Discodermolide: A New Bioactive Polyhydroxylated Lactone from the Marine Sponge *Discodermia dissoluta*

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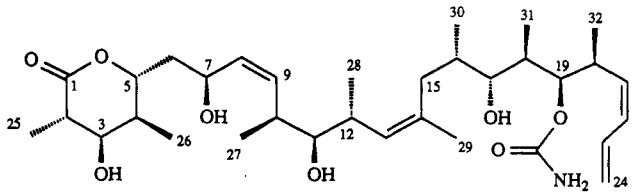
A new polyhydroxylated lactone, discodermolide (1), was isolated from a Caribbean marine sponge, *Discodermia dissoluta*, and its structure was elucidated through a combination of spectroscopic techniques, in particular NMR spectroscopy, and verified by X-ray crystallographic analysis. The carbon skeleton displayed by discodermolide is new; discodermolide is immunosuppressive and cytotoxic.

In our search for biologically active substances from marine organisms, an extract from the marine sponge *Discodermia dissoluta* was discovered to inhibit in vitro proliferation of P388 murine leukemia cells, to inhibit growth of *Candida albicans*, and to be active in the two-way mixed-lymphocyte culture assay.[1] The genus *Discodermia* has been previously recognized as the source of several structurally unusual and potent biological agents, calyculins A–D[2] and discodermins A–D.[3]

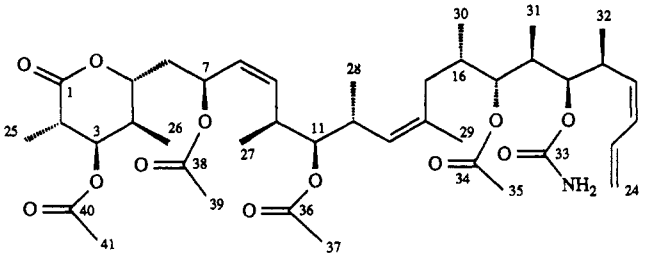
The sponge *D. dissoluta* was collected by scuba at Lucay, Grand Bahama Island, at a depth of 33 m. Methanol/toluene (3:1) solvent extraction of the sponge yielded an extract that was partitioned between EtOAc and water. By silica gel and reversed-phase chromatography, discodermolide was purified from the EtOAc-soluble material; the yield was 0.002% (w/w from frozen sponge). Discodermolide is a crystalline solid that decomposes upon drying under vacuum at room temperature but is relatively stable in solutions of MeOH or EtOAc. A UV absorption at λ_{max} 235 nm (ϵ 12 500) indicated the presence of a conjugated diene group. Infrared absorptions at 3600–3500 and 1725 cm^{-1} revealed the presence of hydroxyl and carbonyl functionalities, respectively. The ^1H and ^{13}C NMR spectra of 1 (Table I) eventually assigned as the



1

result of COSY experiments, long-range COSY experiments,[4] 2D C–H correlation experiments,[5] 2D long-range C–H correlation experiments,[6] and decoupling experiments suggested the presence of a lactone carbonyl, one carbamate carbonyl, seven secondary methyls, one olefinic methyl, two methylenes, six oxygen-bearing methine carbons, seven carbon methines, a monosubstituted double bond, two disubstituted double bonds, a trisubstituted double bond, and at least three exchangeable protons. Due to the lability of the parent hydroxylated compound and to the overlap of proton NMR signals of 1 in several solvents, discodermolide was acetylated under standard conditions and the structure of the acetate was elucidated in the following manner.

The acetylated derivative (2) is a noncrystalline solid and was found to be stable at room temperature and under high vacuum. The molecular formula was determined to



