New Rearranged Limonoids from *Harrisonia perforata*. III

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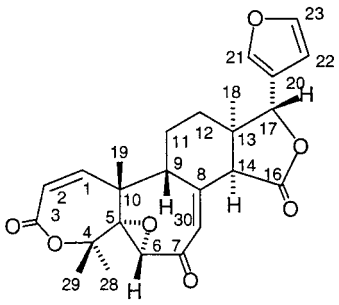
Three new limonoids, named haperforins C2 (**1**), F (**2**), and G (**3**), were isolated from a sample of *Harrisonia perforata* leaves collected in Central Vietnam. Their structures were determined by single-crystal X-ray diffraction analyses, and their NMR and mass spectral data are reported.

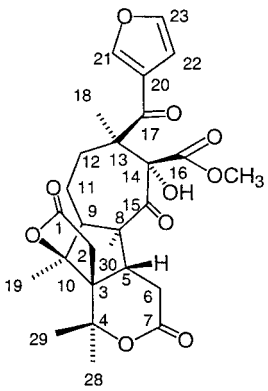
During the course of identification of the limonoids present in the leaves of *Harrisonia perforata* (Blanco) Merr. (Simaroubaceae) collected in the Daklak district in Central Vietnam, we have isolated three new limonoids, namely, haperforins C2 (**1**), F (**2**), and G (**3**). In two preceding papers,[1,2] we have described the isolation and structural elucidation of five new limonoids, haperforin A, haperforin E, 12-desacetylhaperforin A,[1,3] haperforin B1, and haperforin D,[2,3] from the same plant sample. The carbon skeletons of these rearranged limonoids are unrelated to one another, and we could observe that in this plant different types of limonoids were present. Thus, perforatin,[4,5] perforatinolone,[6] perforin A,[7] haperforin A, and 12-desacetylhaperforin A belong to the obacunol series (rings A and D opened),[8] while haperforin B1, haperforin D, haperforin E, and foritin[9] belong to the isovorensate series (rings A, B, and D opened).[8]

The extraction of limonoids from ground dried leaves of *H. perforata* was performed according to the procedure described by J. Polonsky with slight modifications.[10] Successive column and thin-layer chromatography with various eluting systems allowed the separation of the compounds **1**−**3**. Details of the isolation of the limonoïds are presented in the Experimental Section.

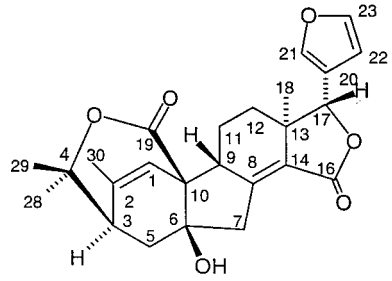
The NMR spectra of haperforin C2 (**1**, $C_{25}H_{26}O_7$) showed the presence of a C-3-substituted furan ring (δ_H 6.38, 7.30, and 7.37 for H-22, H-23, and H-21, respectively), four methyl groups (δ_H 0.90, 1.25, 1.40, and 1.68, as singlets), three singlets (δ_H 3.07, 3.48, and 5.00), and signals for a methine and three methylenes. Three carbonyls were attributed to a ketone (δ_C 197.0) conjugated to a trisubstituted double bond (δ_H 5.76, s), a γ-lactone (δ_C 174.7), and an ester or lactone (δ_C 165.4) conjugated to a disubstituted double bond (δ_H 5.92 and 6.14, AB). The complete structure and relative stereochemistry of **1** were determined by an X-ray crystallographic study.[11] The crystal structure is shown in Figure 1, consistent with the absolute configuration of the limonoids isolated previously from the same plant.[4,6] The molecule belongs to the obacunol series in which rings A and D are seven- and five-membered lactones, respectively. The tetracyclic skeleton of **1** includes two seven-membered rings with a *trans*-junction along the C-5−C-10 bond. The first seven-membered ring (lactone C-1 to C-10, ring A) shows a symmetric conformation in



Haperforin C2 (**1**)



Haperforin F (**2**)



