

HETEROCYCLES, Vol. 100, No. 10, pp. 1678 - 1685. © 2020 The Japan Institute of Heterocyclic Chemistry
Received, 6th July, 2020, Accepted, 6th August, 2020, Published online, 20th August, 2020
DOI: 10.3987/COM-20-14315

AMPHIRIONINS-3 AND -6, NEW POLYKETIDES FROM THE CULTURED MARINE DINOFLAGELLATE *AMPHIDINIUM* SPECIES

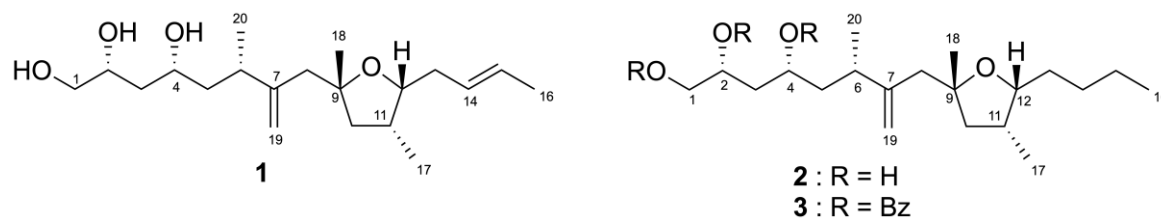
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Abstract – Amphirionins-3 (**1**) and -6 (**2**) have been isolated from the marine dinoflagellate *Amphidinium* species. The structures were elucidated by detail analyses of the spectroscopic data, and chemical conversions. Compounds **1** and **2** exhibited moderate cytotoxic activity against human cervix adenocarcinoma HeLa cells.

Marine dinoflagellates of the genus *Amphidinium* are well known to produce polyketide-like metabolites.^{1,2} Cytotoxic macrolides^{3,4} and polyhydroxy long-chain polyketide compounds^{5,6} have been isolated from the marine symbiotic and free-swimming *Amphidinium* species. On the other hand, certain low-polarity polyketide compounds with a relatively-small molecule size, represented by amphidinins^{7,8} and amphidinoketides,⁹ constitute the third class of *Amphidinium* dinoflagellates metabolites. Recently, we have also discovered a series of new polyketides, amphirionins-2,¹⁰ -4,¹¹ and -5,^{12,13} from the marine benthic dinoflagellate *Amphidinium* species collected off Iriomote Island, Okinawa Prefecture, Japan. Our continuing search for new polyketides from laboratory-cultured marine dinoflagellate *Amphidinium* species¹⁴⁻¹⁶ resulted in the isolation of two new linear polyketides, amphirionins-3 (**1**) and -6 (**2**), from the benthic dinoflagellate *Amphidinium* species (strains KCA09057 and KCA09056). The structures were elucidated by detailed analyses of the spectroscopic data and chemical conversions. The absolute

configuration was assigned on the basis of the CD chirality method with a tribenzoate derivative (**3**). In this paper, we describe the isolation and structure elucidation of **1** and **2** (Scheme 1).



Scheme 1. Structures of amphirionins-3 (**1**) and -6 (**2**)

The dinoflagellate *Amphidinium* species (strain KCA09057) was monoclonally separated from benthic sea sand samples collected off Iriomote Island, Japan, and cultured uniaxially in a 1% Provasoli's enriched seawater (PES) medium with a light and dark cycle of 16 h and 8 h, respectively, for 2 weeks at 27–29 °C. The cultured algal cells (53.54 g, dry weight) of the strain obtained from 2000 L of the medium were extracted with MeOH–toluene (3:1). The toluene-soluble materials of the extract were subjected to a SiO₂ gel, C₁₈, and amino silica gel column chromatography followed by C₁₈ HPLC to afford amphirionin-3 (**1**, 0.002% from dry weight). Meanwhile, amphirionin-6 (**2**) was isolated in 0.028% yield from the toluene-soluble materials of the algal cells of the *Amphidinium* strain KCA09056.