2

be $C_{41}H_{63}NO_{12}$ (high-resolution FABMS of $M^+ - CH_3COO$, m/z 702.4203 for $C_{39}H_{60}NO_{10}$, Δ 1.4 μm; low-resolution FABMS of MH^+, m/z 762). Similar to the case of 1, the UV spectrum of 2 exhibited an absorption indicative of a conjugated double bond (λ_{max} (MeOH) 235 nm (ϵ 12 000)). The IR absorptions at 3537 and 3423 cm^{-1} indicated the presence of an NH_2 functionality, while the presence in 2 of carbonyls was suggested by bands at 1730 and 1720 cm^{-1}. Resonances in the ^1H and ^{13}C NMR spectra of 2 indicated the presence of four acetates (^{13}C resonances: 169.8, 170.4, 170.6, and 170.9 ppm). The presence of a lactone was suggested by the IR absorptions in 1 and 2, the ^{13}C NMR resonances observed at 175.2 and 171.7 ppm in 1 and 2, respectively, and the ^1H NMR resonances observed at 4.50 and 4.26 ppm in 1 and 2, respectively, which are attributed to a methine proton attached to the oxygen-bearing carbon of the lactone ring. The lactone carbonyl, four acetate carbonyls, carbamate carbonyl, and four double bonds in 2 account for 10 of the 11 degrees of unsaturation. Therefore, the carbon skeleton contains a single ring formed by the lactone.

Interpretation of the data from a COSY experiment of 2 and from decoupling experiments gave rise to the partial structures C2–C13 (**A**) and C16–C24 (**B**). Further interpretation of the data from difference NOE experiments[7] allowed for the assignment of the relative stereochemistry of the substituents in the lactone ring and the geometries of the double bonds. The two segments **A** and **B** are separated by a fully substituted sp^2 carbon that bears a methyl group and a methylene group in which the proton

(1) Gunasekera, S. P.; Cranick, S.; Longley, R. E. *J. Nat. Prod.* **1989**, *52*, 757.
(2) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 2780. Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Koseki, K. *J. Org. Chem.* **1988**, *53*, 3930.
(3) Matsunaga, S.; Fusetani, N.; Konosu, S. *Tetrahedron Lett.* **1984**, *25*, 5165; *Ibid.* **1985**, *26*, 855.
(4) Derome, A. *Modern NMR Techniques for Chemistry Research*; Pergamon: New York, 1987.
(5) Bax, A.; Morris, G. A. *J. Magn. Reson.* **1981**, *42*, 501.
(6) Same as XHCORR with suitable delay values.
(7) Hall, L. D.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1980**, *1021*, 5703.

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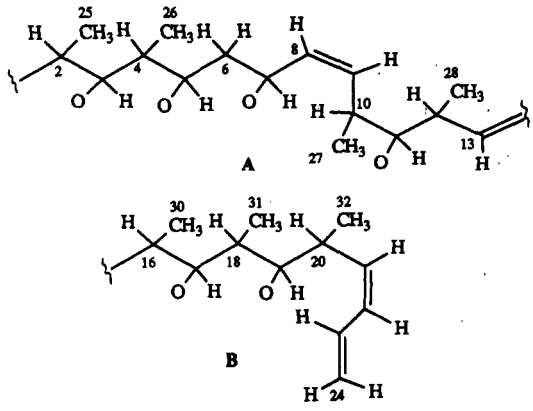

signal appeared as a multiplet that overlaps with other signals. The technique of ^{1}H-detected heteronuclear multiple-bond correlation (HMBC)[8] enabled the assignment of the lactone carbonyl C1, quaternary sp^2 carbon C14, tertiary methyl C29, and the methylene group C15. This experiment also confirmed all the connectivities assigned by COSY and decoupling experiments in the partial structures **A** and **B**. The proton–carbon correlation experiment optimized for the detection of one-bond coupling (HMQC) and the HMBC experiment confirmed unambiguously the chemical shift values of all the carbon atoms in discodermolide tetraacetate (**2**).

