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Hamigeromycins C–G, 14-membered macrolides from the fungus *Hamigera avellanea* BCC 17816

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ABSTRACT

Five new 14-membered macrolides, hamigeromycins C–G, together with the previously described compounds, hamigeromycin A and 89-250904-F1 (radicicol analog A), were isolated from the fungus *Hamigera avellanea* BCC 17816. Hamigeromycins A, C, D, and E are stereoisomers differing from one another in the absolute configurations of the 4′,5′-diol moiety. Hamigeromycins F and G are unusual 5′-keto-analogs, and they are 6′-epimers to each other. The structures and the stereochemistry of the new compounds were deduced by analyses of the NMR spectroscopic and mass spectrometry data in combination with chemical means.

1. Introduction

Recently, we reported the isolation of two new 14-membered nonaketide macrolides, hamigeromycins A (**1**) and B (**8**), and two novel cyclopropyl diketones, hamavellones A and B, together with the known macrolide 89-250904-F1 (radicicol analog A, **7**), pseurotin A, and four anthraquinone derivatives from the soil fungus *Hamigera avellanea* BCC 17816.[1] Since this fungal strain proved to be a potent source of bioactive compounds, we have further chemically investigated its secondary metabolites by altering a liquid fermentation medium. When the fungus was fermented in peptone yeast glucose medium (PYGM, see Experimental Section), the production of hamigeromycin A (**1**) and related macrolides was efficient, whilst metabolites of other chemical classes (hamavellones, pseurotin A, and anthraquinones) were absent. A 7 L fermentation broth (PYGM) provided five new macrolides, hamigeromycins C–G (**2**–**6**), along with two major constituents, hamigeromycin A (**1**)[1] and 89-250904-F1 (**7**).[2,3] This culture extract lacked hamigeromycin B (**8**), which was isolated in very low quantity in our previous study. Herein, we report the structure elucidation and assignments of the stereochemistry of the new macrolides.

2. Results and discussion

Hamigeromycin C (**2**) was isolated as a colorless solid, and its molecular formula was established to be $C_{20}H_{26}O_8$ by HRESIMS, which was the same as the most abundant macrolide constituent, hamigeromycin A (**1**). The UV, IR, and ^1H and ^{13}C NMR spectra of **2** were similar to those of **1** (Tables 1 and 2). The planar structure of **2** was elucidated on the basis of the 2D NMR (COSY, NOESY, HMQC, and HMBC) spectroscopic data (Fig. 1). Thus, the structure of the pentasubstituted benzene ring was addressed from the HMBC correlations: from a chelated OH proton (δ_H 11.41, 2-O*H*) to C-1, C-2, and C-3, from H-3 (δ_H 6.44, s) to C-1, C-2, C-4, and C-5, and from methoxy protons resonating at δ_H 3.88 (3H, s) and 3.60 (3H, s), respectively, to C-4 and C-5. The aromatic methine proton (H-3) showed a weak four-bond correlation to the δ_C 170.6 carbonyl, which confirmed the attachment of the ester carbonyl to C-1. The benzene ring was attached to a *trans*-olefin (C-1′/C-2′) at C-6 position as indicated by the HMBC correlations from the olefinic proton H-1′ (δ_H 6.72, d, J=16.3 Hz) to C-1, C-5, and C-6, and from H-2′ (δ_H 6.03, ddd, J=16.3, 7.8, 6.2 Hz) to C-6. The connection from C-1′ to C-5′ as well as the local structure from C-7′ to C-11′ were addressed on the basis of the COSY correlations. The δ_C 210.9 ketone was placed in the C-6′ position, since the HMBC spectrum exhibited correlations from H-5′, H_2-7′, and H_2-8′ to this carbon. The macrolactone ring was required to account for a downfield shift of H-10′ (δ_H 5.31) and from the molecular formula (HRMS). Thus, the planar structure of hamigeromycin C (**2**) was established to be the same as that of hamigeromycin A (**1**). Hamigeromycins D (**3**) and E (**4**) also possessed the same molecular formula ($C_{20}H_{26}O_8$, HRESIMS), and detailed analyses of the NMR spectroscopic data in the similar manner as described above led to the establishment of the same planar structure as **1** and **2** (Tables 1 and 2). These results implied that compounds **1**–**4** are diastereomers differing from each one other by the absolute configurations of the 4′,5′-diol chiral centers.

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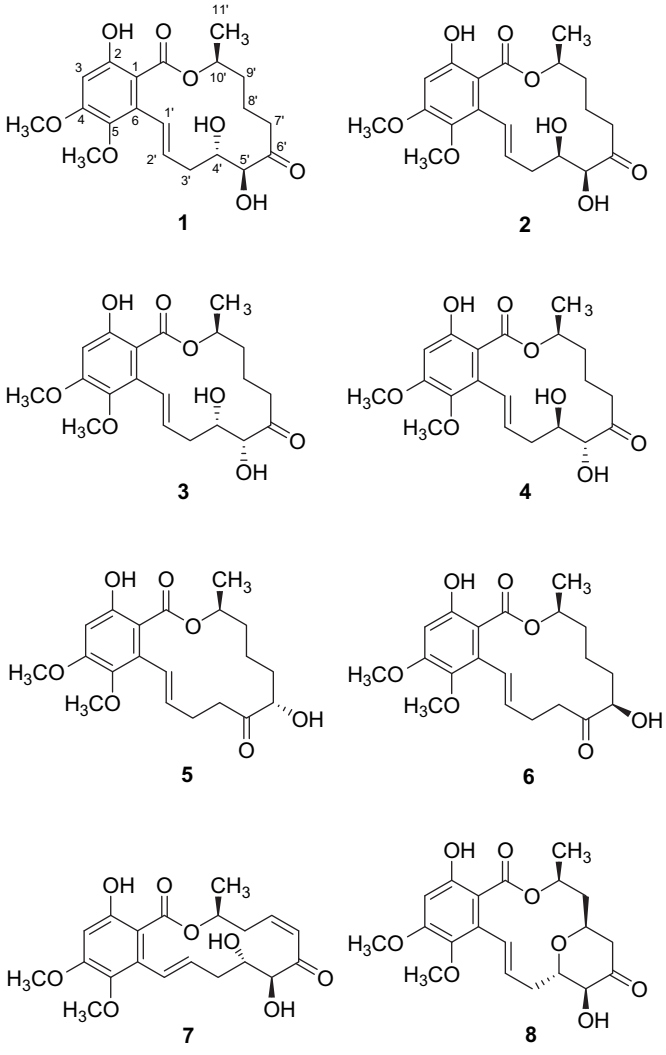


The 4′*S*,5′*S*-configuration of hamigeromycin A (**1**) was previously established by chemical correlation with **7**.[1] To assign the absolute configurations of the other three isomers, compounds **1**–**4** were treated with *p*-TsOH·H_2O in 2,2-dimethoxypropane, which

Table 1
^{13}C NMR data for hamigeromycins A (**1**), C (**2**), D (**3**), and E (**4**) ($CDCl_3$, 125 MHz)

