Semisynthetic Analogues of the Microtubule-Stabilizing Agent Discodermolide: Preparation and Biological Activity

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Received July 18, 2002

A series of 12 semisynthetic discodermolide analogues, **2**−**13**, have been prepared using natural (+)-discodermolide (**1**) and evaluated for in vitro cytotoxicity against cultured murine P-388 leukemia and A-549 human adenocarcinoma cells. These semisynthetic analogues showed a significant variation of cytotoxicity and confirmed the importance of the C-7 through C-19 molecular fragment for potency. Specifically, these analogues suggested the importance of the C-11 and C-17 hydroxyl groups and the C-13 double bond for the potency of discodermolide. The preparation, structure elucidation, and biological activity of these new analogues are described.

Earlier, we reported the preparation, structure elucidation, biological activity, and structure−activity relationship of eight acetylated discodermolide analogues.[1−3] Recently, our group reported the isolation, structure determination, and biological activity of five new naturally occurring discodermolide analogues from a sponge sample of *Discodermia* sp.[4] Herein, we report the preparation, structural elucidation, biological activity, and structure−activity relationship of 12 (**2**−**13**) new semisynthetic analogues of natural (+)-discodermolide (**1**). Discodermolide (**1**) was first reported in 1990,[5] and since then, studies by our group and others have indicated its immunosuppresive[6−8] and antimitotic properties[9−11] with a mechanism of action similar to that of paclitaxel.[9,10] Discodermolide has been shown to promote the rapid polymerization of purified tubulin and to hyperstabilize the microtubule complex in cultured cells. (+)-Discodermolide inhibits the in vitro growth of several cancer cell lines, including paclitaxel-resistant ovarian and colon cancer cells.[11−13] The Schreiber group has synthesized both antipodes of discodermolide, establishing the absolute configuration,[14] and prepared a number of structural variants.[15] Since then, several other groups have synthesized (+)-discodermolide,[16,17] antipode (−)-discodermolide,[18,19] or various fragments of discodermolide using different synthetic approaches.[20−33] In 2001, the Paterson group[34] synthesized (+)-discodermolide and three epimeric discodermolides.

Results and Discussion

The starting material for this study, natural (+)-discodermolide (**1**), was isolated from the sponge *Discodermia* sp. and crystallized using the reported procedure.[5] The preparation of various discodermolide acetates used in this study was described in our earlier publication.[1] Structurally, discodermolide possesses 13 stereogenic centers, a tetrasubstituted δ-lactone (C-1 to C-5), four secondary hydroxyl groups (C-3, C-7, C-11, and C-17), a pendant carbamate moiety (C-19), one di- (C-8, *Z*) and one trisubstituted (C-13, *Z*) double bond, and a terminal (*Z*)-diene (C-21 to C-24). Both in solid state[5] and in solution,[35] discodermolide adapts a hairpin confirmation where the two internal (*Z*)-olefins in the side chain act as conformational locks by minimizing (1,3) strain between their respective substituents in concert with the avoidance of *syn*-pentane interactions. The molecular structure of discodermolide is amenable to other simple modifications; however, for this study, we focused on the four olefinic double bonds and the four hydroxy groups present in the molecule to prepare the selectively hydrogenated analogues (**2**−**6**), dehydroxylated analogues (**7**−**11**), and *seco* analogues (**12**, **13**). The ^{1}H NMR data of all analogues were compared to those reported for discodermolide (see Table 1) and discodermolide acetates,[1] and the chemical shifts were assigned using ^{1}H−^{1}H COSY data. DEPT, HMQC, and in some instances HMBC data were used to assign ^{13}C data of all analogues and are presented in Tables 5 and 6.

HRFABMS of 8,13,21,23-octahydrodiscodermolide (**2**) supported the molecular formula $C_{33}H_{64}NO_8$ [$(M + H)^+$, *m*/*z* 602.4618] as expected for the octahydro product. The ^{1}H NMR spectrum (see Table 1) indicated the saturation of all olefinic signals present in discodermolide. Similarly, the ^{13}C spectrum (see Table 5) showed no olefinic carbons and instead indicated the presence of six additional triplets (δ 36.3, C-8; 29.0, C-9; 42.3, C-13; 23.6, C-21; 31.9, C-22 and 29.9, C-23), a doublet (δ 28.0, C-14), and a quartet (δ 14.3, C-24), which is expected for the saturation of the four double bonds in discodermolide. These data confirmed the structure of 8,13,21,23-octahydrodiscodermolide (**2**). The relative stereochemistry of the C-29 methyl group was not determined.

HRFABMS of 8,21,23-hexahydrodiscodermolide (**3**) supported the molecular formula $C_{33}H_{62}NO_8$ [$(M + H)^+$, *m*/*z* 600.4478] as expected for the hexahydro product. The ^{1}H NMR spectrum (see Table 1) showed the presence of one olefinic doublet at δ 5.04 (J = 9.8 Hz). The COSY spectrum indicated the coupling of this proton to the C-12 multiplet at δ 2.54, which was in turn coupled to the C-11 hydroxymethine proton (δ 3.03, ddd, J = 5.2, 5.1, 5.7 Hz). The ^{13}C NMR spectrum (see Table 5) showed the presence of one olefinic doublet (δ 131.5) and one olefinic singlet (δ 133.6), and these ^{1}H and ^{13}C data established the position of the double bond in hexahydrodiscodermolide. Comparison of ^{1}H and ^{13}C data with those of discodermolide (see Tables 1 and 5) confirmed the structure of 8,21,23-hexahydrodiscodermolide (**3**).

HRFABMS supported the molecular formula $C_{33}H_{60}NO_8$ [$(M + H)^+$, *m*/*z* 598.4338] expected for tetrahydrodiscodermolide (**4**). The ^{1}H NMR spectrum (see Table 2) showed

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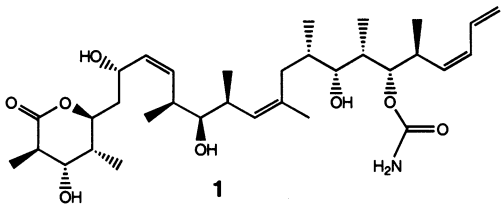
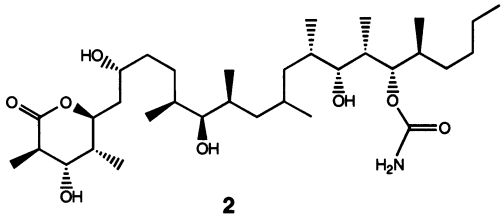
10.1021/np0203234 CCC: $22.00
Published on Web 10/25/2002

Chart 1

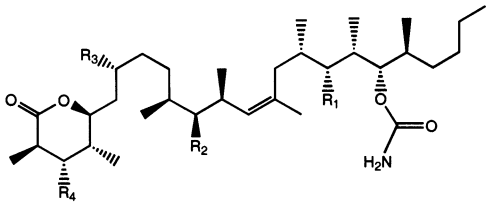


1

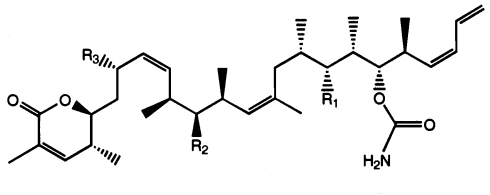


2

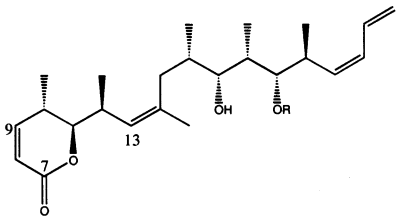
4: Δ 8, Δ 13



	R_1	R_2	R_3	R_4
3:	OH	OH	OH	OH
5:	OH	OH	H	OH
6:	OAc	OAc	H	OAc



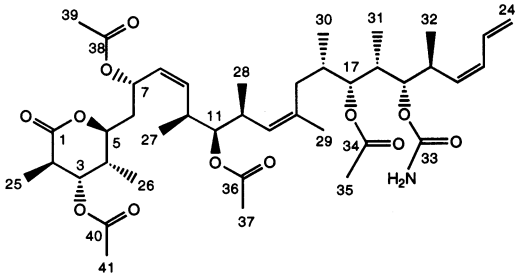
	R_1	R_2	R_3
7:	OH	OH	OH
8:	OH	OAc	OH
9:	OAc	OH	OH
10:	OAc	OAc	OH
11:	OAc	OAc	OAc