Haperforin G (**3**)

which the C-1, C-2, and C-4 atoms deviate by 0.329(3), 0.376(3), and 0.735 (3) Å, respectively, from the mean plane of the other four atoms (C-3, O-4, C-5, C-10). The second seven-membered ring (C-5 to C-10, ring B), incorporating C-30 in an intracyclic double bond, adopts a conformation in which the C-7 and C-10 atoms are situated above the mean plane formed by the other five atoms by 0.393(3) and 0.758(3) Å, respectively. It bears an α-oxirane ring at C-5 and a carbonyl at C-7. The oxygen atoms O-3, O-4, O-5, and O-7 thus lie on the α-face of the molecule. The six-membered ring (C-8 to C-14, ring C), exhibiting a chair conformation, is *cis*-fused along the C-13−C-14 bond to a γ-lactone, placing the oxygen atoms O-16 and O-17 on the β-face of the molecule. This lactone (ring D) adopts an envelope conformation with C-13 away from the mean plane of the other four atoms by 0.596(3) Å. The furan ring at C-17 is fixed perpendicularly to it (dihedral angle of 101°) with the oxygen O-21 oriented on the α-face of the molecule.

The NMR spectra of haperforin F (**2**, $C_{27}H_{32}O_{10}$) showed the presence of four methyl groups (δ_H 1.45, 1.53, 1.61, and

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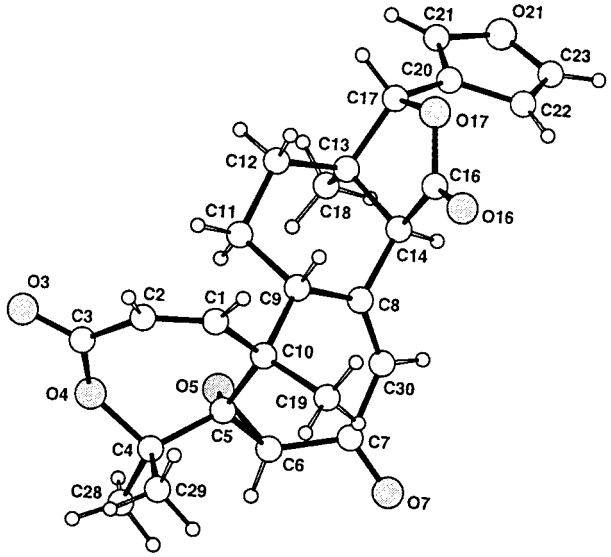

Figure 1. Crystal structure of **1**.

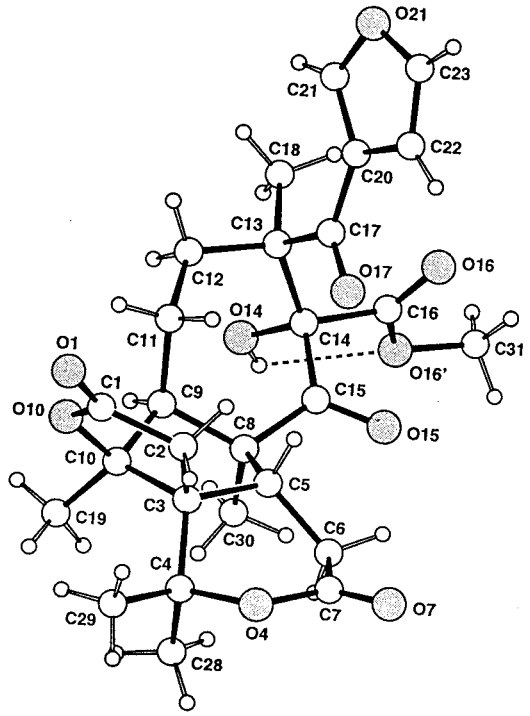

Figure 2. Crystal structure of **2**.