Position	Mult.	1	2	3	4
1-COO–	C	171.2	170.6	170.7	170.6
1	C	103.6	103.8	104.7	105.3
2	C	161.5	160.7	159.8	159.4
3	CH	99.8	99.9	99.9	99.7
4	C	158.9	158.7	158.2	158.4
4-O*C*H$_3$	CH_3	55.9	55.9	55.9	55.9
5	C	140.0	140.5	140.6	140.7
5-O*C*H$_3$	CH_3	60.4	60.3	60.2	59.9
6	C	133.5	133.4	133.2	131.7
1′	CH	126.9	128.7	128.7	127.2
2′	CH	130.4	129.3	129.9	130.4
3′	CH_2	38.0	36.0	38.2	38.0
4′	CH	73.3	71.4	71.1	72.8
5′	CH	79.8	75.5	75.7	80.4
6′	C	209.7	210.9	211.2	210.1
7′	CH_3	39.5	40.2	38.7	39.6
8′	CH_2	20.9	19.0	20.8	20.2
9′	CH_2	34.9	35.0	34.9	35.1
10′	CH	73.0	72.7	73.0	73.3
11′	CH_3	20.1	20.2	20.7	19.6

Table 2
^{1}H NMR data for hamigeromycins A (**1**), C (**2**), D (**3**), and E (**4**) ($CDCl_3$, 500 MHz)

Position	1	2	3	4
2-O*H*	11.94, s	11.41, s	10.96, s	10.68, s
3	6.44, s	6.44, s	6.46, s	6.43, s
4-OC*H*$_3$	3.89, s	3.88, s	3.89, s	3.89, s
5-OC*H*$_3$	3.60, s	3.60, s	3.64, s	3.62, s
1′	6.64, dd (15.9, 1.9)	6.72, d (16.3)	6.73, d (16.3)	6.43, d (16.0)
2′	6.03, ddd (15.9, 10.7, 3.1)	6.04, ddd (16.3, 7.8, 6.2)	5.98, ddd (16.3, 8.4, 6.3)	6.39, ddd (16.0, 8.5, 3.8)
3′	2.70, m	2.74, m	2.71, dt (13.9, 8.8)	2.68, m
	2.18, ddd (15.8, 10.7, 5.0)	2.57, m	2.61, m	2.26, ddd (15.4, 8.5, 5.0)
4′	4.11, m	3.99, m	4.04, m	4.21, m
5′	4.42, d (1.7)	4.33, m	4.45, d (2.7)	4.45, d (2.4)
7′	2.81, m; 2.42, m	3.01, m; 2.41, m	2.88, ddd (15.6, 6.8, 4.7) 2.43, ddd (15.6, 10.7, 6.7)	2.68, m; 2.64, m
8′	1.88, m; 1.76, m	1.89, m; 1.78, m	1.90, m; 1.77, m	1.87, m; 1.82, m
9′	1.75, m; 1.73, m	1.77, m; 1.76, m	1.74, m; 1.69, m	1.84, m; 1.70, m
10′	5.16, m	5.31, m	5.25, m	5.13, m
11′	1.40, d (6.2)	1.40, d (6.3)	1.33, d (6.2)	1.38, d (6.2)

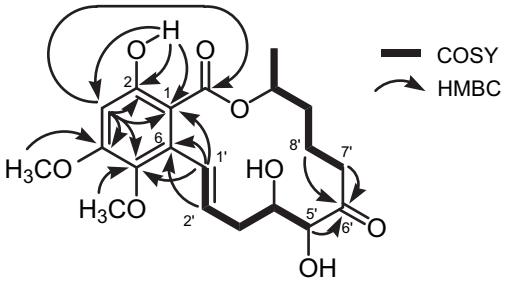


Figure 1. Proposed planar structure of hamigeromycin C (**2**).

gave respective acetonide derivatives **9**–**12** (Fig. 2). Interestingly, the major reaction product from hamigeromycins C (**2**) and D (**3**) were the C-6′ dimethyl acetal derivatives, whereas the ketone functionality was retained in the reactions of hamigeromycins A (**1**) and E (**4**). The acetonide derivatives **9**–**12** were purified by

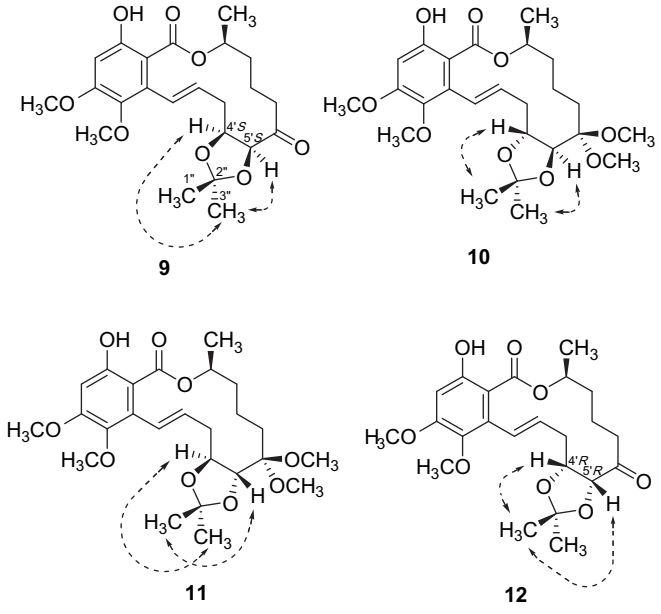


Figure 2. Structures and key NOESY correlations of acetonide derivatives **9**–**12**.

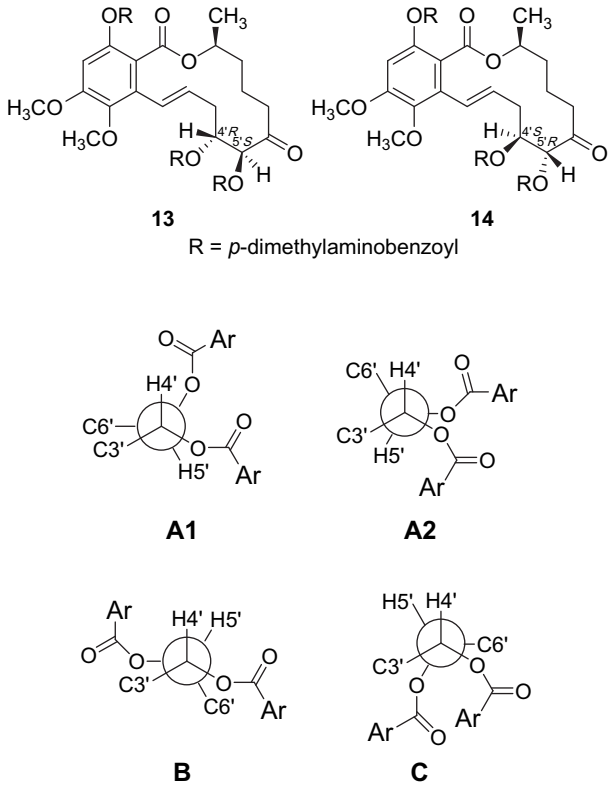


Figure 3. Newman projections showing possible local conformations (**A1**, **A2**, **B**, and **C**) in the 4′*R*,5′*S*-isomer (**13**).

