Polyacetylenes from the Roots of *Polyalthia debilis*

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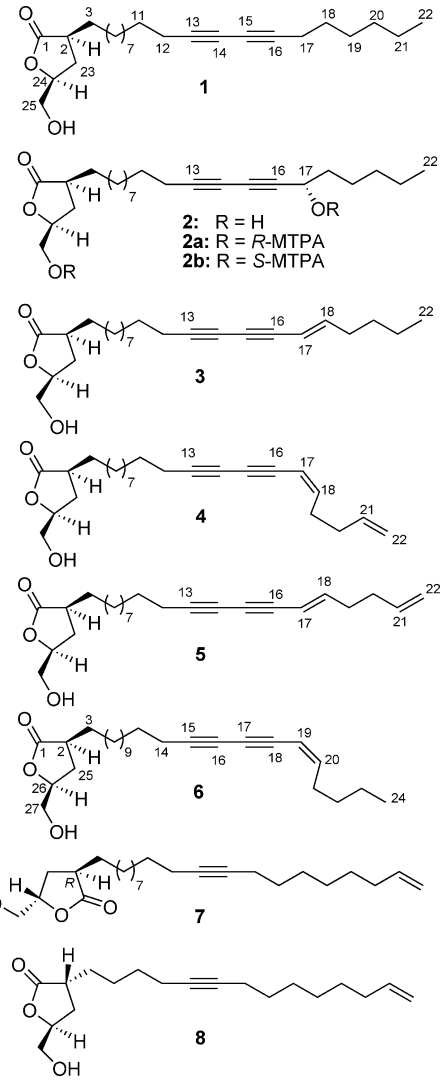
Six new linear polyacetylenic C25 and C27 acetogenins (**1**−**6**), named debilisones A−F, have been isolated from a methanol extract of roots of *Polyalthia debilis*. Structures of these compounds were determined by spectroscopic techniques. The absolute configuration at C-17 of **2** was assigned by the modified Mosher's method. Compounds **2**, **3**, and **5** exhibited moderate antimycobacterial activity against *Mycobacterium tuberculosis* with MIC values of 25.0, 12.5, and 25.0 μg/mL, respectively.

Polyalthia debilis (Piere) Finet & ganep (Annonaceae) is a Thai herbal plant growing widely in the northeastern part of Thailand. It is known as "Kon Krok" in Thai, and water decoctions of its roots are used traditionally by the local people for treatment of abdominal pain.[1] Phytochemical investigations on *Polyalthia* species demonstrated the presence of clerodane diterpenes,[2−4] triterpenes,[5,6] benzopyran derivatives,[7] polyacetylene compounds,[8−11] and azaanthracene,[12] aporphine,[4,13,14] bisaporphine,[11,15−18] indolesesquiterpene,[19] seco-benzyltetrahydroisoquinoline,[20] and oxoprotoberberine alkaloids.[4,21] Compounds isolated from the genus *Polyalthia* have been reviewed.[22] In a previous paper we reported the isolation and characterization of bis-dehydroaporphine alkaloids, bidebilines A−D, from a dichloromethane extract of *P. debilis* roots.[18] As part of our search for bioactive compounds from Thai plants, a methanol extract of air-dried roots of *P. debilis* was shown to be active against *Mycobacterium tuberculosis* (MIC 12.5 μg/mL). This paper describes the isolation, characterization, and bioactivities of six isolated linear C25 (**1**−**5**) and C27 (**6**) acetogenins from the MeOH extract of roots of *P. debilis*.

Results and Discussion

Compound **1** was obtained as a white, amorphous solid, and it was assigned the molecular formula $C_{25}H_{40}O_3$ from HRESITOFMS, *m*/*z* 411.2875 $[M + Na]^+$. The IR spectrum indicated the presence of OH (3461 cm^{-1}), conjugated acetylene (2230 cm^{-1}), and lactone carbonyl (1769 cm^{-1}) groups. The ^1H and ^{13}C NMR data of **1** (Table 1) were similar to those of linear acetogenins goniothalamusin (**7**)[23] and oropheolide,[24] except that the side chain of **1** contained a conjugated acetylene group, which was evidenced by signals at δ_C 77.5, 66.3, 66.3, and 77.5.[10] The γ-hydroxymethyl-γ-lactone moeity displayed signals at δ_H 4.55 (m, H-24), 3.82 (dd, $J = 3.6$, 12.4 Hz, H-25a), 3.60 (dd, $J = 4.6$, 12.4 Hz, H-25b), and 2.67 (m, H-2) and H_2-23 protons at δ_H 1.95, 2.28 (m). However, the chemical shifts for H-2 and H_2-23 of **1** differed from those reported for oropheolide [δ_H/δ_C 2.25 m/32.1 (H-2/C-2) and 2.70 m/39.5 (H-23/C-23)].[24] The complete interpretation of the NMR data of **1** was established as a result of conclusive DEPT, COSY, HMBC, and NOESY experiments.

