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ARTICLE *in* JOURNAL OF NATURAL PRODUCTS · MARCH 2007

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Biogenetic Relationships between Annonaceous Acetogenins: Squamocin Is Not a Precursor of Chamuvarinin Based on a Semisynthetic Study

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Received August 1, 2006

In the course of reactivity studies on squamocin (**1**), a highly cytotoxic acetogenin from the plant family Annonaceae, two diastereomers, **3** and **4**, of chamuvarinin (**2**) were synthesized. Based on this, a plausible relative configuration was proposed for **2**, demonstrating the absence of any biogenetic link between **1** and **2**. The new analogues **3**, **4**, and **7** were also tested for their ability to induce apoptosis.

Acetogenins of the Annonaceae constitute a broad group of secondary metabolites with potent biological activities such as their cytotoxic properties.[1] In consequence, they have been considered as important leads for new anticancer drugs.[2] However, more recently, Annonaceous acetogenins have been suspected as causative factors in neurodegenerative disorders such as atypical parkinsonism.[3] The high activity of the acetogenins of the Annonaceae in conjunction with this new public health issue necessitates a better understanding of the exact mechanisms of action of these compounds. Therefore, we have embarked on synthetic investigations on squamocin (**1**),[4] a common acetogenin of the Annonaceae[5] extracted in our case from the seeds of *Annona reticulata* L. Squamocin (**1**), as depicted in Figure 1, possesses a terminal α,β-unsaturated γ-lactone (which is believed to be the main pharmacophore for complex I inhibition) and a central polar part consisting of two tetrahydrofuran rings and three secondary alcohol functions. On the other hand, chamuvarinin (**2**, Figure 1), a new acetogenin, was recently isolated with squamocin from a cyclohexane extract of the roots of *Uvaria chamae* P. Beauv. (Annonaceae).[6] It features an unusual tetrahydropyran (THP) ring[7] adjacent to the common bis-tetrahydrofuran (THF) system found in numerous acetogenins. The concomitant presence of both **1** and **2** in *U. chamae* suggests a possible biogenetic link between these two structures. In the present investigation, it was intended to investigate the feasibility of accessing the THP ring of **2** from **1** as a way demonstrating this plausible link and also to gain further information concerning the stereochemistry of chamuvarinin (**2**).

Recently, a selective iodination of alcohols was described using sodium iodide and the ion-exchange resin Amberlyst 15 under very mild conditions.[8] It was considered that this reactivity could promote interesting reactions in biomimetic conditions with squamocin (**1**). Treatment of **1** under these conditions for 24 h in acetonitrile at room temperature gave rise to a less polar compound **3** with a molecular mass of 604 Da (**1**−H_2O), corresponding to that of chamuvarinin (**2**) (Scheme 1, route a). Concomitantly, **1** was subjected to Mitsunobu-type conditions. Three major compounds were isolated from the reaction: **3** was found again along with **4** and iodo derivative **5** (Scheme 1, route b). Compound **4**, which also shares with **2** the same mass, was assigned as a diastereomer of **3** by NMR spectroscopic analysis. Finally, squamocin (**1**) was reacted in acidic conditions in THF with Amberlyst 15 but in the absence of NaI (Scheme 1, route c). Isomeric **3** and **4** were isolated from the crude mixture as well as a dehydrated derivative, **6** (the exact position of the double bond has not been clarified). The Mitsunobu reaction performed with 2 equiv of triphenylphosphine and diethylazodicarboxylate but without any nucleophilic reagent

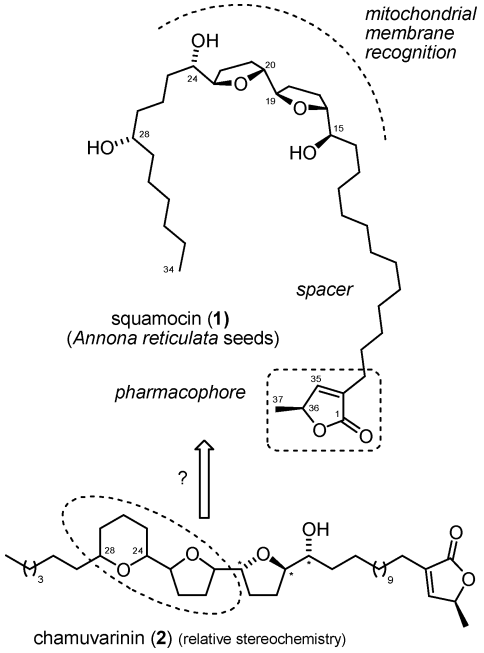

Figure 1. Structures of **1** and **2** and key SAR elements.