preparative HPLC (ODS column) and the gross structures were confirmed by HRMS and interpretation of the 2D NMR spectroscopic data. The NOESY correlations indicated that **9** and **12** were *cis*-acetonide derivatives, whereas **10** and **11** exhibited *trans*-acetonide configurations (Fig. 2). Since hamigeromycin A (**1**) possesses 4′*S*,5′*S* configuration, the other *cis*-acetonide from hamigeromycin E (**4**) should be the 4′*R*,5′*R*-isomer. What remained then was the assignment of the absolute configurations of **2** and **3**, one of which had to be the 4′*R*,5′*S*-isomer and the other the 4′*S*,5′*R*-isomer. Conformational analysis of their acetonide derivatives, **10** and **11**, based on the available NMR spectroscopic data (^{1}H–^{1}H *J*-values and NOESY correlations) did not lead to a conclusive proposal of their stereochemistry. Therefore, we employed the exciton chirality method.[4] Compounds **2** and **3** were converted to their tris-*p*-dimethylaminobenzoate derivatives **13** and **14**, respectively. The circular dichroism (CD) spectrum of **13** in MeOH showed a negative first Cotton effect (330 nm, $\Delta\varepsilon$=−16.0) and a positive second Cotton effect (307 nm, $\Delta\varepsilon$=+22.4) centered at the *p*-dimethylaminobenzoate chromophore λ_{max} (318 nm). In contrast, the CD spectrum of **14** exhibited a positive first Cotton effect (327 nm, $\Delta\varepsilon$=+26.1) and a negative second Cotton effect (304 nm, $\Delta\varepsilon$=−8.5). The ^{1}H NMR spectra of **13** and **14** in CD_3OD showed $^3J_{H4'-H5'}$ values of 4.5 and 4.8 Hz, respectively. Figure 3 shows Newman projections of four possible conformations for the 4′*R*,5′*S*-isomer; A1, A2, B, and C. Examinations of the macrolide ring conformations with a molecular model strongly suggested that conformations corresponding to the projections B and C are disfavored due to steric hindrance of the two *p*-dimethylaminobenzoyloxy groups, which would be forced into close contact with the macrocyclic ring. On the basis of the exciton chirality rule, compound **13**, exhibiting negative chirality, was proposed to possess the 4′*R*,5′*S* configuration, while in turn **14** was assigned as the 4′*S*,5′*R*-isomer.

The molecular formula of hamigeromycin F (**5**) was determined by HRESIMS to be $C_{20}H_{26}O_7$, which was lacking one oxygen atom compared to compounds **1**–**4**. The ^{1}H and ^{13}C NMR, DEPT135, and HMQC spectroscopic data demonstrated that an oxymethine (C-4′) of **1** was replaced by a methylene in **5**. The HMBC correlations (Table 3) revealed that the pentasubstituted benzene moiety was identical to **1**. The connection from C-1′ to C-4′ and the linkage from C-6′ to C-11′ was addressed by COSY and HMBC correlations. HMBC correlations from H_2-3′ (δ_H 2.81 and 2.55), H-7′ (δ_H 2.06), and 6′-OH to the ketone carbon at δ_C 211.5 indicated that this ketone should be placed in the C-5′ position. Consequently, hamigeromycin F (**5**) was identified as a 4′-deoxy derivative of **1**–**4**, and the positions of the ketone and the remaining secondary alcohol functions were exchanged. The molecular formula of hamigeromycin G (**6**) was determined to be $C_{20}H_{26}O_7$ (HRESIMS), which was the same as **5**. Detailed analyses of the NMR spectroscopic data (Table 3) resulted

Table 3
NMR data for hamigeromycins F (**5**) and G (**6**) in $CDCl_3$ (500 MHz for ^{1}H, and 125 MHz for ^{13}C)

Position	**5**			**6**		
	δ_C, mult.	δ_H, mult. (*J* in Hz)	HMBC	δ_C, mult.	δ_H, mult. (*J* in Hz)	HMBC
1-*C*OO-	171.1, C			168.8, C		
1	104.0, C			105.8, C		
2	160.9, C			158.3, C		
2-O*H*		11.70, s	1,2,3		10.06, s	1,2,3
3	99.6, H	6.41, s	1,2,4,5,*C*OO	99.6, CH	6.40, s	1,2,4,5,*C*OO
4	158.6, C			157.7, C		
4-O*C*H_3	55.8, CH_3	3.87, s	4	55.8, CH_3	3.87, s	4
5	140.3, C			140.6, C		
5-O*C*H_3	60.5, CH_3	3.59, s	5	60.3, CH_3	3.62, s	5
6	133.6, C			133.8, C		
1′	125.7, CH	6.62, d (16.1)	1,5,6,2′,3′	125.9, CH	6.54, br d (15.8)	1,5,3′
2′	132.1, CH	5.94, ddd (16.1, 8.2, 4.1)		132.9, CH	5.75, ddd (15.8, 6.8, 6.4)	6,3′
3′	28.4, CH_2	2.81, m; 2.55, m	1′,5′	27.2, CH_2	2.78, m; 2.50, m	1′,2′,4′
4′	37.7, CH_2	2.84, m; 2.58, m	2′,3′	37.2, CH_2	2.80, m; 2.52, m	3′
5′	211.5, C			211.8, C		
6′	76.6, CH	4.36, m		76.0, CH	4.40, m	
6′-O*H*		3.51, d (4.6)	5′,6′		3.57, d (4.9)	5′
7′	33.0, CH_2	2.06, m; 1.84, m	5′,6′,8′	33.0, CH_2	2.11, m; 1.81, m	5′,6′
8′	20.1, CH_2	1.50, m; 121, m	7′	18.0, CH_2	1.63, m; 1.04, m	
9′	36.1, CH_2	1.69, m; 1.65, m	8′	35.5, CH_2	1.77, m; 1.57, m	7′,8′,10′
10′	73.5, CH	4.99, m		71.4, CH	5.30, m	8′
11′	20.7, CH_3	1.36, d (6.2)	9′,10′	20.0, CH_3	1.36, d (6.3)	9′,10′

