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ON THE SYNTHESIS OF 4-KETO-STEROIDAL ALKALOIDS

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ABSTRACT.—To obtain 4-keto-steroidal alkaloids from solasodine, two routes were tried: allylic acetoxylation of (22*S*,25*R*)-22,26-*N*-Cbz-epiminocholest-5-ene-3β,16β-diol-acetate [**3**]; and hydroboration of (22*S*,25*R*)-16β-acetyl-22,26-*N*-Cbz-epiminocholest-4-en-3-one [**11**]. The first route yielded (22*S*,25*R*)-3β-hydroxy-16β-acetoxy-22,26-*N*-Cbz-epiminocholestan-5,6-oxido-4-one [**10**]. The second one yielded two products: (22*S*,25*R*)-3β-hydroxy-16β-ethoxy-22,26-*N*-Cbz-epimino-5α-cholestan-4-one [**22**] and its 16β-acetoxy homologue [**23**].

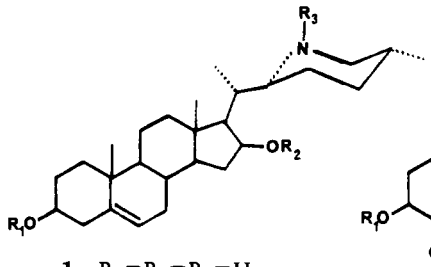
Steroidal alkaloids with a 3-hydroxy-4-keto moiety on ring A have been found in two species of Solanaceae, *Solanum oblongifolium* Bitter (1) and *Solanum ecuadorensis* Bitter (2). The interesting pharmacological properties of these alkaloids (3) led us to consider the convenience of obtaining them by synthesis. As a first approach to the problem, the introduction of a 4-keto group in the steroid nucleous was tried. Solasodine was used as starting material because it was available and is easily transformed into an epiminocholestane type alkaloid with a lateral chain where the nitrogen atom is α-oriented, as in solaphyllidine (4) and related alkaloids (5).

Allylic oxydation of cholesteryl acetate using SeO_2 has been reported by Rosenheim and Starling (6) with rather low yields. On the other hand $Pb(OAc)_4$ oxidation of cholest-5-en-3-one (7) introduces a 4-equatorial hydroxyl group which is difficult to oxidize. Therefore, it was considered convenient to try allylic acetoxylation (8) to introduce a 4-axial hydroxyl.

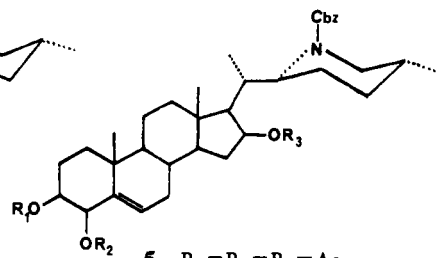
Reduction of solasodine with $NaBH_4$ (9) produced (22*S*,25*R*)-22,26-epiminocholest-5-ene-3β-16β-diol [**1**]. To protect the amino group, **1** was treated with benzyl chloroformate (Cbz). It is interesting to note that the aromatic ring of the Cbz moiety interacts with the H-26eq, deshielding it strongly, causing this proton to appear at δ 3.80 in the ^{1}H-nmr spectrum. The H-26eq is coupled to the H-26ax ($J = 14$ Hz), and the latter is also coupled to the H-25ax ($J = 5$ Hz). Finally, the H-25ax is coupled to the C-27 methyl. Decoupling experiments established these relationships, and a similar situation is present in certain sapogenins (10).

To obtain a compound amenable to allylic acetoxylation, the *N*-CBz derivative [**2**] was treated with Ac_2O/C_5H_5N to yield the 3,16-diacetoxy derivative [**3**]. Treatment with Br_2 and silver acetate in $CHCl_3$ at low temperature produced a mixture of starting material **3** and three products: (22*S*,25*R*)-*N*-Cbz-22,26-epiminocholest-5-ene-3β,4β,16β-triol-acetate [**5**], (22*S*,25*R*)-3β,16β-di-*O*-acetyl-22,26-*N*-Cbz-epiminocholest-5-en-4β-ol [**6**], and its 4β,16β-di-*O*-acetyl-3β-ol isomer **7**. Unfortunately the desired product **6** was obtained in lowest yield; therefore **5**, **7**, and a mixture of **6** and **7** were subjected to mild hydrolysis with K_2CO_3 in MeOH, conditions that do not affect the acetate on C-16. The 3β,4β-diol **8** was obtained almost quantitatively. Selective acetylation of **8** with Ac_2O/C_5H_5N at 0° gave **6** in 54% yield. Mild oxidation of **6** with Jones reagent yielded **9**, which, upon treatment with K_2CO_3/MeOH at room temperature, gave **10**.