was performed. It did not lead to **4** as expected but to a mixture of **7** and **8**, separated by flash chromatography (Scheme 2). The relatively high yield of the monosubstituted carbamate **7** confirmed the possibility of modulating selectively position C-28 of the acetogenin using Mitsunobu conditions.[9] Treatment of squamocin (**1**) in strong acidic conditions such as HBr (48%) as previously reported for the construction of a cyclic ether unit from diols[10] led to the complete degradation of **1**.

Disappearance of the H-24 and H-28 protons of **1** (3.85 and 3.60 ppm, respectively) as observed in the ^{1}H NMR spectrum of **3** and **4** demonstrated the occurrence of a reaction of the attached hydroxyl functions, while new ^{1}H NMR signals (**3**: 3.21−3.23 ppm, **4**: 3.45 and 3.64 ppm) suggested the formation of a tetrahydropyran ring. The relative configuration of the newly created ring was deduced from careful NMR analysis and by comparison with literature data.[7,11] A *cis* relationship was established for **3** (shielded α and α′ protons) and a *trans* configuration for **4** (deshielded α and α′ protons).

Assuming a more likely reaction at the less hindered 28 position, Scheme 3 provides a mechanistic rationale for the sequences of reactions that led to diastereomeric **3** and **4** and compounds **5** and **6**. Two sequential S_N2-type reactions may explain the formation of **3** via either the acidic mediated pathway (path a) or the

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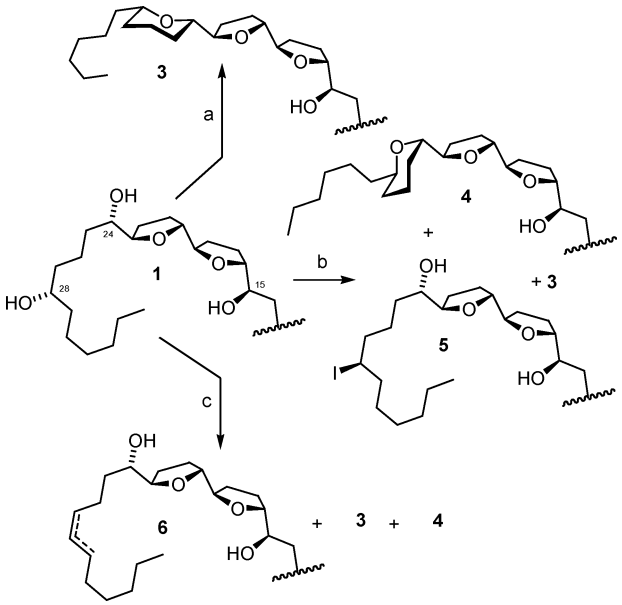
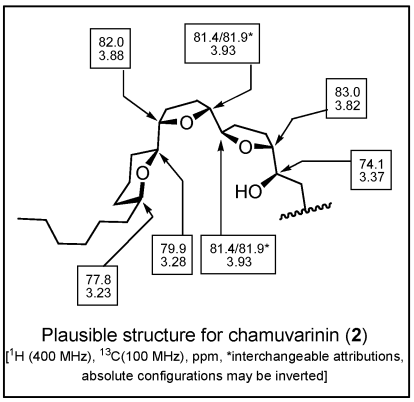
10.1021/np060376b CCC: $37.00
Published on Web 02/06/2007

Scheme 1. Semisynthetic Derivatives of **1** and Plausible Structure of **2**[a]



