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MINOR POLYHYDROXYLATED STEROLS FROM THE STARFISH *PROTOREASTER NODOSUS*[1]

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ABSTRACT.—Three minor polyhydroxylated sterols—5α-cholestane-3β,4β,6α,8,15α,16β,26-heptol (**4**), 24ξ-methyl-5α-cholestane-3β,6α,8,15α,16β,26-hexol (**5**), and (22E) 24ξ-methyl-5α-cholest-22-en-3β,4β,6α,8,15α,16β,26-heptol (**6**)—have been isolated from the Pacific starfish *Protoreaster nodosus*.

The number of known polyhydroxylated steroids from marine animals is steadily growing. They have been isolated from soft corals, gorgonians, nudibranchs, and starfish (1-6). Recently, we have described the occurrence of three highly hydroxylated steroids, with moderate cytotoxicity, from the starfish *Protoreaster nodosus* L. (7).

A common feature of these compounds is the 3β,6α,8β,15α,16β,26-hexahydroxy moiety, one of them is simply the hexol (**1**), the second is related to **1** with the introduction of an additional hydroxyl group at 7α-position (**2**), and the third is the octol (**3**) with two additional hydroxyl groups at the 7α- and 4β-positions.

We now wish to report the isolation of three very minor hydroxylated sterols, 5α-cholestane-3β,4β,6α,8,15α,16β,26-heptol (**4**), 24ξ-methyl-5α-cholestane-3β,6α,8,15α,16β,26-hexol (**5**), and (22E)-24ξ-methyl-5α-cholest-22-en-3β,4β,6α,8,15α,16β,26-heptol (**6**) from *P. nodosus*.

EXPERIMENTAL

The animals (*P. nodosus*, identified by P. Laboute and P. Tirard, ORSTOM de Nouméa) were collected off Nouméa, Nouvelle Caledonie in August 1981, and lyophilized (2 kg). The lyophilized animals were extracted in a Soxhlet apparatus with light petroleum ether (bp 40-70°), then with MeOH-$CHCl_3$ (1:9), followed by MeOH. The MeOH-$CHCl_3$ extract (50 g) was extracted again with EtOAc and then MeOH. The MeOH extract (22 g) was separated by short column chromatography using 500 g of silica gel (15μ) in $CHCl_3$-MeOH (9:1) and increasing amounts of MeOH. The fractions eluted with $CHCl_3$-MeOH (3:1), and (7:3) gave 1.6 g and 1.1 g of residue, respectively, which were combined and chromatographed on Sephadex LH-60 (90×3 cm, 58 g of resin) by using MeOH as eluent. Fractions of 10 ml were collected and monitored by SiO_2-tlc in $CHCl_3$-MeOH-H_2O (80:18:2). The fractions 40-58 (1.1 g) were rechromatographed on Sephadex LH-20 and 7.5 ml fractions were eluted with MeOH. Fractions 45-61 gave 0.49 g of residue, which was submitted to droplet counter current chromatography (DCC-A apparatus, Tokyo Rikakikai, 300 tubes, solvent system: $CHCl_3$-MeOH-H_2O (7:13:8), flow rate 12 ml/h, ascending mode; the eluants were collected in 5 ml fractions and monitored by tlc-SiO_2). Fractions 65-78 (34 mg) contained mainly **4** and the glycoside nodososide (8); fractions 90-93 (16 mg) contained mainly **5** and small amounts of **6** and the previously reported **1** (7); fractions 111-124 contained **6** and major amounts of the previously reported **2** (7). Each of these DCC fractions was chromatographed by hplc on a Whatman Partisil M-9 10/50 ODS column (eluant, MeOH-H_2O, 7:3; M6000 pump, R401 refractometer, U6K injector, all from Waters) to give the individual minor hydroxylated sterols, **4** (9 mg), **5** (8 mg), and **6** (1.5 mg), with elution times of 13.2, 17.2, and 14.2 min, respectively.