1.67, as singlets), a 3-ketofuran ring (δ_H 6.77, 7.44, and 7.99 for H-22, H-23, and H-21, respectively), five carbonyls with three ester(s) and/or lactone(s) (δ_C 172.0, 172.1, and 174.2) and two ketones (δ_C 196.5 and 208.9), a carbomethoxy group (δ_H 3.76), a hydroxyl (δ_{OH} 3.95), a methylene α to a carbonyl (δ_H 2.82 and 3.05, AB), and two methines and three methylenes. Two lactones including an oxygen atom from a tertiary alcohol were present in the molecule. The complete structure and relative stereochemistry of **2** were determined by an X-ray crystallographic study.[11] The crystal structure is shown in Figure 2, consistent with the absolute configuration of limonoids isolated previously from the same plant.[4,6] The molecule is represented by an arrangement of four rings, all *cis*-junctioned. Torsion angle analysis shows that the seven-membered ring (C-8 to C-15, ring C) exhibits a twist-chair conformation with atoms C-11 and C-14 deviating by 0.733(3) and −0.727 (3) Å, respectively, from the mean plane of

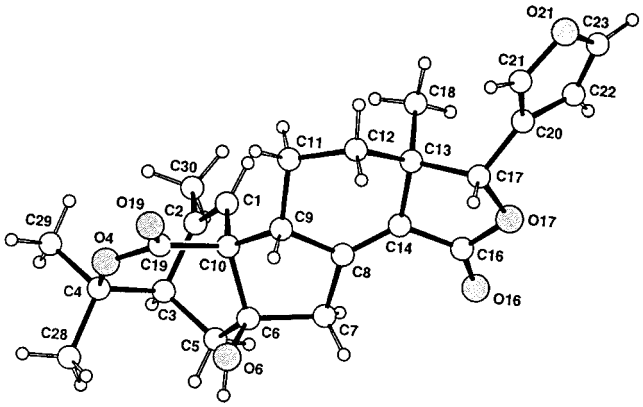

Figure 3. Crystal structure of **3**.

the other five atoms. At C-13, the methyl group is equatorial, while the bulky ketofuran group is axial and oriented perpendicularly to the mean plane of this ring (dihedral angle 97.5°), such that oxygen O-17 is projected nearly on the center of the seven-membered ring. The carbomethoxy group at C-14 is equatorial, tilted out of this plane by 58° and held in this position by an intramolecular hydrogen bond established between the hydroxyl OH-14 and the oxygen O-16′ (distances O-14···O-16′ = 2.682(3) Å, H_{O-14}···O-16′ = 2.27 Å, angle O−H−O = 111.3°). The five-membered ring (C-8, C-9, C-10, C-3, C-5, ring B), with a *cis*-junction to the seven-membered ring along the C-8−C-9 bond, adopts a half-chair conformation with atoms C-8 and C-9 deviating by only −0.229(3) and 0.420(3) Å from the mean plane of the other three atoms. Noteworthy is the *cis*-junction of this ring, along the C-3−C-5 and the C-3−C-10 bonds, respectively, to two lactones formed from ring A. This arrangement places all the oxygen atoms, except O-14 and O-16′, on the β-face of the molecule, while the six methyl groups C-19, C-28, C-29, C-30, C-18, and C-31 are situated on the α-face. With rings A and D opened, haperforin F belongs to the obacunol series but presents an unusual rearrangement of ring A in two lactone rings.

The NMR spectra of haperforin G (**3**, $C_{25}H_{28}O_6$) showed the presence of an unconjugated 3-substituted furan ring (δ_H 6.38, 7.38, and 7.45 as singlets for H-22, H-23, and H-21, respectively), four methyl groups (δ_H 0.89, 1.42, 1.55, and 1.91, as singlets), two carbonyl groups represented by two lactones (δ_C 168.76 and 168.14), a tertiary hydroxyl group (δ_{OH} 2.35, exchangeable with D_2O), a trisubstituted double bond bearing a methyl group (δ_C 118.77 and 145.38), and a tetrasubstituted double bond. Peaks for CH−CH_2−CH_2 and CH−CH_2 structural elements and one methylene as an AB system (δ_H 2.88 and 2.61) were also identified. The complete structure and relative stereochemistry of **3** were determined by an X-ray crystallographic study.[11] The crystal structure is shown in Figure 3, consistent with the absolute configuration of limonoids previously isolated from the same plant.[4,6] As for **1**, ring D is a γ-lactone in an envelope conformation, with atom C-13 deviating out of the mean plane of the other four atoms by −0.544(7) Å, bearing at C-17 a furan ring tilted out of the lactone mean plane by 129°. The six-membered ring C (C-8 to C-14), including the C-8−C-14 double bond, exhibits a half-chair conformation with atoms C-11 and C-12 deviating by −0.231(7) and 0.476(7) Å, respectively, from the mean plane of the four remaining atoms. H-9 is β-oriented. The central cyclopentane ring (C-6 to C-10, ring B) exhibits an envelope conformation, with atom C-10 situated out of the mean plane of the other four atoms by −0.647(6) Å, and a *cis*-junction along the C-6−C-10 bond to the six-membered ring