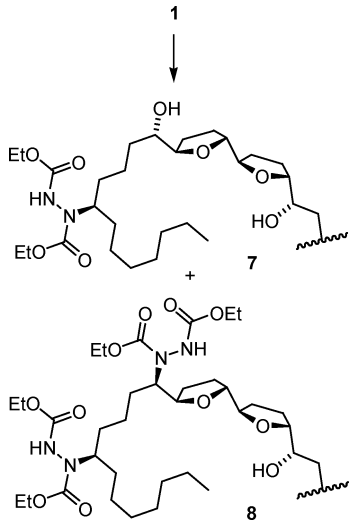


[a] Reagents and conditions: (a) NaI (33 equiv), Amberlyst H-15 (excess), CH_3CN, rt, 24 h (17%); (b) PPh_3 (4.5 equiv), I_2 (4.5 equiv), DEAD (4.5 equiv), THF, rt, 24 h (**3**: 21%, **4**: 21%, **5**: 22%); (c) Amberlyst H-15 (excess), THF, reflux, 5 d (**3**: 11%, **4**: 11%, **6**: 26%).

Mitsunobu-type pathway (path b). In both cases, competition with intramolecular nucleophilic substitution involving OH-24 may bypass the process and give rise to **4**.

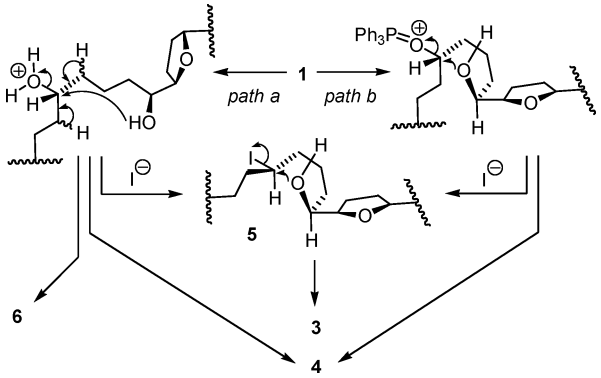
Neither **3** nor **4** was a perfect match with natural **2**. From all information gathered through chemical synthesis and reanalysis of the spectroscopic data of chamuvarinin (**2**),[6] a plausible stereostructure for **2** is proposed (Scheme 1, see ^1H and ^{13}C NMR data). First, chamuvarinin (**2**) presents unambiguously *cis* geometry at the tetrahydropyran ring (e.g., ^1H NMR: shielded H-24 and H-28; ^{13}C NMR: deshielded C-24 and C-28). Furthermore, chemical shifts of the central THF ring could account for a *cis* relationship by comparison with literature data of other acetogenins (e.g., H-21: 1.72 ppm; H-22: 1.92 ppm).[12] In agreement with a low Δ ppm between protons in a *threo* geometry compared to the *erythro*, the observed chemical shifts for **2** are consistent with a C-19/C-20 and a C-23/C-24 *threo* structure. Chamuvarinin (**2**) is therefore unlikely to be derived from squamocin (**1**) in nature. Among many possibilities, a plausible biogenetic pathway is depicted in Scheme 4. Starting from an unsaturated precursor like chatenaytrienine-4,[13] one can explain the formation of chamuvarinin (**2**) via regio- and stereoselective oxidations followed by a cascade of favored *exo*-tet S_N2 openings of the epoxides. Further studies for proving the relative stereochemistry and elucidating the absolute stereochemistry of **2** and its possible origin are underway.

Scheme 2. Reaction with DEAD[a]

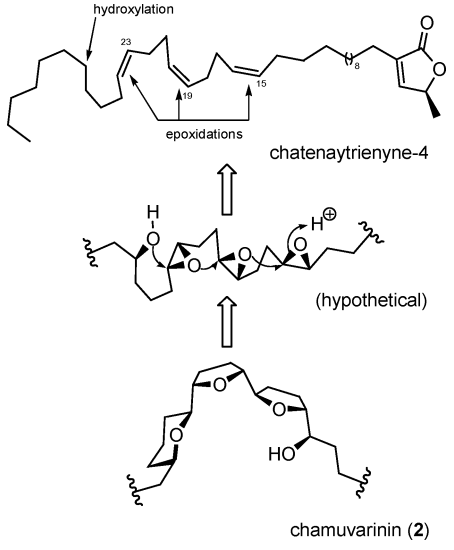


[a] Reagents and conditions: PPh_3 (2 equiv), DEAD (2 equiv), THF, rt, 24 h (**7**: 32%, **8**: 11%).