Compound **4**: mp 241-243° (from MeOH in the presence of CH_2Cl_2 vapors); $[\alpha]_D = +28.4$ (c, 1, MeOH); eims (70 eV) *m/z* (%) 466 (M^+ -H_2O, 8), 448 (62), 430 (37), 412 (15), 347 (10), 337 (M^+ -side chain, 15), 319 (32), 301 (30), 283 (42), 265 (25), 241 (*a*, 42), 225 (b -H_2O, 100), 223 (25) and 207 (60); pmr (CD_3OD) δ 0.94 (d, *J*=6.5Hz, CH_3-21), 0.96 (d, *J*=6.5Hz, CH_3-27), 1.14 (s, CH_3-18), 1.22 (s,

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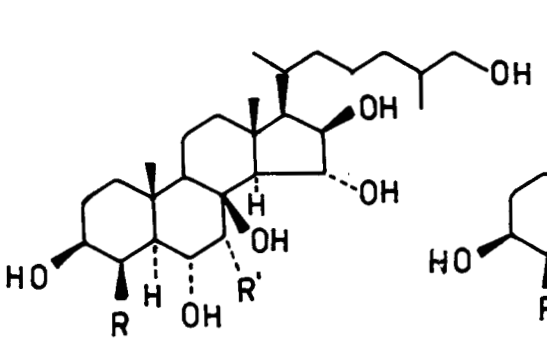
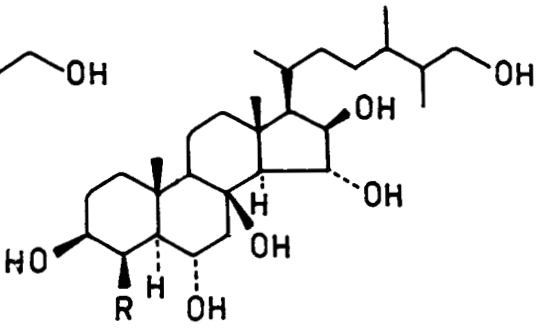
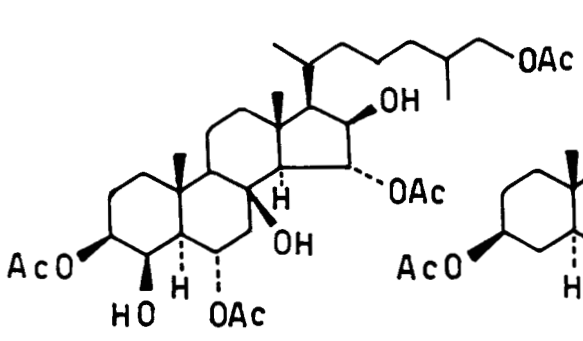


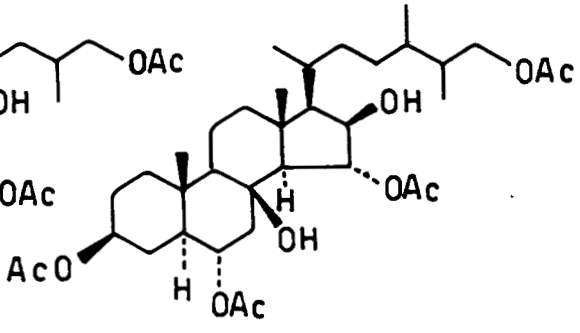
1 R=H, R′=H
2 R=H, R′=OH
3 R=R′=OH
4 R=OH, R′=H



5 R=H
6 R=OH Δ^{22}-*trans*



4a



5a

CH_3-19), 2.50 (dd, J=13 and 3Hz, 7β-H), 3.43-3.49 (2H, one dd with J=10.5 and 6.0 Hz superimposed on a broad signal, 26- and 3α-H), 4.01 (dd, J=7.5 and 3Hz, 16α-H), 4.09 (2H, one dd with J=10.5 and 3Hz, 15β-H superimposed on the signal for 6β-H), 4.28 (br s, W½=6Hz, 4α-H).