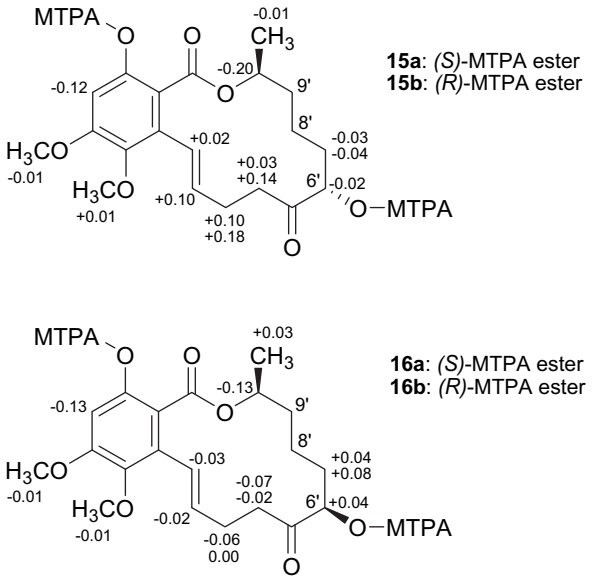
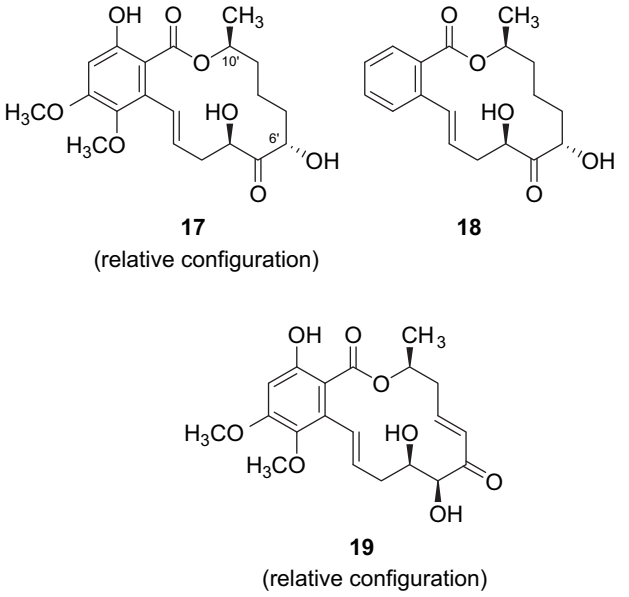


Figure 4. $\Delta\delta$-Values (δ_S–δ_R) of the bis-(*S*)- and bis-(*R*)-MTPA esters **15a** and **15b** of hamigeromycin F (**5**), and **16a** and **16b** of hamigeromycin G (**6**). The assignments of proton resonances are based on the COSY data. Accurate chemical shifts of H_2-8′ and H_2-9′ of these compounds could not be estimated due to the signal overlap with H_2O or lipid.



in establishing the same planar structure as **5**, which implied that **5** and **6** are C-6′ epimers. The absolute configuration of these compounds was addressed by application of modified Mosher method.[5,6] Hamigeromycin F (**5**) was reacted with (*R*)- and (*S*)-MTPACl to give, respectively, bis-(*S*)- and bis-(*R*)-MTPA ester derivatives (**15a** and **15b**). Based on the $\Delta\delta$ values (δ_S–δ_R) of the bis-MTPA ester derivatives (Fig. 4), the 6′*S* configuration of **5** was established. Similarly hamigeromycin G (**6**) was converted to its bis-(*S*)- and bis-(*R*)-MTPA ester derivatives **16a** and **16b**, the ^{1}H NMR spectroscopic data of which unambiguously indicated the 6′*R* configuration of **6**.

The 5′-keto-derivatives, hamigeromycins F (**5**) and G (**6**), resemble queenslandon (**17**), which was previously isolated from *Chrysosporium queenslandicum* IFM 51121 and proposed to have the 4′*R**,6′*S**,10′*S** relative configuration on the basis of NMR spectroscopic data.[7] Comparison of the ^{1}H and ^{13}C NMR spectroscopic data in $CDCl_3$ reported for queenslandon with those of hamigeromycins showed several marked differences in chemical shifts of protons and carbons. Significantly, δ_H 3.95 (H-10′) of queenslandon was not consistent with δ_H 4.99 (H-10′) for **5**, whereas H-6′ of queenslandon (δ_H 5.18) was shifted far more downfield than the corresponding proton of **5** (δ_H 4.36). The oxymethine proton (H-10′) of compounds **1**–**7** resonated within a range of δ_H 5.36–4.99. Maier and co-workers recently reported the synthesis of a core structure (**18**) of queenslandon.[8] Selected chemical shifts of protons for **18** in $CDCl_3$, δ_H 5.14–5.23 (H-10′), and δ_H 4.30–4.37 (H-6′),[8] were reasonably close to those of **5**. Furthermore, the carbon chemical shifts reported for **18**, δ_C 75.1 (C-6′), 33.1 (C-7′), 20.4 (C-8′), 35.3 (C-9′), and 72.1 (C-10′),[8] were consistent with those of **5** (Table 3), but different from those of queenslandon, δ_C 73.0 (C-6′), 20.9 (C-7′), 34.9 (C-8′), 39.5 (C-9′), and 74.2 (C-10′).[7] We therefore cast some doubts on the proposed structure (**17**) of queenslandon. Recently, structurally related nematicidal macrolides caryospomycins A–C were isolated from *Caryospora calliparpa* YMF1.01026.[9] Hamigeromycin C (**2**) is the 7′,8′-dihydro analog of caryospomycin C (**19**), which was proposed to possess the 4′*R**,5′*S**,10′*S** relative configuration.

Macrolides **1**–**5** were subjected to a cytotoxicity assay against three human cancer cell lines (KB, MCF-7, and NCI-H187) and noncancerous Vero cells (African green monkey kidney fibroblasts). All compounds were inactive against cancer cell lines at a concentration of 50 μg/mL, whilst compounds **1** and **2** showed weak growth inhibition against Vero cells with respective IC_{50} values of 42 and 13 μg/mL. All compounds were inactive in an antimalarial activity assay against *Plasmodium falciparum* K1 at 10 μg/mL.

3. Experimental

3.1. General procedures

Melting points were measured with an Electrothermal IA9100 digital melting point apparatus. Optical rotations were measured with a JASCO P-1030 digital polarimeter. UV spectra were recorded on a GBC Cintra 404 spectrophotometer. CD spectra were recorded on a JASCO J-180 spectropolarimeter. FTIR spectra were recorded on a Bruker VECTOR 22 spectrometer. NMR spectra were recorded on Bruker AV500D and DRX400 spectrometers. ESI-TOF mass spectra were measured with Micromass LCT and Bruker micrOTOF mass spectrometers.