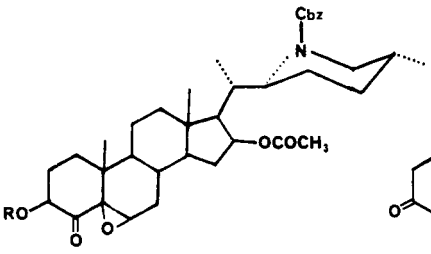
Even though **10** is an interesting compound, the desired product was an alkaloid with a 3β-OH, 4-keto moiety with no neighboring epoxy group. Therefore, a new scheme was tried to obtain a compound devoid of the Δ5 double bond. To obtain such a compound, **3** was treated with K_2CO_3/MeOH, and the product **4** of hydrolysis was subjected to Oppenauer oxidation to yield **11**, which is a suitable compound to intro-



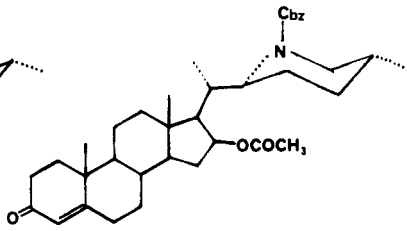
1 $R_1=R_2=R_3=H$
2 $R_1=R_2=H$, $R_3=Cbz$
3 $R_1=R_2=Ac$, $R_3=Cbz$
4 $R_1=H$, $R_2=Ac$, $R_3=Cbz$



5 $R_1=R_2=R_3=Ac$
6 $R_1=R_3=Ac$, $R_2=H$
7 $R_1=H$, $R_2=R_3=Ac$
8 $R_1=R_2=H$, $R_3=Ac$



9 R=Ac
10 R=H



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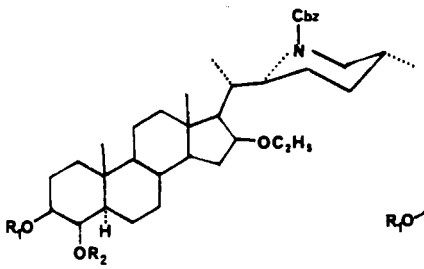
duce a hydroxyl at C-4 by hydroboration. The hydroboration reaction, which was performed according to Zweifel and Herbert (11), rendered two products in about equal proportions. The less polar product **12**, R_f 0.27, showed an ethoxy group at C-16, while the other product **16**, R_f 0.16, had an *O*-acetyl. The formation of **12** was probably caused by an excess of diborane, as reduction of carbonyls under these conditions has been reported in the literature (12).

In order to oxidize the hydroxyl at C-4 without affecting the one at C-3, selective acetylation of **12** and **16** was conducted as previously described for **8**. In each case three acetylated derivatives were obtained: **13**, **14** and **15** from **12**, and **17**, **18**, and **19** from **16**. Mild oxidation of **14** with Jones reagent yielded the 3-*O*-acetyl-4-keto derivative **20**. The ^{13}C-nmr spectrum of **20** showed the signal of C-3 at 76.2 ppm, that of C-5 at 57.4 ppm, and the carbonyl (C-4) at 205.3 ppm, which agrees with values reported for solaphyllidine acetate (13). In a similar manner, **21** was obtained by mild oxidation of **18**.

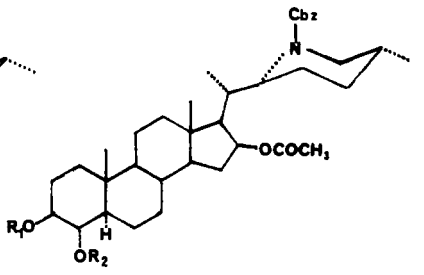
For comparison, **15** was treated with Jones reagent, yielding **24**. In this compound C-4 appears at 77.2 ppm and C-5 at 51.5 ppm. Treatment of **20** and **21** with K_2CO_3/MeOH produced the corresponding 3-OH, 4-keto derivatives **22** and **23**. These compounds show the C-4 carbonyl at 212.4 ppm as observed in solaphyllidine.