A (C-1, C-2, to C-10). The latter presents a C-1−C-2 double bond of 1.32 Å and adopts a boat conformation, where atoms C-3 and C-10, occupying the prow and stern positions, deviate by 0.647(7) and 0.549(7) Å, respectively, from the mean plane of the other four atoms. Between C-3 and C-10, a bridge including atoms C-4, O-4, and C-19 forms an oxabicyclo[3.2.2]nonane system on the β-face of the molecule. A tertiary hydroxyl group is present at C-6 in β-axial position, while the three methyl groups C-18, C-30, and C-29 appear on the α-face of the molecule.

Experimental Section

General Experimental Procedures. Melting points were determined in capillary tubes and are uncorrected. Optical rotations were measured in $CHCl_3$ with 0.5% EtOH, at room temperature, on a Perkin-Elmer 241 polarimeter. IR spectra were determined with a Nicolet FT-IR 205 spectrometer, and UV spectra with a Perkin-Elmer Lambda 205 spectrometer. ^{1}H NMR spectra were performed in $CDCl_3$, unless otherwise stated; chemical shifts δ were expressed in ppm; and coupling constants were expressed in Hz and were registered with Bruker WP-300 and WP-400 instruments. ^{13}C NMR spectra were recorded on the Bruker WP-300. Mass spectra (MS) were run on AEI MS-50 or AEI MS-9 mass spectrometers. Column chromatography was performed on Merck Kieselgel 60, and flash column chromatography on Merck Kieselgel 60H. Analytical thin-layer chromatography was performed using Si gel precoated foils, visualized by spraying with 1% anisaldehyde reagent and 50% aqueous H_2SO_4 and heating. For X-ray crystal structure analyses, intensity data were measured on an Enraf-Nonius CAD-4 diffractometer using graphite-monochromated Cu Kα radiation (1.5418 Å) and the (θ−2θ) scan technique up to θ = 68°. Cell parameters were refined from 25 well-centered reflections. The structures were solved by direct methods using SHELXS86[12] and refined by full-matrix least-squares based upon unique F^2 using SHELXL93.[13] All the H atoms were located in difference Fourier maps and refined as riding models. They were assigned an isotropic displacement parameter equivalent to that of the bonded C atom, plus 20% or 30% for those of the methyl or hydroxyl groups.

Plant Material. The aerial parts of *H. perforata* were collected in the Daklal district in Central Vietnam in March 1995. The plant material was identified by the Museum of the Botanical Garden of Ho-Chi-Minh-City, where a voucher sample has been deposited.

Extraction and Isolation. The 25% aqueous EtOH extract from the dried leaves (1000 g and 2.5 L of EtOH) was treated with lead acetate (400 mL of a 30% aqueous solution) and filtered. Addition of a Na_2SO_4 solution to the filtrate gave a precipitate of lead sulfate, which was separated by filtration. Limonoids were adsorbed on activated charcoal (30 g), which was filtered, dried at 50 °C for 24 h, and extracted with $CHCl_3$ in a Soxhlet apparatus. Evaporation of the solvent gave a residue (2.42 g, 0.25%) of crude limonoids.

