New Xenia Diterpenoids from a Soft Coral, *Xenia* Species Containing Fatty Acyl Side Chains[1)]

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Seven new diterpenoids with an opened A-ring containing an aliphatic acid, called azamilides A—G (**1**—**7**), have been isolated from an acetone extract of *Xenia* sp. and their structures elucidated on the basis of spectroscopic analysis.

Soft corals of the family Xeniidae have proven to be a rich source of xenia diterpenoids containing a 9-membered monocarbocyclic ring.[2)] The structures of the xenia diterpenoids have been divided into three groups: xenicins (**8**),[3)] xeniolides (**9**),[4)] and xeniaphyllanes (**10**) (Chart 1),[5)] all of which are plausibly derived from geranylgeraniol or geranyllinalool. Many variants of xenia diterpenoids might be expected to be found in *Xenia* sp., since no investigation of their chemical constituents has been as extensive as that for the cembranoid group of metabolites isolated from soft corals of the family Alcynoiidae.[2)] We have isolated eleven new xenia diterpenoids, including three artifacts, from the methanol extract of *Xenia* sp., collected in the area of Bonotsu, Kagoshima prefecture.[6,7)] In this study we used acetone extraction of the same corals, since the methanol extract likely give artifacts due to methanolysis. The concentrated acetone extract was partitioned between CH_2Cl_2 and water. The organic soluble portion was subjected to silica-gel, gel-filtration (Sephadex LH-20), and reversed-phased HPLC column chromatograpraphies. This yielded a series of new xenia diterpenoids, called azamilides A—G (**1**—**7**), containing a 9-membered monocarbocyclic ring, which were acylated with a series of C_{16}—C_{20} saturated fatty acids.[8)] The diterpenoids (**1**—**7**) were isolated as oils, and their molecular formulas were determined by a combination of mass spectrometry and the ^1H and ^{13}C NMR data. The present paper deals with the isolation and structure elucidation of **1**—**7**.