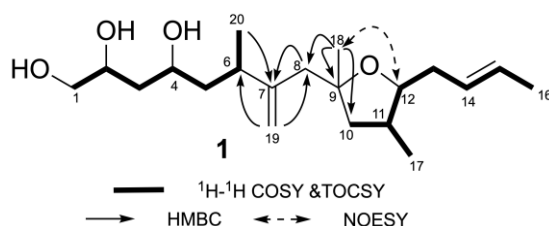
Amphirionin-3 (**1**) was obtained as a colorless oil and was optically active {[α]_D²⁰ -26 (c 0.1, CHCl₃)}. The molecular formula of **1** was established to be C₂₀H₃₆O₄ by HRESIMS (*m/z* 363.25026 [M+Na]⁺, Δ -0.87 mmu). The ¹H and ¹³C NMR data (Table 1) of **1** in CDCl₃ and C₆D₆ presented a total of 20 carbon resonances, arising from an sp² quaternary carbon, sp² methylene, oxygenated sp³ quaternary carbon, two sp² methines, five sp³ methines, six sp³ methylenes, and four methyls. As two of the three degrees of unsaturation were accounted for, **1** was inferred to possess a single ring system.

Interpretation of ¹H-¹H COSY and TOCSY spectra revealed one isolated methylene (H₂-8) and two proton-proton networks from H₂-1 to H-6 and H₃-20 and from H₂-10 to H₃-16 and H₃-17 (Figure. 1). The disubstituted C-14–C-15 double bond was assigned to be *E*, as suggested by the *J*(H-14/H-15) value (15.2 Hz). The presence of the exomethylene unit at C-7 was suggested by HMBC correlations for H₂-8 (δ_H 2.26 and 2.24)/C-7 (δ_C 150.8), H₃-20 (δ_H 1.00)/C-7, H₂-19 (δ_H 4.85 and 4.84)/C-6 (δ_C 34.4), and H₂-19/C-8 (δ_C 50.5). HMBC correlations from a singlet of methyl protons (H₃-18; δ_H 1.17) to C-8, C-9 (δ_C 82.6), and C-10 (δ_C 47.7) indicated that the oxygenated quaternary carbon at C-9 connects to C-8, C-10, and C-18. The NOESY correlation for H-12 (δ_H 3.97)/H₃-18 suggested that C-9 was involved in an ether linkage with C-12. Thus, the planar structure of **1** was assigned to be a linear polyketide triol associated with a tetrahydrofuran ring and four one-carbon branches.

Table 1. ^1H and ^{13}C NMR data of amphirionin-3 (**1**) in CDCl_3 and C_6D_6

positn.	CDCl_3^a				C_6D_6			
	^{13}C		^1H		^{13}C		^1H	
1	67.0	CH_2	3.60 3.48	m m	67.2	CH_2	3.67 3.58	dd, 10.8, 4.0 dd, 10.8, 5.5
2	72.6	CH	3.94	m	72.8	CH	4.02	m
3	39.1	CH_2	1.62 1.51	m m	39.8	CH_2	1.75 1.40	m m
4	69.1	CH	4.00	m	69.4	CH	4.10	m
5	44.3	CH_2	1.56 1.45	m m	44.6	CH_2	1.49 ^b	m
6	34.4	CH	2.65	m	34.5	CH	2.80	m
7	150.8	C			151.0	C		
8	50.5	CH_2	2.26 2.24	d, 12.9 d, 12.9	50.5	CH_2	2.15 2.05	d, 13.0 d, 13.0
9	82.6	C			82.4	C		
10	47.7	CH_2	1.99 1.49	dd, 12.3, 7.3 m	47.4	CH_2	1.57 1.15	dd, 12.3, 7.4 dd, 12.3, 7.6
11	35.1	CH	2.39	m	35.1	CH	2.01	m
12	81.5	CH	3.97	m	81.5	CH	3.72	m
13	34.5	CH_2	2.13 ^b	brt, 6.8	34.8	CH_2	2.00 ^b	m
14	127.3	CH_2	5.35	dtq, 15.2, 6.8, 1.5	127.6	CH	5.38	m
15	127.8	CH_2	5.49	brdq, 15.2, 6.3	127.9	CH	5.42	m
16	18.2	Me	1.65 ^c	dd, 6.3, 1.5	18.2	Me	1.70 ^c	brd, 4.3
17	14.8	Me	0.99 ^c	d, 7.0	14.5	Me	0.74 ^c	d, 6.5
18	25.8	Me	1.17 ^c	s	25.5	Me	1.05 ^c	s
19	111.9	CH_2	4.85 4.84	s s	111.9	CH_2	4.87 4.82	s s
20	24.0	Me	1.00 ^c	d, 6.8	24.1	Me	1.06 ^c	d, 6.8

^aOH signals were observed at δ_{H} 4.88 (1H, t, $J = 2.2$ Hz), 4.76 (1H, brs), and 2.36 (1H, brs). ^b2H. ^c3H.