Haperforin C2 (1). The dry crude extract (10 g) prepared as described above (from 4 kg of dried leaves) was dissolved in heptane−EtOAc (8:2) and chromatographed over a Si gel 60H column (350 g). Each fraction (20 mL) was collected and analyzed by TLC. Fractions 311−330 showed the presence of a major compound and were evaporated to give a residue (530 mg), which by crystallization from MeOH afforded pure **1** (100 mg): mp 270 °C (MeOH); $[\alpha]_D$ −284° ($CHCl_3$, *c* 0.9); UV (EtOH) λ_{max} (log ϵ) 211 (4.60), 251 (4.32) nm; IR (film) ν_{max} 1768, 1712, 1668 (C=O), 1381, 1306, 1131, 1025, 1000 (C−O) cm^{-1}; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 0.90 (3H, s, CH_3-18), 1.25 (3H, s, CH_3-29), 1.40 (3H, s, CH_3-19), 1.68 (3H, s, CH_3-28), 1.74 (2H, m, CH_2-12), 1.94 (2H, m, H-9, H-11β), 2.13 (1H, m, H-11α), 3.07 (1H, s, H-14), 3.48 (1H, s, H-6), 5.0 (1H, s, H-17), 5.76 (1H, s, H-30), 5.92 (1H, AB, *J* = 15 Hz, H-2), 6.14 (1H, AB, *J* = 15 Hz, H-1) 6.38 (1H, s, H-22), 7.30 (1H, s, H-23), 7.37 (1H, s, H-21); ^{13}C NMR ($CDCl_3$ 75 MHz) δ 20.2 (CH_3-18), 25.0 (CH_3-28), 26.8 (CH_3-29), 27.7 (CH_3-19), 28.2 (CH_2-11), 37.0 (CH_2-12), 47.9 (C-13), 48.5 (C-10), 53.9 (CH-9), 58.3 (CH-14), 64.3 (CH-6), 72.1 (CH-17), 83.1 (C-4), 83.4 (C-5), 109.0 (CH-22), 121.3 (C-20), 123.6 (CH-1), 126.8 (CH-30), 140.5 (CH-23), 144.6 (CH-21), 149.0 (CH-2), 150.5 (C-8), 165.4 (C-3), 174.7 (C-16), 197.0 (C-7); HRCIMS *m/z* 439.1747 (calcd for $C_{25}H_{27}O_7$ 439.1756).

Crystal Data. Crystal of **1** (0.53 × 0.16 × 0.07 mm) grown from methanol solution: $C_{25}H_{26}O_7$, M_w = 438.46, orthorhombic, space group $P2_12_12_1$, Z = 4, a = 8.154(6) Å, b = 9.773(4) Å, c = 27.519(18) Å, V = 2193 Å^3, d_c =1.328 g cm^{-3}, F(000) = 928, λ(Cu Kα) = 1.5418 Å, μ = 0.801 mm^{-1}; 6416 intensities measured (−9 ≤ h ≤ 9, −10 ≤ k ≤ 11, l 0 to 27) of which 3527 were unique (R_{int} = 0.048). No intensity decay. Refinement of 296 variables converged to $R_1(F)$ = 0.0495 for 3112$F_o \geq 4\sigma(F_o)$ and $wR_2(F^2)$ = 0.1284 for all the 3527 data with goodness-of-fit S = 1.063. The residual electron density was found between −0.24 and 0.20 e Å^{-3} in the final difference map. Only normal van der Waals contacts were observed in the packing of the molecules.