Because catalytic reduction could not be used to cleave the Cbz group (14), because it would reduce the carbonyl, acid hydrolysis with HBr/HOAc (15) was tried unsuccessfully. On the other hand, removal of the Cbz group using a strong Lewis acid such as $AlCl_3$ (16) proved equally inadequate. This demonstrated the convenience of using a protecting group like *t*-butyloxycarbonyl (BOC) (17), which can be removed by acid hydrolysis (18), or thiothiazolone (19).

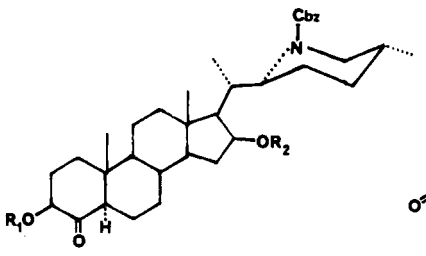
The overall yield for compound **10** was approximately 7%, while the yield of **23** from solasodine was about 4%. The yield of the latter could be doubled if partial reduction of the 16-*O*-acetate during hydroboration is avoided; this could be accomplished if this group is hydrolyzed prior to hydroboration.



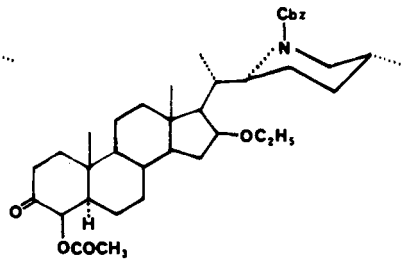
12 $R_1=R_2=H$
13 $R_1=R_2=Ac$
14 $R_1=Ac$, $R_2=H$
15 $R_1=H$, $R_2=Ac$



16 $R_1=R_2=H$
17 $R_1=R_2=Ac$
18 $R_1=Ac$, $R_2=H$
19 $R_1=H$, $R_2=Ac$



20 $R_1=Ac$, $R_2=Et$
21 $R_1=R_2=Ac$
22 $R_1=H$, $R_2=Et$
23 $R_1=H$, $R_2=Ac$



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EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Tlc was performed on Si gel plates, using C_6H_{14}-EtOAc (2:1) as a solvent unless otherwise stated, and spots were visualized with I_2 vapor. Melting points were determined on a Fisher-Johns hot stage and are uncorrected. Optical rotations were measured in a Schmidt-Haensch polarimeter. The ir spectra were recorded using a Perkin-Elmer spectrometer model Fx-1720 as KBr disks. The ^{1}H-nmr and ^{13}C-nmr spectra were determined in $CDCl_3$ with TMS as internal standard, and chemical shifts are expressed in ppm; a Varian Ft-80 apparatus was used, and standard proton noise-decoupled and attached proton test (APT) spectra were recorded for all compounds. Microanalyses were conducted at Prof. Melissa & G. Reuter's Analytical Laboratories, D-5270 Gummersbach, Germany. Solasodine dihydrochloride was obtained from Oss-Diosynth (Holland).

(22*S*,25*R*)-22,26-EPIMINOCHOLEST-5-ENE-3β,16β-DIOL [**1**].—To an ice-cold solution of 60 g (0.145 mol) of solasodine in 3.5 liters of MeOH/CH_2Cl_2, 22 g (0.58 mol) of $NaBH_4$ was added slowly with stirring. After 2 h, ice-H_2O was added and the mixture was extracted twice with $CHCl_3$. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum to dryness. The crude product was crystallized from MeOH to give 53.1 g (88%) of dihydrosolasodine: mp 259–262°, [lit. (20) 265–266°]; ir ν max cm^{-1} 3410, 3190, 1170, 1080; ^{1}H nmr (80 MHz, $CDCl_3$) δ 0.85 (3H, d, J = 6 Hz, 27-Me), 0.94 (3H, s, Me-18), 1.03 (3H, s, Me-19), 1.08 (3H, d, J = 6 Hz, Me-21), 2.95 (1H, d, J = 12 Hz, H-26), 3.45 (1H, m, H-3α), 4.40 (1H, m, H-16α), 5.30 (1H, bd, J = 4 Hz, H-6).