Results and Discussion

Azamilide A (**1**), $C_{40}H_{68}O_6$, had IR absorption bands assigned to a hydroxyl group (3450 cm^{-1}), an ester group (1740 and 1240 cm^{-1}), and an olefinic group (1630 cm^{-1}). The molecular formula indicated seven degrees of unsaturation. An acetyl resonance [δ = 21.0 (q) and 170.9 (s)], an acyl resonance [δ = 173.6 (s)] and eight olefinic resonances [δ = 117.0 (t), 123.2 (d), 130.4 (d), 132.8 (d), 133.3 (d), 136.9 (s), 142.0 (d), 149.0 (s)] in the ^{13}C NMR spectrum accounted for six equivalents of unsaturation, suggesting that **1** was monocyclic. The gross structure was determinated by using extensive NMR techniques, including ^1H–^1H COSY and ^{13}C–^1H COSY NMR experiments, and by a comparison of the NMR spectra of **1** with those of xeniatine A (**11**).[6)] Resonances due to a 9-membered carbocyclic ring were readily assigned as follows. Resonances due to methyl protons on a carbon bearing a hydroxyl group (δ = 1.32; 3H, s, H-18) and doubly allylic methylene protons (δ = 2.57; 1H, dd, J = 7.3 and 12.4 Hz and δ = 3.65; 1H, br t, J = 12.4 Hz, H-10) were observed. The methylene protons were coupled to an olefinic proton at δ = 5.80—5.87 (1H, m, H-9), which in turn was coupled to another olefinic proton at δ = 5.25 (1H, d, δ = 11.7 Hz, H-8). Two broad singlets at δ = 4.98 and 5.00 (1H each) were assigned to exo methylene protons at C-19. Resonances due to H-4a (δ = 4.02; 1H, br t, J = 11.7 Hz, δ_C = 34.9) were coupled to one of the H-5 protons (δ = ca. 1.40, 1H, overlapped, δ_C = 28.8), which were geminally coupled to H-5 (δ = 1.83; 1H, br t, J = 13.9 Hz). The latter H-5 was coupled to one of the H-6 protons (δ = ca. 1.69, 1H, overlapped, δ_C = 36.0), which was also coupled to another H-6 (δ = 1.25; 1H, overlapped). The H-4a proton was further coupled to H-11a (δ = ca. 2.57; 1H, overlapped, δ_C = 50.5), which was also coupled to H-1 oxymethylene protons (δ = 3.85; 1H, dd, J = 3.3 and 11.0 Hz; δ = 3.98; 1H, dd, J = 9.0 and 11.0 Hz, δ_C = 65.4). Another oxymethylene protons appeared at δ = 4.65 (2H, s, H-3, δ_C = 64.5). The two methylene groups were determined to be acylated on the basis of the low-field chemical shifts. This also implied that the A-ring was cleaved, unlike xeniatine A. The presence of the 5-hydroxyl-5-methyl-1,3-hexadiene moiety was indicated by the following data. Thus, resonances due to two methyl protons on a carbon bearing a hydroxyl group (δ = 1.35; 3H×2, s) and olefinic protons at δ = 5.86 (1H, d, J = 15.4 Hz, H-14), 6.24 (1H, br d, J = 11.0 Hz, H-12) and 7.07 (1H, br dd, J = 11.0 and 15.4 Hz, H-13), which were coupled to each other, were observed. Resonances due to protons of a straight-chain fatty acyl group were assigned; δ = 0.88; 3H, t, J = 7.0 Hz, $C\underline{H}_3CH_2$–; δ = 1.25; s, $-(CH_2)_n-$; δ = 2.33 (2H, t, J = 7.5 Hz, $-COOC\underline{H}_2CH_2-$) as well as resonances due to acetyl protons (δ = 1.98; 3H, s). The acyl group was concluded to be a stearoyl group by a fragment ion, *m/z* 283, corresponding to $[C_{17}H_{35}COO]^-$ in the negative FAB mass