R

12: $CONH_2$

13: H



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the presence of two additional olefinic signals (δ 5.35, ddd, J = 2.2, 9.1, 10.9 Hz and δ 5.49 ddd, J = 1.0, 10.1, 10.9 Hz) compared to that of hexahydrodiscodermolide (**3**). The COSY spectrum revealed a coupling of the δ 5.35 olefinic signal to the H-7 hydroxymethine signal at δ 4.46 and coupling of the δ 5.49 signal to the H-10 signal at δ 2.65, which was in turn coupled to the H-11 hydroxymethine signal at δ 3.09. The ^{13}C NMR spectrum (see Table 5) showed the presence of only three olefinic doublets (δ 133.8, C-8; 133.7, C-9; 131.2, C-13) and one olefinic singlet (δ 133.8, C-14), indicating the saturation of two conjugated terminal double bonds in the discodermolide molecule. These data confirmed the structure of 21,23-tetrahydrodiscodermolide (**4**).

HRFABMS supported the molecular formula $C_{33}H_{62}NO_7$ [$(M + H)^+$, m/z 584.4512] expected for the deoxy-hexahydrodiscodermolide (**5**). The ^1H NMR spectrum closely resembled that of 8,21,23-hexahydrodiscodermolide. The presence of an H-13 doublet (δ 5.03, d, J = 9.8 Hz) in the ^1H spectrum together with the olefinic doublet (δ 130.0, C-13) and a singlet (δ 133.2, C-14) in the ^{13}C spectrum established compound **5** to be an analogue of 8,21,23-hexahydrodiscodermolide (**3**). Comparison of the ^1H NMR spectrum of **5** with that of **3** (see Tables 1 and 2) indicted that **5** has one less hydroxymethine proton. The COSY spectrum of **5** indicated that H-5 (δ 4.30) is coupled to H-6 methylene protons (δ 1.55 and 1.65), and these were in turn coupled to another methylene group at δ 1.39 (H-7) and 1.47 (H-7). These data suggested that deoxygenation has taken place at C-7 during the hydrogenation of discodermolide and thus confirmed the structure of **5** as 7-deoxy-hexahydrodiscodermolide.

The 7-deoxy-hexahydrodiscodermolide on acetylation furnished its triacetate **6**. HRFABMS supported the molecular formula $C_{39}H_{68}NO_{10}$ [$(M + H)^+$, m/z 710.4827] expected for the triacetate (**6**). The ^1H NMR spectrum of **6** (see Table 2) when compared with that of **5** showed the presence of three acetoxymethyls (δ 2.08, 2.05, and 2.07) and downfield-shifted signals for H-3 (Δ 1.18 ppm), H-11 (Δ 1.50 ppm), and H-17 (Δ 1.51 ppm). The ^{13}C spectrum (see Table 5) when compared with that of **5** showed the presence of three additional methyl signals (δ 21.0, 20.9, 20.8) and three additional carbonyl signals (δ 171.0, 170.4, 170.3) for the presence of three acetoxy groups. These data confirmed the structure of the acetylated product of **5** as 7-deoxy-hexahydrodiscodermolide-3,11,17-triacetate (**6**).

Discodermolide-3-acetate on deacetylation under alkaline conditions gave the 3-deoxy analogue **7**. HRFABMS supported the molecular formula $C_{33}H_{54}NO_7$ [$(M + H)^+$, m/z 576.3931] expected for the deoxy-discodermolide (**7**). The ^1H NMR spectrum of 3-deoxy-discodermolid-2-ene (**7**) (see Table 2) was similar to that of discodermolide (see Table 1). The ^1H NMR spectrum of **7** indicated signals for eight methyl groups as in discodermolide. However, it showed the presence of two vinylic methyl singlets compared to one vinylic methyl singlet present in discodermolide. The comparison of the ^1H NMR spectrum of **7** with that of discodermolide indicated that the downfield methyl doublet

Table 1. ^{1}H NMR Data of Discodermolide (**1**) and Semisynthetic Analogues **2** and **3**[a]

position	**1**	**2**	**3**
2	2.56 (dq, 4.2, 7.2)	2.56 (dq, 4.6, 7.3)	2.57 (dd, 4.2, 7.4)
3	3.61 (ddd, 4.2, 4.2, 4.6)	3.63 (ddd, 2.3, 3.5, 4.7)	3.64 (ddd, 4.0, 4.0, 4.5)
3-OH	3.27 (4.6)	3.27 (d, 4.7)	3.31 (d, 4.5)
4	1.83 (ddq, 2.0, 4.2, 6.9)	1.87 (m)	1.87 (m)
5	4.45 (dt, 2.0, 10.1)	4.47 (dt, 2.0, 9.5)	4.48 (dt, 2.0, 10.0)
6	1.72 (m)	1.32 (m)	1.59 (m)
6	1.47 (ddd, 2.4, 10.8, 13.0)	1.61 (m)	1.65 (m)
7	4.44 (m)	3.72 (m)	3.70 (m)
7-OH	2.75 (d, 5.3)	2.77 (d, 5.2)	2.84 (d, 5.5)
8	5.38 (ddd, 2.2, 9.1, 10.9)	1.27 (m)	1.24 (m)
9	5.54 (ddd, 1, 10.1, 10.9)	1.70 (m)	1.65 (m)
		1.10 (m)	1.00 (m)
10	2.62 (m)	1.51 (m)	1.48 (m)
11	3.05 (m)	3.02 (m)	3.03 (ddd, 5.2, 5.1, 5.7)
11-OH	2.64(d, 5.2)	2.44 (d, 5.5)	2.43 (d, 5.7)
12	2.29 (ddq, 5.2, 6.6, 10.0)	1.71 (m)	2.54 (m)
13	4.97 (d, 10.0)	1.28 (m)	5.04 (d, 9.8)
		0.97 (m)	
14		1.55 (m)	
15	1.76 (m)	1.20 (m)	2.09 (m)
15	1.63 (dd, 3.6, 12.2)	0.95 (m)	1.93 (dd, 3.6, 12.2)
16	1.76 (m)	1.80 (m)	1.93 (m)
17	3.27 (dd, 3.5, 6.2)	3.16 (ddd, 5.0, 6.1, 6.2)	3.54 (ddd, 5.2, 5.1, 5.9)
17-OH	2.59 (d, 6.5)	2.59 (d, 6.1)	2.80 (d, 5.9)
18	1.72 (m)	1.87 (m)	1.87 (m)
19	4.71 (dd, 4.1, 8.0)	4.53 (dd, 4.2, 7.3)	4.54 (dd, 4.5, 7.7)
20	3.07 (m)	1.74 (m)	1.75 (m)
21	5.42 (dd, 10.6, 10.7)	1.25 (m)	1.26 (m)
		1.09 (m)	1.01 (m)
22	6.06 (dd, 10.7, 11.0)	1.38 (m)	1.40 (m)
22		1.19 (m)	1.19 (m)
23	6.68 (ddd, 10.5, 11.0, 16.6)	1.25 (m)	1.26 (m)
		1.35 (m)	1.35 (m)
24	5.21 (d, 16.6)	0.89 (t, 6.6)	0.90 (t, 6.6)
24	5.10 (d, 10.1)		
25	1.18 (d, 7.2)	1.20 (d, 7.4)	1.21 (d, 7.4)
26	0.97 (d, 6.9)	0.97 (d, 6.6)	0.97 (d, 6.7)
27	1.00 (d, 6.9)	0.85 (d, 6.7)	0.88 (d, 6.8)
28	0.88 (d, 6.6)	0.85 (d, 6.6)	0.92 (d, 6.6)
29	1.57 (s)	0.82 (d, 6.6)	1.63 (s)
30	0.73 (d, 6.2)	0.89 (d, 6.5)	0.78 (d, 6.5)
31	0.80 (d, 6.5)	0.81 (d, 6.5)	0.90 (d, 6.6)
32	0.93 (d, 6.7)	0.78 (d, 6.7)	0.87 (d, 6.6)
NH_2	5.05 (br s)	5.10 (br s)	5.08 (br s)