(22*S*,25*R*)-*N*-CBZ-22,26-EPIMINOCHOLEST-5-ENE-3β,16β-DIOL [**2**].—A solution of 45 g (0.108 mol) of **1** in 1.3 liters of $CHCl_3$ was mixed with 647 ml of 5% $NaHCO_3$ and 34 g (0.22 mol) of benzyl chloroformate (Cbz-Cl) in toluene, prepared according to Carter *et al.* (21). After shaking for 9.5 h an additional amount (11 g) of CbzCl was added and left overnight at room temperature. The $CHCl_3$ phase was shaken several times with H_2O, dried over anhydrous Na_2SO_4, and concentrated to dryness. The residue was chromatographed on a Si gel column. Elution with C_6H_6-EtOAc (10:1) yielded 34.75 g (58.4%) of **2**, which crystallized from EtOH-Me_2CO (1:1): mp 170–171°; $[\alpha]^{25}D$ −14.5 (c = 0.31, MeOH). Calcd for $C_{35}H_{51}NO_4$, C 76.46, H 9.35, N 2.55; found C 76.09, H 9.11, N 2.44. Ir ν max 3440, 1693 cm^{-1}; ^{1}H

nmr (80 MHz, $CDCl_3$) δ 0.84 (3H, d, J = 6 Hz, Me-21), 0.86 (3H, s, Me-18), 0.98 (3H, s, Me-19), 1.00 (3H, d, J = 6 Hz, Me-27), 3.01 (1H, dd, J = 14, 5 Hz, H-26ax), 3.80 (1H, d, J = 14 Hz, H-26eq), 4.12 (1H, m, H-16α), 5.10 (2H, ABq, J = 22, 12 Hz, H-Bz), 7.34 (5H, bs, aromatic H).

(22*S*,25*R*)-*N*-Cbz-22,26-EPIMINOCHOLEST-5-ENE-3β,16β-DIOL-ACETATE [**3**].—To a solution of 30 g of **2** in pyridine, 150 ml of Ac_2O was added. After 3 days at room temperature cold H_2O was added, and the precipitate was filtered, washed with H_2O, and crystallized from MeOH, yielding 34 g of diacetate: mp 110–112°; ir ν max 1732, 1686, 1245 cm^{-1}; ^1H nmr (80 MHz, $CDCl_3$) δ 0.84 (3H, s, Me-18), 0.90 (3H, d, J = 6 Hz, Me-21), 0.96 (3H, d, J = 6 Hz, Me-27), 1.04 (3H, s, Me-19), 2.00 (3H, s, OAc), 2.04 (3H, s, OAc), 4.6 (1H, m, H-3α), 5.07 (2H, ABq, J = 23, 13 Hz, H_2-Bz), 5.26 (1H, bs, H-4), 7.35 (5H, bs, aromatic H).