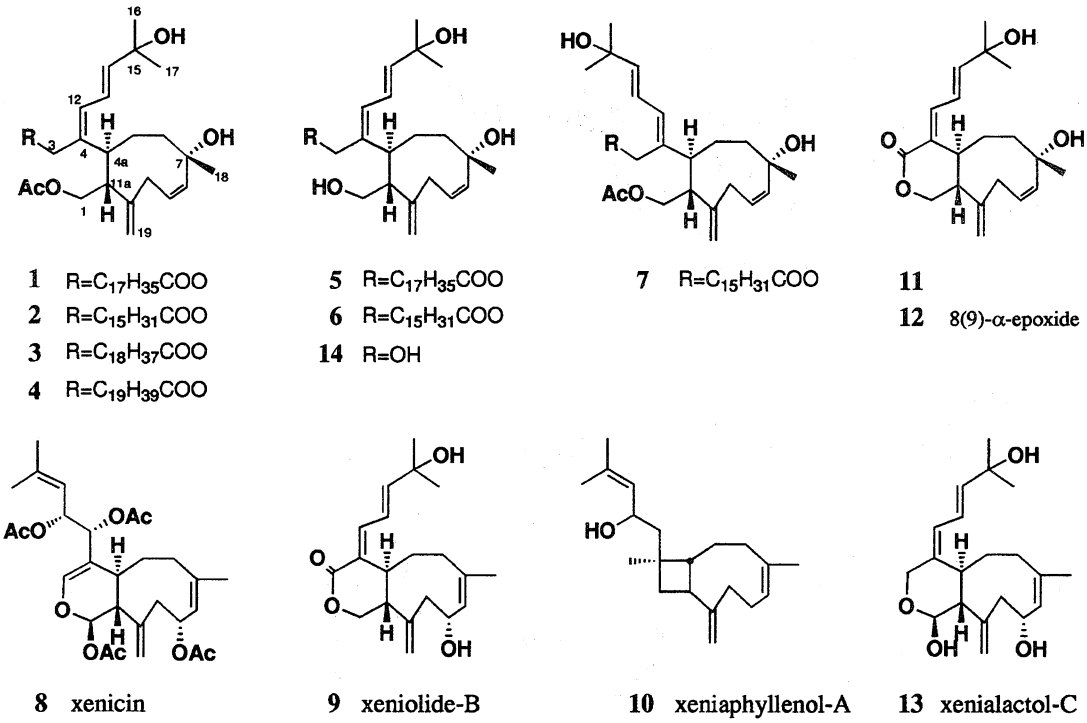

Chart 1.

spectrum. This assumption was further supported by the alkaline hydrolysis of **1** followed by a treatment with diazomethane, leading to methyl stearate, which was confirmed by the GC-MS chromatography. At this stage, the position of the stearoyl group at C-1 or C-3 could not be determined. The β configuration of the methyl group at C-7 was established by a comparison of the NOE data (Fig. 1) of **1** with those of xeniatine A epoxide[7] (**12**): H-4a→H-10*endo* (4.8%) and H-13 (15.3%); H-8→Me-18 (3.1%); H-19→H-11a (13.0%). No correlation was observed between Me-18 and H-4a or Me-18 and H-10. The stereochemistry between H-4a and H-11a was determined to be *trans* due to the large coupling constant ($J = 11.7$ Hz) between H-4a and H-11a. This was consistent with the fact that substituents as theses positions in other xenia diterpenoids so far isolated have also been in the *trans* position. The low-field chemical shift of H-4a, when compared to that of **7** ($\delta = 3.23$), which is mentioned later, was due to a deshielding effect of the 13(14)-olefinic bond.

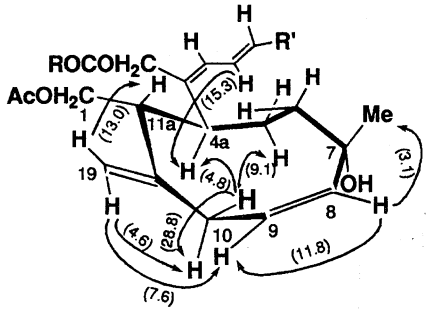

Fig. 1. NOEs (%) observed for **1**. R=alkyl group, R′=side moiety.

The ^{1}H and ^{13}C NMR spectra of azamilides B—D (**2**—**4**) were indistinguishable with those of **1**, though the optical rotation and mass spectral data were all different. The negative FAB mass spectra of compounds **2**, **3**, and **4** have fragment ions showing *m/z* 255, 297, and 311, respectively, indicating the presence of $C_{15}H_{31}COO$–, $C_{18}H_{37}COO$–, and $C_{19}H_{39}COO$– groups respectively. On the basis of these results, the structures of azamilides B, C, and D were concluded to be **2**, **3**, and **4**, respectively.

The ^{1}H NMR spectrum of azamilide E (**5**), $C_{38}H_{66}O_5$, was closely related to that of **1**, except that the NMR resonances due to the acetyl group in **1** [$\delta_H = 1.98$ (3H, s); $\delta_C = 21.0$ (q) and 170.9 (s)] were missing, and the resonances for H-1 [$\delta = 3.13$ (t, $J = 10.4$ Hz)] were shifted to a higher field ($\Delta_H - 0.5$ ppm) compared to that of **1**. This located the acyl group at C-3, which was identified as a stearoyl group by the appearance of a fragment ion (*m/z* 283) in the negative FAB mass spectrum. To further clarify the structural relationship between **1** and **5**, the latter was acetylated with Ac_2O in pyridine to yield a monoacetate, (*m/z* 667 $[M+Na]^+$), the ^{1}H and ^{13}C NMR spectral data of which were identical with those of **1**. Thus, the structure of **5** is the deacetyl derivative of azamilide A (**1**). Therefore, the aliphatic groups in **1**—**4** are attached to C-3 and the acetyl groups to C-1.

