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Miyakosynes A–F, cytotoxic methyl branched acetylenes from a marine sponge *Petrosia* sp.

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ABSTRACT

Cytototoxic linear acetylenes, miyakosynes A–F, were isolated from a marine sponge *Petrosia* sp. Their structures were elucidated by a combination of spectroscopic analyses and chemical methods. The absolute configuration of the secondary alcohols at each terminus was determined by the modified Mosher's analysis. Miyakosynes show cytotoxicity against HeLa cells at submicromolar concentrations.

1. Introduction

Fatty acid derived linear acetylenes are characteristic metabolites of Asteraceae plants and *Haplosclerida* sponges.[1] Petrosynol and duryne are the first members of symmetrical C_{30}-metabolites with a common highly unsaturated terminus in both ends.[2,3] Together with melynenes and pellynols,[4,5] they comprise a class of metabolites characterized by the presence of a double bond in the central part of the long aliphatic chain with both termini unsaturated or oxidized in divergent ways. As a departure from this group, a few compounds containing a branched methyl group have been reported, but the position of the methyl branch was defined only in one compound.[6–8] In the course of our study to explore biomedical potential of marine invertebrates, the extract of a marine sponge *Petrosia* sp. collected at Miyako sea-knoll exhibited significant cytotoxicity against HeLa cells. Bioassay-guided fractionation of the extract afforded six linear acetylenes with a branched methyl group, which we named miyakosynes A–F (**1**–**6**). The structure elucidation and biological activity of miyakosynes were described below.

2. Result and discussion

The sponge *Petrosia* sp. was extracted with EtOH and $CHCl_3$/MeOH (1:1), and the extracts were combined, concentrated, and partitioned between $CHCl_3$ and H_2O. The organic layer was further partitioned between MeOH/H_2O (9:1) and *n*-hexane. The aqueous MeOH fraction was successively fractionated by flash chromatography on SiO_2 and ODS, and the resultant active fractions were purified by ODS HPLC to yield miyakosynes A–F (**1**–**6**, Fig. 1).

Miyakosyne A (**1**) had the molecular formula of $C_{29}H_{48}O_2$ as assigned by HRESIMS. An interesting feature of the ^{1}H NMR spectrum was that a methyl doublet (δ 0.84, J=6.7 Hz) was integrated for 1.5H compared to other isolated ^{1}H signals. This observation was accounted for by the presence of one methyl group in otherwise symmetrical structure. The ^{1}H NMR and HSQC data showed the presence of characteristic terminal structure comprised of terminal acetylene, carbinol, and *E*-olefin, in this order, as found in duryne and petrosynol (Table 1).[2,3] The molecular formula and NMR data indicated that the two termini were linked through a saturated linear aliphatic chain with one methyl branch. The branched methyl group was shown not to be located near the termini by interpretation of HMBC spectrum. The position of the methyl branch was investigated by analysis of tandem FABMS data. Because the molecule has an identical polar group placed at both ends, it is likely that each end comprises the charged site with the same probability. Therefore, we considered the tandem FABMS data as a summation of product ion spectra with each end charged. When a methyl branch is present, the regularity of the appearance of product ions separated by 14 units, corresponding to the C–C bond cleavages in the aliphatic chain, is broken by the absence of one peak, resulting in the separation of two adjacent ions by 28 units.[9] In the tandem FABMS of **1**, such phenomenon was not observed. Instead, significant fluctuation in the intensities of the ion peaks at