The specific rotation of **1** (+22.0) was the same sign as its analogue, **7** [+14.6 (*c* 0.206, $CHCl_3$)].[23] However, there are two closely related γ-lactone acetogenins, oropheolide and saccopetrin A (**8**), that have the opposite sign of specific rotation [−12 (*c* 1.0, $CHCl_3$)[24] and −10 (*c* 0.25, $CHCl_3$),[25] respectively]. Also, the absolute configuration of the γ-lactone ring of **8** was reported as 2*R* and 24*S* and proposed to be the enantiomer of **7**.[25] The NOESY spectrum of **1** showed a correlation between H-2 and H-24 (Figure 1), suggesting that the two protons are located on the same side of the lactone ring. From the above evidence, the relative configuration



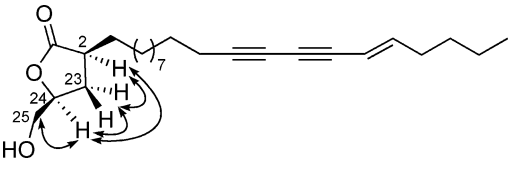


Figure 1. Selected NOESY correlations of **1**.

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Table 1. ^{1}H and ^{13}C NMR Data for **1**−**3** in $CDCl_3$

	1		**2**		**3**	
no.	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1		180.7		170.7		179.9
2	2.67 m	39.6	2.78 m	39.6	2.68 m	39.6
3	1.36 m[c], 1.77 m	31.2	1.41 m[c], 1.80 m	31.2	1.35 m[c], 1.80 m	31.2
4−10	1.22−1.40 m[a]	27.2−29.6[a]	1.26−1.45 m[a]	27.2−29.6[a]	1.28−1.52 m[a]	27.2−29.6[a]
11	1.47 quint (6.9)[b]	29.0	1.51 quint (7.3)	28.1	1.50 quint (6.9)	28.2
12	2.20 t (6.9)	19.6	2.26 t (7.3)	19.2	2.22 t (6.9)	19.5
13		77.5		81.7		83.6
14		66.3		69.8		65.2
15		66.3		64.4		72.8
16		77.5		76.6		74.0
17	2.20 t (6.9)	19.6	4.40 t (6.6)	62.9	5.46 d (15.8)	108.6
18	1.47 q (6.9)	28.3	1.69 m	37.6	6.25 dt (7.0, 15.8)	148.2
19	1.22−1.40 m[a]	27.2−29.6[a]	1.41 m[c]	24.7	2.09 q (7.0)	29.8
20	1.23 brs[c]	31.2	1.26 brs[c]	31.4	1.28 brs[c]	30.6
21	1.23 brs[c]	22.5	1.26 brs[c]	22.5	1.28 brs[c]	22.1
22	0.85 t (6.8)	14.0	0.88 t (6.8)	14.0	0.87 t (6.9)	13.8
23	1.95 m, 2.28 m	29.4	2.00 m, 2.31 m	29.3	1.98 m, 2.31 m	29.2
24	4.55 m	78.0	4.60 m	78.6	4.56 m	78.7
25	3.82 dd (3.6, 12.4)	64.4	3.85 dd (3.0, 12.3)	64.5	3.84 dd (2.8, 12.4)	65.8
	3.60 dd (4.6, 12.4)		3.63 dd (4.7, 12.3)		3.62 dd (4.6, 12.4)	

[a] Signals may be interchanged. [b] Values in parentheses are coupling constants in Hz. [c] Overlapping of the signals.

at C-2 and C-24 in the γ-lactone ring of **1** was proposed to be 2*S* and 24*S*. Finally, the location of the conjugated acetylene moiety between C-13 and C-16 was established by EIMS fragmentations at *m*/*z* 147, 133, and 109. Thus, **1** was determined to be a new linear acetogenin, and it was named debilisone A.