[a] All spectra run at 500 MHz in CD_3CN. Chemical shifts are reported in ppm, and J values in Hz.

corresponding to the C-25 methyl (δ 1.18, d, J = 7.2 Hz, H_3-25) in discodermolide has been changed to a vinylic methyl singlet (δ 1.81, s) and has been shifted downfield (Δ 0.63 ppm) as expected. The ^{1}H−^{1}H COSY spectrum of **7** indicated allylic coupling between the vinylic methyl at 1.81 ppm and the newly formed broad olefinic singlet at 6.42 ppm. Although no coupling was seen between the olefinic singlet at 6.42 ppm and the H-4 at 2.44 ppm, the allylic nature of the H-4 established the position of the new unsaturation. The remainder of the ^{1}H NMR spectrum was identical to that of discodermolide. The ^{13}C spectrum of **7** showed the presence of a conjugated olefinic singlet (δ 127.5) and an olefinic doublet (δ 147.0) instead of an oxygenated carbon and a methine carbon present in the ^{13}C spectrum of discodermolide. These data confirmed the structure of 3-deoxy-discodermolid-2-ene (**7**).

The ^{1}H NMR data of the four acetylated products **8**, **9**, **10**, and **11** of 3-deoxy-discodermolide (**7**) were compared with the ^{1}H NMR data of discodermolide and 3-deoxy-discodermolide. Using the ^{1}H−^{1}H COSY data in combination with the HMQC data, the proton chemical shift values of these analogues were assigned (see Tables 3 and 4). The ^{1}H NMR spectra of these analogues indicated a significant downfield shift of the signals corresponding to the acetoxymethines (see Tables 3 and 4), and these data were used to determine the position of acetylation in each analogue. The HRMS data of **8** and **9** are consistent with the presence of one acetoxy group in each compound and established the molecular formula $C_{35}H_{55}NO_8$. Comparison of the ^{1}H NMR spectra of **8** and **9** with that of 3-deoxy-discodermolid-2-ene (**7**) showed the presence of one acetoxymethyl in each compound and downfield shifts of H-11 (Δ 1.65 ppm) in **8** and H-17 (Δ 1.65 ppm) in **9**. The combination of these data confirmed the structures of 3-deoxy-discodermolid-2-en-11-acetate (**8**) and 3-deoxy-discodermolid-2-en-17-acetate (**9**).

HRESIMS supported the molecular formula $C_{37}H_{57}NNaO_9$ [$(M + Na)^+$, m/z 682.3896] expected for the 3-deoxy-discodermolid-2-ene-diacetate (**10**). The ^{1}H NMR spectrum of **10** (see Table 4) when compared with that of **7** (see Table 3) showed the presence of two additional acetoxymethyls (δ 2.04 and 2.08) and a downfield shift of H-11 (Δ 1.58 ppm) and H-17 (Δ 1.64 ppm). These data are supported by the ^{13}C data, which showed signals for two acetoxy groups (δ 20.9, q; 21.0, q; 171.0, s; 170.7, s). Combination of these data confirmed the structure of 3-deoxy-discodermolid-2-en-11,17-diacetate (**10**).

The molecular formula $C_{39}H_{59}NO_{10}$ expected for the triacetate **11** was supported by HRESIMS data [m/z 702.4204, for $C_{39}H_{60}NO_{10}$ $(M + H)^+$]. The ^{1}H NMR spectrum of **11** (see Table 4) when compared with that of **7** (see Table 3) showed the presence of three additional aectoxym-

Table 2. ^{1}H NMR Data of Discodermolide Analogues **4**, **5**, and **6**[a]

position	**4**[b]	**5**[c]	**6**[c]
2	2.56 (dq, 4.2, 7.2)	2.64 (dq, 3.7, 7.4)	2.71 (dd, 3.7, 7.4)
3	3.62 (ddd, 4.2, 4.2, 4.6)	3.71 (dd, 3.7, 3.7)	4.89 (dd, 3.7, 3.7)
3-OH	3.30 (4.6)		
4	1.83 (m)	1.91 (m)	2.05 (m)
5	4.47 (dt, 2.0, 10.1)	4.30 (ddd, 2.8, 8.2, 8.2)	4.28 (ddd, 2.0, 8.5, 8.5)
6	1.72 (m)	1.55 (m)	1.53 (m)
6	1.46 (ddd, 2.4, 10.8, 13.0)	1.65 (m)	1.65 (m)
7	4.46 (m)	1.39 (m)	1.35 (m)
7		1.47 (m)	1.45 (m)
7-OH	2.80 (d, 5.3)		
8	5.35 (ddd, 2.2, 9.1, 10.9)	1.22 (m)	1.24 (m)
9	5.49 (ddd, 1.0, 10.1, 10.9)	1.70 (m)	1.65 (m)
		1.10 (m)	1.00 (m)
10	2.65 (m)	1.53 (m)	1.65 (m)
11	3.09 (m)	3.13 (dd, 4.7, 6.4)	4.63 (dd, 4.3, 7.9)
11-OH	2.64 (d, 5.2)		
12	2.38 (ddq, 5.2, 6.6, 10.0)	2.57 (ddq, 4.7, 3.4, 10.0)	2.60 (ddq, 4.7, 3.4, 10.0)
13	5.03 (d, 10.0)	5.03 (d, 9.8)	4.94 (d, 9.8)
15	1.95 (m)	1.87 (m)	1.75 (m)
15	1.75 (dd, 3.6, 12.2)	2.11 (m)	1.62 ((m)
16	1.83 (m)	1.97 (m)	2.21 (m)
17	3.15 (ddd, 3.5, 6.1, 6.2)	3.29 (dd, 5.3, 5.4)	4.80 (dd, 4.2, 7.7)
17-OH	2.64 (d, 6.1)		
18	1.87 (m)	1.90 (m)	2.04 (m)
19	4.55 (dd, 4.1, 8.0)	4.58 (dd, 3.8, 7.7)	4.56 (dd, 3.8, 7.8)
20	1.74 (m)	1.72 (m)	1.75 (m)
21	1.25 (m)	1.27 (m)	1.27 (m)
	1.09 (m)	1.05 (m)	1.08 (m)
22	1.38 (dd, 10.7, 11.0)	1.38 (m)	1.40 (m)
22	1.19 (m)	1.19 (m)	1.16 (m)
23	1.25 (m)	1.25 (m)	1.26 (m)
	1.35 (m)	1.35 (m)	1.35 (m)
24	0.91 (t, 6.6)	0.87 (t, 6.6)	0.87 (t, 6.6)
25	1.19 (d, 7.4)	1.29 (d, 7.3)	1.31 (d, 7.4)
26	0.97 (d, 6.9)	1.03 (d, 6.7)	0.96 (d, 6.7)
27	0.99 (d, 6.9)	0.90 (d, 6.8)	0.81 (d, 6.8)
28	0.91 (d, 6.6)	0.95 (d, 6.8)	0.84 (d, 6.7)
29	1.61 (s)	1.65 (s)	1.63 (s)
30	0.75 (d, 6.6)	0.80 (d, 6.6)	0.72 (d, 6.5)
31	0.85 (d, 6.5)	0.94 (d, 6.7)	0.86 (d, 6.6)
32	0.84 (d, 6.7)	0.86 (d, 6.7)	0.85 (d, 6.6)
NH_2	5.05 (br s)	4.70 (br s)	4.65 (br s)
35			2.08 (s)
37			2.05 (s)
41			2.07 (s)