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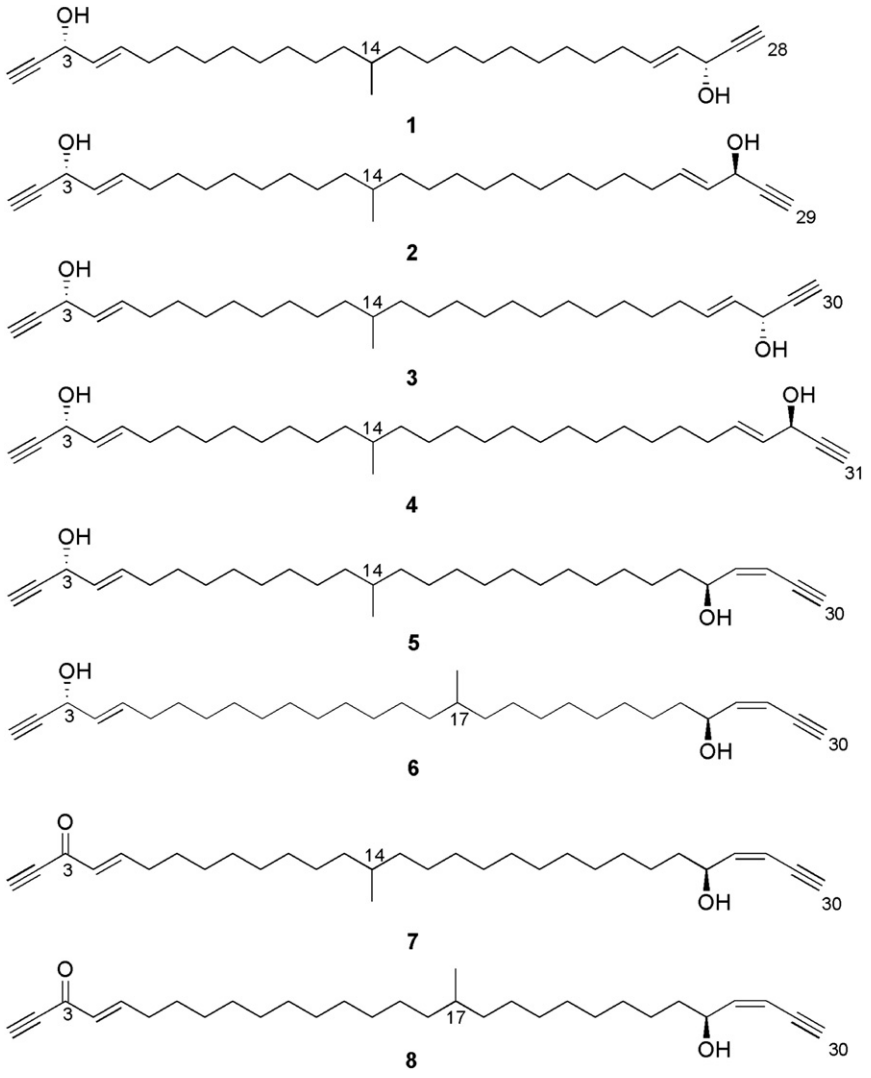

Fig. 1. Structures of miyakosynes A–F (**1**–**6**) and keto-alcohols **7** and **8**.