Figure 1. Selected 2D NMR correlations for amphirionin-3 (**1**)

The gross structure of **1** was reminiscent of the amphidin A^{7.17} (**4**) structure. Therefore, the elucidation of the relative stereochemistry of **1** was performed by comparing the ^1H and ^{13}C NMR chemical shifts for **1** with those obtained for amphidin A (**4**). Figure 2 illustrates ^1H and ^{13}C chemical shift differences [$\Delta\delta$ (in ppm) = δ for **1** – δ for **4**] for C-1–C-12 and the four branched C_1 moieties at C-6, C-7, C-9, and C-11. The ^{13}C chemical shift differences for C-1–C-7 and the C-20 methyl were negligible (≤ 0.3 ppm),

indicating that the relative stereochemistry for C-2, C-4, and C-6 of **1** were *R**, *R**, and *S**-configurations, respectively, i.e., the same as those of **4**.¹⁷ The relative configuration for the tetrahydrofuran ring at C-9–C-12 was elucidated by analysis of the NOESY correlations observed for **1** in CDCl₃ (Figure. 3). NOESY correlations for H-6/H-8a, H-8a/H₃-20, and H-8b/H₃-18 suggested the 6*S**- and 9*R**-relations. Thus, total six stereocenters in **1** were established to have the same relative configurations as those of **4**.