[a] All spectra run at 500 MHz. Chemical shifts are reported in ppm, and *J* values in Hz. [b] In CD_3CN. [c] In $CDCl_3$.

ethyls (δ 2.01, 2.08, 1.99) and the downfield shift of H-7 (Δ 1.20 ppm), H-11 (Δ 1.57 ppm), and H-17 (Δ 1.65 ppm) acetoxymethine protons. The ^{13}C data supported the presence of three acetoxy groups in the molecule (δ 20.9, q; 21.0, q; 21.2, q; 171.0, s; 170.6, s; 169.8, s). These data confirmed the structure of 3-deoxy-discodermolid-2-en-7,11,17-triacetate (**11**).

Discodermolide (**1**) on mild oxidation with MnO_2 at room temparature gave 6,7-*seco*-discodermolide instead of the expected 7-ketodiscodermolide. HRESIMS supported the molecular formula $C_{25}H_{40}NO_5$ [$(M + H)^+$, *m*/*z* 434.2911] expected for the 6,7-*seco*-discodermolide (**12**). The ^{1}H NMR spectrum **12** (see Table 4) was quite different from that of discodermolide (see Table 1) and showed the absence of all signals corresponding to the C-1 through C-7 fragment of the discodermolide molecule. The ^{1}H spectrum indicated the presence of one vinylic methyl singlet (δ 1.64, s) corresponding to the C-14 methyl group and five methyl doublets. The presence of a conjugated double bond was apparent from the downfield shift of C-8 to 5.91 ppm and C-9 to 6.64 ppm. The signals corresponding to the C-21 through C-24 diene system were present in the spectrum. The presence of the carbamate group was evident from the characteristic NH_2 signal at 4.48 ppm. The ^{13}C spectrum indicated signals for 25 carbons including the α,β-unsaturated δ-lactone (δ 164.0, s) and the characteristic carbamate group (δ 158.0, s). These data suggested that the C-7 allylic hydroxyl group in discodermolide had undergone a complete oxidation to an acid group and that in turn had esterified with the C-11 hydroxy group to yield the α,β-unsaturated δ-lactone. These data confirmed the structure of 6,7-*seco*-discodermolide (**12**).

The ^{1}H NMR spectrum of 19-*des*-aminocarbonyl-6,7-*seco*-discodermolide closely resembled that of **12** (see Table 4). The characteristic differences observed were the absence of the carbamate NH_2 functionality and the upfield shift of the C-19 oxymethine proton (Δ 1.31 ppm). HRESIMS supported the molecular formula $C_{24}H_{39}O_4$ [$(M + H)^+$, *m*/*z* 391.2858] expected for the *des*-aminocarbonyl compound. The ^{13}C NMR spectrum indicated the absence of the characteristic carbon signal for the carbamate group. The remaining ^{13}C NMR spectral data were very similar to those of **12**. These data confirmed the structure of 19-*des*-aminocarbonyl-6,7-*seco*-discodermolide (**13**).

Biological Activity of Discodermolide (1) and Semisynthetic Analogues 2−13. Discodermolide (**1**) and its semisynthetic analogues **2**−**13** were tested for their in vitro cytotoxicity against cultured murine P-388 leukemia and human lung adenocarcinoma A-549 cell lines.[36] These compounds inhibited the in vitro proliferation of the P-388

Table 3. ^{1}H NMR Data of Discodermolide Analogues **7**, **8**, and **9**[a]

position	**7**[b]	**8**[c]	**9**[c]
1			
2			
3	6.42 (s)	6.33 (s)	6.32 (s)
4	2.44 (dq, 9.5, 7.3)	2.44 (dq, 9.8, 7.1)	2.43 (m)
5	4.23 (ddd, 2.5, 9.5,9.5)	4.32 (ddd, 2.2, 9.8, 9.8)	4.32 (ddd, 2.2, 9.8, 9.8)
6	1.80, 1.60 (2H, m)	1.77, 1.70 (m)	1.80, 1.60 (m)
7	4.45 (ddd, 2, 8.1, 8.0)	4.75 (dd, 8.0, 9.0)	4.72 (ddd, 2.0, 8.0, 8.0)
8	5.38 (dd, 8.0, 10.5)	5.38 (dd, 8.0, 10.5)	5.47 (dd, 8.0, 10.5)
9	5.55 (dd, 10.5, 10.5)	5.44 (dd, 10.5, 10.5)	5.41 (dd, 10.5, 10.1)
10	2.63 (ddq, 6.1, 10.5, 6.9)	2.88 (ddq, 10.5, 6.7, 6.1)	2.73 (ddq, 10.1, 10.1, 6.6)
11	3.08 (dd, 6.1, 6.1)	4.73 (m)	3.12 (m)
12	2.27 (ddq, 6.6, 9.9, 6.1)	2.62 (ddq, 6.1, 6.7, 9.7)	2.43 (m)
13	4.97 (d, 9.7)	4.94 (d, 9.7)	5.12 (d, 9.8)
14			
15	1.75, 1.6 (m)	1.9, 1.6 (m)	1.87, 1.65 (m)
16	1.72 (m)	1.90 (m)	2.05 (m)
17	3.13 (dd, 5.1, 5.3)	3.25 (dd, 5.1, 4.9)	4.79 (dd, 5.5, 5.7)
18	1.75 (m)	1.85 (m)	2.01 (m)
19	4.72 (dd, 4.3, 7.2)	4.71 (dd, 6.0, 6.0)	4.62 (dd, 6.2, 6.1)
20	3.07 (m)	3.00 (ddq, 6.0, 6.7 10.8)	3.13 (m)
21	5.40 (dd, 10.5, 10.9)	5.34 (dd, 10.8, 10.9)	5.33 (dd, 10.9,10.5)
22	6.06 (dd, 10.9, 10.9)	6.01 (dd, 10.9, 11.0)	6.03 (dd, 10.9, 11.0)
23	6.66 (ddd, 10.2, 10.9, 16.3)	6.60 (ddd, 10.2, 11.0, 16.5)	6.71 (ddd, 10.2, 11.0, 16.3)
24	5.14 (d, 10.2)	5.11 (d, 10.2)	5.14 (d, 10.2)
24	5.24 (d, 16.3)	5.20 (d, 16.5)	5.21 (d, 16.3)
25	1.81 (s)	1.88 (s)	1.88 (s)
26	1.07 (d, 7.3)	1.09 (d, 7.1)	1.09 (d, 7.3)
27	1.01 (d, 7.2)	0.98 (d, 6.9)	0.98 (d, 6.6)
28	0.88 (d, 6.6)	0.87 (d, 6.7)	0.90 (d, 6.6)
29	1.60 (s)	1.61 (s)	1.62 (s)
30	0.74 (d, 6.2)	0.80 (6.0)	0.71 (d, 7.5)
31	0.75 (d, 6.8)	0.97 (d, 6.7)	0.91 (d, 6.8)
32	0.95 (d, 7.0)	0.99 (d, 6.7)	0.96 (d, 7.0)
35			2.07 (s)
37		2.02 (s)	
NH_2	5.04 (br s)	4.53 (br s)	4.51 (br s)

[a] All spectra run at 500 MHz. Chemical shifts are reported in ppm, and *J* values in Hz. [b] In CD_3CN. [c] In $CDCl_3$.