Table 1
^{1}H and ^{13}C NMR data of Miyakosynes A-D (**1**–**4**) in $CDCl_3$

No.	Miyakosyne A (**1**)		Miyakosyne B (**2**)		Miyakosyne C (**3**)		Miyakosyne D (**4**)	
	δ_H, mult.	δ_C[a]	δ_H, mult.	δ_C[a]	δ_H, mult.	δ_C[b]	δ_H, mult.	δ_C[b]
1	2.57, d (2.1)	74.2	2.56, d (2.2)	74.1	2.56, d (2.1)	74.0	2.57, d (2.1)	74.0
2		83.5		83.6		83.4		83.4
3	4.84, br d (6.2)	63.0	4.83, br d (6.2)	62.9	4.84, br d (6.2)	62.8	4.84, br d (6.1)	62.9
4	5.61, dd (15.1, 6.2)	128.5	5.61, dd (15.4, 6.2)	128.5	5.61, dd (15.1, 6.2)	128.3	5.62, dd (15.3, 6.1)	128.4
5	5.92, dt (15.1, 6.9)	134.9	5.91, dt (15.4, 6.9)	134.7	5.91, dt (15.1, 6.8)	134.5	5.93, dt (15.3, 6.9)	134.7
6	2.07, m	32.2	2.07, m	32.1	2.07, m	31.9	2.07, m	31.9
7	1.39, m	29.0	1.39, m	29.0	1.39, m	29.0	1.40, m	28.9
8–12	1.24–1.31	29.3–30.2	1.23–1.30	29.3–30.2	1.23–1.30	29.0–30.2	1.23–1.30	29.0–30.2
13	1.08, m	37.3	1.07, m	37.3	1.07, m	37.0	1.08, m	37.1
14	1.36, m	32.9	1.35, m	32.9	1.35, m	32.7	1.35, m	32.8
15	1.08, m	37.3	1.07, m	37.3	1.07, m	37.0	1.08, m	37.1
16-21	1.24–1.31	29.3–30.2	1.23–1.30	29.3–30.2	1.23–1.30	29.0–30.2	1.23–1.30	29.0–30.2
22	1.39, m	29.0	1.23–1.30	29.3–30.2	1.23–1.30	29.0–30.2	1.23–1.30	29.0–30.2
23	2.07, m	32.2	1.39, m	29.0	1.23–1.30	29.0–30.2	1.23–1.30	29.0–30.2
24	5.92, dt (15.1, 6.9)	134.9	2.07, m	32.1	1.39, m	29.0	1.23–1.30	29.0–30.2
25	5.61, dd (15.1, 6.2)	128.5	5.91, dt (15.4, 6.9)	134.7	2.07, m	31.9	1.40, m	28.9
26	4.84, br d (6.2)	63.0	5.61, dd (15.4, 6.2)	128.5	5.91, dt (15.1, 6.8)	134.5	2.07, m	31.9
27		83.5	4.83, br d (6.2)	62.9	5.61, dd (15.1, 6.2)	128.3	5.93, dt (15.3, 6.9)	134.7
28	2.57, d (2.1)	74.2		83.6	4.84, br d (6.2)	62.8	5.62, dd (15.3, 6.1)	128.4
29			2.56, d (2.2)	74.1		83.4	4.84, br d (6.1)	62.9
30					2.56, d (2.1)	74.0		83.4
31							2.57, d (2.1)	74.0
14-Me	0.84, d (6.7)	19.9	0.84, d (6.6)	19.9	0.84, d (6.6)	19.7	0.84, d (6.6)	19.8

[a] ^{13}C NMR was measured at 150 MHz.
[b] ^{13}C NMR chemical shifts were determined by HSQC data.