Compound **5**: mp 253-256° (from MeOH in the presence of CH_2Cl_2 vapors); [α]D=+27.8° (c, 0.8, MeOH); eims (70 eV) *m/z* (%) 464 (M^+ -H_2O, 62), 449 (8), 446 (44), 431 (20), 428 (30), 413 (22), 410 (11), 331 (20), 321 (M^+ -side-chain, 23), 303 (40), 285 (38), 267 (26), 239 (b -H_2O, 100), 225 (a, 45), 221 (b-2H_2O, 60); pmr (CD_3OD) δ 0.82 (d, J=6.5Hz, CH_3-28 or CH_3-27), 0.84 (d, J=6.5Hz, CH_3-27 or CH_3-28), 0.95 (d, J=6.5Hz), CH_3-21), 1.05 (s, CH_3-19), 1.15 (s, CH_3-18), 2.43 (dd, J=12 and 3Hz, 7β-H), 3.40 (1H, dd, J=10.5 and 6Hz, 26-H), 3.51 (broad m, 3α-H), 3.64 (dt, J=3 and 10Hz, 6β-H), 4.01 (dd, J=8.0 and 2.5 Hz, 16α-H), 4.06 (dd, J=11.0 and 2.5Hz, 15β-H).

Compound **6**: mp 185-188° (from MeOH in the presence of CH_2Cl_2 vapors), [α]D=+20.0° (c, 0.4, MeOH); eims (70 eV) *m/z* (%) 478 (M^+ -H_2O, 25), 460 (100), 442 (60); pmr (CD_3OD) δ 0.91 (d, J=6.5Hz, CH_3-27), 0.99 (d, J=6.5Hz, CH_3-28), 1.045 (d, J=6Hz, CH_3-21), 1.17 (s, CH_3-18), 1.22 (s, CH_3-19), 2.10 (m, H-24), 2.50 (dd, J=13.5 and 3.5Hz, 7β-H), 2.55 (m, 20-H), 3.41 (2H, one dd with J=10.5 and 6Hz, partially superimposed on a broad signal, 26-H and 3α-H), 3.56 (1H, dd, J=10.5 and 6.5Hz, 26-H), 3.93 (dd, J=7.5 and 2.5Hz, 16α-H), 4.09 (2H, one dd with J=11.0 and 2.5Hz, 15β-H superimposed on the 6β-H signal), 4.28 (m, W½=6Hz, 4α-H), 5.45 (2H, m, 22 and 23-H).

5α-*Cholestane-3β,4β,6α,8,15α,16β,26-heptol 3,6,15,26-tetraacetate* **4a**: The mixture of **4** (3 mg) and excess of Ac_2O in 0.1 ml of dry pyridine was kept at room temperature overnight. The excess reagents were evaporated under vacuum, and the residue pyridine was removed by coevaporation with C_6H_6. The dark brown polar materials were removed by dissolving the residue in $CHCl_3$ and passing it through a Pasteur pipette fitted with a slurry of a silica gel in $CHCl_3$. The eluate was evaporated to give a residue (2.3 mg) containing the tetraacetate, **4a**. Eims (70 eV) (*m/z*) (%) 592 (M^+-CH_3CO_2H, 15), 574 (10), 532 (18), 514 (55), 496 (18), 472 (25), 454 (M^+-3CH_3CO_2H-H_2O, 100); pmr ($CDCl_3$) δ 0.91 (d, J=6.5Hz, CH_3-21 or CH_3-27), 0.92 (d, J=6.5Hz, CH_3-27 or CH_3-21), 1.19 (s, CH_3-18), 1.29 (s, CH_3-19), 2.05, 2.09, 2.10 and 2.11 (four s, 12H, O=C-CH_3), 3.83 (1H, dd, J=10.0 and 6.5Hz, 26-H), 3.96 (3H, br signal, 4α-, 16α- and 26-H), 4.72 (2H, broad signal, 3α- and 15β-H), 5.28 (1H, dt, J=4 and 10.5Hz, 6β-H).