Compound **2** was isolated as a white wax, and it was assigned the molecular formula $C_{25}H_{40}O_4$ from HRESITOFMS, *m*/*z* 427.2824 $[M + Na]^+$. The IR spectrum indicated the presence of OH (3420 cm^{-1}), conjugated acetylene (2253 cm^{-1}), and lactone carbonyl (1732 cm^{-1}) groups. The ^{1}H and ^{13}C NMR spectra of **2** (Table 1) were similar to those of **1**, except for the chemical shift of the oxymethine proton at C-17, which appeared as a triplet at δ_H 4.40, whereas the carbon signal appeared at δ_C 62.9. This was confirmed by the HMBC correlation of H-17 to C-16 (76.6), C-15 (64.4), C-18 (37.6), and C-19 (24.7). Complete interpretation of the NMR data was established as a result of conclusive DEPT, COSY, HSQC, HMBC, and NOESY experiments.

Assignment of the absolute configuration at C-17 was carried out using the modified Mosher's ester method.[26] Reaction of **2** with (*R*)- and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA-Cl) gave the *S*- and *R*-MTPA esters, respectively. The difference in the ^{1}H NMR chemical shifts between the *S*- and *R*-MTPA derivatives ($\Delta\delta_H = \delta_S - \delta_R$) near C-17 determined the absolute configuration at this position to be *S* (Figure 2). The EIMS of **2** (Figure 3) contained ion peaks at *m*/*z* 163, 149, 125, and 333, indicating that the conjugated acetylene unit was located between C-12 and C-17. Thus, compound **2** was determined to be another new linear acetogenin, and it was named debilisone B.

The ^{1}H and ^{13}C NMR data of compound **3** (Table 1) were similar to those of **1**. The molecular formula $C_{25}H_{38}O_3$ (from the HRESITOFMS) indicated two fewer protons and one more degree of unsaturation than **1**. These data agree well with the presence of an *E* alkene group at $\delta_{H/C}$ 5.46 (d, J = 15.8 Hz, H-17)/108.6 (C-17) and 6.25 (dt, J = 7.0, 15.8 Hz, H-18)/148.2 (C-18). The COSY and HMBC data were examined to verify the position of this double bond. Finally, the EIMS fragmentation ion peaks at *m*/*z* 83, 107, 131, and 145 agreed with the diacetylene unit being connected to C-12 and C-17. Thus, the structure of **3** was deduced as shown, and it was was named debilisone C.

Compound **4** had the molecular formula $C_{25}H_{36}O_3$ (HRESITOFMS), two fewer protons and one more degree of unsaturation than **3**. The ^{1}H and ^{13}C NMR data of **4** (Table 2) were similar to those of **3**, except for the appearance of a *Z* alkene at C-17 [$\delta_{H/C}$ 5.48 (d, J = 10.8 Hz, H-17)/108.6 (C-17), 6.01 (dt, J = 7.4, 10.8 Hz, H-18)/146.5 (C-18)] and a terminal alkene at C-21 [$\delta_{H/C}$ 5.80 (m, H-21)/137.6 (C-21) and 5.03 (d, J = 17.0 Hz, H-22a) and 4.84 (d, J = 10.1 Hz, H-22b)/115.1(C-22)]. This structure was supported by COSY and HMBC data. Finally, the EIMS fragmentation ion peaks at *m*/*z* 81, 105, 129, and 143 again revealed that the diacetylene unit was connected between C-12 and C-17. Thus, the structure of **4** was as indicated, and it was named debilisone D.

Compound **5** was assigned the molecular formula $C_{25}H_{36}O_3$ from HRESITOFMS, *m*/*z* 407.2562 $[M + Na]^+$. The ^{1}H and ^{13}C NMR spectra of **5** (Table 2) were similar to those of **4**, except for the configuration of the double bond at C-17−C-18, which was assigned as *E* [δ_H 5.45 (d, J = 15.9 Hz, H-17) and 6.25 (dt, J = 6.8, 15.9 Hz, H-18)]. The EIMS fragmentation ion peaks of **5** were similar to those of **4**. Thus, compound **5** was determined to be new, and it was named debilisone E.