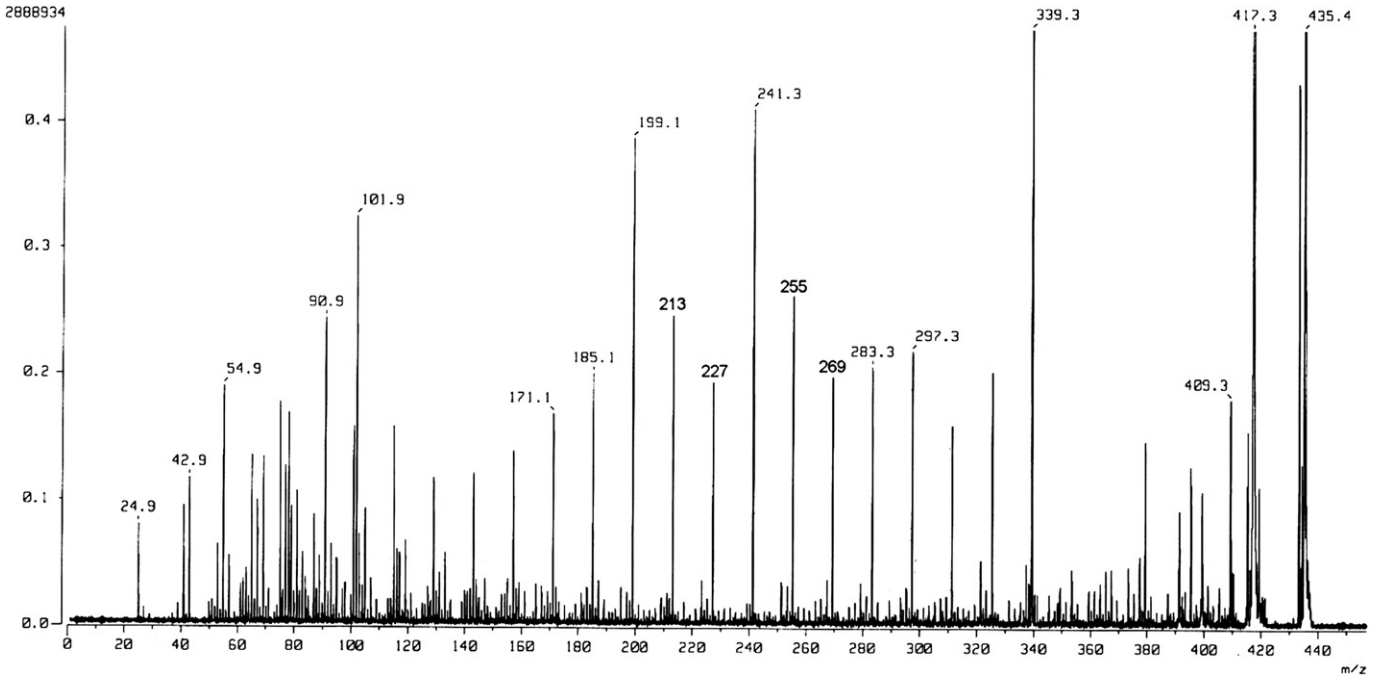

Fig. 2. Tandem FABMS spectrum of miyakosyne A (**1**).

m/*z* 199, 213, 227, and 241 was observed, while the intensity changes of larger or smaller ions (e.g., *m*/*z* 171, 185, 255, and 269) were within statistical errors (Fig. 2). In the tandem FABMS of methyl branched fatty acids, the incidence of cleavage between α-carbon and β-carbon of the branching points is twice as that between the neighboring methylene carbons.[9] With this tendency in mind, we can predict the relative intensity of product ions for a specific methyl branch (Fig. 3, Table 2). In the spectrum with C-13 methyl branch, the ratio of ion peaks at *m*/*z* 185, 199, 213, 227, 241, and 255 was expected to be 3:1:3:3:1:3, whereas that with C-14 methyl branch in a ratio of 2:3:2:2:3:2 (Table 2), the latter ratio being matched well with the observed value (Fig. 2). Compounds with methyl branch at C-11 and C-12 would give different ratios from the observed value (Table 2). Therefore, we concluded that **1** had C-14 methyl branch. Because of the limited precision of the analysis, it is not possible to eliminate the possibility of the presence of small amounts of other positional isomers. The absolute configurations of the carbinol carbons were determined as *R*, because the ^{1}H NMR data of the terminal portions of the (*R*)-MTPA esters of **1** were superimposable on those of the (*S*)-MTPA ester of petrocortyne A:[10] petrocortyne A contains the corresponding terminal moiety with the *S*-configuration.

Table 2
Predicted relative intensities of ions for methyl branches at C-11 (a), C-12 (b), C-13 (c), and C-14 (d) in **1**

m/*z*	157	171	185	199	213	227	241	255	269	283
a: C-11	+++	+	+++	++	++	++	++	+++	+	+++
b: C-12	++	+++	+	+++	++	++	+++	+	+++	++
c: C-13	++	++	+++	+	+++	+++	+	+++	++	++
d: C-14	++	++	++	+++	++	++	+++	++	++	++

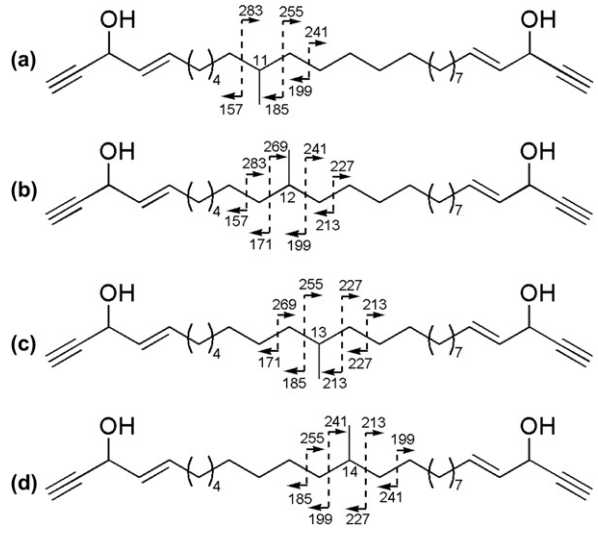

Fig. 3. Estimated intensities of product ions in tandem FABMS for isomeric structures of **1** with a methyl branch at C-11 (**a**), C-12 (**b**), C-13 (**c**), and C-14 (**d**).