3.2. Fungal material

H. avellanea Stock & Samson, accession # BCC 17816 was isolated from a soil sample collected in the Queen Sirikit Botanic Garden, Chiang Mai province, Thailand, and identified based on morphology and ITS rDNA sequence data by Dr. J. Jennifer Luangsa-ard as described previously.[1]

3.3. Fermentation and isolation

The fungus BCC 17816 was maintained on potato dextrose agar at 25 °C, which was then cut into plugs and inoculated in 3×250 mL Erlenmeyer flasks containing 25 mL of potato dextrose broth (PDB; potato starch 4.0 g, dextrose 20.0 g, per liter). After incubation at 25 °C for 6 days on a rotary shaker (200 rpm), each primary culture was transferred into a 1 L Erlenmeyer flask containing 250 mL of the same liquid medium (PDB), and incubated for 6 days under identical conditions. These secondary cultures (700 mL) were transferred into a 10 L bioreactor containing 6.3 L of

peptone yeast glucose medium (PYGM: bacteriological peptone 5.0 g, yeast extract 20.0 g, glucose 10.0 g, KH_2PO_4 1.0 g, $MgSO_4 \cdot 7H_2O$ 0.5 g, per liter), and final fermentation was carried out at 25 °C for 7 days. The culture was filtered to separate the residue (mycelium) and the filtrate (broth). The broth was extracted with EtOAc (3×5.5 L) and concentrated to yield a yellow solid (1.30 g; extract A). The mycelium was macerated in MeOH (1.5 L, room temperature, 2 days) and filtered. This extraction was repeated one more time. The filtrate was defatted with hexane (2.1 L), and the MeOH phase was evaporated. The residue was diluted with EtOAc (3 L), washed with H_2O (300 mL), concentrated under reduced pressure to give a pale brown gum (1.06 g, extract B). Extract A was subjected to column chromatography (CC) on Si gel (3.0×21 cm) using CH_2Cl_2/MeOH as eluent to obtain 14 fractions (1–14). Fraction 3 (44 mg) was fractionated by CC on Si gel (1.5×20 cm, step gradient elution with CH_2Cl_2/MeOH) to obtain eight fractions (3-1–3-8). Fractions 3-3 (6.5 mg) and 3-4 (3.3 mg) were combined and further purified by HPLC using a reverse phase column (Phenomenex Luna 10u C18(2) 100A, 21.2×250 mm; mobile phase MeCN/H_2O 27:73, flow rate 15 mL/min) to furnish **6** (1.8 mg, t_R 25 min) and **5** (3.7 mg, t_R 38 min). Fraction 10 (300 mg) was subjected to HPLC (MeCN/H_2O 27:73) to obtain **3** (26 mg, t_R 21 min), **4** (37 mg, t_R 27 min), and a mixture of **2** and **1** corresponding to the broad peak around t_R 43 min (165 mg). This mixture was separated by CC on Si gel (CH_2Cl_2/EtOAc) to furnish pure compounds **2** (30 mg) and **1** (70 mg). Fraction 11 (20 mg) was also purified by HPLC (MeCN/H_2O 27:73) to afford **3** (1.9 mg, t_R 21 min) and **1** (7.0 mg, t_R 35 min). Fraction 10 (240 mg) was triturated in CH_2Cl_2 (3 mL) and MeOH (3 mL) to leave uracil (70 mg) as a residual colorless solid. The mycelial extract (extract B) was also subjected to the NMR-guided chromatographic fractionation, however, no new compound was found.

*3.3.1. Hamigeromycin C (**2**).* Colorless solid; mp 102–105 °C; $[\alpha]_D^{28}$ −11 (*c* 0.12, MeOH); UV (MeOH) λ_{max} (log ε) 230 (4.37), 267 (3.90), 321 (3.71) nm; IR (KBr) ν_{max} 3446, 1710, 1644, 1596, 1359, 1317, 1247, 1053, 1020, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) data, see Tables 1 and 2; HRMS (ESI-TOF) *m*/*z* 395.1707 $[M+H]^+$ (calcd for $C_{20}H_{27}O_8$, 395.1706).

*3.3.2. Hamigeromycin D (**3**).* Colorless solid; mp 115–117 °C; $[\alpha]_D^{27}$ +24 (*c* 0.10, MeOH); UV (MeOH) λ_{max} (log ε) 221 (4.37), 259 sh (3.88), 268 sh (3.78), 309 (3.61) nm; IR (KBr) ν_{max} 3489, 1713, 1645, 1595, 1248, 1029 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) data, see Tables 1 and 2; HRMS (ESI-TOF) *m*/*z* 395.1716 $[M+H]^+$ (calcd for $C_{20}H_{27}O_8$, 395.1706).

*3.3.3. Hamigeromycin E (**4**).* Colorless solid; mp 139–142 °C; $[\alpha]_D^{28}$ +44 (*c* 0.10, MeOH); UV (MeOH) λ_{max} (log ε) 231 (4.43), 260 sh (3.99), 269 sh (3.93), 315 (3.73) nm; IR (KBr) ν_{max} 3423, 1710, 1656, 1599, 1360, 1314, 1249, 1225, 1020 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) data, see Tables 1 and 2; HRMS (ESI-TOF) *m*/*z* 395.1703 $[M+H]^+$ (calcd for $C_{20}H_{27}O_8$, 395.1706).

*3.3.4. Hamigeromycin F (**5**).* Colorless amorphous solid; $[\alpha]_D^{26}$ +41 (*c* 0.13, MeOH); UV (MeOH) λ_{max} (log ε) 219 (4.41), 257 sh (3.89), 268 sh (3.75), 307 (3.61) nm; IR (KBr) ν_{max} 3455, 1710, 1646, 1597, 1247, 1023, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) data, see Table 3; HRMS (ESI-TOF) *m*/*z* 401.1570 $[M+Na]^+$ (calcd for $C_{20}H_{26}O_7Na$, 401.1576).

*3.3.5. Hamigeromycin G (**6**).* Colorless amorphous solid; $[\alpha]_D^{26}$ +17 (*c* 0.08, MeOH); UV (MeOH) λ_{max} (log ε) 219 (4.24), 258 sh (3.69), 267 sh (3.58), 305 (3.45) nm; IR ($CHCl_3$) ν_{max} 3451, 1711, 1643, 1594, 1245, 1023, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) data, see Table 3; HRMS (ESI-TOF) *m*/*z* 401.1568 $[M+Na]^+$ (calcd for $C_{20}H_{26}O_7Na$, 401.1576).

3.4. Preparation of the acetonide derivatives

To a solution of hamigeromycin C (**2**; 1.3 mg) in 2,2-dimethoxypropane (0.3 mL) was added *p*-TsOH·H_2O (ca. 0.5 mg), and the mixture was stirred at room temperature for 4 h. The mixture was diluted with EtOAc and washed with 1 M $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to obtain a colorless solid, which was purified by HPLC using a reverse phase column (MeCN/H_2O 50:50) to afford compound **10** (1.1 mg) as a colorless solid. Using the same procedure, compounds **9**, **11**, and **13** were obtained as major reaction products, respectively, from **1**, **3**, and **4**.