NMR data of compound **6** (Table 2) indicated a structural relationship to compound **3**, except for signals of olefinic protons at δ_H 5.45 (d, J = 10.8 Hz, H-19) and 6.06 (dt, J = 7.5, 10.8, Hz, H-20) indicating a *Z* configuration. The molecular formula of **6** ($C_{27}H_{42}O_3$) was consistent with two more methylene units than **3**. Finally, the EIMS fragmentation ion peaks at *m*/*z* 84, 107, 131, and 145 supported a diacetylene unit between C-14 and C-19. Thus, the structure of **6** was determined, and it was named debilisone F.

Compounds **2**, **3**, and **5** showed moderate antimycobacterial activity against *Mycobacterium tuberculosis* with MIC values of 25.0, 12.5, and 25.0 μg/mL, respectively. Since some polyacetylenes have been reported to possess antimalarial activity against *Plasmodium falciparum* and weak cytotoxicity against BC1, KB, and NCI-H187 cell lines,[10,11] all isolated compounds were evaluated for these tests. The compounds were also tested against the fungus *Candida albicans*. No activity was evident in the latter tests.

Experimental Section

General Experimental Procedures. Optical rotations were obtained using a JASCO DIP-1000 digital polarimeter. UV spectra were measured on an Agilent 8453 UV−visible spectrophotometer. IR spectra were taken on a Perkin-Elmer Spectrum One spectrophotometer. NMR spectra were recorded in $CDCl_3$ on a Varian Mercury Plus 400 spectrometer, using residual $CHCl_3$ as internal standard. HRESITOFMS and EIMS were recorded on Micromass Q-TOF-2 and Varian CP-3800 GC 1200 L Quadrupole MS/MS spectrometers, respectively. Column chromatography (CC) was carried out on Merck silica gel 60 (230−400 mesh), Cosmosil (75C_{18}−OPN), Lichroprep RP-18 (particle size 40−63 μm), and Sephadex LH-20 (Amersham Pharmacia Biotech AB, Sweden). TLC was performed with precoated Merck silica gel 60 PF_{254}

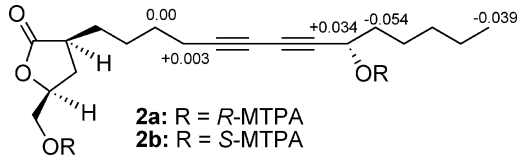

Figure 2. $\Delta\delta$ values ($\Delta\delta = \delta_S - \delta_R$ in ppm) obtained for MTPA esters **2a** and **2b**.

aluminum sheets; the spots were visualized under UV light (254 and 366 nm) and further by spraying with anisaldehyde then heating until charred.

Plant Materials. Roots of *P. debilis* were collected at Nampong District, Khon Kaen Province, Thailand, in February 2008. A plant specimen (voucher number S. Kanokmedhakul-1) was identified by Prof. Pranom Chantaranothai and was deposited at the herbarium of the Department of Biology, Faculty of Science, Khon Kaen University, Thailand.

Extraction and Isolation. Air-dried roots of *P. debilis* (2.1 kg) were ground into powder and then extracted with MeOH. The MeOH solution was filtered and evaporated. The filtrate was partitioned successively between water−hexane, water−EtOAc, and water−BuOH to yield crude hexane (15.4 g), EtOAc (38 g), and BuOH (8 g) extracts, respectively. The EtOAc extract (38 g) was separated by silica gel flash CC, eluted with a gradient system of hexane−CH_2Cl_2 and MeOH, to give fractions F_1−F_6. Fraction F_3 was separated by Sephadex LH-20 CC, eluted with MeOH, to yield subfractions $F_{3.1}$−$F_{3.3}$. Fraction $F_{3.2}$ was purified by silica gel flash CC, eluted with 20% EtOAc−hexane, to obtain subfractions $F_{3.2.1}$−$F_{3.2.3}$. Subfraction $F_{3.2.2}$ was subjected to RP-18 CC, eluted with 85% MeOH−H_2O, to give **1** (286 mg) and **6** (23 mg). Fraction F_4 was fractionated by Sephadex LH-20 CC, eluted with MeOH, to afford subfractions $F_{4.1}$−$F_{4.3}$. Subfraction $F_{4.2}$ was subjected to silica gel flash CC, eluted with 30% EtOAc−hexane, to yield subfractions designated $F_{4.2.1}$−$F_{4.2.3}$. Subfraction $F_{4.2.2}$ was separated on RP-18 CC, eluted with 85% MeOH−H_2O, to give **3** (15 mg), **4** (190 mg), **5** (90 mg), and an additional amount of **1** (106 mg). Purification of $F_{4.2.3}$ on RP-18 CC, eluted with 85% MeOH−H_2O, gave additional amounts of **3** (11 mg) and **5** (16.9 mg). Fraction F_5 was applied to Sephadex LH-20 CC and eluted with MeOH to afford subfractions $F_{5.1}$−$F_{5.3}$. Subfraction $F_{5.2}$ was purified by silica gel flash CC, eluted with 30% EtOAc−hexane, to yield **2** (215 mg).