The NMR data for azamilide F (**6**), $C_{36}H_{62}O_5$, were almost identical with those of **5**, and the molecular formula of **6** suggested that it contained a palmitoyl group rather than a stearoyl group. This was confirmed by the fragmentation ion (*m/z* 255) in the negative FAB mass spectrum; hence, **6** is acylated at C-3 with palmitic acid.

The ^{1}H NMR spectrum of azamilide G(**7**), $C_{38}H_{64}O_6$, was similar to that of **2**, except that the chemical shifts of H-4a

and H-13 were shifted to a higher field by 0.79 and 0.60 ppm, respectively, compared to those of **2**. This suggested that **7** and **2** were geometrical isomers with regard to the 4(12) configuration. Irradiation of H-12 (δ = 6.18; 1H, d, J = 11.0 Hz) caused an 11.2% enhancement of H-4a (δ = 3.23; 1H, m), indicating the 4(12)*E* configuration.

To our knowledge, this is the first isolation of xenia diterpenoids possessing saturated fatty acyl chains. The fatty acid chains found were stearic (C_{18}), palmitic (C_{16}), and nonadecanoic (C_{20}). The nonadecanoic is less common. In addition, azamilides A—G (**1**—**7**) are the first example of xenia diterpenoids with an opened A-ring, though diterpenoids with a similar carbon skeleton have been isolated from marine algae, *Dictyota* sp.[2]

The discovery of azamilides A—G (**1**—**7**) is further evidence that the 1,3-diol **14** is a common precursor for xenicins, xenialactols, and xeniolides.[6,7]

Experimental

UV and IR spectra were recorded on a Shimadzu UV-210 and a Shimadzu IR-408, respectively. The optical rotations were measured on a JASCO J-20A spectropolarimeter. NMR spectra were recorded with a JEOL JNM-GX 400 spectrometer. The mass spectra were obtained with a JEOL DX-303 or a JEOL D-300 spectrometer.

Extraction and Isolation. Specimens of *Xenia* sp. were collected at a depth of −2 m at Bonotsu, Kagoshima prefectrue. The reference of sample (collection #114) was identified by Dr. Y. Imahara (Wakayama Prefectural Museum of National History). The organisms (dry weight: 750 g) were chopped into small pieces and extracted twice with acetone. The combined acetone solns were concd to afford a dark-reddish residue. The residue was suspended into H_2O and extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried over Na_2SO_4, filtered, and evaporated to dryness. A portion of the CH_2Cl_2 extract (15 g) was absorbed on silica-gel and subjected to column chromatography of silica-gel packed in hexane, frs (200 ml) being collected as follows: A: CH_2Cl_2–hexane, 1 : 9, B: CH_2Cl_2, C: EtOH–CH_2Cl_2, 1 : 49, D: EtOH–CH_2Cl_2, 1 : 19, E: EtOH–CH_2Cl_2, 1 : 9, F: EtOH–CH_2Cl_2, 1 : 16, G: EtOH–CH_2Cl_2, 1 : 1, H: EtOH). Xeniaethers D (**4**) (0.7 mg) and E (**5**) (4.2 mg) were isolated from the fr B using Sephadex LH-20 with MeOH–CH_2Cl_2 (1 : 1), prep. TLC with hexane–ether (1 : 1), and HPLC on ODS with H_2O–MeCN (2 : 3). Azamilides B (**2**) (4.8 mg), C (**3**) (1.3 mg), D (**4**), (1.1 mg), and xeniaether C (**3**) (4.4 mg) were isolated from the fr D using Sephadex LH-20 with MeOH–CH_2Cl_2 (1 : 3 to 1 : 1), prep. TLC with hexane–ether (1 : 1) and ether–CH_2Cl_2 (1 : 3), and HPLC on ODS with H_2O–MeOH (1 : 9). The fr E was further subjected to silica-gel chromatography with ether–CH_2Cl_2 (1 : 4 to 1 : 1) and then EtOH–CH_2Cl_2 (1 : 19 to 3 : 22), to a column of Sephadex LH-20 with MeOH–CH_2Cl_2 (1 : 1), and to HPLC on ODS with H_2O–MeOH (1 : 19) to afford azamilides A (**1**) (16 mg), G (**7**) (1.4 mg), E (**5**) (4.5 mg), and F (**6**) (1.0 mg).