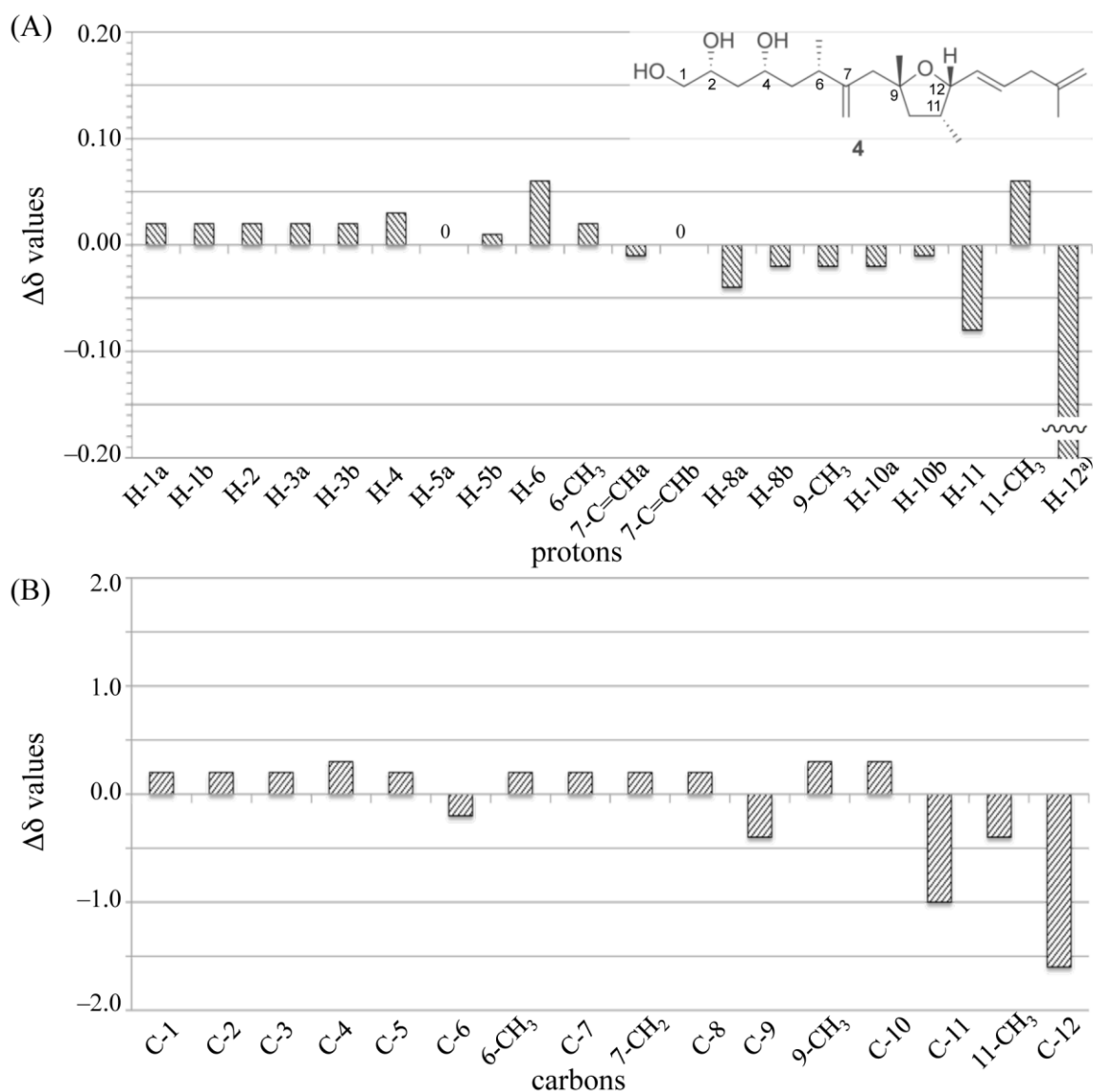


Figure 2. Differences between NMR chemical shifts of amphirionins-3 (**1**) and amphidin A (**4**) in CDCl₃. (A) $\Delta\delta_H$ (in ppm) = δ_H of **1** – δ_H of **4**. (B) $\Delta\delta_C$ (in ppm) = δ_C of **1** – δ_C of **4**. “a” and “b” for geminal proton pairs denoted low- and high-field resonances, respectively. a) $\Delta\delta_H$ values for H-12 was -0.43.

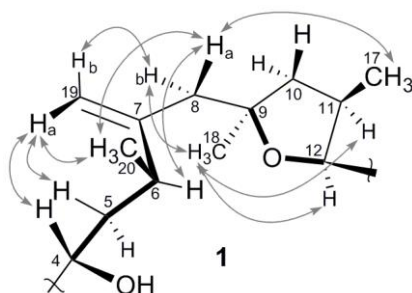


Figure 3. Stereostructure for the C-4–C-12 portion in amphirionin-3 (**1**).

Arrows show the NOESY correlations in CDCl₃.

The molecular formula, C₂₀H₃₈O₄, of amphirionin-6 (**2**) was revealed by [ESIMS *m/z* 365.26675 (M+Na)⁺, Δ -0.03 mmu]. The ¹³C NMR data of **2** in C₆D₆ presented a total of 20 carbon resonances, arising from an sp² quaternary carbon, sp² methylene, oxygenated sp³ quaternary carbon, five sp³ methines, eight sp³ methylenes, and four methyls. The planar structure of **2** elucidated on the basis of detailed NMR studies in C₆D₆ was established to be a 14,15-dihydro derivative of amphirionin-3 (**1**). The reduction of **1** using palladium–charcoal under hydrogen atmosphere afforded **2**, thus indicating that **2** possessed identical stereochemistry to that of **1**. The absolute stereochemistry of C-4 in **2** was assigned as *R* on the basis of the CD spectrum of the tribenzoate derivative (**3**) of **2**, where the negative and positive Cotton effects were detected at 233 (Δε -5.61) and 220 (+2.60) nm, respectively.¹⁸ Therefore, the absolute configurations of the six chiral centers of **1** and **2** were concluded to be 2*R*, 4*R*, 6*S*, 9*R*, 11*R*, and 12*R*.

Two new low-polarity polyketide compounds, amphirionins-3 (**1**) and -6 (**2**), are congeners of amphidinins A⁷ and G.⁸ Compounds **1** and **2** exhibited medium growth inhibition against human cervix adenocarcinoma HeLa cells with equal IC₅₀ values of 30 μM, indicating that the double bond at C-14 do not affect the cytotoxic activity.

EXPERIMENTAL

General information. The optical rotations were measured on a JASCO DIP-370 and P-2300 polarimeters, IR spectra were recorded on a JASCO FT/IR-5300 spectrophotometer. The CD spectrum was obtained on a JASCO J-1500 spectropolarimeter. NMR data for **1** were recorded on an Agilent NMR400WB spectrometer equipped with a PFG-HX or XH nanoprobe. NMR spectra of **2** were measured on a Bruker AMX-500 spectrometer using 2.5–mm microcells (Shigemi Co. Ltd.). The ¹H and ¹³C chemical shifts in CDCl₃ were reported in ppm relative to the residual signals of CDCl₃ (δ_H 7.16 and δ_C 77.16). Chemical shifts in C₆D₆ are reported in ppm with reference to the residual proton and carbon signals (δ_H 7.20 and δ_C 128.0) of the solvent. ESIMS spectra were obtained on an LTQ Orbitrap XL and Exactive spectrometers (ThermoFisher Scientific Inc.).