Debilisone A (1): white, amorphous solid; $[\alpha]^{23}_D$ +22.0 (*c* 0.206, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 208 (3.3), 214 (4.4), 241 (3.5), 253 (3.7), 267 (3.9), 283 (3.8); IR (KBr) ν_{max} 3461, 2919, 2849, 2230, 1769, 4169, 1172, 1047 cm^{-1}; ^1H and ^{13}C NMR data, see Table 1; HRESITOFMS *m/z* 411.2875 $[M + Na]^+$ (calcd for $C_{25}H_{40}O_3Na$, 411.2875).

Debilisone B (2): white wax; $[\alpha]^{21}_D$ +113.4 (*c* 0.206, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 200 (2.9), 215 (3.1), 241 (2.8), 254 (2.7), 268 (2.8), 284 (2.5); IR ν_{max} 3420, 2927, 2855, 2253, 1732, 1458, 1205, 1185 cm^{-1}; ^1H and ^{13}C NMR data, see Table 1; HRESITOFMS *m/z* 427.2824 $[M + Na]^+$ (calcd for $C_{25}H_{40}O_4Na$, 427.2824).

Debilisone C (3): white, amorphous solid; $[\alpha]^{24}_D$ +52.9 (*c* 0.206, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 208 (4.2), 215 (4.3), 241 (3.6), 253 (3.8), 268 (3.9), 284 (3.8); IR (KBr) ν_{max} 3467, 2931, 2851, 2233, 2144, 1768, 1464, 1172, 1046 cm^{-1}; ^1H and ^{13}C NMR data, see Table 1; HRESITOFMS *m/z* 409.2711 $[M + Na]^+$ (calcd for $C_{25}H_{38}O_3Na$, 409.2719).

Debilisone D (4): white, amorphous solid; $[\alpha]^{23}_D$ +34.9 (*c* 0.206, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 208 (4.5), 215 (4.6), 241 (3.8), 253 (4.0), 268 (4.2), 284 (4.1); IR (KBr) ν_{max} 3458, 2918, 2849, 2231, 1770, 1640, 1470, 1172, 1048 cm^{-1}; ^1H and ^{13}C NMR data, see Table 2; HRESITOFMS *m/z* 407.2562 $[M + Na]^+$ (calcd for $C_{25}H_{36}O_3Na$, 407.2562).

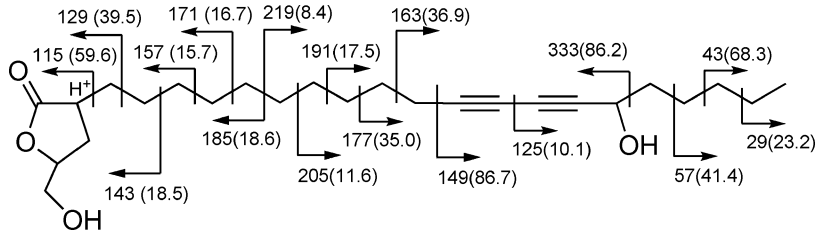

Figure 3. EIMS fragmentation of **2** with relative intensity values in parentheses.