Partial structure **A** was established by interpretation of the ^{1}H COSY spectrum and confirmed by long-range C–H correlations. In the COSY spectrum of **2** the proton observed at 2.70 ppm (H2) revealed couplings to the methyl group observed at 1.29 ppm (H25) and to the proton observed at 4.89 ppm (H3). The chemical shift of H2 and the absence of any other couplings suggested that the proton was attached to the carbon adjacent to the lactone carbonyl. The presence of three-bond cross-peaks between C1 (171.7 ppm) and the methyl protons H25 and between C1 and proton H3 unambiguously established the attachment of the lactone carbonyl to C2. Proton H3 was found to be coupled to H4 (2.09 ppm), which in turn was coupled to methyl protons H26 (0.97 ppm). Proton H5 exibited two cross-peaks to the two methylene protons H6 (2.10, 1.64 ppm), and in turn these two signals showed couplings to the methine proton H7 (5.65 ppm). Proton H7 was further coupled to the olefinic proton H8 (5.28 ppm), which in turn was coupled to the olefinic proton H9 (5.49 ppm). The 10.7-Hz coupling constant between H8 and H9 is consistent with a *Z* olefinic bond and was confirmed by a difference NOE experiment. Proton H10 (2.89 ppm) revealed cross-peaks to H9 and H11 (4.27 ppm) and to the methyl protons H27 (0.95 ppm). Similarly, proton H12 (2.47 ppm) showed cross-peaks to H11, the olefinic proton H13 (4.94 ppm), and the methyl protons H28 (0.85 ppm). The olefinic proton H13 (d, J = 9.9 Hz) did not exhibit further couplings and thus established the partial structure **A**.

Similarly, the partial structure **B** was established by interpreting data from a COSY experiment and from long-range C–H correlations. The COSY experiment of **2** in $CDCl_3$ afforded connectivities for the diene part C21 to C24: H24′ (5.15 ppm)/H23 (6.71 ppm, J = 16.1 Hz); H24 (5.21 ppm)/H23 (J = 10.0 Hz); H23/H22 (6.03 ppm, J = 11.3 Hz); H22/H21 (5.31 ppm, J = 10.5 Hz). The coupling constant and difference NOE experiment confirmed a *Z* configuration of Δ^{21} double bond. In the COSY experiment H21 revealed a coupling to H20 (3.12 ppm), which in turn was coupled to H19 (4.60 ppm) and to the methyl protons H32 (0.96 ppm). The difference double-resonance (DDR) experiment revealed a coupling of H19 to H18 (1.98 ppm), which was partly covered under a proton multiplet. The ^{1}H NMR spectrum of **2** in C_6D_6 partially resolved this overlapping multiplet. From comparison of the COSY spectra in $CDCl_3$ and C_6D_6, proton H18 (1.98 ppm) in $CDCl_3$ was found to be coupled to H17 (4.78 ppm), which in turn was coupled H16 (2.03 ppm). The H15 signal appeared as a complicated multiplet, and unambiguous assignment of the connectivity was not possible by COSY and DDR experiments. The three-bond long-range C–H coupling between H17/C30, H17/C31, and H18/C16 established the partial structure **B**.

The remaining methylene carbon C15 (35.6 ppm) exhibited a three-bond C–H coupling to H17 and also to the methyl protons H30 and thus established the connectivity between C15 and C16. Long-range C–H correlations were essential in joining the two partial structures across the C14 quarternary carbon atom. In the long-range C–H correlated spectrum there were cross-peaks appearing from H12 (2.47 ppm) to C14 (133.4 ppm), the H29 (1.61 ppm) methyl protons to C13 and C15 (35.6 ppm), and H13 (4.94 ppm) to C29 (22.8 ppm). These connectivities established connection between the two partial structures **A** and **B**. The *Z* geometry of the Δ^{13} double bond was assigned on the basis of difference NOE experiment in which the irradiation of H29 methyl protons caused enhancement of H13. Finally, the presence of a carbamate moiety[9] was suggested from the ^{13}C NMR signal observed at 156.7 ppm and a ^{1}H NMR signal observed at 4.60 ppm (2 H, br s, exchangeable). The long-range C–H correlation observed between H19 and the carbamate carbonyl C33 (156.7 ppm) fixed the carbamate group at C19.

The ^{1}H NMR spectrum of discodermolide (**1**) in $CDCl_3$/5% CD_3OD exhibited proton signals at 3.57, 4.50, 4.60, 3.09, and 3.15 ppm and were assigned to H3, H5, H7, H11, and H17, respectively. Acetylation of discodermolide shifted four of these signals, H3, H7, H11, and H17, downfield to 4.89, 5.65, 4.27, and 4.78 ppm, respectively. The absence of a downfield shift for H5 after acetylation was consistant with the assignment of the C5 oxygen being part of the lactone ring. However, a three-bond coupling between H5 and C1 was not observed. The long-range C–H correlations observed between H3 and C40 (170.4 ppm), H7 and C38 (169.8 ppm), H11 and C36 (170.6 ppm), and H17 and C34 (170.9 ppm) unambiguously established the positions of the four acetoxy groups. The relative stereochemistry of the lactone ring of discodermolide was established by difference NOE experiments. Irradiation of H5 resulted in an enhancement of the resonances for H2 and $CH_3$26. Similarly, irradiation of H3 enhanced the resonances for H2, H4, $CH_3$25, and $CH_3$26. Irradiation of $CH_3$25 enhanced resonances for H2, H3, and H4 while the irradiation of $CH_3$26 enhanced H3, H4, and H5. Combining of the above data established the structures for discodermolide and discodermolide tetraacetate.