Miyakosynes B–D (**2**–**4**) had molecular formulas of $C_{30}H_{50}O_2$, $C_{31}H_{52}O_2$, and $C_{32}H_{54}O_2$, respectively, as assigned by HRESIMS. ^{1}H and ^{13}C NMR data of **2**–**4** were almost identical with those for **1**, indicating that **2**–**4** have the common terminal structures and a methyl branch (Table 1). This was confirmed by analyses of 2D NMR data. The positions of the methyl branch in **2**–**4** were all assigned to be at C-14 by application of similar arguments on interpretation of tandem FABMS data as described above. The absolute configurations of the carbinol carbons in all these compounds were determined as *R* by interpretation of the ^{1}H NMR spectra of the bis-(*R*)-MTPA esters as described above.

Miyakosynes E (**5**) and F (**6**), obtained as an inseparable mixture, were both isomeric with **3**. ^{1}H NMR spectrum of the mixture showed one set of resonances for the common terminal structure and its rearranged form comprised of an conjugated enyne system linked to an allylic secondary alcohol, with a *Z*-olefin ($J_{H27,H26}$=11.0 Hz, Table 3). There was a branched methyl group in this molecule as well. The mixture of **5** and **6** gave the tandem FABMS spectrum almost identical with that of **3**, allowing us to locate the methyl group in the aliphatic chain, but it was not possible to differentiate the two terminal polar groups, which had identical compositions. Fortunately, the reactivity of the two

Table 3
^{1}H and ^{13}C NMR data of Miyakosynes E (**5**) and F (**6**) in $CDCl_3$

Miyakosynes E (**5**) and F (**6**)		
No.	δ_H, mult.	δ_C[a]
1	2.57, d (2.1)	74.0
2		83.3
3	4.84, br d (6.2)	62.8
4	5.62, dd (15.1, 6.2)	128.3
5	5.92, dt (15.1, 6.9)	134.7
6	2.07, m	31.9
7	1.40, m	28.7
8-12 (8-15)[b]	1.23–1.30	29.0–30.2
13 (16)[b]	1.08, m	37.0
14 (17)[b]	1.35, m	32.7
15 (18)[b]	1.08, m	37.0
16-24 (16-19)[b]	1.23–1.30	29.0–30.2
25α	1.63, m	36.5
25β	1.53, m	
26	4.68, m	70.0
27	6.00, dd (11.0, 8.3)	147.5
28	5.54, dd (11.0, 1.4)	108.8
29		82.7
30	3.14, d (1.4)	79.4
14-Me (17-Me)	0.84, d (6.6)	19.7

[a] ^{13}C NMR chemical shifts were determined by HSQC data.
[b] Parenthetic carbon numbers were assigned for **6**.

secondary alcohols was different: allylic propargylic alcohol was much more susceptible to oxidation. DDQ oxidation of the mixture afforded a mixture of keto-alcohols (**7** and **8**), which was derivatized with Girard's T reagent[11] and subjected to the tandem FABMS analysis. In the Girard's T derivatives, the newly introduced positive charge was considered as the sole ionization site. The fixed charged site allowed the tandem FABMS data to be interpreted unambiguously. We expected the disruption of the regularity of fragments of 14 mass units differences by the presence of a branched methyl. Such a disruption was not observed. Instead, intensities of ions at *m*/*z* 318 and 360 were weaker than their neighboring ions, implying that **5** and **6** were a mixture of two compounds with a branched methyl group at either C-14 or C-17 (Fig. 4). The absolute configurations of **5** and **6** were both determined to be (3*R*, 26*S*) by the modified Mosher's method (Fig. 5).

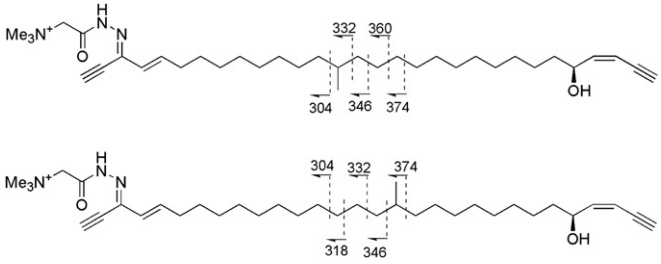

Fig. 4. Diagnostic tandem FABMS fragment ions for the Girard's T derivatives of a mixture of **7** and **8**.