24ξ-Methyl-5α-Cholestane-3β,6α,8,15α,16β,26-hexol 3,6,15,26-tetraacetate **5a**: This compound was prepared and purified by the method described above; eims (70 eV) (*m/z*) (%) 590 (M^+-CH_3CO_2H, 35), 582 (10), 530 (60), 512 (M^+-$2CH_3CO_2H$-H_2O, 100), 494 (20), 470 (45), 452 (70); pmr ($CDCl_3$) δ 0.80 (d, *J*=6.5Hz, CH_3-28 or CH_3-27), 0.84 (d, *J*=6.5Hz, CH_3-27 or CH_3-28), 0.90 (d, *J*=7.0Hz, CH_3-21), 1.09 (s, CH_3-19), 1.19 (s, CH_3-18), 2.03, 2.04, 2.05, 2.07 (four s, 12H, O=C-CH_3), 3.88 (1H, dd, *J*=10.5 and 7.0Hz, 26-H), 3.99 (2H, broad m, 26 and 16α-H), 4.69 (2H, one dd, *J*=12 and 2.5Hz emerging from a broad m, 15β and 3α-H), 4.92 (dt, *J*=4 and 12Hz, 6β-H).

HYDROGENATION OF **6**.—The Δ^{22}-unsaturated sterol **6** (1 mg) was hydrogenated for 12 h at room temperature and atmospheric pressure using Pd/C (5%, 1 mg) as catalyst and MeOH as solvent. Filtration and evaporation of the solvent gave a residue whose pmr showed in the methyl region the following signals, δ 0.82 (d, *J*=6.5Hz), 0.85 (d, *J*=6.5Hz), 0.95 (d, *J*=7.0Hz), 1.14 (s, CH_3-18), 1.22 (s, CH_3-19); the olefinic signal had disappeared.

INSTRUMENTAL.—Pmr and cmr spectra were recorded on Bruker WX-270 and WM-250 instruments. Eims were obtained on an AEI MS-30 mass spectrometer. Optical rotation was measured on a Perkin Elmer 141 polarimeter in MeOH. Mps were measured on a Kofler hot-stage apparatus and are uncorrected.

RESULTS AND DISCUSSION

5α-Cholestane-3β,4β,6α,8,15α,16β,26-heptol (**4**), had mp 241-243°, $[\alpha]_D$=+28.4°. In the eims the highest molecular weight ion observed (*m/z* 466) corresponded to loss of H_2O from the molecular formula $C_{27}H_{48}O_7$. The fragmentation pattern, with ions for stepwise H_2O loss (*m/z* 448, 430, and 412) and ions corresponding to the loss of an hydroxylated C_8 side chain (*m/z* 337) together with H_2O loss (*m/z* 319, 301, 283, and 265), closely resembled that observed in the spectrum of the heptol **2** (7). The spectrum also contained two intense ions at *m/z* 241 (42%) and 225 (100%), each accompanied by loss of H_2O (*m/z* 223 and 207). An intense peak at *m/z* 225 was already observed in the hexol **1** and in the heptol **2**; in the spectrum of this latter a peak at *m/z* 223 (i.e., 241-H_2O) was also present. We propose that these fragments can originate by cleavages of the 12,13 and 8,14 bonds promoted by the 8β-hydroxy function as illustrated in Figure 1. The ms of compound **5**, the 24-methyl homologue of the hexol **1**, with ions at *m/z* 225 (**a**, 40%), 239 (**b** -H_2O, 100%) and 221 (**b** -$2H_2O$, 68%), gives support to our suggestion. The pmr spectrum of **4** contained several features, two doublets of doublets at δ 4.01 (*J*=7.5 and 3Hz) and 4.09 (*J*=10.5 and 3Hz), this latter superimposed on the signal for 6β-H, and the A portion of an ABX system at δ 3.43 (J_{AB}=10.5Hz, J_{AX}=6Hz; the B portion, resonated under the MeOH signal) was already observed in the spectrum of the hexol **1** (7) and assigned to 16α-H, 15β-H and 26-H, respectively. When we measured the spectrum of the derived tetraacetate **4a** the overlapping methine protons at δ 4.09 were shifted to lower field at δ 4.72 (15β-H) and 5.28. This latter signal had the characteristic shape (dt with *J* of 4 and 10.5 Hz) of the axial proton associated with the 6α-acetoxyl group (9).