Haperforin F (2). A crude extract (1.48 g) was dissolved in CH_2Cl_2 (40 mL) and chromatographed on a Si gel column (75 g). Each 8 mL fraction eluted by CH_2Cl_2−OEtAc (9:1) was collected and analyzed by TLC. Fractions 62−102 were evaporated to give a mixture (833 mg) in which one main product was present. The components were crudely separated by flash chromatography over Si gel 60H (30 g). Elution was conducted with toluene containing increasing amounts of diethyl ether. The fraction eluted by toluene−ether (1:1) (350 mg) was evaporated, dissolved in toluene, and purified by column chromatography over Si gel 60 (10 g). Each 4 mL fraction eluted by toluene−ether (1:1) was collected and analyzed by TLC. Fractions 103−134 were evaporated, and the residue (230 mg) was purified by preparative TLC (CH_2Cl_2−MeOH, 95:5) to afford **2** (71 mg): mp 224 °C (MeOH), $[\alpha]_D$ + 16.9° ($CHCl_3$, *c* 0.93); UV (EtOH) λ_{max} (log ϵ) 211 (4.54), 251 nm (4.02); IR (film) ν_{max} 1762, 1740, 1690, 1658 (C=O), 1272 cm^{-1}; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 1.45 (3H, s, CH_3-18) 1.48 (1H, m, CH_2-11α), 1.53 (3H, s, CH_3-29), 1.61 (3H, s, CH_3-30), 1.67 (3H, s, CH_3-28), 1.77 (1H, m, CH_2-12α), 1.85 (3H, s, CH_3-19), 2,0 (1H, dm, *J* = 12 Hz, CH_2-11β), 2,26 (1H, tt, *J* = 12 Hz, *J* = 2 Hz, H-12β), 2.54 (1H, dd, *J* = 12 Hz, *J* = 2 Hz, H-9), 2.82 and 3.05 (2H, AB, *J* = 20 Hz, CH_2-2), 2.96 and 3.15 (2H, ABX, *J* = 17 Hz, J_{AX} = 7 Hz, J_{BX} = 9 Hz, CH_2-6), 3.44 (1H, t, *J* = 8 Hz, H-5), 3.76 (3H, s, OCH_3), 3.95 (1H, s, OH), 6.77 (1H, s, H-22), 7.44 (1H, s, H-23), 7.99 (1H, s, H-21); ^{13}C NMR ($CDCl_3$ 75 MHz) δ 21.7 (CH_3-18), 24.1 (CH_2-11), 26.5 (CH_3-30), 27.6 (CH_3-28), 27.6 (CH_3-29), 27.8 (CH_3-19), 32.3 (CH_2-6), 35.2 (CH_2-12), 46.0 (CH-2), 50.1 (CH-5), 53.1 (OCH_3), 56.1 (C-3), 56.6 (C-13), 59.3 (CH-9), 59.5 (C-8), 81.6 (C-4), 87.7 (C-14), 94.6 (C-10), 110.0 (CH-22), 124.9 (C-20), 142.8 (CH-23), 145.8 (CH-21), 172.0 (C-16), 172.1 (C-7), 174.2 (C-1), 196.5 (C-17), 209.0 (C-15); HRCIMS *m/z* 517.2101 (calcd for $C_{27}H_{33}O_{10}$ 517.2073).

Crystal Data. Crystal of **2** (0.45 × 0.35 × 0.30 mm) grown from methanol solution: $C_{27}H_{32}O_{10}$, M_w = 516.53, orthorhombic, space group $P2_12_12_1$, Z = 4, a = 7.852(5) Å, b = 9.285(7) Å, c = 35.285(27) Å, V = 2572 Å^3, d_c =1.334 g cm^{-3}, F(000) =1096, λ(Cu Kα) = 1.5418 Å, μ = 1.15 mm^{-1}; 3420 intensities measured (−6 ≤ h ≤ 9, k 0 to 9, l 0 to 42) of which 3233 were unique (R_{int} = 0.035). No intensity decay. Refinement of 341 variables converged to $R_1(F)$ = 0.0504 for 3065 $F_o \geq 4\sigma(F_o)$ and $wR_2(F^2)$ = 0.1320 for all the 3233 data with goodness of fit S = 1.069. The residual electron density was found between − 0.22 and 0.49 e Å^{-3} in the final difference map. In the crystal, the molecules are linked in infinite chains, along the direction of the *b* axis, by means of intermolecular hydrogen bonds established between the OH-14 group of each molecule and the oxygen atom O-1 of the nearest one at (x, 1+y, z) with the characteristics O14···O1 = 2.757(4) Å, H_{O-14}···O1 = 2.07 Å, angle O−H−O = 141°.

Haperforin G (3). A crude extract (6.4 g) was dissolved in toluene and chromatographed over a Si gel column (300 g) and eluted with toluene containing increasing amounts of diethyl ether. Each 300 mL fraction was collected and analyzed by TLC. The fractions eluted by toluene−ether (4:6) gave a