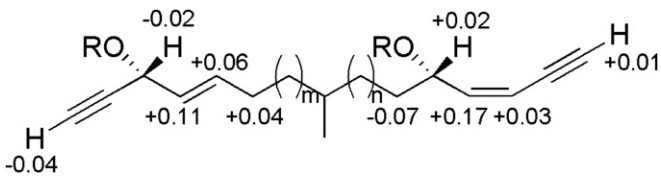

Fig. 5. Result of the modified Mosher's method for the MTPA ester of **5** (m=7, n=10) and **6** (m=10, n=7). $\Delta\delta$ ($\delta_S-\delta_R$) values are shown.

Miyakosynes A–D (**1**–**4**) and a mixture of miyakosynes E (**5**) and F (**6**) exhibited cytotoxic activity against HeLa cells with IC_{50} values of 0.10, 0.13, 0.04, 0.15, and 0.30 μg/mL, respectively. Miyakosynes were equipotent to duryne,[3] a C_{30}-acetylene with one double bond at the center of the chain and without methyl branch. From these data, we reason that neither methyl branch nor the central olefin is indispensable for the potent cytotoxicity of this class of metabolites.

3. Experimental section

3.1. General procedures

Optical rotations were measured on a JASCO DIP-1000 digital polarimeter in MeOH. NMR spectra were recorded on a JEOL alpha 600 NMR spectrometer at 300 K. Chemical shifts were referenced to solvent peaks: δ_H 7.27 and δ_C 77.2 for $CDCl_3$. ESI mass spectra were measured on a JEOL JMS-T100LC. FABMS and FABMSMS were measured on a JEOL JMS-700T mass spectrometer.

3.2. Animal material

The sponge *Petrosia* sp. was collected at Miyako sea-knoll, at depth of 415 m, and identified by Dr. Yuji Ise, The University of Tokyo.

3.3. Extraction and isolation

The sponge was frozen after collection and kept frozen until extraction. The sponge (730 g, wet weight) was homogenized and extracted with EtOH (1.8 L×3) and $CHCl_3$/MeOH (1:1, 1.8 L). The combined extracts were concentrated, and partitioned between H_2O (300 mL) and $CHCl_3$ (300 mL×3). The $CHCl_3$ layer was further partitioned between *n*-hexane (300 mL) and MeOH/H_2O (9:1, 300 mL). The aqueous MeOH layer was concentrated and separated by ODS column chromatography eluting with 50% MeOH, 70% MeOH, 90% MeOH, MeOH, and $CHCl_3$/MeOH/H_2O (6:4:1). The MeOH eluate was concentrated and separated by silica gel column chromatography eluting with $CHCl_3$, $CHCl_3$/MeOH (98:2), $CHCl_3$/MeOH (95:5), $CHCl_3$/MeOH (9:1), $CHCl_3$/MeOH/H_2O (8:2:0.1), and $CHCl_3$/MeOH/H_2O (7:3:0.5). The $CHCl_3$ eluate was separated by silica gel column chromatography eluting with *n*-hexane/EtOAc (9:1), *n*-hexane/EtOAc (8:2), and *n*-hexane/EtOAc (1:1). The *n*-hexane/EtOAc (8:2) eluate was concentrated and separated by ODS HPLC (Cosmosil AR-II; 20×250 mm) with 90%–100% MeOH to afford 14 fractions. One fifth of the second and seventh fractions were purified by ODS HPLC (Cosmosil MS-II; 20×250 mm) with 85% MeCN to afford **1** (21.6 mg) and **3** (37.0 mg), respectively. The fifth, sixth, and ninth fractions were purified by ODS HPLC with 90% MeCN to afford **2** (66.0 mg), a mixture of **5** and **6** (7.2 mg), and **4** (8.6 mg), respectively.