Cultivation and Isolation. A seawater medium was added to benthic sea sand samples collected off Iriomote Island, Japan, and the mixture was incubated for several weeks. Two dinoflagellate strain KCA09056 and KCA09057 were isolated monoclonally by micropipetting. The voucher specimens were deposited at the Center for Advanced Marine Core Research, Kochi University. The KCA09057 strain was cultured at 27–29 °C for two weeks in seawater medium enriched with 1% PES supplement, with light and dark cycles of 16 h and 8 h, respectively. The dried algal cells (53.54 g from 2,000 L culture) were extracted with MeOH–toluene (3:1), and partitioned between toluene and H₂O. The toluene-soluble materials (2.94 g) were subjected to silica gel column chromatography using a gradient elution of 0–5% MeOH in CHCl₃. The fraction eluted with CHCl₃–MeOH (95:5) was then chromatographed on C₁₈ (MeCN–H₂O, 7:3) and amino silica gel (hexane–EtOAc, 1:1–1:4) columns. The fraction eluted with hexane–EtOAc (1:4) was separated by C₁₈ HPLC [YMC-Pack Pro C₁₈, 10 mm × 250 mm; eluent, MeCN–H₂O (70:30); flow rate, 2 mL/min; UV detection at 230 nm] to afford amphirionin-3 (**1**, 1.0 mg, 0.002%). The strain KCA09056 was cultured under the above-described conditions. The harvested cells (15.3 g, from 400 L culture) were extracted with MeOH–toluene (3:1), and the extract was partitioned between toluene and water. The toluene-soluble fractions (2 g) were subjected to SiO₂ column chromatography using a stepwise elution of CHCl₃ and CHCl₃–MeOH (98:2). The fraction eluted with (CHCl₃–MeOH, 98:2) was chromatographed successively on a C₁₈ column (MeCN–H₂O, 7:3) followed by C₁₈ HPLC [YMC-Pack Pro C₁₈, 5 μm, YMC Co., Ltd., 10 x 250 mm; eluent, MeCN–H₂O (60:40); flow rate, 2 mL/min; UV detection at 210 nm] to afford amphirionin-6 (**2**, 4.3 mg, 0.028%).

Amphirionin-3 (1): colorless oil; $[\alpha]_D^{20}$ -26 (*c* 0.1, CHCl₃); IR (neat) ν_{\max} 3450 (broad) and 2980 cm⁻¹; ¹H and ¹³C NMR data (CDCl₃ and C₆D₆, see Table 1); HRESIMS *m/z* 363.25026 [calcd for C₂₀H₃₆O₄Na, (M+Na)⁺: 363.25113].

Amphirionin-6 (2): colorless oil; $[\alpha]_D^{20}$ -34 (*c* 0.08, CHCl₃); $[\alpha]_D^{20}$ -15 (*c* 0.05, C₆H₆); $[\alpha]_D^{20}$ -29 (*c* 0.05, MeOH); IR (neat) ν_{\max} 3446 (broad) and 2920 cm⁻¹; ¹H NMR (C₆D₆) δ 0.76 (3H, d, *J* = 6.8 Hz, H₃-17), 0.94 (3H, t, *J* = 6.7 Hz, H₃-16), 1.07 (3H, d, *J* = 7.0 Hz, H₃-20), 1.09 (3H, s, H₃-18), 1.18 (1H, dd, *J* = 12.2 and 6.8 Hz, H-10b), 1.24 (2H, m, H-14b and H-15b), 1.26 (1H, m, H-13b), 1.30 (1H, m, H-15a), 1.38 (2H, m, H-3b and H-14a), 1.39 (1H, m, H-13a), 1.50 (2H, m, H₂-5), 1.62 (1H, dd, *J* = 12.2 and 7.2 Hz, H-10a), 1.75 (1H, dt, *J* = 14.7 and 10.8 Hz, H-3a), 1.97 (1H, m, H-11), 2.07 (1H, d, *J* = 12.9 Hz, H-8b), 2.20 (1H, d, *J* = 12.9 Hz, H-8a), 2.82 (1H, m, H-6), 3.57 (1H, dd, *J* = 10.5 and 5.5 Hz, H-1b), 3.66 (1H, m, H-1a), 3.67 (1H, m, H-12), 4.01 (1H, m, H-2), 4.13 (1H, m, H-4), 4.83 (1H, s, H-19b), and 4.87 (1H, s, H-19a); ¹³C NMR (C₆D₆) δ 14.2 (CH₃, C-16), 14.6 (CH₃, C-17), 23.1 (CH₂, C-15), 24.0 (CH₃, C-20), 25.4 (CH₃, C-18), 28.6 (CH₂, C-14), 30.6 (CH₂, C-13), 34.7 (CH, C-6), 35.2 (CH, C-11), 39.9 (CH₂, C-3), 44.5 (CH₂, C-5), 47.7 (CH₂, C-10), 50.6 (CH₂, C-8), 67.2 (CH₂, C-1), 69.3 (CH, C-4), 72.8