Scheme 3. Proposed Mechanism for the Conversion of **1** to **3**−**6**



Scheme 4. Plausible Biogenetic Origin for Chamuvarinin (**2**)



Squamocin (**1**) is known to be a proapoptotic agent.[4a] Compounds **3** and **4** were tested for their ability to induce apoptosis of Jurkat T cells. The measurement, by flow cytometry, of the early stage disruption of mitochondrial transmembrane potential, a constant event of apoptosis, permitted the evaluation, through a simple screening procedure, of the ability of the semisynthetic analogues to induce programmed cell death. Chamuvarinin diastereomers **3**

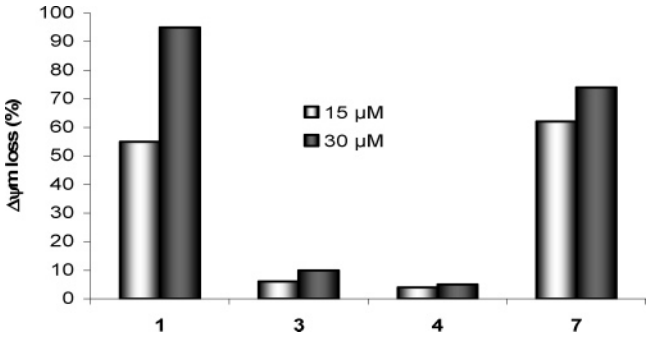


Figure 2. Evaluation of pro-apoptotic potential for **1** and its semisynthetic analogues **3** and **4** by measurement of $\Delta\Psi_m$ disruption in Jurkat T cells. After 24 h of the indicated treatment, Jurkat cells were labeled with both $DiOC_6(3)$ and propidium iodide and analyzed by flow cytometry. Percentages refer to cells with low $DiOC_6(3)$ staining. As positive control, etoposide (10 μM) induced $\Delta\Psi_m$ loss on 80 ± 10% of the cells (three independent experiments).

and **4** were poor apoptotic inducers compared to squamocin (**1**) and analogue **7** (Figure 2).

Experimental Section

General Experimental Procedures. See ref 4a.

Procedures for the Preparation of Compounds 3−6 from 1. Scheme 1, Route a. To a solution of squamocin (**1**, 50 mg, 80 μmol) in dry CH_3CN were added sodium iodide (389 mg, 2.6 mmol, 33 equiv) and a large excess of Amberlyst H-15. The heterogeneous mixture was stirred under reflux for 24 h. Amberlyst H-15 was eliminated by filtration and rinsed with CH_2Cl_2. The organic layer was washed with an aqueous saturated solution of $NaHCO_3$ (3 × 10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2−MeOH, 9:1) to afford compound **3** (R_f = 0.40 (CH_2Cl_2−MeOH, 95:5), 8 mg, 17%).

Scheme 1, Route b. To a solution of **1** (20 mg, 32 μmol) in dry THF (1 mL) were added triphenylphosphine (36 mg, 144 μmol, 4.5 equiv), iodide (36 mg, 144 μmol, 4.5 equiv), and diethylazodicarboxylate (24 mg, 21 μL, 144 μmol, 4.5 equiv). The mixture was stirred at room temperature overnight, concentrated under reduced pressure, and submitted successively to flash chromatography (silica gel, CH_2Cl_2 followed by CH_2Cl_2−MeOH, 98:2, 95:5, 9:1) and Sephadex LH-20 (CH_2Cl_2) to give compounds **3** (4 mg, 21%), **4** (R_f = 0.35 (CH_2Cl_2−MeOH, 95:5), 4 mg, 21%), and **5** (R_f = 0.25 (CH_2Cl_2−MeOH, 95:5), 5 mg, 22%).