The relative stereochemistry of discodermolide was determined by X-ray crystallography on a crystal measuring 0.37 × 0.37 × 0.25 mm mounted in a sealed glass capillary. Diffraction measurements were made on a Rigaku AFC5S fully automated diffractometer using graphite-monochromated Cu Kα radiation (λ = 1.541 78 Å) and the low-temperature apparatus. The data were collected at −50 °C. Preliminary indications of the unit cell based on 25 randomly selected reflections revealed

(8) Bax, A.; Summers, M. F. *J. Am. Chem. Soc.* **1986**, *108*, 1093. Bax, A.; Aszalos, A.; Dinya, Z.; Sudo, K. *J. Am. Chem. Soc.* **1986**, *108*, 8056.

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Table I. ^1H and ^{13}C NMR Data for 1 and 2 and the Long-Range Connectivities Observed in the HMBC Experiment

	1		2		
C	H[a]	C[a]	H[b]	C[b]	HMBC (^1H)[b]
1		175.2		171.7 (s)	H2, H3, H25
2	2.58	42.9	2.70 (dq, 5.8, 7.3)	40.0 (d, 130)	H3, H25
3	3.57	72.5	4.89 (dd, 5.8, 5.8)	74.5 (d, 156)	H2, H25, H26
4	1.82	35.4	2.09 (ddq, 2.0, 5.8, 6.9)	33.7 (d, 127)	H2, H26
5	4.50	77.0	4.26 (dt, 2.0, 9.7)	76.8 (d, 147)	H3, H26
6	1.59	40.9	1.64 (ddd, 1.8, 9.7, 12.6)	38.7 (t, 126)	H5
6	1.74		2.10 (ddd, 8.3, 9.7, 12.6)		
7	4.60	63.4	5.65 (ddd, 8.3, 9.7, 12.6)	66.5 (d, 148)	H5, H9
8	5.37	132.4	5.28 (ddd, 1.0, 10.0, 10.7)	128.2 (d, 161)	H9
9	5.84	133.8	5.49 (dd, 10.7, 10.7)	135.1 (d, 160)	H7, H8, H11, H27
10	2.65	36.0	2.89 (ddq, 6.4, 6.6, 10.7)	35.1 (d, 124)	H8, H27
11	3.09	78.9	4.27 (dd, 4.8, 6.4)	80.2 (d, 151)	H9, H12, H27, H28
12	2.45	35.1	2.47 (ddq, 4.8, 6.6, 9.9)	34.1 (d, 126)	H11, H13, H28
13	5.05	129.9	4.94 (d, 9.9)	128.9 (d, 147)	H11, H28, H29
14		132.7		133.4 (s)	H12, H29
15	1.70	35.6	1.67 (dd, 10.0, 12.6)	35.6 (t, 125)	H13, H29, H30
15	1.84		1.86 (dd, 11.8, 12.6)		
16	1.80	33.0	2.03 (dddq, 5.8, 6.6, 10.0, 11.8)	31.8 (d, 124)	H17, H30
17	3.15	75.6	4.78 (dd, 5.6, 5.8)	77.9 (d, 145)	H19, H30
18	1.80	37.1	1.98 (ddq, 5.6, 6.1, 6.8)	36.4 (d, 123)	H17, H19, H31
19	4.63	78.8	4.60 (dd, 6.1, 6.1)	77.8 (d, 145)	H31, H32
20	2.95	34.4	3.12 (ddq, 6.1, 6.6, 10.5)	34.1 (d, 126)	H22, H32
21	5.28	133.3	5.31 (ddd, 10.5, 10.5, 13.0)	133.0 (d, 159)	H19, H20, H22
22	5.95	129.7	6.03 (ddd, 1.1, 10.5, 11.3)	130.2 (d, 159)	H20, H23, H24
23	6.54	131.9	6.71 (dddd, 1.3, 10.0, 11.3, 16.6)	132.2 (d, 153)	H21, H24
24′	5.05	117.8	5.15 (dd, 1.1, 16.6)	118.2 (t, 160)	H22
24	5.13		5.21 (d, 10.0)		
25	1.22	15.5	1.29 (d, 7.3)	15.3 (q, 124)	H2, H3
26	0.97	12.4	0.97 (d, 6.9)	12.4 (q, 124)	H3
27	0.94	18.0	0.95 (d, 6.6)	17.5 (q, 124)	H9, H11
28	0.86	15.6	0.85 (d, 6.6)	16.6 (q, 124)	H11, H12, H13
29	1.54	22.9	1.61 (s)	22.8 (q, 123)	H13
30	0.74	13.7	0.68 (d, 6.6)	13.6 (q, 124)	H17
31	0.87	8.6	0.89 (d, 6.8)	9.5 (q, 121)	H17, H19
32	0.92	17.3	0.96 (d, 6.6)	17.5 (q, 124)	H19, H20
33		157.7		156.7 (s)	H19
34				170.9 (s)	H17, H35
35			2.08 (s)	20.8 (q, 127)	
36				170.6 (s)	H11, H37
37			2.02 (s)	20.9 (q, 127)	
38				169.8 (s)	H7, H39
39			2.00 (s)	20.9 (q, 127)	
40				170.4 (s)	H3, H41
41			2.08 (s)	21.2 (q, 127)	
NH_2			4.60 (br s)		