residue (440 mg), which was purified by preparative thin-layer chromatography (CH_2Cl_2−MeOH, 95:5, as eluent). Pure **3** (38 mg) was obtained: mp 251 °C (CH_2Cl_2−OEtAc); $[\alpha]_D$ + 24.1° ($CHCl_3$, *c* 0.9); IR (film) ν_{max} 3650 (OH), 1764, 1707 (C=O), 1271, 1201, 1089 (C−O) cm^{-1}; ^1H NMR ($CDCl_3$ 300 MHz) δ 0.89 (3H, s, CH_3-18), 1.42 (3H, s, CH_3-29), 1.55 (3H, s, CH_3-28), 1.72 (2H, m, CH_2-11a, CH_2-12a), 1.91, 2.04 (1H, dd, J = 14 Hz, J = 4,5 Hz, CH_2-5a), 2.26 (1H, m, H-11β), 2.30 (1H, m, H-3), 2.35 (1H, s, OH), 2.61 (2H, dd, J = 14 Hz, J = 1.5 Hz, CH_2-5b), 2.88 and 3.04 (2H, AB, J = 21 Hz, CH_2-7), 3.48 (1H, m, H-9), 4.96 (1H, s, H-17), 5.39 (1H, s, H-1), 6.38 (1H, s, H-22), 7.45 (1H, s, H-23), 7.45 (1H, s, H-21); ^{13}C NMR ($CDCl_3$ 75 MHz) δ 18.6 (CH_2-11), 21.4 (CH_3-18), 23.4 (CH_3-30), 27.4 (CH_3-28), 28.6 (CH_3-29), 31.3 (CH_2-12), 38.3 (CH_2-5), 42.4 (C-13), 46.3 (CH_2-7), 46.9 (CH-9), 48.2 (CH-3), 61.3 (C-10), 82.8 (C-6), 83.6 (CH-17), 85.3 (C-4), 108.0 (CH-22), 118.8 (CH-1), 119.8 (C-20), 125.6 (C-14), 139.3 (CH-23), 143.1 (CH-21), 145.4, (C-2), 151.8 (C-8), 168.1 (C-19), 168.8 C-16); HRCIMS *m*/*z* 425.1972 (calcd for $C_{25}H_{29}O_6$ 425.1963).

Crystal Data. A small crystal of **3** (0.33 × 0.15 × 0.12 mm), grown from ethanol, was placed in a glass capillary with a drop of solvent to avoid decay during recording. $C_{25}H_{28}O_6$, C_2H_6O, M_w = 470.54, orthorhombic, space group $P2_12_12_1$, Z = 4, a = 7.515(6) Å, b = 12.233(10) Å, c = 27.961(15) Å, V = 2570 $Å^3$, d_c =1.216 g cm^{-3}, $F(000)$ = 1008, λ(Cu Kα) = 1.5418 Å, μ = 0.712 mm^{-1}; 4330 intensities (h k l and $-h$ $-k$ l) measured ($-7 \le h \le 9$, $-12 \le k \le 14$, l 0 to 33) of which 2685 were unique (R_{int} = 0.084). An ethanol molecule was found in a crystal void, showing large thermal displacement parameters. This molecule was thus refined as a rigid model, its hydrogen atoms were not calculated, and only the oxygen atom was treated anisotropically. Moreover, the methylene carbon of this molecule was found disordered, with two positions of respective weights 0.80:0.20 causing the OH group of the ethanol to be hydrogen-bonded either to the oxygen atom O-19 of the molecule by 2.98(1) Å (major situation) or to the oxygen atom O-4 by 3.09(1) Å (minor situation). Thus, refinement of 306 variables converged to $R_1(F)$ = 0.0740 for the1539 $F_o \ge 4\sigma(F_o)$ and to $wR_2(F^2)$ = 0.2464 for all the 2685 data with goodness-of-fit S = 1.040. The residual electron density was found between −0.18 and 0.43 e $Å^{-3}$ in the final difference map. In the crystal, the molecules are linked in helical chains along the direction of the *b* axis, through hydrogen bonds built between the hydroxyl OH-6 of one molecule (x, y, z) and the oxygen O-16 of the nearest one located at ($1-x$, $0.5+y$, $1.5-z$), according to the scheme O-6···O-16 = 2.776 (8) Å, H_{O-6}···O-16 = 2.01 Å, angle O−H−O = 155.6°.

Supporting Information Available: Crystallographic data are available free of charge via the Internet at htpp://pubs.acs.org.

References and Notes

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(11) Crystallographic data for the structures reported in this paper have been deposited as CIF files with the Cambridge Crystallographic Data Centre and allocated the deposition numbers CCDC 156787, 156788, and 156789. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)223−336033 or e-mail: deposit@ccdc.cam.ac.uk].
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