Scheme 1, Route c. To a solution of **1** (20 mg, 32 μmol) in dry THF was added a large excess of Amberlyst H-15. The heterogeneous mixture was stirred under reflux for 5 days. Amberlyst H-15 was eliminated by filtration and rinsed with CH_2Cl_2. The organic layer was concentrated under reduced pressure and the residue purified by flash chromatography (CH_2Cl_2−MeOH, 98:2) to afford compounds **3** (2 mg, 11%), **4** (2 mg, 11%), and **6** (R_f = 0.20 (CH_2Cl_2−MeOH, 95:5), 5 mg, 26%). **3**: colorless oil; $[\alpha]_D$ +30 (*c* 0.5, CH_2Cl_2); IR (film, CH_2Cl_2) ν_{max} 3473, 2924, 2853, 1755, 1459, 1372, 1318, 1242, 1198, 1067 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (3H, m, H-34), 1.15 (1H, m, H-25a or H-27a), 1.25 (25H, s, H-25a or H-27a, -CH_2-), 1.30 (2H, m, H-33), 1.37 (1H, m, H-25b or H27b), 1.39 (5H, m, H-14, H-37), 1.52−1.56 (5H, m, H-4, H-25b or H-27b, H-29), 1.63 (4H, m, H-17a, H-18a, H-21a, H-22a), 1.84 (2H, m, H-26), 1.94−2.00 (4H, m, H-17b, H-18b, H-21b, H-22b), 2.26 (2H, t, *J* = 7.5 Hz, H-3), 3.21−3.23 (2H, m, H-24, H-28), 3.40 (1H, m, H-15), 3.82 (1H, m, H-16), 3.84−3.91 (3H, m, H-19, H-20, H-23), 4.99 (1H, t, *J* = 6.0 Hz, H-36), 6.98 (1H, s, H-35); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.1 (C-34), 19.2 (C-37), 22.6, 23.4 (C-26), 25.2, 25.6, 25.7, 27.4, 28.0, 28.4, 28.8, 28.9, 29.2, 29.3, 29.5, 29.6, 29.7, 31.8, 31.9, 33.5, 36.5, 74.1 (C-15), 77.3 (C-36), 77.8 (C-28), 80.3 (C-24), 81.9, 82.0, 82.5, 83.0, 83.2 (C-16, C-19, C-20, C-23), 134.4 (C-2), 148.8 (C-35), 173.9 (C-1); ESIMS *m*/*z* 627 [M + Na]$^+$; HRESIMS *m*/*z* [M + Na]$^+$ 627.4612 (calcd for $C_{37}H_{64}NaO_6$ 627.4601). **4**: colorless oil; $[\alpha]_D^{20}$ +50 (*c* 0.1, CH_2Cl_2); IR (film, CH_2Cl_2) ν_{max} 3488, 2924, 2853, 1753, 1462, 1437, 1317, 1195, 1069, 1028 cm^{-1}; ^{1}H NMR 0.87 (3H, m, H-34), 1.20 (1H, m, H-25a), 1.27 (25H, s, H-27a, -CH_2-), 1.37 (2H, m, H-33), 1.40 (5H, m, H-14, H-37), 1.54 (3H, m, H-4, H-25b), 1.64 (5H, m, H-18, H-27b, H-29), 1.73 (2H, m, H-21), 1.86 (2H, m, H-26), 1.95 (2H, m, H-17), 2.04 (2H, m, H-22), 2.26 (2H, t, $^3J_{3-4}$ = 7.5 Hz, H-3), 3.37 (1H, m, H-15), 3.45 (1H, m, H-24), 3.64 (1H, m, H-28), 3.81 (1H, m, H-16), 3.83−3.86 (2H, m, H-19, H-20), 4.07 (1H, m, H-23), 4.99 (1H, t, $^3J_{36-37}$ = 6.0 Hz, H-36), 6.98 (1H, s, H-35); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.1 (C-34), 18.4, 19.2 (C-37), 22.6, 25.2, 25.7, 25.8, 27.4, 28.4, 28.7, 28.9, 29.0, 29.2, 29.3, 29.5, 29.6, 29.7, 29.9, 30.4, 31.9, 33.0, 33.4, 72.2 (C-28), 73.2 (C-24), 74.1 (C-15), 77.3 (C-36), 80.0, 81.8, 81.9, 83.1 (C-16, C-19, C-20, C-23), 134.4 (C-2), 148.8 (C-35), 173.9 (C-1); ESIMS *m*/*z* 627 [M + Na]$^+$; HRESIMS *m*/*z* 627.4623 [M + Na]$^+$ calcd for $C_{37}H_{64}NaO_6$ 627.4601. **5**: colorless oil; $[\alpha]_D^{20}$ 0 (*c* 0.1, CH_2Cl_2); IR (film, CH_2Cl_2) ν_{max} 3462, 2925, 2854, 1756, 1460, 1374, 1318, 1198, 1118, 1071 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.87 (3H, m, H-34), 1.26 (26H, s, −CH_2−), 1.33 (2H, m, H-33), 1.40 (7H, m, H-14, H-25, H-37), 1.54 (2H, m, H-4), 1.65 (6H, m, H-17, H-18, H-21), 1.84 (4H, m, H-27, H-29), 1.98 (2H, m, H-22), 2.26 (2H, t, $^3J_{3-4}$ = 7.5 Hz, H-3), 3.39 (1H, m, H-15), 3.82 (1H, m, H-16), 3.86−3.89 (3H, m, H-19, H-20, H-24), 3.92 (1H, m, H-23), 4.11 (1H, m, H-28), 4.99 (1H, t, $^3J_{36-37}$ = 6.0 Hz, H-36), 6.98 (1H, s, H-35); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.1 (C-34), 19.2 (C-37), 22.6, 25.2, 25.7, 27.4, 28.4, 29.2, 29.3, 29.5, 29.6, 29.7, 30.9, 31.9, 34.4, 35.3, 40.4 (C-28), 71.4 (C-24), 74.1, 77.3, 82.0, 82.5, 134.4, 148.8, 173.9; ESIMS *m*/*z* 755 [M + Na]$^+$; HRESIMS *m*/*z* 755.3716 [M + Na]$^+$ calcd for $C_{37}H_{65}INaO_6$ 755.3724. **6**: colorless oil; $[\alpha]_D$ 0 (*c* 0.1, CH_2Cl_2); IR (film, CH_2Cl_2) ν_{max} 3460, 2924, 2854, 1754, 1461, 1318, 1200, 1065 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, m, H-34), 1.27 (24H, s, −CH_2−), 1.33 (2H, m, H-33), 1.40 (7H, m, H-14, H-25, H-37), 1.55 (2H, m, H-4), 1.65 (4H, m, H-18, H-21), 1.83−1.98 (4H, m, H-17, H-22), 1.98 (4H, m, H-26 and H-29 or H-27 and H-30), 2.26 (2H, t, $^3J_{3-4}$ = 7.5 Hz, H-3), 3.39 (1H, m, H-15), 3.87 (1H, m, H-16), 3.90−3.93 (4H, m, H-19, H-20, H-23, H-24), 4.99 (1H, t, $^3J_{36-37}$ = 6.0 Hz, H-36), 5.40 (2H, m, H-27 and H-28 or H-28 and H-29), 6.98 (1H, s, H-35); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.1 (C-34), 19.2 (C-37), 22.6, 25.2, 25.7, 27.4, 28.3, 28.9, 29.2, 29.3, 29.5, 29.6, 31.9, 32.5, 33.4, 33.5, 71.4 (C-24), 74.1 (C-15), 77.3 (C-36), 82.5, 82.6, 82.8, 83.2 (C-16, C-19, C-20, C-23), 129.8 (C-27 and C-28 or C-28 and C-29), 134.4 (C-2), 148.8 (C-35), 173.9 (C-1); ESIMS *m*/*z* 627 [M + Na]$^+$; HRESIMS *m*/*z* 627.4609 [M + Na]$^+$ calcd for $C_{37}H_{64}NaO_6$ 627.4601.