[a] $CDCl_3$ and 5% CD_3OD. [b] $CDCl_3$. [c] Chemical shifts (ppm) from solvent (multiplicity, J (Hz)).

monoclinic symmetry. The data were processed[10] in the high-angle cell, giving the following lattice parameters: a = 11.236 (4) Å, b = 12.411 (2) Å, and c = 13.816 (3) Å with β = 112.92 (2)°. The space group was assigned as $P2_1$ (No. 4), Z = 2, with one molecule of composition $C_{33}H_{55}O_8N$ and one molecule of water forming the asymmetric unit. The volume was 1774.3 (8) Å^3, and the calculated density was 1.11 g/cm^3. There were 2784 reflections collected with $2\theta \leq 120°$; of those reflections, 1804 (65%) with $I \geq 3\sigma(I)$ were judged observed.

The structure shown in Figure 1 was solved with a combination of MITHRIL[11] and DIRDIF[12] programs. The initial phasing model was obtained from a MITHRIL run that used three special reflections and six general reflections. This effort produced 640 different phase sets for which the one with highest combined figure of merit yielded 33 out of the 42 non-hydrogen atoms. Anisotropic refinement of the non-hydrogen atoms and inclusion of the hydrogen scattering factors have resulted in R = 0.053 and R_w = 0.065 factors. The absolute configuration of 1 was not determined.

Discodermolide inhibits the in vitro proliferation of cultured murine P388 leukemia cells with an IC_{50} of 0.5 μg/mL and suppresses the two-way mixed-lymphocyte response of both murine splenocytes and human peripheral blood lymphocytes at 0.5 and 5 μg/mL, respectively, with greater than 85% viability of the splenocyte cells.

Experimental Section

NMR spectra were recorded at 360 MHz for ^1H and 90.5 MHz for ^{13}C. All chemical shifts were recorded with respect to the solvent ($CDCl_3$, 7.24 ppm; C_6D_6, 7.15 ppm). Melting point on is uncorrected.