The spectrum of **4** also included one-proton double doublet at δ 2.50 (*J*=13 and 3Hz), already observed in the hexol **1** and assigned to 7β-H. These data suggested the presence of a 6α,8β-dihydroxy moiety. Several features of the pmr spectra indicated a new hydroxyl group at 4β-position. The spectrum of the heptol **4** displayed an isolated signal at δ 4.28, which was quite narrow ($W_{1/2}$=6Hz) as would be expected for an equatorial proton and a methyl singlet at δ 1.22 (CH_3-19) downfield shifted by 0.20 ppm relative to hexol **1** in agreement with the postulation of a 4β-OH in **4** (7,10). The remaining three methyl signals, δ 0.94d, 0.96d, and 1.14s, were close to the values for CH_3-21, CH_3-27 and CH_3-18, respectively, observed in the spectrum of the hexol **1** (7). Further, the pmr spectrum of the tetraacetate **4a** still contained overlapping hydroxyl and acetoxyl methine signals, δ *ca* 4.72 (2H, 3α-H, 15β-H) and 3.96 (3H, 4α-H, 16α-H and 26-H), but irradiation around 3.96 ppm in a double resonance experiment simplified the complexity of signal at δ 4.72 from which distinctly emerged a sharp

doublet (J=10.5 Hz, 15β-H) and a signal clearly composed of four peaks, evidently a doublet of doublets with J=11.5 and 4Hz, as would be expected for the axial proton associated with the 3β-OH still coupled with two other protons. On these bases, the position for the new hydroxyl group was narrowed down to C-2β or C-4β. The peak due to 6β-H in **4** (δ~4.10, overlapping with 15β-H) and in **4a** (δ 5.28), was significantly downfield shifted by ~0.50 and 0.30 ppm relative to the hexol **1** and its tetraacetate (3,6,15,26-tetraacetate), respectively (7). These data clearly show that the new hydroxyl group is located at position 4β.