(CH, C-2), 81.6 (CH, C-12), 82.1 (C, C-9), 112.0 (CH₃, C-19), and 150.9 (C, C-7); HRESIMS m/z 365.26675 [calcd for C₂₀H₃₈O₄Na, (M+Na)⁺: 365.26678].

Reduction of Amphirionin-3 (1). Amphirionin-3 (**1**, 0.3 mg) was dissolved in EtOAc (200 μ L), and treated with 10% palladium-charcoal (1 mg) under hydrogen atmosphere at room temperature for 1 h. After filtration and evaporation of the solvent, the residue was purified by silica gel column chromatography (hexane–EtOAc, 2:1) to afford **2** (0.1 mg). **2**: colorless oil; $[\alpha]_D^{20}$ -40 (c 0.05, CHCl₃); ¹H NMR (C₆D₆) δ 0.76 (3H, d, J = 6.7 Hz), 0.95 (3H, t, J = 6.7 Hz), 1.07 (3H, d, J = 6.9 Hz), 1.09 (3H, s), 1.13 ~ 1.30 (5H, m), 1.35 ~ 1.42 (3H, m), 1.50 (2H, m), 1.62 (1H, dd, J = 12.4 and 7.4 Hz), 1.76 (1H, brdt, J = 14.7 and 10.8 Hz), 1.97 (1H, m), 2.07 (1H, d, J = 13.0 Hz), 2.20 (1H, d, J = 13.0 Hz), 2.82 (1H, m), 3.57 (1H, dd, J = 10.5 and 5.5 Hz), 3.62 ~ 3.69 (2H, m), 4.02 (1H, m), 4.14 (1H, m), 4.84 (1H, s), and 4.87 (1H, s); HRESIMS m/z 365.26573 [calcd for C₂₀H₃₈O₄Na, (M+Na)⁺: 365.26678].

1,2,4-Tris-*O*-benzoyl Ester (3) of amphirionin-6 (2). To a solution of amphirionin-6 (**2**, 1 mg) in pyridine (40 μ L) was added benzoyl chloride (6 μ L), and the mixture was stirred at room temperature for 2 h. After addition of water, the mixture was extracted with EtOAc, and the combined extract was washed with 1 M aqueous HCl, saturated aqueous NaHCO₃, and water. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane–Et₂O, 9:1) to afford the 1,2,4-tris-*O*-benzoyl ester (**3**, 0.61 mg) of **2**. **3**: CD (MeOH) λ_{ext} 233 ($\Delta\epsilon$ -5.61) and 220 nm (+2.60) nm; ¹H NMR (CDCl₃) δ 0.84 (3H, t, J = 7.0 Hz), 0.87 (3H, d, J = 7.0 Hz), 1.04 (3H, s), 1.06 (3H, d, J = 7.0 Hz), 1.18 ~ 1.35 (4H, m), 1.46 (1H, m), 1.48 ~ 1.60 (2H, m), 1.73 (1H, m), 1.76 ~ 1.90 (2H, m), 2.21 (1H, d, J = 14.1 Hz), 2.25 (1H, d, J = 14.1 Hz), 2.25 (1H, m), 2.28 (1H, m), 2.34 (1H, m), 2.47 (1H, m), 3.73 (1H, m), 4.50 (1H, d, J = 6.1 and 12.2 Hz, H-1), 4.64 (1H, dd, J = 2.9, and 12.2 Hz, H-1), 4.75 (1H, s, H-18), 4.79 (1H, brs, H-18), 5.34 (1H, m), 5.64 (1H, m), 7.39 (6H, m), 7.52 (3H, m), and 7.98 (6H, m); HRESIMS m/z 677.34426 [calcd for C₄₁H₅₀O₇Na, (M+Na)⁺: 677.34542].

ACKNOWLEDGEMENTS

We thank S. Oka from the Equipment Management Center, Hokkaido University and T. Matsuzaki from the Institute of Scientific and Industrial Research, Osaka University, for the measurement of the ESIMS spectra.

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