Procedure for the Preparation of Compounds 7 and 8. To a solution of squamocin (**1**, 34 mg, 55 μmol) in dry THF (1 mL) under stirring were added triphenylphosphine (29 mg, 110 μmol, 2 equiv) and diethylazodicarboxylate (19 mg, 17 μL, 110 μmol, 2 equiv). The mixture was stirred overnight at room temperature, concentrated under reduced pressure, and purified by flash chromatography (CH_2Cl_2, CH_2Cl_2−MeOH, 98:2, 95:5) to give two fractions. Both fractions were purified over a column of Sephadex LH-20 impregnated with CH_2Cl_2 to give **7** (14 mg, 32%) and **8** (6 mg, 11%). **7**: colorless oil; $[\alpha]_D$ +15 (*c* 0.3, CH_2Cl_2); IR (film, CH_2Cl_2) ν_{max} 3470, 3290, 2924, 2854, 1752, 1708, 1522, 1464, 1439, 1412, 1376, 1317, 1259, 1227, 1117, 1061, 1028, 953, 875, 759, 722, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, s, H-34), 1.27 (32H, s, H-40, H-43, −CH_2−), 1.37 (2H, m, H-33), 1.41 (3H, d, $^3J_{37-36}$ = 6.0 Hz, H-37), 1.43 (2H, m, H-25), 1.52−1.54 (6H, m, H-4, H-27, H-29), 1.64 (5H, m, H-14a, H-18, H-21), 1.85−1.97 (4H, m, H-17, H-22), 2.26 (2H, t, $^3J_{3-4}$ = 7.5 Hz, H-3), 2.51 (1H, m, H-14b), 3.39 (1H, m, H-15), 3.83−3.92 (6H, m, H-16, H-19, H-20, H-23, H-24, H-28), 4.17 (4H, m, H-39, H-43), 4.99 (1H, t, $^3J_{36-37}$ = 6.0 Hz, H-36), 6.98 (1H, s, H-35); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.1 (C-34), 14.6 (C-40, C-43), 19.2 (C-37), 22.6, 25.1, 25.7, 27.4, 28.3, 28.9, 29.2, 29.3, 29.5, 29.6, 29.7, 30.5, 31.8, 33.4, 39.4, 62.0 (C-39, C-42), 67.7 (C-28), 71.2 (C-24), 74.1 (C-15), 77.3 (C-36), 82.2, 82.4, 82.8, 83.2 (C-16, C-19, C-20, C-23), 134.4 (C-2), 148.8 (C-35), 173.6 (C-1); ESIMS *m*/*z* 803 [M + Na]$^+$. **8**: colorless oil; IR (film, CH_2Cl_2) ν_{max} 3470, 3290, 2924, 2854, 1752, 1708, 1522, 1464, 1439, 1412, 1376, 1317, 1259, 1227, 1117, 1061, 1028, 953, 875, 759, 722, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, s, H-34), 1.27 (38H, s, H-40, H-43, H-46, H-49, -CH_2-), 1.37 (2H, m, H-33), 1.41 (3H, d, $^3J_{37-36}$ = 6.0 Hz, H-37), 1.52−1.54 (8H, m, H-4, H-25, H-27, H-29), 1.64 (5H, m, H-14a, H-18, H-21), 1.85−1.97 (4H, m, H-17, H-22), 2.26 (2H, t, $^3J_{3-4}$ = 7.5 Hz, H-3), 2.51 (1H, m, H-14b), 3.39 (1H, m, H-15), 3.83−3.92 (5H, m, H-16, H-19, H-20, H-23, H-28), 4.17 (8H, m, H-39, H-43, H-45, H-48), 4.34 (1H, m, H-24), 4.99 (1H, t, $^3J_{36-37}$ = 6.0 Hz, H-36), 6.98 (1H, s, H-35); ^{13}C NMR (50 MHz, $CDCl_3$) δ

14.1 (C-34), 14.4 14.5 (C-40, C-43, C-46, C-49), 19.2 (C-37), 22.6, 25.1, 25.7, 27.4, 28.8, 29.2, 29.3, 29.5, 29.6, 29.7, 31.8, 33.4, 39.4, 62.7 (C-39, C-42), 67.7 (C-28), 68.2 (C-24), 74.1 (C-15), 77.3 (C-36), 81.5, 83.1 (C-16, C-19, C-20, C-23), 134.4 (C-2), 148.8 (C-35), 173.6 (C-1); ESIMS *m*/*z* 961 $[M + Na]^+$.

Biological Activities. Jurkat cell culture treatments and cytofluorimetric determination of apoptosis were performed according to previously described procedures; see ref 4a.

Acknowledgment. We thank J. C. Jullian for assistance with the NMR studies.

References and Notes

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NP060376B