*3.4.1. Acetonide of hamigeromycin A (**9**).* Colorless amorphous solid; IR ($CHCl_3$) ν_{max} 1726, 1645, 1597, 1247, 1222, 1059, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 11.85 (1H, s, 2-O*H*), 6.67 (1H, dd, *J*=16.1, 2.2 Hz, H-1′), 6.45 (1H, s, H-3), 6.01 (1H, ddd, *J*=16.1, 9.4, 3.0 Hz, H-2′), 5.26 (1H, m, H-10′), 4.59 (1H, d, *J*=6.3 Hz, H-5′), 4.55 (1H, m, H-4′), 3.89 (3H, s, 4-OCH_3), 3.57 (3H, s, 5-OCH_3), 3.13 (1H, ddd, *J*=19.4, 8.6, 4.3 Hz, Ha-7′), 3.05 (1H, dq, *J*=16.3, 3.0 Hz, Ha-3′), 2.38 (1H, m, Hb-7′), 2.35 (1H, m, Hb-3′), 2.06 (1H, m, Ha-8′), 1.83 (1H, m, Ha-9′), 1.80 (1H, m, Hb-9′), 1.67 (3H, s, H_3-1″), 1.49 (1H, m, Hb-8′), 1.40 (3H, s, H_3-3″), 1.34 (3H, d, *J*=6.3 Hz, H_3-11′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.5 (C, C-6′), 171.1 (C, -*C*OO-), 161.3 (C, C-2), 158.8 (C, C-4), 140.3 (C, C-5), 132.7 (C, C-6), 130.0 (CH, C-2′), 127.0 (CH, C-1′), 110.0 (C, C-2″), 103.6 (C, C-1), 99.9 (CH, C-3), 80.7 (CH, C-5′), 77.5 (CH, C-4′), 74.7 (CH, C-10′), 60.2 (CH_3, 5-O*C*H_3), 55.9 (CH_3, 4-O*C*H_3), 41.6 (CH_2, C-7′), 33.8 (CH_2, C-3′), 32.7 (CH_2, C-9′), 26.5 (CH_3, C-1″), 25.9 (CH_3, C-3″), 20.2 (CH_3, C-11′), 18.6 (CH_2, C-8′); HRMS (ESI-TOF) *m*/*z* 457.1843 $[M+Na]^+$ (calcd for $C_{23}H_{30}O_8Na$, 457.1833).

*3.4.2. Acetonide of hamigeromycin C (**10**).* Colorless amorphous solid; IR ($CHCl_3$) ν_{max} 1651, 1599, 1249, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 11.77 (1H, s, 2-O*H*), 6.74 (1H, dd, *J*=16.1, 2.0 Hz, H-1′), 6.42 (1H, s, H-3), 6.13 (1H, ddd, *J*=16.1, 9.6, 3.3 Hz, H-2′), 4.94 (1H, m, H-10′), 4.20 (1H, dt, *J*=9.2, 3.2 Hz, H-4′), 3.97 (1H, d, *J*=9.2 Hz, H-5′), 3.88 (3H, s, 4-OCH_3), 3.58 (3H, s, 5-OCH_3), 3.46 (3H, s, 6′-OCH_3), 3.28 (3H, s, 6′-OCH_3), 3.05 (1H, m, Ha-3′), 2.42 (1H, ddd, *J*=16.7, 9.6, 2.9 Hz, Hb-3′), 1.93 (1H, m, Ha-7′), 1.72 (1H, m, Ha-8′), 1.68 (1H, m, Ha-9′), 1.57 (1H, m, Hb-9′), 1.46 (3H, s, H_3-1″), 1.39 (3H, d, *J*=6.1 Hz, H_3-11′), 1.35 (3H, s, H_3-3″), 1.30 (1H, m, Hb-8′), 1.28 (1H, m, Hb-7′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4 (C, –*C*OO–), 161.0 (C, C-2), 158.8 (C, C-4), 140.4 (C, C-5), 133.8 (C, C-6), 129.5 (CH, C-2′), 126.9 (CH, C-1′), 107.6 (C, C-2″), 104.0 (C, C-1), 100.0 (C, C-6′), 99.5 (CH, C-3), 80.1 (CH, C-5′), 75.9 (CH, C-4′), 74.0 (CH, C-10′), 60.4 (CH_3, 5-O*C*H_3), 55.8 (CH_3, 4-O*C*H_3), 50.8 (CH_3, 6′-O*C*H_3), 49.1 (CH_3, 6′-O*C*H_3), 33.6 (CH_2, C-7′), 35.1 (CH_2, C-3′), 36.6 (CH_2, C-9′), 27.0 (CH_3, C-1″), 27.0 (CH_3, C-3″), 21.0 (CH_3, C-11′), 20.5 (CH_2, C-8′); HRMS (ESI-TOF) *m*/*z* 503.2256 $[M+Na]^+$ (calcd for $C_{25}H_{36}O_9Na$, 503.2252).

*3.4.3. Acetonide of hamigeromycin D (**11**).* Colorless amorphous solid; IR ($CHCl_3$) ν_{max} 1646, 1597, 1246 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 11.66 (1H, s, 2-O*H*), 6.49 (1H, d, *J*=16.1 Hz, H-1′), 6.41 (1H, s, H-3), 6.38 (1H, dt, *J*=16.1, 6.9 Hz, H-2′), 5.28 (1H, m, H-10′), 4.03 (1H, ddd, *J*=9.1, 5.9, 2.8 Hz, H-4′), 3.95 (1H, d, *J*=9.1 Hz, H-5′), 3.88 (3H, s, 4-OCH_3), 3.59 (3H, s, 5-OCH_3), 3.42 (3H, s, 6′-OCH_3), 3.31 (3H, s, 6′-OCH_3), 2.95 (1H, m, Ha-3′), 2.42 (1H, dt, *J*=15.9, 6.3 Hz, Hb-3′), 1.88 (1H, m, Ha-7′), 1.71 (1H, m, Ha-9′), 1.67 (1H, m, Hb-7′), 1.62 (1H, m, Hb-9′), 1.60 (1H, m, Ha-8′), 1.53 (1H, m, Hb-8′), 1.46 (3H, s, H_3-1″), 1.42 (3H, s, H_3-3″), 1.35 (3H, d, *J*=6.4 Hz, H_3-11′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0 (C, –*C*OO–), 160.8 (C, C-2), 158.7 (C, C-4), 140.5 (C, C-5), 132.8 (C, C-6), 130.4 (CH, C-2′), 126.6 (CH, C-1′), 107.8 (C, C-2″), 104.2 (C, C-1), 100.6 (C, C-6′), 99.5 (CH, C-3), 80.3 (CH, C-

5′), 76.9 (CH, C-4′), 72.4 (CH, C-10′), 60.1 (CH_3, 5-OCH_3), 55.8 (CH_3, 4-OCH_3), 50.0 (CH_3, 6′-OCH_3), 49.1 (CH_3, 6′-OCH_3), 36.1 (CH_2, C-3′), 34.9 (CH_2, C-9′), 32.8 (CH_2, C-7′), 27.1 (CH_3, C-1″), 27.1 (CH_3, C-3″), 18.1 (CH_3, C-11′), 17.0 (CH_2, C-8′); HRMS (ESI-TOF) *m*/*z* 503.2255 $[M+Na]^+$ (calcd for $C_{25}H_{36}O_9Na$, 503.2252).