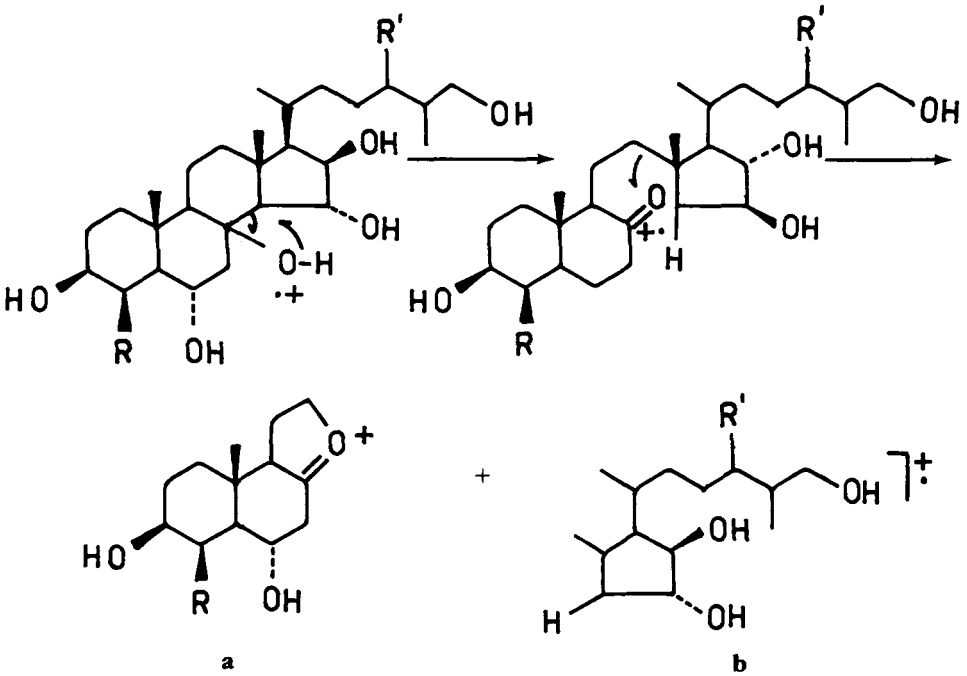


FIGURE 1. Fragments in the mass spectra of 8-hydroxysteroids.

During our investigation of biologically active marine steroids from Echinoderms, we have been working on the extractives of the Pacific starfish *Acanthaster planci* and have isolated in 10-mg amounts a polyhydroxylated sterol identical with **4**. Thus, it was possible to run a cmr spectrum and confirm that **4** was related to **1** by introduction of the seventh hydroxyl group at the 4β-position. The cmr chemical shift assignments are shown in Table 1. The most significant features of the spectrum of **4**, which suggested the location of the new hydroxyl group at C-4β, were the upfield shifts exhibited by C-2 (5.2 ppm) and C-6 (2.9 ppm), and the downfield shifts experienced by C-3

TABLE 1. Cmr Shifts in **4** (CD_3OD)

C-1	39.9	C-10	38.0	C-19	17.0
C-2	26.3	C-11	18.9	C-20	30.6
C-3	73.6	C-12	43.2	C-21	18.3
C-4	69.2	C-13	45.4	C-22	37.2
C-5	57.2	C-14	64.6	C-23	24.8
C-6	64.7	C-15	80.8	C-24	35.0
C-7	50.5	C-16	83.1	C-25	37.0
C-8	76.0	C-17	60.7	C-26	68.6
C-9	58.4	C-18	16.9	C-27	17.2

(1.4 ppm), C-5 (3.5 ppm), and C-19 (2.8 ppm) relative to the hexol **1** (7). Similar shifts have been observed in 4β-hydroxysteroids (e.g., in 5α-cholestane-3β,4β-diol relative to 3β-cholestanol the β shifts at C-3 and C-5 are +0.8 and +4.0 ppm, respectively; the γ-shifts at C-2 and C-6 are −5.0 and −2.8 ppm, respectively; and the δ shift at C-19 is +2.4 ppm (11,12). Small shifts were also exhibited by C-9 and C-11, i.e., +1.0 and −0.5 ppm, respectively, relative to the hexol **1** (+1.0 and −0.7 ppm in 5α-cholestane-3β,4β-diol *vs* 3β-cholestanol; + denotes downfield shifts, and − denotes upfield shifts).

24ξ-Methyl-5α-Cholestane-3β,6α,8,15α,16β,26-hexol (**5**) had mp 253-256°, $[\alpha]_D = +27.8°$. In the eims the highest molecular weight ion observed (*m/z* 464) corresponded to loss of H_2O from the molecular formula $C_{28}H_{50}O_6$. In addition to intense peaks for stepwise H_2O loss, the ms showed also the loss of the side-chain with peaks at *m/z* 321, 303, 285, 267, identical to those that we had previously seen for the cholestane-hexol **1** (7), indicating an additional methyl group in the hydroxylated side-chain. The base peak at *m/z* 239 (see Figure 1) confirmed the presence of an hydroxylated C_9-side-chain. The pmr spectrum of **5** was very similar with that of the hexol **1** (7); the only difference being observed in the methyl region. In the spectrum of **5** there were two methyl doublets at δ 0.82 (J=6.5Hz) and 0.84 (J=6.5Hz) instead of the three protons of the methyl doublet observed at δ 0.91 in the spectrum of **1**, the remaining methyl signals, 0.95d, 1.05s, and 1.15s were close to the values for CH_3-21, CH_3-19, and CH_3-18, respectively, observed in the spectrum of **1**.