The IR, ^{1}H, and ^{13}C NMR data of Azamilides (**1**—**4**) could not be distinguished from one another. Azamilides (**1**—**4**): Oil; IR (film) ν_{max} 3450, 1740, 1630, and 1240 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.88 (3H, t, J = 7.0 Hz, C$\underline{H}_3$CH$_2$–), 1.25 [s, –(CH$_2$)$_n$–], ca. 1.25 (1H, overlapped, H-6), 1.32 (3H, s, H-18), 1.35 (3H×2, s, H-16 and H-17), ca. 1.40 (1H, overlapped, H-5*endo*), ca. 1.69 (1H, overlapped, H-6), 1.83 (1H, br t, J = 13.9 Hz, H-5*exo*), 1.98 (3H, s, CH_3COO–), 2.33 (2H, t, J = 7.5 Hz, –COC$\underline{H}_2$CH$_2$–), ca. 2.57 (1H, overlapped, H-11a), 2.57 (1H, dd, J = 7.3 and 12.4 Hz, H-10*exo*), 3.65 (1H, br t, J = 12.4 Hz, H-10*endo*), 3.85 (1H, dd, J = 3.3 and 11.0 Hz, H-1), 3.98 (1H, dd, J = 9.0 and 11.0 Hz, H-1), 4.02 (1H, br t, J = 11.7 Hz, H-4a), 4.65 (2H, s, H-3), 4.98 and 5.00 (1H, each, br s, H-19), 5.25 (1H, d, J = 11.7 Hz, H-8), 5.80—5.87 (1H, m, H-9), 5.86 (1H, d, J = 15.4 Hz, H-14), 6.24 (1H, br d, J = 11.0, H-12), and 7.07 (1H, br dd, J = 11.0 and 15.4 Hz, H-13); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.1 [C$\underline{H}_3$(CH$_2$)$_n$–], 21.0 (C$\underline{H}_3$COO), 22.7—34.5 [CH$_3$(C$\underline{H}_2$)$_n$COO–], 27.1 (C-10), 28.8 (C-5), 30.5 (C-18), 34.5 (C-16 and C-17), 34.9 (C-4a), 36.0 (C-6), 50.5 (C-11a), 64.5 (C-3), 65.4 (C-1), 71.4 (C-15), 77.2 (C-7), 117.0 (C-19), 123.2 (C-13), 130.4 (C-12), 132.8 (C-8), 133.3 (C-9), 136.9 (C-4), 142.0 (C-14), 149.0 (C-11), 170.9 (CH$_3$C$\underline{O}$O), and 173.6 (–C$\underline{O}$O–).

Azamilide A (1): Oil, $[\alpha]_D$ +77.1° (*c* 0.07, MeOH), UV (MeOH) λ_{max} 240 nm (ε 25000); FABMS: *m/z* 667 $[M+Na]^+$, 283 $[C_{17}H_{35}COO]^-$. HREIMS Found: *m/z* 626.4858 ($M^+ - H_2O$). Calcd for $C_{40}H_{66}O_5$: M, 626.4909.

Azamilide B (2): $[\alpha]_D$ +99.0° (MeOH, *c* 0.05); UV (MeOH) λ_{max} 240 nm (ε 16000); FABMS: *m/z* 639 $[M+Na]^+$, 255 $[C_{15}H_{31}COO]^-$.