Collection and Extraction. The sponge *D. dissoluta* was collected from Lucay, Grand Bahama Island, at a depth of 30 m in March 1987 and was immediately frozen. A voucher specimen is deposited in the Indian River Coastal Museum of the Harbor

(10) Least-squares function minimized: $\sum w(|F_o| - |F_c|)^2$ where $w = 4F_o^2/\sigma^2(F_o^2)$, $b^2(F_o^2) = [S^2(C + R^2B) + (pF_o^2)^2]/Lp^2$, S = scan rate, C = total integrated peak count, R = ratio of scan time to background counting time, B = total background count, Lp = Lorentz-polarization factor, and p = p factor. Standard deviation of an observation of unit weight: $\sum w(|F_o| - |F_c|^2/(N_o - N_v)]^{1/2}$, where N_o = number of observations and N_v = number of variables.

(11) Gilmore, C. J. *J. Appl. Cryst.* **1984**, *17*, 42.

(12) Beurskens, P. T. DIRDIF: Direct Methods for Difference Structures - an automatic procedure for phase extension and refinement of difference structure factors. Technical Report 1984/1; Crystallography Laboratory: Toernooiveld, 6525 Ed Nijmegen, The Netherlands.

(13) URANUS, a program to generate plots written by Simon K. Kearsley, Yale University, 1985.

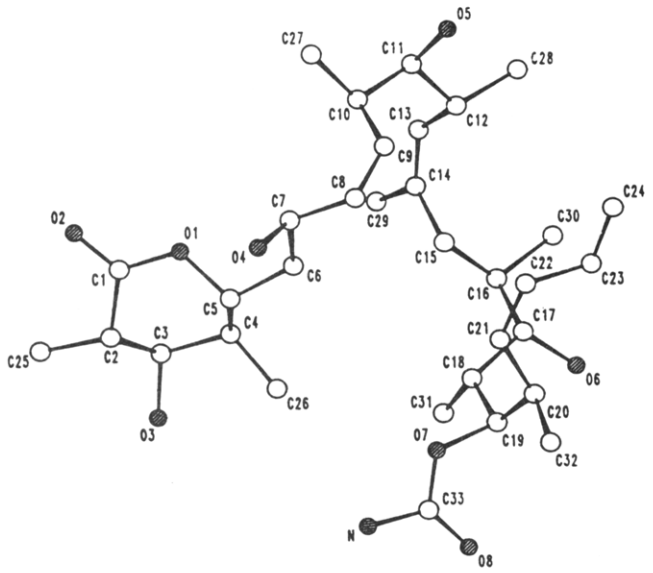

Figure 1. URANUS drawing[13] of discodermolide (1) with numbering scheme.

Branch Oceanographic Institution, Inc. The freshly thawed sponge (434 g) was extracted exhaustively with a mixture of methanol and toluene (3:1). The solvent was removed in vacuo from the combined extracts. The resulting extract was partitioned between EtOAc and H_2O. The EtOAc soluble fraction was chromatographed on silica gel (Kieselgel 60H) with a CH_2Cl_2/MeOH step gradient. The fraction that was eluted with 10% MeOH/CH_2Cl_2 was chromatographed on reversed-phase C_{18} with a MeOH/H_2O gradient. The semipure compound that separated with the 20% H_2O/MeOH mixture was then subjected to HPLC (RP C_{18}, 5 μm, 250 × 10 mm) with 48% H_2O/MeOH to give pure discodermolide, 7 mg (0.002% from frozen sponge).

Discodermolide (1): white crystals; mp 115–6 °C; $[\alpha]^{25}_D$ 7.2° (*c* 0.72, MeOH); UV λ_{max} (MeOH) 235 nm (ε 12500), 226 sh (19500), 210 (35400); IR ($CHCl_3$), 1725 cm^{-1}; ^1H and ^{13}C NMR, Table I; LRFABMS, *m/z* (relative intensity) 550 (4%, $(M + 1)^+ - CONH_2$), 542 (3), 517 (3), 488 (25), 445 (23), 427 (10), 393 (12), 375 (10), 155 (95), 135 (80), 119 (100).

Acetylation of Discodermolide. A solution of discodermolide (5.0 mg) in pyridine (1 mL) and acetic anhydride (0.5 mL) was stirred overnight. The solvents were removed in vacuo, and the resulting oil was purified by reversed-phase HPLC (C_{18}, 5 μm, 250 × 10 mm) with 20% H_2O/CH_3CN to give discodermolide tetraacetate, 4.5 mg.