cell line, with IC_{50} (nM) values of **1**, 35; **2**, >8292; **3**, 33.8; **4**, 10; **5**, 309; **6**, >7052; **7**, 33.6; **8**, 519; **9**, >8103; **10**, >7587; **11**, 7076; **12**, 3686, and **13**, >12787, and the A-549 cell line, with IC_{50} (nM) values of **1**, 13.5; **2**, >8292; **3**, 67.7; **4**, 8.4; **5**, 377; **6**, not determined; **7**, 21.7; **8**, 3128; **9**, >8103; **10**, >7587; **11**, >7133; **12**, 6774, and **13**, >12787. The cytotoxicity data of compounds **2**−**5** indicated that double bonds play a significant role in the activity of discodermolide (**1**). The comparable cytotoxicity value of tetrahydrodiscodermolide (**4**) and discodermolide (**1**) in both cell lines suggested that the terminal conjugated diene system is not contributing significantly to the cytotoxicity of discodermolide. Further saturation of discodermolide (**1**) to hexahydrodiscodermolide (**3**) showed a 5-fold reduction in activity against the A-549 cell line but comparable activity against the P-388 cell line. These activity data indicated that the C-8 *Z*-double bond is not contributing significantly to the cytotoxicity of discodermolide (**1**). The 7-deoxy-hexahydrodiscodermolide (**5**) showed a 10-fold reduction in P-388 activity and a 5-fold reduction in A-549 activity compared to that of hexahydrodiscodermolide (**3**), suggesting the importance of the C-7 hydroxy group for cytotoxicity. A significant reduction of activity in hexahydrodiscodermolide triacetate (**6**) clearly indicated the contribution of hydroxy groups to the folding of the molecule via hydrogen bonds. A remarkable loss of activity is indicated in the fully saturated octahydrodiscodermolide (**2**). These data suggested that the C-13 *Z*-double bond, which partly controls the folding of the discodermolide molecule, is important for cytotoxicity. The series of 3-deoxy compounds **7**−**11** clearly shows the contribution of each hydroxy group toward the cytotoxicity of discodermolide (**1**). The activity data indicated that the C-3 hydroxy group is not essential for cytotoxicity, the C-7 hydroxy group is partly contributing toward cytotoxicity, and the C-17 hydroxy group is essential for the cytotoxicity of discodermolide. The complete loss of cytotoxicity in the *seco*-compounds **12** and **13** indicated that the combination of C-11 and C-17 hydroxy groups contribute to the optimum cytotoxicity of discodermolide. These results are consistent with our earlier findings[1,2] that acetylation at C_{11} and more specifically at C_{17} caused a dramatic reduction in activity and further support our earlier inference[1,2] that the C_7 through C_{17} moiety contributes to the overall cytotoxicity of discodermolide. The complete biological activity profile, including the effects of analogues on tubulin polymerization both within cells and using purified tubulin and G_2/M blocking activity, will be published elsewhere. The details of the P-388 and A-549 assays were described previously.[1,2]

Experimental Section

General Experiment Procedures. UV spectra were measured with a Hitachi U-3010 spectrophotometer. IR spectra were obtained on a Midac M-1200 with Galactic GRAMS/386 software. 1D and 2D NMR spectra were measured on a Bruker AMX-500 instrument. The ^{1}H NMR chemical shifts were assigned using a combination of data from COSY and HMQC experiments. Similarly, ^{13}C NMR chemical shifts were assigned on the basis of DEPT and HMQC experiments. The HRFABMS and HRESIMS were obtained on Finnigan MAT95Q and MAT95 Hybrid Sector mass spectrometers, respectively, at the Spectroscopic Services Group, University of Florida, Gainesville.

Preparation of 8,13,21,23-Octahydrodiscodermolide (2). Discodermolide (2.0 mg) in absolute EtOH (5.0 mL) and a

Table 4. ^{1}H NMR Data of Discodermolide Analogues **10**, **11**, **12**, and **13**[a]

position	**10**	**11**	**12**	**13**
1				
2				
3	6.33 (s)	6.30 (s)		
4	2.46 (m)	2.42 (m)		
5	4.30 (ddd, 2.0, 9.9,9.9)	4.04 (ddd, 2.2, 9.9, 9.9)		
6	1.77 (m)	1.90 (m)		
6	1.67 (m)	1.75 (m)		
7	4.66 ((m)	5.65 (ddd, 2.0, 8.2, 9.0)		
8	5.39 (dd, 8.0, 10.5)	5.28 (dd, 9.0, 10.5)	5.92 (d, 9.3)	5.92 (d, 9.3)
9	5.49 (dd, 10.5, 10.5)	5.48 (dd, 10.5, 10.5)	6.64 (dd, 4.0, 9.3)	6.64 (dd, 4.0, 9.3)
10	2.86 (ddq, 6.1, 10.5, 6.9)	2.85 (ddq, 10.5, 6.7, 6.1)	2.54 (ddq, 4.0, 6.0, 7.4)	2.54 (4.0, 6.0, 7.4)
11	4.66 (m)	4.65 (dd, 6.1, 6.1)	3.91 (dd, 6.0, 6.0)	3.92 (dd, 6.0, 6.0)
12	2.46 (m)	2.51 (ddq, 6.1, 6.8, 10.0)	2.75 (ddq, 6.0, 6.7, 10.0)	2.78 (m)
13	4.94 (d, 10.0)	4.95 (d, 10.0)	5.18 (d, 10.0)	5.18 (d, 10.0)
14				
15	1.95, 1.65 (m)	1.8, 1.6 (m)	1.94, 1.85 (m)	1.90, 1.80 (m)
16	2.02 (m)	2.0 (m)	1.88 (m)	1.90 (m)
17	4.77 (dd, 5.1, 5.3)	4.78 (dd, 5.8, 5.7)	3.25 (dd, 5.2, 5.5)	3.42 (dd, 5.2, 5.5)
18	1.96 (m)	1.95 (m)	1.86 (m)	1.80 (m)
19	4.59 (m)	4.60 (dd, 6.0, 6.0)	4.69 (dd, 4.4, 7.7)	3.38 (dd, 4.0, 8.5)
20	3.15 (ddq, 6.0, 7.0, 10.5)	3.14 (ddq, 6.0, 6.6, 10.6)	2.98 ddq, 7.0, 7.7, 10.4)	2.74 (m)
21	5.33 (dd, 10.5, 10.9)	5.33 (dd, 10.6, 10.9)	5.33 (dd, 10.4, 10.5)	5.27 (dd, 10.4, 10.5)
22	6.04 (dd, 10.9, 11.0)	6.03 (dd, 10.9, 11.0)	6.01 (dd, 10.5, 11.0)	6.19 (dd, 10.5, 10.9)
23	6.74 (ddd, 10.2, 11.0, 16.5)	6.72 (ddd, 10.1, 11.0, 16.5)	6.60 (ddd, 10.2, 11.0, 16.3)	6.62 (ddd, 10.2, 10.9, 16.3)
24	5.16(d, 10.2)	5.15 (d, 10.1)	5.10 (d, 10.2)	5.17 (d, 10.2)
24	5.22 (d, 16.5)	5.21 (d, 16.5)	5.21 (d, 16.3)	5.21 (d, 16.3)
25	1.88 (s)	1.88 (s)		
26	1.09 (d, 7.2)	1.10 (d, 7.0)		
27	0.94 (d, 6.6)	0.96 (d, 6.6)	1.14 (d, 7.4)	1.15 (d, 7.4)
28	0.83 (d, 6.7)	0.87 (d, 6.8)	1.01 (d, 6.3)	1.02 (d, 6.3)
29	1.61 (s)	1.60 (s)	1.64 (s)	1.65 (s)
30	0.67 (d, 6.5)	0.68 (d, 6.7)	0.80 (d, 6.5)	0.82 (d, 6.5)
31	0.89 (d, 7.0)	0.90 (d, 6.7)	0.97 (d, 6.8)	0.87 (d, 6.8)
32	0.94 (d, 7.0)	0.96 (d, 6.6)	0.99 (d, 7.0)	0.96 (d, 7.0)
35	2.04 (s)	2.01 (s)		
37	2.08 (s)	2.08 (s)		
39		1.99 (s)		
NH_2	5.04 (br s)	4.53 (br s)	4.48 (br s)	

[a] All spectra run at 500 MHz in $CDCl_3$. Chemical shifts are reported in ppm, and *J* values in Hz.

catalytic amount of Pt(IV) oxide was allowed to shake in a hydrogen atmosphere under a balloon pressure for 12 h at room temparature. The reaction mixture was filtered, and the filtrate was evaporated under a stream of N_2 to give a colorless residue (~2 mg). The residue was subjected to HPLC on a SiO_2 gel (Lichrosorb 5μ, Phenomenex 250 × 10 mm) column using a mixture of 6% MeOH in CH_2Cl_2 to yield 8,13,21,23-octahydrodiscodermolide (**2**, 1.8 mg).