Azamilide C (3): Oil, $[\alpha]_D$ +68.3° (*c* 0.07, MeOH); UV (MeOH) λ_{max} 240 nm (ε 14000); FABMS: *m/z* 681 $[M+Na]^+$, 297 $[C_{18}H_{37}COO]^-$.

Azamilide D (4): Oil, $[\alpha]_D$ +100.0° (*c* 0.07, MeOH); UV (MeOH) λ_{max} 240 nm (ε 24000); FABMS: *m/z* 695 $[M+Na]^+$, 311 $[C_{19}H_{39}COO]^-$.

The spectroscopic data of Azamilides (**5**) and (**6**) were also almost identical and could not be distinguished from each other. Azamilides (**5**) and (**6**): Oil, IR (film) ν_{max} 3450, 1740, 1630, and 1240 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.88 (3H, t, J = 7.0 Hz, C$\underline{H}_3$CH$_2$–), 1.25 [s, –(CH$_2$)$_n$–], ca. 1.25 (1H, overlapped, H-6), 1.32 (3H, s, H-18), 1.35 (3H×2, s, H-16 and H-17), ca. 1.40 (1H, overlapped, H-5*endo*), ca. 1.66 (1H, overlapped, H-6), 1.82 (1H, br t, J = 14.1 Hz, H-5*exo*), 2.35 (2H, t, J = 7.5 Hz, –COC$\underline{H}_2$CH$_2$–), 2.42 (1H, br t, J = 9.5 Hz, H-11a), 2.56 (1H, dd, J = 7.7 and 12.1 Hz, H-10*exo*), 3.13 (1H, t, J = 10.4 Hz, H-1), 3.43—3.49 (1H, m, H-1), 3.65 (1H, br t, J = 12.1 Hz, H-10*endo*), 3.95 (1H, br dd, J = 8.4 and 10.4 Hz, H-4a), 4.63 (2H, s, H-3), 5.06 (1H, br s, H-19), 5.14 (1H, s, H-19), 5.26 (1H, d, J = 11.7 Hz, H-8), 5.80—5.88 (1H, obscured, H-9), 5.87 (1H, d, J = 15.1 Hz, H-14), 6.24 (1H, br d, J = 10.6 Hz, H-12), and 7.04 (1H, br dd, J = 10.6 and 15.1 Hz, H-13); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.1 [C$\underline{H}_3$(CH$_2$)$_n$–], 22.7—34.5 [CH$_3$(C$\underline{H}_2$)$_n$COO–], 26.9 (C-10), 29.1 (C-5), 30.6 (C-18), 34.5 (C-16 and C-17), 34.8 (C-4a), 36.0 (C-6), 54.6 (C-11a), 62.6 (C-1), 64.4 (C-3), 71.4 (C-15), 77.2 (C-7), 117.7 (C-19), 123.1 (C-13), 130.2 (C-12), 133.0 (C-8 and C-9), 137.2 (C-4), 141.8 (C-14), 149.4 (C-11), and 173.7 (–C$\underline{O}$O–).

Azamilide E (5): Oil, $[\alpha]_D$ +81.8° (*c* 0.067, MeOH); UV (MeOH) λ_{max} 241 nm (ε 25000); FABMS: *m/z* 625 $[M+Na]^+$, 283$[C_{17}H_{35}COO]^-$. HREIMS Found: *m/z* 584.4778 ($M^+ - H_2O$). Calcd for $C_{38}H_{64}O_4$; M, 584.803.

Azamilide F (6): Oil, $[\alpha]_D$ +128.6° (*c* 0.005, MeOH); UV (MeOH) λ_{max} 241 nm (ε 25000); FABMS: *m/z* 597 $[M+Na]^+$, 255$[C_{15}H_{31}COO]^-$.