Discodermolide tetraacetate (2): colorless gum; $[\alpha]^{25}_D$ 19.2° (*c* 0.3, $CHCl_3$); UV λ_{max} (EtOH) 235 nm (ε 12000), 227 sh (21000), 222 (21400), 205 (41000); IR ($CHCl_3$) 1735, 1727 cm^{-1}; ^1H ($CDCl_3$/5% CD_3OD) and ^{13}C NMR, Table I; ^1H NMR (C_6D_6) δ 6.87 (1 H, dddd, *J* = 16.6, 11.3, 10.0, 1.3 Hz, H23), 6.09 (1 H, ddd, *J* = 11.3, 10.5, 1.1 Hz, H22), 6.04 (1 H, ddd, *J* = 10.0, 8.3, 1.8 Hz, H7), 5.76 (1 H, dd, *J* = 10.7, 10.7 Hz, H9), 5.46 (1 H, ddd, *J* = 11.3, 10.5, 1.3 Hz, H21), 5.19 (1 H, dd, *J* = 16.6, 1.1 Hz, H24), 5.12 (1 H, dd, *J* = 5.8, 5.6 Hz, H17), 5.07 (1 H, d, *J* = 10.0 Hz, H24′), 5.02 (1 H, d, *J* = 9.9 Hz, H13), 4.97 (1 H, dd, *J* = 6.4, 4.8 Hz, H11), 4.96 (1 H, dd, *J* = 6.1, 6.1 Hz, H19), 4.95 (1 H, ddd, *J* = 10.7, 10.0, 1.0 Hz, H8), 4.91 (1 H, dd, *J* = 5.8, 5.8 Hz, H3), 4.32 (1 H, dt, *J* = 9.7, 2.0 Hz, H5), 4.14 (2 H, br s, NH_2), 3.29 (1 H, ddq, *J* = 10.5, 6.6, 6.1 Hz, H20), 3.15 (1 H, ddq, *J* = 10.7, 6.6, 6.4 Hz, H10), 2.68 (1 H, dq, *J* = 7.1, 5.8 Hz, H2), 2.68 (1 H, ddq, *J* = 9.9, 6.6, 4.8 Hz, H12), 2.29 (1 H, dddq, *J* = 11.8, 10.0, 6.6, 5.8 Hz, H16), 2.13 (1 H, ddq, *J* = 6.9, 5.8, 2.0 Hz, H4), 2.05 (1 H, dd, *J* = 12.6, 11.8 Hz, H15), 2.04 (1 H, ddq, *J* = 6.8, 6.1, 5.6 Hz, H18), 2.04 (1 H, ddd, *J* = 12.6, 9.7, 8.3 Hz, H6), 1.97 (1 H, dd, *J* = 12.6, 10.0 Hz, H15), 1.85 (1 H, ddd, *J* = 12.6, 9.7, 1.8 Hz, H6), 1.85 (3 H, s, H29), 1.83 (3 H, s, H35), 1.79 (3 H, s, H37), 1.70 (3 H, s, H39), 1.52 (3 H, s, H41), 1.17 (3 H, d, *J* = 6.6 Hz, H27), 1.17 (3 H, d, *J* = 7.1 Hz, H25), 1.07 (3 H, d, *J* = 6.8 Hz, H31), 0.98 (3 H, d, *J* = 6.6 Hz, H32), 0.98 (3 H, d, *J* = 6.6 Hz, H28), 0.85 (3 H, d, *J* = 6.6 Hz, H30), 0.76 (3 H, d, *J* = 6.9 Hz, H26); HRFABMS, *m/z* 702.4203, Δ 1.4 μm for $C_{39}H_{60}NO_{10}$ $(M - CH_3COO)^+$; LRFABMS, *m/z* (relative intensity) 762 (3%, MH^+), 702 (5), 642 (2), 581 (2), 521 (7), 439 (3), 427 (5), 411 (4), 399 (5), 387 (12), 359 (9), 334 (11), 327 (5), 299 (5), 285 (5), 259 (6), 232 (20), 217 (75), 173 (42), 161 (72), 147 (50), 133 (80), 126 (100).

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Supplementary Material Available: Positional parameters, *B*(eq) values, bond distances and angles, torsion or conformational angels, and *U* values for compound 1 (6 pages). Ordering information is given on any current masthead page.