ALLYLIC ACETOXYLATION OF **3**.—A solution of **3** (10 g, 0.016 mol) in 71 ml $CHCl_3$ was cooled at −60° and mixed under stirring with 0.64 g (0.008 mol) of Br_2 and a solution of 14.25 g (0.085 mol) AgAc in pyridine. The mixture was stirred until it reached ambient temperature and then left to stand 24 h in the dark. The mixture was treated with dilute HCl to complete precipitation of AgCl, filtered, and washed with H_2O. The aqueous layer was extracted with $CHCl_3$, and the $CHCl_3$ phase was shaken with $NaHCO_3$ solution, dried over anhydrous Na_2SO_4, and concentrated to dryness. The residue (9 g) was purified by vacuum chromatography using Si gel. Elution with C_6H_{14}-EtOAc (10:1) yielded 1.59 g of starting compound **3** and 0.88 g of **5**, which crystallized out of the column solvent: mp 85–88°; $[\alpha]^{25}D$ −31.6° (c = 0.0155, MeOH) ir ν max cm^{-1} 1745, 1690, 1245; ^1H nmr (80 MHz, $CDCl_3$) δ 0.84 (3H, s, Me-18), 0.90 (3H, d, J = 6 Hz, Me-21), 0.98 (3H, d, J = 6 Hz, Me-27), 1.18 (3H, s, Me-19), 1.98 (6H, s, OAc), 2.03 (3H, s, OAc), 3.06 (1H, dd, J = 14, 5 Hz, H-26ax), 3.80 (1H, d, J = 14 Hz, H-26eq), 4.75 (1H, m, H-3α), 5.08 (2H, ABq, J = 23, 13 Hz), 5.50 (1H, d, J = 4 Hz, H-6), 5.75 (1H, m, H-4α), 7.3 (5H, bs, aromatic H); ^{13}C nmr (20 MHz, $CDCl_3$) ppm 138.5 (C-5), 131.0 (C-6), 76.9 (C-4), 76.5 (C-16), 72.8 (C-3), 56.4 (C-22), 55.8 (C-17), 54.4 (C-14), 50.0 (C-9), 45.9 (C-26), 42.5 (C-13), 39.5 (C-12), 36.8 (C-1), 36.1 (C-20), 36.0 (C-10), 34.8 (C-15), 31.6 (C-7), 31.1 (C-8), 28.8 (C-25), 27.4 (C-23), 25.4 (C-24), 22.5 (C-2), ,20.2 (C-11 and C-27), 18.9 (C-19), 13.8 (C-21), 12.6 (C-18). Elution with C_6H_{14}-EtOAc (4:1) yielded 0.08 g of **6**: mp 87–90°; $[\alpha]^{25}D$ −20.3 (c = 0.04 MeOH). Calcd for $C_{39}H_{55}NO_7$, C 72.07, H 8.53, N 2.16; found C 71.90, H 8.17, N 2.14. Ir ν max cm^{-1} 3456, 1735, 1695, 1245; ^1H nmr (80 MHz, $CDCl_3$) δ 0.82 (3H, s, Me-18), 0.93 (3H, d, J = 6 Hz, Me-21), 0.98 (3H, d, J = 6 Hz, Me-27), 1.18 (3H, s, Me-19), 2.00 (6H, s, OAc), 2.09 (3H, s, OAc), 3.02 (1H, dd, J = 14, 5 Hz, H-26ax), 3.80 (1H, d, J = 14 Hz, H-26eq), 4.20 (1H, d, J = 4 Hz, H-4α), 4.70 (1H, m, H-3α), 5.10 (2H, ABq, J = 22, 12), 5.70 (1H, m, H-6), 7.3 (5H, bs, aromatic H); ^{13}C nmr see Table 1. Increasing the polarity of the solvent gave a 4.5 g mixture of **6** and **7**. Finally, 0.78 g of **7**, mp 82–85°, was obtained: $[\alpha]^{25}D$ −31.4 (c = 0.27, MeOH); ir ν max cm^{-1} 3450, 1735, 1694, 1244; ^1H nmr (80 MHz, $CDCl_3$) δ 0.83 (3H, s, Me-18), 0.94 (3H, d, J = 6 Hz, Me-21), 0.98 (3H, d, J = 6 Hz, Me-27), 1.10 (3H, s, Me-19), 3.02 (1H, dd, J = 14, 5 Hz, H-26ax), 3.40 (1H, m, H-3α), 3.80 (1H, d, J = 14 Hz, H-26eq), 5.10 (2H, ABq, J = 2, 12, H-Bz), 5.35 (1H, m, H-4α), 5.70 (1H, d, J = 4 Hz, H-6), 7.30 (5H, bs, aromatic H); ^{13}C nmr see Table 1.

HYDROLYSIS OF ALLYLIC ACETOXYLATION PRODUCTS.—To a mixture of **5**, **7**, and **6** + **7** dissolved in MeOH, a 5% solution of K_2CO_3 was added to slight turbidity and the mixture left at ambient temperature for 6 h. After addition of H_2O the product was extracted with $CHCl_3$. The organic phase was dried over anhydrous Na_2SO_4 and concentrated to dryness. Crystallization from MeOH afforded 4.7 g of **8**: mp 168–172°; $[\alpha]^{25}D$ −11.2 (c = 0.0187, MeOH). Calcd for $C_{37}H_{53}NO_6$, C 73.11, H 8.79, N 2.30; found C 73.15, H 8.73, N 2.31. Ir ν max cm^{-1} 3474, 1735, 1695, 1243; ^1H nmr (80 MHz, $CDCl_3$) δ 0.84 (3H, s, Me-18), 0.90 (3H, d, J = 6 Hz, Me-21), 0.95 (3H, d, J = 6 Hz, Me-27), 1.12 (3H, s, Me-19), 1.97 (3H, s, OAc), 2.99 (1H, dd, J = 14, 5 Hz, H-26ax), 3.40 (1H, m, H-3α), 3.76 (1H, d, J = 14 Hz, H-26eq), 4.05 (1H, d, J = 4 Hz, H-4α), 5.10 (2H, ABq, J = 23, 13 Hz, H-Bz), 5.65 (1H, m, H-6), 7.28 (5H, bs, aromatic H); ^{13}C nmr (20 MHz, $CDCl_3$) ppm 143.0 (C-5), 127.9 (C-6), 76.6 (C-4 and C-17), 72.4 (C-3), 56.4 (C-22), 55.9 (C-17), 54.5 (C-14), 50.2 (C-9), 45.9 (C-26), 42.6 (C-13), 39.5 (C-12), 37.0 (C-1), 36.0 (C-10), 34.8 (C-15), 31.6 (C-7 and C-8), 28.7 (C-25), 27.4 (C-23), 26.0 (C-2), 25.3 (C-24), 20.8 (C-11 and C-19), 19.9 (C-27), 13.8 (C-21), 12.6 (C-18).