Table 2. ^1H and ^{13}C NMR Data for **4**−**6** in $CDCl_3$

	4		**5**		**6**	
no.	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1		179.8		179.7		179.9
2	2.70 m	39.6	2.70 m	39.6	2.69 m	39.6
3	1.32 m[c], 1.82 m	31.2	1.37 m[c], 1.82 m	31.2	1.38 m[c], 1.82 m	30.9
4−10	1.20−1.45 m[a]	27.2−29.5[a]	1.26−1.43 m[a]	27.2−29.6[a]	1.26−1.44 m[a]	27.2−29.6[a]
11	1.53 quint (7.2)	28.2	1.52 quint (7.2)	28.2	1.26−1.44 m[a]	27.2−29.6[a]
12	2.32 t (7.2)	19.6	2.23 t (7.2)	19.5	1.26−1.44 m[a]	27.2−29.6[a]
13		85.1		83.3	1.53 quint (7.1)	28.2
14		65.1		65.1	2.31 t (7.1)	19.2
15		71.8		73.1		84.8
16		78.5		73.8		65.1
17	5.48 d (10.8)	108.6	5.45 d (15.9)	109.2		72.1
18	6.01 dt (7.4, 10.8)	146.5	6.25 dt (6.8, 15.9)	147.0		78.1
19	2.42 q (7.4)	29.8	2.21 m	32.5	5.45 d (10.8)	108.5
20	2.16 q (7.2)	32.8	2.15 m	32.6	6.06 dt (7.5, 10.8)	147.7
21	5.80 m	137.6	5.76 m	137.3	2.31 t (7.1)	30.4
22	5.03 d (17.0)	115.1	5.01 d (17.1)	115.3	126 brs[c]	31.2
	4.84 d (10.1)		4.96 d (10.1)			
23	2.06 m, 2.27 m	29.3	2.00 m, 2.31 m	29.3	126 brs[c]	22.2
24	4.58 m	78.6	4.58 m	78.6	0.85 t (6.8) xx	13.9
25	3.85 dd (3.0,12.3)	64.5	3.85 dd (2.9, 12.3)	64.6	1.99 m, 2.23 m	29.4
	3.63 dd (4.7, 12.3)		3.63 dd (4.7, 12.3)			
26					4.58 m	78.6
27					3.82 dd (3.4, 12.4)	64.5
					3.62 dd (4.7, 12.0)	

[a] Signals may be interchanged. [b] Values in parentheses are coupling constants in Hz. [c] Overlapping of the signals.

Debilisone E (5): white, amorphous solid; $[\alpha]^{25}_{D}$ +42.7 (*c* 0.206, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 208 (4.2), 214 (4.3), 241 (3.5), 253 (3.8), 268 (4.0), 284 (3.9); IR (KBr) ν_{max} 3429, 2919, 2849, 2225, 1769, 1640, 1469, 1171, 1046 cm^{-1}; ^1H and ^{13}C NMR data, see Table 2; HRESITOFMS *m*/*z* 407.2562 $[M + Na]^+$ (calcd for $C_{25}H_{36}O_3Na$, 407.2562).

Debilisone F (6): white, amorphous solid; $[\alpha]^{20}_{D}$ +50.2 (*c* 0.206, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 208 (5.4), 214 (5.5), 240 (4.7), 253 (3.9), 267 (5.0), 283 (4.9); IR ν_{max} 3413, 2909, 2851, 2224, 1757, and 1174 cm^{-1}; ^1H and ^{13}C NMR data, see Table 2; HRESITOFMS *m*/*z* 437.3032 $[M + Na]^+$ (calcd for $C_{27}H_{42}O_3Na$, 437.3032).

Preparation of the (*R*)- and (*S*)-α-Methoxy-α-(trifluoromethyl)phenyl Acetate of 2. Dimethylaminopyridine (2.0 mg) and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MPTA-Cl) (20 μL)) were added to a solution of **2** (10 mg) in pyridine (1.5 mL). The mixture was stirred under N_2 at room temperature for 3 h, and the solvent was removed in vacuo. The product was purified by preparative TLC (EtOAc−hexane, 30:70) to provide the *R*-ester (**2a**, 2 mg). The (*S*)-α-methoxy-α-(trifluoromethyl)phenyl acetate of **2** was prepared using the method described above [alcohol **2** (13 mg), pyridine (1.5 mL), dimethylaminopyridine (2.0 mg), and MPTA-Cl (26 μL)] to yield ester **2b** (3 mg).

Antimycobacterial Assay. Antimycobacterial activity was assessed against *Mycobacterium tuberculosis* H37Ra using the Microplate Alamar Blue Assay (MABA).[27] The standard drugs isoniazid and kanamycin sulfate showed respective MIC values of 0.04−0.09 and 2.0−5.0 μg/mL.

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Supporting Information Available: ^1H NMR, ^{13}C NMR, NOESY, and EIMS spectra for debilisones A−F (**1**−**6**) and ^1H NMR data of **2a** and **2b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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