Preparation of 8,21,23-Hexahydrodiscodermolide (3), 21,23-Tetrahydrodiscodermolide (4), and 7-Deoxy-8,21,-23-hexahydrodiscodermolide (5). Discodermolide (34.0 mg) in absolute EtOH (20.0 mL) and a catalytic amount of Pt(IV) oxide was maintained at 10 °C and treated with hydrogen under a balloon pressure for 0.5 h. The reaction mixture was filtered, and the filtrate was evaporated under a stream of N_2 to give a colorless residue (~34 mg). The residue was subjected to HPLC on a SiO_2 gel (Lichrosorb 5μ, 250 × 10 mm) column using a mixture of 7% MeOH in CH_2Cl_2 to yield 8,21,23-hexahydrodiscodermolide (**3**, 21.0 mg), 21,23-tetrahydrodiscodermolide (**4**, 2.0 mg), and 7-deoxy-8,21,23-hexahydrodiscodermolide (**5**, 2.3 mg).

Preparation of 7-Deoxy-8,21,23-hexahydrodiscodermolide-3,11,17-triacetate (6). 7-Deoxy-8,21,23-hexahydrodiscodermolide (1.0 mg) in pyridine (0.3 mL) and acetic anhydride (0.3 mL) was stirred overnight at 23 °C. The solvents were removed in a vacuum, and the resulting gum on purification on a Si Sep-Pak with 1% MeOH/CH_2Cl_2 gave 7-deoxy-8,21,23-hexahydrodiscodermolide-3,11,17-triacetate (**6**, 1.0 mg).

Preparation of 3-Deoxy-discodermolid-2-ene (7). Discodermolide-3-acetate[1] (2.4 mg) was treated with saturated aqueous Na_2CO_3 in ethanol (1:9, 2 mL), and the mixture was stirred at room temparature for 24 h. The solvent was removed by distillation under reduced pressure. The residue was partitioned between EtOAc (5 mL) and H_2O (5 mL), and the EtOAc-soluble fraction on purification by HPLC (SiO_2, 5 μm, 250 × 10 mm) with 4.5% MeOH−CH_2Cl_2 gave 3-deoxy-discodermolid-2-ene (**7**) as a white solid (1.2 mg).

Preparation of 3-Deoxy-discodermolid-2-en-11-acetate (8). Discodermolide-3,7,11-triacetate[1] (3.0 mg) was treated with saturated aqueous Na_2CO_3 in ethanol (1:9, 2 mL), and the mixture was stirred at room temparature for 24 h. The solvent was removed by distillation under reduced pressure. The residue was partitioned between CH_2Cl_2 (4 mL) and H_2O (4 mL), and the CH_2Cl_2-soluble fraction on purification by HPLC (SiO_2, 5μ, 250 × 10 mm) with 2.5% MeOH−CH_2Cl_2 gave 3-deoxy-discodermolid-2-en-11-acetate (**8**) as a white solid (1.5 mg).

Preparation of 3-Deoxy-discodermolid-2-en-17-acetate (9) and 3-Deoxy-discodermolid-2-en-11,17-diacetate (10). Discodermolide-3,7,11,17-tetraacetate[5] (**14**, 4.0 mg) was treated with saturated aqueous Na_2CO_3 in ethanol (1:9, 2 mL), and the mixture was stirred at 40 °C for 2 h. The solvent was removed by distillation under reduced pressure. The residue was partitioned between EtOAc (5 mL) and H_2O (5 mL), and the EtOAc-soluble fraction on purification by HPLC (SiO_2, 5μ, 250 × 10 mm) with 3.5% MeOH−CH_2Cl_2 gave 3-deoxy-discodermolid-2-en-17-acetate (**9**) as a white solid (1.0 mg) and 3-deoxy-discodermolid-2-en-11,17-diacetate (**10**) as a white solid (2.0 mg).

Preparation of 3-Deoxy-discodermolid-2-en-7,11,17-triacetate (11). 3-Deoxy-discodermolid-2-en-11,17-diacetate (**10**, 1.0 mg) in pyridine (0.3 mL) and acetic anhydride (0.3 mL) was stirred overnight at 23 °C. The solvents were removed

Table 5. ^{13}C NMR Data of Compounds **1**−**6**[a]

position	**1**[b]	**2**[b]	**3**[b]	**4**[b]	**5**[c]	**6**[c]
1	174.7 (s)	174.8 (s)	174.9 (s)	174.6 (s)	174.2 (s)	172.9 (s)
2	44.1 (d)	44.0 (d)	44.1 (t)	44.0 (d)	43.2 (d)	40.37 (d)
3	73.2 (d)	73.2 (d)	73.2 (d)	73.1 (d)	73.4 (d)	74.9 (d)
4	36.4 (d)	37.9 (d)	38.0 (d)	37.6 (d)	37.1 (d)	35.8 (d)
5	77.6 (d)	78.3 (d)	78.3 (d)	77.6 (d)	80.2 (d)	78.7 (d)
6	42.2 (t)	42.0 (t)	41.9 (t)	42.2 (t)	33.1 (t)	33.1 (t)
7	63.5 (d)	68.1 (d)	68.1 (d)	63.6 (d)	24.9 (t)	24.4 (t)
8	133.9 (d)	36.3 (t)	37.3 (t)	133.8 (d)	30.3 (t)	30.4 (t)
9	133.8 (d)	29.0 (t)	31.8 (t)	133.7 (d)	29.2 (t)	29.2 (d)
10	36.4 (d)	36.8 (d)	36.9 (d)	36.2 (d)	35.7 (d)	34.8 (d)
11	79.8 (d)	80.1 (d)	80.7 (d)	79.6(d)	80.8 (d)	81.5 (d)
12	37.1 (d)	32.9 (d)	36.2 (d)	36.4 (d)	35.5 (d)	34.5 (d)
13	131.2 (d)	42.3 (t)	131.5 (d)	131.2 (d)	130.0 (d)	129.1 (d)
14	133.9 (s)	28.0 (d)	133.6 (s)	133.8 (s)	133.2 (s)	133.1 (s)
15	36.3 (t)	43.6 (t)	36.9 (t)	36.9 (t)	36.5 (t)	36.4 (d)
16	34.3 (d)	32.8 (d)	33.8 (d)	34.0 (d)	33.2 (d)	31.4 (d)
17	76.0 (d)	76.3 (d)	76.9 (d)	77.0 (d)	77.2 (d)	78.3 (d)
18	38.5 (d)	35.9 (d)	35.7 (d)	35.3 (d)	34.9 (d)	32.7 (d)
19	79.3 (d)	79.4 (d)	79.6 (d)	80.0 (d)	80.2 (d)	80.8 (d)
20	34.8 (d)	36.1 (d)	36.1 (d)	36.1 (d)	35.5 (d)	33.8 (d)
21	134.3 (d)	23.6 (t)	23.6 (t)	23.6 (t)	22.9 (t)	22.9 (t)
22	130.4 (d)	31.9 (t)	130.6 (d)	31.2 (t)	31.4 (t)	31.2 (t)
23	133.3 (d)	29.9 (t)	29.9 (t)	29.9 (t)	27.1 (t)	27.1 (t)
24	118.3 (t)	14.3 (q)	13.6 (t)	14.4 (q)	14.0 q)	14.0 (t)
25	15.8 (q)	15.7 (q)	15.7 (q)	15.7 (q)	15.8 (q)	16.6 (q)
26	13.1 (q)	12.9 (q)	13.8 (q)	13.0 (q)	12.6 (q)	12.4 (q)
27	19.7 (q)	20.7 (q)	17.6 (q)	19.4 (q)	17.1 (q)	16.9 (q)
28	17.5 (q)	16.3 (q)	16.9 (q)	17.1 (q)	16.4 (q)	16.5 (q)
29	23.3 (q)	16.6 (q)	23.6 (q)	23.4 (q)	23.4 (q)	22.9 (q)
30	15.5 (q)	14.5 (q)	14.3 (q)	14.5 (q)	13.1 (q)	12.7 (q)
31	9.2 (q)	9.8 (q)	9.7 (q)	9.3 (q)	8.7 (q)	9.5 (q)
32	18.2 (q)	13.0 (q)	16.4 (q)	16.5 (q)	15.7 (q)	15.8 (q)
33	158.4 (s)	158.4 (s)	158.4 (s)	158.5 (s)		156.9 (s)
34						171.0 (s)
35						21.0 (s)
36						170.4 (s)
37						20.9 (s)
40						170.3 (s)
41						20.8 (s)