SELECTIVE ACETYLATION OF **8**.—To an ice-cold solution of 3.7 g of **8** in 25 ml of pyridine, 20 ml of Ac_2O was added. After 35 min cold H_2O was added, and the mixture was left at ambient temperature for 1 h. The precipitate was filtered, washed with H_2O, and dried overnight in an oven at 45°. The residue was dissolved in toluene and taken to dryness under vacuum, and the products were separated by vacuum chromatography on Si gel. Elution with C_6H_{14}-EtOAc (3:1) yielded 0.79 g of **5**. Further elution with C_6H_{14}-EtOAc (2:1) yielded 2.08 g of **6**.

(22,25*R*)-3β,16β-DIACETOXY-22,26-*N*-Cbz-EPIMINOCHOLESTAN-5,6-OXIDO-4-ONE [**9**].—To

TABLE 1. ^{13}C Chemical Shifts of *N*-Cbz-dihydrosolasodine [**2**] and Derivatives.[a]

Carbon	Compound																		
	2	**3**	**6**	**7**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
C-1	37.3	38.1	37.0	36.9	38.0	34.8	37.9	37.3	36.1	37.7	37.9	37.2	36.0	37.4	36.0	36.0	35.9	35.8	38.8
C-2	31.6	27.8	21.7	31.8	30.3	33.8	31.5	26.0	25.8	31.3	31.6	25.6	25.7	31.1	28.5	28.5	32.2	32.4	31.0
C-3	71.6	73.8	75.4	71.6	65.2	198.6	75.5	74.0	79.3	74.4	75.4	74.0	79.3	74.3	76.2	76.1	74.5	74.4	204.7
C-4	42.3	37.0	75.3	79.1	204.7	123.0	76.7	75.4	72.5	78.4	76.7	75.4	72.5	78.3	205.3	205.0	212.2	212.1	77.2
C-5	141.0	139.5	141.8	139.0	69.5	170.4	50.9	49.4	51.5	49.2	50.9	49.1	51.5	49.2	57.4	57.4	56.9	56.8	51.5
C-6	121.1	122.2	128.4	130.0	63.2	32.6	22.9	22.9	27.7	22.9	23.0	22.4	22.6	23.0	21.5	21.4	21.5	21.3	24.1
C-7	31.6	31.4	31.6	31.5	29.8	31.7	31.2	31.2	31.4	29.1	31.0	30.8	31.2	29.3	30.1	29.9	30.2	30.1	29.1
C-8	31.5	31.3	31.2	31.1	34.2	35.1	34.5	34.7	34.8	34.7	34.5	34.5	34.5	34.5	34.5	34.7	34.0	33.9	34.7
C-9	50.1	50.1	50.2	50.2	48.6	53.6	53.9	58.9	53.9	54.0	53.0	54.9	51.5	54.0	53.7	54.2	54.0	53.8	53.8
C-10	36.5	36.6	36.1	36.0	46.2	37.0	36.5	36.1	36.8	36.2	36.3	36.0	36.8	36.0	42.6	42.8	43.2	43.1	36.8
C-11	20.7	20.7	20.2	20.2	21.2	20.7	20.8	20.8	20.8	20.8	21.2	21.2	20.7	20.7	20.2	20.1	20.2	20.1	21.0
C-12	39.9	39.6	39.5	39.5	39.3	39.5	39.8	39.9	39.9	39.9	39.8	39.2	39.7	39.7	39.9	39.6	40.0	39.8	39.9
C-13	42.3	42.6	42.6	42.5	42.9	42.6	42.7	42.2	42.2	42.3	42.8	42.8	42.8	42.7	42.3	42.3	42.4	42.4	43.0
C-14	54.4	54.4	54.5	54.5	54.1	53.6	54.3	54.2	54.4	54.3	54.3	54.1	54.2	54.3	54.3	53.8	54.3	54.0	54.0
C-15	37.3	34.8	34.8	34.7	34.7	34.8	33.6	33.6	33.6	33.6	33.8	34.8	34.7	34.8	33.6	34.4	33.7	34.4	33.6
C-16	73.0	76.6	76.5	76.4	75.9	76.3	79.6	79.6	79.6	79.6	76.4	76.5	76.6	76.6	76.6	76.4	79.6	76.3	79.6
C-17	57.0	55.9	55.9	55.8	55.9	55.8	58.3	58.2	58.2	58.2	55.9	55.9	55.9	55.9	58.2	55.9	58.2	55.9	58.2