*3.4.4. Acetonide of hamigeromycin E (**12**).* Colorless solid; IR ($CHCl_3$) ν_{max} 1723, 1648, 1598, 1247, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 11.73 (1H, s, 2-O*H*), 6.48 (1H, d, *J*=16.3 Hz, H-1′), 6.43 (1H, s, H-3), 6.19 (1H, ddd, *J*=16.3, 8.6, 4.5 Hz, H-2′), 5.19 (1H, m, H-10′), 4.65 (1H, dt, *J*=1.1, 7.6 Hz, H-4′), 4.61 (1H, d, *J*=7.6 Hz, H-5′), 3.88 (3H, s, 4-OC*H*$_3$), 3.55 (3H, s, 5-OC*H*$_3$), 2.99 (1H, ddd, *J*=19.9, 9.9, 4.5 Hz, Ha-7′), 2.77 (1H, ddd, *J*=19.9, 5.6, 4.5 Hz, Hb-7′), 2.65 (1H, m, Ha-3′), 2.54 (1H, dd, *J*=16.6, 8.6 Hz, Hb-3′), 2.05 (1H, m, Ha-9′), 1.93 (1H, m, Ha-8′), 1.81 (1H, m, Hb-9′), 1.56 (3H, s, H_3-1″), 1.53 (1H, m, Hb-8′), 1.36 (3H, s, H_3-3″), 1.34 (3H, d, *J*=6.3 Hz, H_3-11′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.4 (C, C-6′), 171.3 (C, –*C*OO–), 160.8 (C, C-2), 158.7 (C, C-4), 140.7 (C, C-5), 133.6 (C, C-6), 130.9 (CH, C-2′), 125.0 (CH, C-1′), 109.5 (C, C-2″), 103.9 (C, C-1), 99.7 (CH, C-3), 82.2 (CH, C-5′), 75.9 (CH, C-4′), 75.2 (CH, C-10′), 60.1 (CH_3, 5-OCH_3), 55.9 (CH_3, 4-OCH_3), 39.0 (CH_2, C-7′), 34.0 (CH_2, C-3′), 32.7 (CH_2, C-9′), 26.2 (CH_3, C-1″), 24.8 (CH_3, C-3″), 20.7 (CH_3, C-11′), 19.6 (CH_2, C-8′); HRMS (ESI-TOF) *m*/*z* 457.1839 $[M+Na]^+$ (calcd for $C_{23}H_{30}O_8Na$, 457.1833).

3.5. Preparation of tris-*p*-dimethylaminobenzoate derivatives

Hamigeromycin C (**2**, 2.0 mg) was treated with *p*-dimethylaminobenzoyl chloride (15 mg) and 4-*N*,*N*-dimethylaminopyridine (DMAP, 2.5 mg) in 0.3 mL pyridine/CH_2Cl_2 1:2 at room temperature for 16 h. The mixture was diluted with EtOAc and washed with H_2O and 1 M $NaHCO_3$, and the organic layer was concentrated in vacuo to obtain a colorless solid (10 mg), which was purified by CC on Si gel (EtOAc/CH_2Cl_2 5:95) to furnish the tris-*p*-dimethylaminobenzoate derivative **13** (2.3 mg). Similarly, tris-*p*-dimethylaminobenzoate **14** (2.5 mg) was prepared from hamigeromycin D (**3**, 2.0 mg).

*3.5.1. Compound **13**.* Colorless gum; UV (MeOH) λ_{max} 228 (3.96), 319 (4.88) nm; CD (MeOH) $\Delta\varepsilon$ 330 (−16.0), 307 (+22.4) nm; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (2H, d, *J*=9.0 Hz, *p*-dimethylaminobenzoyl), 7.97 (2H, d, *J*=9.1 Hz, *p*-dimethylaminobenzoyl), 7.80 (2H, d, *J*=9.1 Hz, *p*-dimethylaminobenzoyl), 6.88 (1H, s, H-3), 6.78 (2H, d, *J*=9.1 Hz, *p*-dimethylaminobenzoyl), 6.74 (2H, d, *J*=9.0 Hz, *p*-dimethylaminobenzoyl), 6.63 (2H, d, *J*=9.1 Hz, *p*-dimethylaminobenzoyl), 6.54 (1H, d, *J*=16.0 Hz, H-1′), 6.28 (1H, ddd, *J*=16.0, 8.8, 6.3 Hz, H-2′), 5.51 (1H, d, *J*=4.5 Hz, H-4′), 5.46 (1H, m, H-5′), 5.12 (1H, m, H-10′), 3.88 (3H, s, 4-OC*H*$_3$), 3.69 (3H, s, 5-OC*H*$_3$), 3.09 (6H, s, *p*-dimethylaminobenzoyl), 3.06 (6H, s, *p*-dimethylaminobenzoyl), 3.04 (6H, s, *p*-dimethylaminobenzoyl), 2.85–2.79 (2H, m, Ha-3′ and Hb-3′), 2.77 (1H, m, Ha-7′), 2.55 (1H, m, Hb-7′), 1.78–1.72 (3H, m, Ha-8′, Hb-8′, and Ha-9′), 1.54 (1H, m, Hb-9′), 0.97 (3H, d, *J*=6.2 Hz, H_3-11′); HRMS (ESI-TOF) *m*/*z* 858.3577 $[M+Na]^+$ (calcd for $C_{47}H_{53}N_3O_{11}Na$, 858.3572).

*3.5.2. Compound **14**.* Colorless gum; UV (MeOH) λ_{max} (log ε) 226 (3.92), 317 (4.89) nm; CD (MeOH) $\Delta\varepsilon$ 327 (+26.1), 304 (−8.5) nm; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (2H, d, *J*=9.1 Hz, *p*-dimethylaminobenzoyl), 7.87 (2H, d, *J*=9.1 Hz, *p*-dimethylaminobenzoyl), 7.84 (2H, d, *J*=9.1 Hz, *p*-dimethylaminobenzoyl), 6.88 (1H, s, H-3), 6.78 (2H, d, *J*=9.1 Hz, *p*-dimethylaminobenzoyl), 6.72 (2H, d, *J*=9.1 Hz, *p*-dimethylaminobenzoyl), 6.69 (2H, d, *J*=9.1 Hz, *p*-dimethylaminobenzoyl), 6.63 (1H, d, *J*=16.3 Hz, H-1′), 6.40 (1H, dt, *J*=16.3, 7.0 Hz, H-2′), 5.63 (1H, m, H-4′), 5.59 (1H, d, *J*=4.8 Hz, H-5′), 5.18 (1H, m, H-10′), 3.88 (3H, s, 4-OC*H*$_3$), 3.71 (3H, s, 5-OC*H*$_3$), 3.09 (6H, s, *p*-dimethylaminobenzoyl), 3.05 (6H, s, *p*-dimethylaminobenzoyl), 3.04 (6H, s, *p*-dimethylaminobenzoyl), 2.85 (1H, m, Ha-3′), 2.81 (1H, m, Ha-7′), 2.66 (1H, m, Hb-7′), 2.48 (1H, m, Hb-3′), 1.85 (1H, m, Ha-8′), 1.75 (1H, m, Hb-8′), 1.72 (1H, m, Ha-9′), 1.64 (1H, m, Hb-9′), 1.00 (3H, d, *J*=6.1 Hz, H_3-11′); HRMS (ESI-TOF) *m*/*z* 858.3579 $[M+Na]^+$ (calcd for $C_{47}H_{53}N_3O_{11}Na$, 858.3572).