*3.3.1. Miyakosyne A (**1**).* Colorless solid; $[\alpha]_D^{24}$ −28 (*c* 0.42, MeOH); HRESIMS $(M+Na)^+$ *m*/*z* 451.3548 (calcd for $C_{29}H_{48}O_2Na^+$, 451.3547); ^{1}H NMR ($CDCl_3$) and ^{13}C NMR ($CDCl_3$) data, see Table 1.

*3.3.2. Miyakosyne B (**2**).* Colorless solid; $[\alpha]_D^{26}$ −27 (*c* 0.60, MeOH); HRESIMS $(M+Na)^+$ *m*/*z* 465.3735 (calcd for $C_{30}H_{50}O_2Na^+$, 465.3704); ^{1}H NMR ($CDCl_3$) and ^{13}C NMR ($CDCl_3$) data, see Table 1.

*3.3.3. Miyakosyne C (**3**).* Colorless solid; $[\alpha]_D^{24}$ −28 (*c* 0.72, MeOH); HRESIMS $(M+Na)^+$ *m*/*z* 479.3856 (calcd for $C_{31}H_{52}O_2Na^+$, 479.3860); ^{1}H NMR ($CDCl_3$) and ^{13}C NMR ($CDCl_3$) data, see Table 1.

*3.3.4. Miyakosyne D (**4**).* Colorless solid; $[\alpha]_D^{26}$ −25 (*c* 0.35, MeOH); HRESIMS $(M+Na)^+$ *m*/*z* 493.4036 (calcd for $C_{32}H_{54}O_2Na^+$, 493.4017); ^{1}H NMR ($CDCl_3$) and ^{13}C NMR ($CDCl_3$) data, see Table 1.

*3.3.5. Miyakosynes E and F (**5**, **6**).* Colorless oil; $[\alpha]_D^{25}$ −34 (*c* 0.32, MeOH); HRESIMS $(M+Na)^+$ *m*/*z* 479.3882 (calcd for $C_{31}H_{52}O_2Na^+$, 479.3860); ^{1}H NMR ($CDCl_3$) and ^{13}C NMR ($CDCl_3$) data, see Table 3.

*3.3.6. Preparation of keto-alkohols **7** and **8**.* To a mixture of **5** and **6** (0.5 mg) was added DDQ solution in dioxane (15 mg/mL, 20 μL). The solution was left at room temperature for a week, and the reaction mixture was purified by silica gel column chromatography eluted with *n*-hexane/EtOAc (95:5) to afford a mixture of keto-alcohols **7** and **8** (0.2 mg).

*3.3.6.1. Keto-alcohols **7** and **8**.* Colorless oil; HRESIMS $(M+Na)^+$ *m*/*z* 477.3698 (calcd for $C_{31}H_{50}O_2Na^+$, 477.3704); ^1H NMR of keto-alcohols **7** and **8** ($CDCl_3$) δ 7.26 (m, H-5), 6.19 (d, *J*=15.6, H-4), 6.00 (dd, *J*=11.0, 8.3, H-27), 5.54 (dd, *J*=11.0, 1.4, H-28), 4.68 (m, H-26), 3.22 (s, H-1), 3.14 (d, *J*=1.4, H-30), 2.32 (m, H-6), 1.63 (m, H-25α), 1.53 (m, H-25β): **7** 1.35 (m, H-14), 1.08–1.40 (H-7–H-13, H-15–H-24), 0.84 (d, *J*=6.6, 14-Me): **8** 1.35 (m, H-17), 1.08–1.40 (H-7–H-16, H-18–H-24), 0.84 (d, *J*=6.6, 17-Me).

3.4. Preparation of Girard's T derivatives

To a portion of a mixture of **7** and **8** (0.1 mg) was added Girard's reagent T in AcOH (50 mg/mL, 20 μL) and the solution was kept at 70 °C for 30 min. The reaction mixture was evaporated by a stream of dry nitrogen and diluted with MeOH (5 μL) before application to tandem FABMS analysis.

3.5. Preparation of MTPA esters

To a solution of a sample (0.1 mg) in dry pyridine (10 μL) was added (*S*)-MTPACl (2 μL). The solution was left at room temperature for 4 h, and the reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The organic layer was purified by reversed-phase HPLC to afford the (*R*)-MTPA ester. (*S*)-MTPA ester of **5** and **6** was prepared in a similar way using (*R*)-MTPACl.