C-18	13.2	12.6	12.6	12.6	12.6	12.7	12.8	13.0	12.8	13.0	12.8	12.8	12.8	12.8	13.0	12.8	13.0	12.8	12.9
C-19	19.3	19.1	20.9	20.2	18.2	17.3	13.5	13.3	13.5	13.4	13.5	13.3	13.5	13.4	13.6	13.4	13.4	13.4	13.7
C-20	35.6	36.0	35.9	35.9	36.4	35.7	36.2	35.9	36.1	36.2	35.9	36.0	36.0	36.0	36.1	36.0	36.0	36.0	36.2
C-21	14.2	13.8	13.8	13.8	13.7	13.7	13.8	13.5	13.8	13.7	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.7
C-22	56.6	56.5	56.4	56.4	56.5	56.5	56.5	56.3	56.4	56.3	56.5	56.5	56.4	56.5	56.3	56.5	56.3	56.5	56.2
C-23	27.7	27.4	27.4	27.3	27.6	27.4	27.8	27.9	27.8	27.9	27.8	27.4	27.4	27.4	27.6	27.4	27.6	27.8	27.8
C-24	24.9	25.4	25.4	25.3	25.7	25.4	25.5	25.8	25.8	25.8	25.7	25.4	25.5	25.5	25.8	25.5	25.8	25.6	25.8
C-25	28.9	28.8	28.7	28.7	29.0	28.7	28.9	29.0	29.1	29.4	28.7	28.8	28.8	28.8	29.1	28.8	29.0	28.9	29.1
C-26	46.1	45.9	45.9	45.8	46.1	45.9	46.0	46.1	46.0	46.1	45.9	45.9	45.9	45.9	46.1	45.9	46.0	46.1	46.1
C-27	19.9	19.9	19.9	19.9	20.3	19.9	20.0	20.4	20.4	20.4	19.9	20.0	20.0	20.3	20.4	20.1	20.4	20.2	20.4

[a]Other signals: 67.1 (Bz-CH_2), 127.9, 128.1, 128.5, 137.0 (Aromatic-C), 157.6 (Bz-CO), Acetate 169.9–170.0 (CO), 20.6–21.1 (Me), Ethoxy group 63.8 (CH_2-O), 15.6 (Me).

a cold solution of 300 mg of **6** in 50 ml of Me_2CO, 1.0 ml of Jones reagent was added (drop by drop). After 4 h at room temperature, MeOH and H_2O were added, the product was extracted with $CHCl_3$, and the organic phase was washed with H_2O, dried with anhydrous Na_2SO_4, and evaporated to dryness. The residue showed two spots on tlc which were separated by preparative tlc on Si gel using three developments with C_6H_{14}-EtOAc (2:1). The upper layer yielded 240 mg of **9** as a yellow powder, mp 95–97°. Calcd for $C_{39}H_{53}NO_8$, C 70.56, H 8.05, N 2.11; found C 70.39, H 8.27, N 2.25. Ir ν max cm^{-1} 1734, 1695, 1242; ^1H nmr (80 MHz, $CDCl_3$) δ 0.85 (3H, s, Me-18), 0.88 (3H, d, $J = 6$ Hz, Me-21), 0.94 (3H, d, $J = 6$ Hz, Me-27), 0.98 (3H, s, Me-19), 2.00 (3H, s, OAc), 2.08 (3H, s, OAc), 3.00 (1H, dd, $J = 14$, 5 Hz, H-26ax), 3.30 (1H, d, $J = 3$ Hz, H-6), 3.78 (1H, d, $J = 14$ Hz, H-26eq), 4.35 (1H, m, H-3α), 5.10 (2H, ABq, $J = 23$, 13, H-Bz), 5.29 (1H, m, H-16α), 7.30 (5H, bs, aromatic H); ^{13}C nmr (20 MHz, $CDCl_3$) ppm 204.0 (C-4), 76.2 (C-17), 68.8 (C-3), 67.7 (C-5), 60.6 (C-6), 56.4 (C-22), 55.8 (C-17), 54.1 (C-14), 49.9 (C-9), 46.2 (C-10), 46.0 (C-26), 42.6 (C-13), 39.4 (C-12), 37.0 (C-1), 34.5 (C-15), 33.8 (C-8), 32.5 (C-7), 28.8 (C-2 and C-25), 27.4 (C-23), 25.5 (C-24), 21.1 (C-11), 20.0 (C-27), 17.5 (C-19), 13.7 (C-21), 12.5 (C-18).