3.6. Preparation of bis-MTPA esters

Hamigeromycin F (**5**, 0.4 mg) was treated with (+)-(*S*)-MTPACl (2 mg) in pyridine (0.1 mL) at room temperature for 16 h. The mixture was diluted with EtOAc and washed with H_2O and 1 M $NaHCO_3$, and the organic layer was concentrated in vacuo. The residue was purified by preparative HPLC (MeCN/H_2O) to furnish the bis-(*R*)-MTPA ester **15b** (1.2 mg). Similarly, bis-(*S*)-MTPA ester **15a** was prepared from **5** and (−)-(*R*)-MTPACl. In the same fashion, bis-(*S*)- and bis-(*R*)-MTPA esters, **16a** and **16b**, were synthesized from hamigeromycin G (**6**). The assignments of protons are based on the COSY data.

*3.6.1. Bis-(S)-MTPA ester **15a**.* Colorless gum; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60–7.40 (10H, m, phenyl of MTPA ×2), 6.576 (1H, s, H-3), 6.398 (1H, d, *J*=16.5 Hz, H-1′), 6.177 (1H, m, H-2′), 5.225 (1H, dd, *J*=6.0, 4.6 Hz, H-6′), 4.736 (1H, m, H-10′), 3.846 (3H, s, 4-OC*H*$_3$), 3.737 (3H, s, 5-OC*H*$_3$), 3.669 (3H, br s, OC*H*$_3$ of MTPA), 3.591 (3H, br s, OC*H*$_3$ of MTPA), 2.738 (1H, m, Ha-3′), 2.600 (1H, m, Ha-4′), 2.460 (1H, m, Hb-3′), 2.445 (1H, m, Hb-4′), 1.850 (1H, m, Ha-7′), 1.813 (1H, m, Hb-7′), 1.65–1.10 (4H, m, Ha-8′, Hb-8′, Ha-9′, and Hb-9′), 0.882 (3H, d, *J*=6.1 Hz, H_3-11′); HRMS (ESI-TOF) *m*/*z* 833.2369 $[M+Na]^+$ (calcd for $C_{40}H_{40}O_{11}F_6Na$, 833.2367).

*3.6.2. Bis-(R)-MTPA ester **15b**.* Colorless gum; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60–7.40 (10H, m, phenyl of MTPA ×2), 6.699 (1H, s, H-3), 6.381 (1H, d, *J*=16.2 Hz, H-1′), 6.155 (1H, m, H-2′), 5.240 (1H, dd, *J*=6.7, 4.2 Hz, H-6′), 4.938 (1H, m, H-10′), 3.852 (3H, s, 4-OC*H*$_3$), 3.730 (3H, s, 5-OC*H*$_3$), 3.584 (3H, br s, OC*H*$_3$ of MTPA), 3.548 (3H, br s, OC*H*$_3$ of MTPA), 2.634 (1H, m, Ha-3′), 2.573 (1H, m, Ha-4′), 2.310 (1H, m, Hb-4′), 2.279 (1H, m, Hb-3′), 1.880 (1H, m, Ha-7′), 1.855 (1H, m, Hb-7′), 1.65–1.10 (4H, m, Ha-8′, Hb-8′, Ha-9′, and Hb-9′), 0.894 (3H, d, *J*=6.3 Hz, H_3-11′); HRMS (ESI-TOF) *m*/*z* 833.2361 $[M+Na]^+$ (calcd for $C_{40}H_{40}O_{11}F_6Na$, 833.2367).

*3.6.3. Bis-(S)-MTPA ester **16a**.* Colorless gum; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60–7.40 (10H, m, phenyl of MTPA ×2), 6.595 (1H, s, H-3), 6.504 (1H, d, *J*=16.2 Hz, H-1′), 6.096 (1H, m, H-2′), 5.312 (1H, dd, *J*=6.1, 3.5 Hz, H-6′), 4.810 (1H, m, H-10′), 3.847 (3H, s, 4-OC*H*$_3$), 3.746 (3H, s, 5-OC*H*$_3$), 3.661 (3H, br s, OC*H*$_3$ of MTPA), 3.524 (3H, br s, OC*H*$_3$ of MTPA), 2.833 (1H, m, Ha-3′), 2.740 (1H, m, Ha-4′), 2.615 (1H, m, Hb-4′), 2.360 (1H, m, Hb-3′), 2.105 (1H, m, Ha-7′), 1.810 (1H, m, Hb-7′), 1.65–1.10 (4H, m, Ha-8′, Hb-8′, Ha-9′, and Hb-9′), 0.887 (3H, d, *J*=6.2 Hz, H_3-11′); HRMS (ESI-TOF) *m*/*z* 833.2370 $[M+Na]^+$ (calcd for $C_{40}H_{40}O_{11}F_6Na$, 833.2367).

*3.6.4. Bis-(R)-MTPA ester **16b**.* Colorless gum; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65–7.40 (10H, m, phenyl of MTPA ×2), 6.729 (1H, s, H-3), 6.530 (1H, d, *J*=16.2 Hz, H-1′), 6.120 (1H, m, H-2′), 5.273 (1H, dd, *J*=5.7, 3.3 Hz, H-6′), 4.939 (1H, m, H-10′), 3.858 (3H, s, 4-OC*H*$_3$), 3.756 (3H, s, 5-OC*H*$_3$), 3.632 (3H, br s, OC*H*$_3$ of MTPA), 3.555 (3H, br s, OC*H*$_3$ of MTPA), 2.894 (1H, m, Ha-3′), 2.806 (1H, m, Ha-4′), 2.638 (1H, m, Hb-4′), 2.360 (1H, m, Hb-3′), 2.070 (1H, m, Ha-7′), 1.728 (1H, m, Hb-7′), 1.65–1.10 (4H, m, Ha-8′, Hb-8′, Ha-9′, and Hb-9′), 0.860 (3H, d, *J*=6.2 Hz, H_3-11′); HRMS (ESI-TOF) *m*/*z* 833.2369 $[M+Na]^+$ (calcd for $C_{40}H_{40}O_{11}F_6Na$, 833.2367).

3.7. Biological assays

Cytotoxicity against KB cells (oral human epidermoid carcinoma), MCF-7 cells (human breast cancer), NCI-H187 cells (human small-cell lung cancer), and Vero cells (African green monkey

kidney fibroblasts) were evaluated using the resazurin microplate assay.[10] Assay for activity against *P. falciparum* (K1, multi-drug resistant strain) was performed using the microculture radioisotope technique described by Desjardins et al.[11]

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Supplementary data

^{1}H and ^{13}C NMR spectra of **1**–**6**, and CD and UV spectra of **13** and **14**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.11.101.

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