Azamilide G (7): Oil, $[\alpha]_D$ +100.0° (*c* 0.07, MeOH); UV (MeOH) λ_{max} 241 nm (ε 23000); IR (film) ν_{max} 3450, 1740, 1630, and 1240 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.88 (3H, t, J = 6.7 Hz, C$\underline{H}_3$CH$_2$–), 1.25 [s, –(CH$_2$)$_n$–], ca. 1.25 (1H, overlapped, H-6), ca. 1.40 (1H, overlapped, H-5*endo*), 1.33 (3H, s, H-18), 1.36 [(3H×2), s, H-16 and H-17), ca. 1.62 (1H, overlapped, H-6), 1.82 (1H, br t, J = 12.3 Hz, H-5*exo*), 2.32 (2H, t, J = 7.8 Hz, –COC$\underline{H}_2$CH$_2$–), ca. 2.56 (2H, overlapped, H-11a and H-10*exo*), 3.23 (1H, m, H-

4a), 3.51 (1H, br t, $J = 11.7$ Hz, H-10*endo*), 3.90 (1H, dd, $J = 3.7$ and 11.0 Hz, H-1), 4.00 (1H, $J = 11.0$ Hz, H-1), 4.69 and 4.77 (AB, $J = 12.3$ Hz, H-3), 4.97 and 4.99 (1H each, br s, H-19), 5.26 (1H, d, $J = 11.7$ Hz, H-8), 5.77—5.85 (1H, m, H-9), 5.90 (1H, d, $J = 15.2$ Hz, H-14), 6.18 (1H, br d, $J = 11.0$, H-12), and 6.49 (1H, dd, $J = 11.0$ and 15.2 Hz, H-13); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 14.1$ [$\underline{C}H_3(CH_2)_n$–], 21.0 ($\underline{C}H_3COO$), 22.7—34.4 [$CH_3(\underline{C}H_2)_nCOO$–], 28.8 (C-10), 29.3 (C-5), 31.9 (C-18), 34.1 (C-16 and C-17), 34.1 (C-4a), 36.4 (C-6), 51.5 (C-11a), 65.5 (C-1), 68.9 (C-3), 70.9 (C-15), 76.1 (C-7), 116.6 (C-19), 121.9 (C-13), 132.5 (C-12 or C-8), 133.3 (C-8 or C-12), 133.3 (C-9), 136.9 (C-4), 143.2 (C-14), 148.9 (C-11), 170.9 ($CH_3\underline{C}OO$), and 173.9 (–$\underline{C}OO$–). FABMS: *m/z* 639 $[M+Na]^+$, 255 $[C_{15}H_{31}COO]^{-1}$; HREIMS Found: *m/z* 598.4636 ($M^+ - H_2O$). Calcd for $C_{38}H_{62}O_5$: M, 598.4596.

Hydrolysis of 1 Followed by Methylation. To a soln of a small amount of **1** in MeOH was added 0.5 M NaOH (M = mol dm^{-3}); the soln was then stirred for 1 h at r.t. The soln was diluted with H_2O and extracted with Et_2O to remove the neutral material. The aq soln was acidified with dil HCl and extracted with Et_2O. The Et_2O extract was washed with H_2O and brine, then dried over Na_2SO_4. The solvent was evaporated, dissolved, in ether, and by treated with CH_2N_2 to give a crude material. The presence of methyl stearate in the material was confirmed by GS-MS chromatography: column, 1.5% OV-17, 2 m×2 mm; column temp, 200 °C; inject. temp, 250 °C: EIMS, *m/z* 298 (M^+). The GC mass spectrum was identical with that of an authentic sample of methyl stearate.

Acetylation of 5. Compound **5** (1.8 mg) was treated with Ac_2O and pyridine to give an acetate (1.8 mg), FABMS: *m/z* 667$[M+Na]^+$. The spectral data were identical with those of **1**.

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