*3.5.1. (R)-MTPA ester of **1**.* ^1H NMR ($CDCl_3$) δ 6.04 (H-3, H-26), 6.02 (H-5, H-24), 5.50 (H-4, H-25), 2.64 (H-1, H-28), 2.05 (H-6, H-23), 1.24–1.64 (H-7–H-12, H-16–H-22), 1.36 (H-14), 1.08 (H-13, H-15), 0.84 (14-Me); ESIMS *m*/*z* 899 $(M+Na)^+$.

*3.5.2. (R)-MTPA ester of **2**.* ^1H NMR ($CDCl_3$) δ 6.04 (H-3, H-27), 6.02 (H-5, H-25), 5.50 (H-4, H-26), 2.64 (H-1, H-29), 2.05 (H-6, H-24), 1.24–1.64 (H-7–H-12, H-16–H-23), 1.35 (H-14), 1.08 (H-13, H-15), 0.84 (14-Me); ESIMS *m*/*z* 913 $(M+Na)^+$.

*3.5.3. (R)-MTPA ester of **3**.* ^1H NMR ($CDCl_3$) δ 6.04 (H-3, H-28), 6.02 (H-5, H-26), 5.50 (H-4, H-27), 2.64 (H-1, H-30), 2.05 (H-6, H-25), 1.24–1.64 (H-7–H-12, H-16–H-24), 1.35 (H-14), 1.08 (H-13, H-15), 0.84 (14-Me); ESIMS *m*/*z* 927 $(M+Na)^+$.

*3.5.4. (R)-MTPA ester of **4**.* ^1H NMR ($CDCl_3$) δ 6.04 (H-3, H-29), 6.02 (H-5, H-27), 5.50 (H-4, H-28), 2.64 (H-1, H-31), 2.05 (H-6, H-26), 1.24–1.64 (H-7–H-12, H-16–H-25), 1.35 (H-14), 1.08 (H-13, H-15), 0.84 (14-Me); ESIMS *m*/*z* 941 $(M+Na)^+$.

*3.5.5. (R)-MTPA esters of **5** and **6**.* ^1H NMR for (*R*)-MTPA ester of **5** and **6** ($CDCl_3$) δ 6.04 (H-3), 6.02 (H-5), 5.95 (H-26), 5.83 (H-27), 5.64 (H-28), 5.50 (H-4), 3.26 (H-30), 2.64 (H-1), 2.05 (H-6), 1.81 (H-25α): (*R*)-MTPA ester of **5** 1.25–1.68 (H-7–H-12, H-16–H-24, H-25β), 1.35 (H-14), 1.08 (H-13, H-15), 0.84 (14-Me); (*R*)-MTPA ester of **6** 1.25–1.68 (H-7–H-15, H-19–H-24, H-25β), 1.35 (H-17), 1.08 (H-16, H-18), 0.84 (17-Me); ESIMS *m*/*z* 911 $(M+Na)^+$.

*3.5.6. (S)-MTPA esters of **5** and **6**.* ^1H NMR for (*S*)-MTPA ester of **5** and **6** ($CDCl_3$) δ 6.08 (H-5), 6.02 (H-3), 6.00 (H-27), 5.97 (H-26), 5.67 (H-28), 5.61 (H-4), 3.27 (H-30), 2.60 (H-1), 2.05 (H-6), 1.74 (H-25α): (*S*)-MTPA ester of **5** 1.23–1.63 (H-7–H-12, H-16–H-24, H-25β), 1.36 (H-14), 1.08 (H-13, H-15), 0.84 (14-Me); (*S*)-MTPA ester of **6** 1.23–1.63 (H-7–H-15, H-19–H-24, H-25β), 1.36 (H-17), 1.08 (H-16, H-18), 0.84 (17-Me); ESIMS *m*/*z* 911 $(M+Na)^+$.

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Supplementary data

NMR spectra for **1**–**6**, and tandem FABMS spectra for **1**–**6**, and Girard's T derivatives. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.04.085.

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