Similarly, treatment of **5** with Ac_2O and pyridine lead to a 3β,6α,15α,26-tetraacetate, **5a**, whose pmr spectrum in the acetoxy, hydroxy-methine and methylene proton regions was superimposable with that of 5α-cholestane-3β,6α,8,15α,16β,26-hexol 3,6,15,26 tetraacetate (7); in the methyl region the methyl doublets were seen at δ 0.80, 0.84, and 0.90. On this basis we suggest that the new sterol is the 24-methyl homologue of the hexol **1**. The location of the primary hydroxyl group at C-26 received support by double resonance experiments. Irradiation around 1.9 ppm in **5a** collapsed only the methyl doublet resonating at δ 0.90, and irradiation around 1.5 ppm collapsed the methyl doublet resonating at δ 0.84 leaving intact the doublet at δ 0.80. These experiments ruled out an isopropyl structure. The location of the "extra" methyl group at C-24 is mainly based on biogenetic grounds.

Upon catalytic hydrogenation, the compound **6**, whose Δ^{22}-24-methyl structure was supported by pmr double resonance experiments, yielded a saturated derivative showing in the pmr spectrum three methyl doublets with chemical shifts δ 0.82, 0.85, and 0.95 virtually the same as in **5**.

(22E) 24-Methyl-5α-Cholest-22-ene-3β,4β,6α,8,15α,16β,26-heptol (**6**) had mp 185-188°, $[\alpha]_D = +20.0°$. In the eims the highest molecular weight ion observed (*m/z* 478) corresponded to loss of H_2O from the molecular formula $C_{28}H_{48}O_7$. In **6**, the chemical shifts and coupling constants for the protons at position 3,4,6,15, and 19 were virtually the same as in **4** (Experimental). The C-16 proton was shifted upfield (δ 3.93 *vs.* 4.01) and the terminal C-26 protons were shifted downfield (δ 3.41, dd, J=10.5 and 6.0Hz and δ 3.55, dd, J=10.5 and 6.5 Hz). The singlet due to C-18 protons was also shifted downfield (δ 1.17 vs. 1.14). The pmr spectrum also showed the presence of a Δ^{22} double bond, which is responsible for the above shifts, and a 24-methyl substituent in the side-chain. In the olefinic region a multiplet around 5.45 ppm and in the methyl region, doublets at δ 1.045 (J=6.5Hz), 0.99 (J=6.5Hz) and 0.91 (J=7Hz) are in agreement with a 26-hydroxy, 24-methyl-Δ^{22}-side-chain. The protons at C-20 and C-24 in an allylic position have also been shifted considerably downfield and are found as isolated multiplets at δ 2.55 and 2.10, respectively. Irradiation of the multiplet at δ 2.55 (20-H) in a double resonance experiment did indeed col-

lapse the doublet at δ 1.045 ppm to a singlet, and also simplified the complexity of the signal for the Δ^{22} protons. Irradiation at 2.11 ppm (H-24) again simplified the Δ^{22} pattern and collapsed the doublet at 0.99 ppm to a singlet.

The stereochemistry at the Δ^{22} double bond is suggested to be *trans*. The C-21 methyl group signal is displayed in "normal" 3β-hydroxy sterols at 1.00-1.01 ppm when it occurs together with a Δ^{22}-*trans* double bond whereas a *cis* double bond shifts it to 0.94-0.95 ppm (13). Our value of 1.045 ppm seems indicative that the double bond is *trans* in **6**.

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