[a] All spectra run at 125.7 MHz. Chemical shifts are reported in ppm. [b] In CD_3CN. [c] In $CDCl_3$.

Table 6. ^{13}C NMR Data of Compounds **7**−**12**[a]

position	**7**[b]	**8**[c]	**9**[c]	**10**[c]	**11**[c]	**12**[c]
1	166.2 (s)	165.5 (s)	165.5 (s)	165.4 (s)	164.8 (s)	
2	127.5 (s)	127.3 (s)	127.3 (s)	127.3 (s)	127.6 (s)	
3	147.0 (d)	145.6 (d)	145.6 (d)	145.5 (d)	144.8 (d)	
4	34.8 (d)	35.0 (d)	35.0 (d)	34.5 (d)	34.1 (d)	
5	80.7 (d)	79.9 (d)	79.9 (d)	79.9 (d)	79.4 (d)	
6	41.8 (t)	40.6 (t)	40.6 (t)	40.5 (t)	38.4 (t)	
7	63.1 (d)	63.4 (d)	63.4 (d)	63.4 (d)	66.8 (d)	164.0 (s)
8	134.1 (d)	132.2 (d)	132.2 (d)	132.3 (d)	128.1 (d)	119.8 (d)
9	133.9 (d)	133.9 (d)	133.9 (t)	133.7 (d)	135.2 (d)	151.1 (d)
10	36.2 (d)	34.7 (d)	34.7 (d)	34.5 (d)	35.0 (d)	34.3 (d)
11	79.8 (d)	80.2 (d)	80.2 (d)	80.3 (d)	80.2 (d)	87.3 (d)
12	37.0 (d)	34.0 (d)	34.0 (d)	34.0 (d)	33.7 (d)	30.3 (d)
13	131.1 (d)	128.4 (d)	128.9 (d)	128.9 (d)	129.0 (d)	128.2 (d)
14	133.1 (s)	133.9 (s)	133.5 (s)	133.5 (s)	133.2 (s)	134.9 (s)
15	36.0 (t)	36.1 (t)	35.4 (t)	35.4 (t)	35.5 (t)	35.8 (t)
16	34.3 (d)	32.8 (d)	31.9 (d)	31.9 (d)	31.9 (d)	33.2 (d)
17	75.9 (d)	75.7 (d)	77.3 (d)	77.3 (d)	77.9 (d)	76.0 (d)
18	38.5 (d)	37.4 (d)	36.5 (d)	36.5 (d)	36.4 (d)	37.3 (d)
19	79.4 (d)	78.6 (d)	77.8 (d)	78.1 (d)	78.0 (d)	78.9 (d)
20	34.6 (d)	34.3 (d)	34.0 (d)	34.0 (d)	34.0 (d)	34.6 (d)
21	134.0 (d)	133.8 (d)	133.8 (d)	132.9 (d)	132.9 (d)	133.4 (d)
22	130.5 (d)	129.9 (d)	130.0 (d)	130.3 (d)	130.2 (d)	129.8 (d)
23	133.6 (d)	132.3 (d)	132.3 (d)	132.3 (d)	132.2 d)	132.0 (d)
24	118.3 (t)	117.8 (t)	118.1 (t)	118.2 (t)	118.2 (t)	117.8 (t)
25	16.9 (q)	16.6 (q)	16.8 (q)	16.8 (q)	16.7 (q)	
26	16.7 (q)	16.3 (q)	16.6 (q)	16.6 (q)	16.3 (q)	
27	19.7 (q)	17.4 (q)	17.5 (q)	17.5 (q)	17.5 (q)	17.4 (q)
28	17.5 (q)	16.8 (q)	16.8 (q)	16.8 (q)	16.8 (q)	15.8 (q)
29	23.2 (q)	23.1 (q)	22.9 (q)	22.9 (q)	22.9 (q)	23.1 (q)
30	15.6 (q)	13.8 (q)	14.0 (q)	14.0 (q)	13.8 (q)	13.6 (q)
31	8.9 (q)	8.9 (q)	9.4 (q)	9.4 (q)	9.4 (q)	8.6 (q)
32	18.1 (q)	18.6 (q)	18.7 (q)	18.7 (q)	15.5 (q)	17.4 (q)
33	158.3 (s)	156.9 (s)	156.7 (s)	156.7 (s)	156.7 (s)	158.0 (s)
34			171.0 (s)	171.0 (s)	171.0 (s)	
35			20.9 (q)	20.9 (q)	20.9 (q)	
36		170.8 (s)		170.7 (s)	170.6 (s)	
37		21.0 (q)		21.0 (q)	21.0 (q)	
38					169.8 (s)	
39					21.2 (q)	

[a] All spectra run at 125.7 MHz. Chemical shifts are reported in ppm. [b] In CD_3CN. [c] In $CDCl_3$.

in a vacuum, and the resulting gum on purification on a Si Sep-Pak with 1% MeOH/CH_2Cl_2 gave 3-deoxy-discodermolid-2-en-7,11,17-triacetate (**11**, 1.0 mg) as a white solid.

Preparation of 6,7-*seco*-Discodermolide (12). Discodermolide (5.0 mg) was dissolved in EtOAc (4.0 mL) and treated with excess of MnO_2 (10 mg, Aldrich Chem. Co., 5μ, ~85% activated). The mixture was stirred at room temperature for 48 h. The product was filtered to remove MnO_2 and evaporated to dryness using a stream of nitrogen. The residue on purification by HPLC (SiO_2, 5 μm, 250 × 10 mm) with 3.5% MeOH−CH_2Cl_2 gave 6,7-*seco*-discodermolide (**12**, 3.4 mg) as a white solid.

