

Extraction and Isolation. The soft coral (0.8 kg, wet weight) was extracted with methanol (1.1 L × 1 and 0.8 L × 1). The extract (44.3 g) was partitioned between EtOAc (500 mL × 3) and water (500 mL). A part (1.0 g) of the EtOAc-soluble materials (12.6 g) was subjected to passage over a silica gel column ($CHCl_3$/MeOH, 95:5) to give fractions I (59.9 mg) and II (56.8 mg). Fraction I was separated by silica gel column chromatography (*n*-hexane/EtOAc, 1:3) to afford brianodin A (**1**, 26.0 mg, 0.0032%, wet wt). Fraction II in the first silica gel column was chromatographed on C18 HPLC (Luna 5u C18(2), Phenomenax Co., Ltd., 10 × 300 mm; flow rate, 2.5 mL/min; eluent, MeOH/H_2O, 40:60 to 70:30; UV detection at 220 nm) to yield brianodins B (**2**, t_R 38.0 min, 4.4 mg, 0.0006%), C (**3**, t_R 28.0 min, 5.7 mg, 0.0007%), and D (**4**, t_R 25.5 min, 10.4 mg, 0.0013%).

Brianodin A (1): colorless solid; mp 255–258 °C; $[\alpha]_D^{25}$ −129 (*c* 1.0, $CHCl_3$); IR (NaCl) ν_{max} 3550, 1780, and 1740 cm^{-1}; ^{1}H and ^{13}C NMR (Tables 1 and 2); FABMS (3-nitrobenzylalcohol) *m/z* 523 [M + H]$^+$; HRFABMS *m/z* 523.2178 [M + H]$^+$, calcd for $C_{26}H_{35}O_{11}$, 523.2179.

Brianodin B (2): colorless solid; mp 170–172 °C; $[\alpha]_D^{25}$ −6 (*c* 1.0, $CHCl_3$); IR (NaCl) ν_{max} 3270, and 1740 cm^{-1}; ^1H and ^{13}C NMR (Tables 1 and 2); FABMS (glycerol) *m/z* 599 $[M + H]^+$; HRFABMS *m/z* 599.2336 $[M + H]^+$, calcd for $C_{28}H_{39}O_{14}$, 599.2339.

Brianodin C (3): colorless solid; mp 286–288 °C; $[\alpha]_D^{25}$ +20 (*c* 0.5, $CHCl_3$); IR (NaCl) ν_{max} 3420, 1730, and 1650 cm^{-1}; ^1H and ^{13}C NMR (Tables 1 and 2); FABMS (glycerol) *m/z* 557 $[M + H]^+$; HRFABMS *m/z* 557.2247 $[M + H]^+$, calcd for $C_{26}H_{37}O_{13}$, 557.2234.

Brianodin D (4): colorless solid; mp 181–183 °C; $[\alpha]_D^{25}$ −79 (*c* 0.5, $CHCl_3$); IR (NaCl) ν_{max} 3270, and 1730 cm^{-1}; ^1H and ^{13}C NMR (Tables 1 and 2); FABMS (glycerol) *m/z* 499 $[M + H]^+$; HRFABMS *m/z* 499.2187 $[M + H]^+$, calcd for $C_{24}H_{35}O_{11}$, 499.2181.

(*S*)- and (*R*)-MTPA Esters of Brianodin C (3). To a solution of **3** (0.3 mg) in pyridine (50 μL) were added *N*,*N*-dimethylaminopyridine (50 μg) and (*R*)-MTPACl (6 μL). The mixture was allowed to stand at room temperature for 30 min. After addition of *N*,*N*-dimethyl-1,3-propanedioamine (6 μL), the residue was concentrated and applied to a silica gel column to give the (*S*)-MTPA ester of **3**. The (*R*)-MTPA ester of **3** was prepared according to the same procedure as described above.

(*S*)-MTPA ester of **3**: ^1H NMR (CD_3OD) δ 6.13 (1H, H-9), 5.93 (1H, H-7), 5.90 (1H, H-13), 5.77 (1H, H-14), 5.43 (1H, H-6), 5.21 (1H, H-12), 5.09 (1H, H-4), 4.79 (1H, H-3), 4.62 (1H, H-2), 2.85 (1H, H-10); ESIMS *m/z* 795 $[M + Na]^+$; HRESIMS *m/z* 795.2445 $[M + Na]^+$, calcd for $C_{36}H_{43}F_3NaO_{15}$, 795.2452.

(*R*)-MTPA ester of **3**: ^1H NMR (CD_3OD) δ 6.17 (1H, H-9), 5.96 (1H, H-7), 5.87 (1H, H-13), 5.72 (1H, H-14), 5.49 (1H, H-6), 5.13 (1H, H-12), 5.05 (1H, H-4), 4.78 (1H, H-3), 4.41 (1H, H-2), 2.87 (1H, H-10); ESIMS *m/z* 795 $[M + Na]^+$; HRESIMS *m/z* 795.2431 $[M + Na]^+$, calcd for $C_{36}H_{43}F_3NaO_{15}$, 795.2452.

(*S*)- and (*R*)-MTPA Esters of Brianodin D (4). The (*S*)- and (*R*)-MTPA esters of **4** were prepared according to the same procedure as described above.

(*S*)-MTPA ester of **4**: ^1H NMR (CD_3OD) δ 6.20 (1H, H-14), 6.15 (1H, H-9), 5.92 (1H, H-13), 5.87 (1H, H-7), 5.69 (1H, H-3), 5.35 (1H, H-6), 5.27 (1H, H-12), 3.02 (1H, H-4), 2.71 (1H, H-10); ESIMS *m/z* 737 $[M + Na]^+$; HRESIMS *m/z* 737.2388 $[M + Na]^+$, calcd for $C_{34}H_{41}F_3NaO_{13}$, 737.2397.

(*R*)-MTPA ester of **4**: ^1H NMR (CD_3OD) δ 6.22 (1H, H-9), 6.13 (1H, H-14), 5.92 (1H, H-7), 5.88 (1H, H-13), 5.67 (1H, H-3), 5.43 (1H, H-6), 5.22 (1H, H-12), 3.01 (1H, H-4), 2.76 (1H, H-10); ESIMS *m/z* 737 $[M + Na]^+$; HRESIMS *m/z* 737.2369 $[M + Na]^+$, calcd for $C_{34}H_{41}F_3NaO_{13}$, 737.2397.

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