Preparation of 19-*des*-Aminocarbonyl-6,7-*seco*-discodermolide (13). 6,7-*seco*-Discodermolide (**12**, 1.0 mg) was dissolved in CH_2Cl_2 (1.0 mL) and treated with titanium isopropoxide (15 μL) at room temparature. The mixture was stirred at room temparature for two weeks. The product was partitioned between CH_2Cl_2 and H_2O. The CH_2Cl_2-soluble layer was evaporated to dryness using a stream of nitrogen. The residue on purification by HPLC (SiO_2, 5 μm, 250 × 10 mm) with 1.5% MeOH−CH_2Cl_2 gave 19-*des*-aminocarbonyl-6,7-*seco*-discodermolide (**13**, 0.6 mg) as a white powder.

8,13,21,23-Octahydrodiscodermolide (2): $[\alpha]^{21}_D$ −50.0° (*c* 0.1, MeOH); UV (MeOH) λ_{max} (log ϵ) 202 (3.25) nm; IR (neat/NaCl) ν_{max} 3365, 2967, 1720, 1602, 1389, 1237, 1028 cm^{-1}; HRFABMS (glycerol) *m/z* 602.4618 $[M + H]^+$ (calcd for $C_{33}H_{64}NO_8$, 602.4628).

8,21,23-Hexahydrodiscodermolide (3): $[\alpha]^{21}_D$ −29.2° (*c* 0.8, MeOH); UV (MeOH) λ_{max} (log ϵ) 202 (3.85) nm; IR (neat/NaCl) ν_{max} 3470, 2968, 1720, 1602, 1382, 1240 cm^{-1}; HRFABMS (glycerol) *m/z* 600.4478 $[M + H]^+$ (calcd for $C_{33}H_{62}NO_8$, 600.4475).

21,23-Tetrahydrodiscodermolide (4): UV (MeOH) λ_{max} (log ϵ) 202 (3.25) nm; IR (neat/NaCl) ν_{max} 3490, 2970, 1720, 1602, 1382, 1235 cm^{-1}; HRFABMS (glycerol) *m/z* 598.4338 $[M + H]^+$ (calcd for $C_{33}H_{60}NO_8$, 598.4346).

7-Deoxy-8,21,23-hexahydrodiscodermolide (5): $[\alpha]^{21}_D$ −19.8° (*c* 0.3, MeOH); UV (MeOH) λ_{max} (log ϵ) 202 (3.25) nm; IR (neat/NaCl) ν_{max} 3480, 2970, 1720, 1602, 1372, 1240 cm^{-1}; HRFABMS (glycerol) *m/z* 584.4512 $[M + H]^+$ (calcd for $C_{33}H_{62}NO_7$, 584.4526).

7-Deoxy-8,21,23-hexahydroxydiscodermolide-3,11,17-triacetate (6): $[\alpha]^{21}_D$ −12.1° (*c* 0.01, MeOH); UV (MeOH) λ_{max} (log ϵ) 202 (3.30) nm; IR (neat/NaCl) ν_{max} 3490, 2967, 1737, 1720, 1602, 1370, 1244 cm^{-1}; HRFABMS (glycerol) *m/z* 710.4827 $[M + H]^+$ (calcd for $C_{39}H_{68}NO_{10}$, 710.4842).

3-Deoxy-discodermolid-2-ene (7): $[\alpha]^{21}_D$ 20.0° (*c* 0.04, MeOH); UV (MeOH) λ_{max} (log ϵ) 237 (3.07), 222 (3.37) nm; IR (neat/NaCl) ν_{max} 3426, 1705, 1404, 1249 cm^{-1}; HRFABMS (glycerol) *m/z* 576.3931 $[M + H]^+$ (calcd for $C_{33}H_{54}NO_7$, 576.3955).

3-Deoxy-discodermolid-2-en-11-acetate (8): $[\alpha]^{21}_D$ 5.1° (*c* 0.04, MeOH); UV (MeOH) λ_{max} (log ϵ) 237 (3.07), 220 (3.40) nm; IR (neat/NaCl) ν_{max} 3490, 2669, 1737, 1707, 1606, 1372, 1240, 1045 cm^{-1}; HRFABMS (glycerol) *m/z* 618.4036 $[M + H]^+$ (calcd $C_{35}H_{56}NO_8$, 618.4005).

3-Deoxy-discodermolid-2-en-17-acetate (9): $[\alpha]^{21}_D$ 6.2° (*c* 0.03, MeOH); UV (MeOH) λ_{max} (log ϵ) 237 (3.07), 220 (3.40) nm; IR (neat/NaCl) ν_{max} 3480, 2970, 1736, 1707, 1605, 1374, 1243, 1045 cm^{-1}; HRESIMS *m/z* 618.4037 $[M + H]^+$ (calcd for $C_{35}H_{56}NO_8$, 618.4007).

3-Deoxy-discodermolid-2-en-11,17-diacetate (10): $[\alpha]^{21}_D$ 3.3° (*c* 0.03, MeOH); UV (MeOH) λ_{max} (log ϵ) 237 (3.07), 221 (3.41) nm; IR (neat/NaCl) ν_{max} 3490, 2973, 1736, 1707, 1374, 1243, 1045 cm^{-1}; HRESIMS *m/z* 682.3896 $[M + Na]^+$ (calcd for $C_{37}H_{57}NNaO_9$, 682.3924).

3-Deoxy-discodermolid-2-en-7,11,17-triacetate (11): UV (MeOH) λ_{max} (log ϵ) 237 (3.07), 221 (3.41) nm; IR (neat/NaCl)

ν_{max} 3490, 2970, 1737, 1707, 1372, 1240, 1045 cm^{-1}; HRESIMS *m/z* 702.4204 $[M + H]^+$ (calcd for $C_{39}H_{60}NO_{10}$, 702.4213).

6,7-*seco*-Discodermolide (12): $[\alpha]^{21}_D$ 37.5° (*c* 0.08, MeOH); UV (MeOH) λ_{max} (log ϵ) 238 (3.94), 220 (4.29) nm; IR (neat/NaCl) ν_{max} 3367, 2928, 1705, 1691, 1384, 1328, 1235 cm^{-1}; HRFABMS (3-nitrobenzyl alcohol) *m/z* 434.2911 $[M + H]^+$ (calcd for $C_{25}H_{40}NO_5$, 434.2906).

19-*des*-Aminocarbonyl-6,7-*seco*-discodermolide (13): UV (MeOH) λ_{max} (log ϵ) 238 (3.94), 219 (4.29) nm; IR (neat/NaCl) ν_{max} 3367, 2928, 1705, 1603, 1384, 1328, 1235 cm^{-1}; ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 164.0 (s, C-7), 119.8 (d, C-8), 151.0 (d, C-9), 34.3 (d, C-10), 87.3 (d, C-11), 30.3 (d, C-12), 128.2 (d, C-13), 134.9 (s, C-14), 35.8 (t, C-15), 32.3 (d, C-16), 76.0 (d, C-17), 37.0 (d, C-18), 78.9 (d, C-19), 34.2 (d, C-20), 133.4 (d, C-21), 129.8 (d, C-22), 132.0 (d, C-23), 117.8 (t, C-24), 17.4 (q, C-27), 15.8 (q, C-28), 23.1 (q, C-29), 13.6 (q, C-30), 8.6 (q, C-31), 17.4 (q, C-32); HRFABMS (3-nitrobenzyl alcohol) *m/z* 391.2858 $[M + H]^+$ (calcd for $C_{24}H_{39}O_4$, 391.2840).

Acknowledgment. We thank S. A. Pomponi and J. K. Reed for the collection and identification of the sponge *Discodermia* sp. and R. K. Boeckman, Jr., University of Rochester, for helpful discussions. We also thank Patricia Linley for her assistance with the cytotoxicity assays, D. Powell of the University of Florida, Gainesville, for the HRMS measurements, and L. McNulty, Florida Atlantic University, Jupiter campus, for allowing us to use the polarimeter. This research was funded in part by a grant from the National Institutes of Health/National Cancer Institute # CA 74227. This is Harbor Branch Oceanographic Institution contribution no. 1486.

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NP0203234