(22*S*,25*R*)-3β-HYDROXY-16β-ACETOXY-22,26-*N*-Cbz-EPIMINO-CHOLESTAN-5,6-OXIDO-4-ONE [**10**].—A solution of 80 mg of **9** in 50 ml MeOH was saturated with a 5% K_2CO_3 solution and left at room temperature 24 h. Extraction with $CHCl_3$ and usual workup gave 65 mg of **10** which did not crystallize: ir ν max cm^{-1} 1732, 1272; ^1H nmr (80 MHz, $CDCl_3$) δ 0.83 (3H, s, Me-18), 0.87 (3H, d, $J = 6$ Hz, Me-21), 0.93 (3H, d, $J = 6$ Hz, Me-27), 1.05 (3H, s, Me-19), 2.99 (1H, dd, $J = 14$, 5, H-26ax), 3.25 (1H, d, $J = 4$ Hz, H-6), 3.75 (1H, d, $J = 14$ Hz, H-26eq), 3.90 (1H, m, H-3α), 5.10 (2H, ABq, $J = 22$, 12, H-Bz), 5.25 (1H, m, H-16α), 7.30 (5H, bs, aromatic H); ^{13}C nmr see Table 1.

(22*S*,25*R*)-16β-ACETOXY-22,26-*N*-Cbz-EPIMINOCHOLEST-5-EN-3β-OL [**4**].—A solution of 6.3 g (0.01 mol) of **3** in 280 ml MeOH was saturated with 18 ml of a 5% K_2CO_3 solution and left at room temperature overnight. Extraction with $CHCl_3$ and usual workup yielded 5.2 g (0.0088 mol) of **4**, which crystallized from EtOH; mp 176–178; ir ν max cm^{-1} 3447, 1734, 1699, 1241; ^1H nmr (80 MHz, $CDCl_3$) δ 0.82 (3H, s, Me-18), 0.91 (3H, d, $J = 6$ Hz, Me-21), 0.95 (3H, d, $J = 6$ Hz, Me-27), 0.99 (3H, s, Me-19), 1.99 (3H, s, OAc), 3.00 (1H, dd, $J = 14$, 5, H-26ax), 3.40 (1H, m, H-3α), 3.80 (1H, dd, $J = 14$ Hz, H-26eq), 5.10 (2H, ABq, $J = 22$, 12 Hz, H-Bz), 5.32 (1H, m, H-6), 7.3 (5H, bs, aromatic H).

(22*S*,25*R*)-16β-ACETOXY-22,26-*N*-Cbz-EPIMINOCHOLEST-4-EN-3-ONE [**11**].—A mixture of 3.0 g of **4**, 135 ml of toluene, and 27 ml of cyclohexanone was heated to complete solution. Aluminum isopropoxide (1.8 g) was added, and 100 ml of toluene was distilled. H_2O was added and the product extracted with CH_2Cl_2. Chromatography over alumina yielded 1.95 g of **11**: mp 112–115°; $[\alpha]^{25}D$ 39.0 ($c = 0.031$, MeOH). Calcd for $C_{37}H_{51}NO_5$, C 75.35, H 8.72, N 2.37; found C 75.10, H 8.59, N 2.35. Ir ν max cm^{-1} 1732, 1693; ^1H nmr (80 MHz, $CDCl_3$) δ 0.83 (3H, s, Me-18), 0.90 (3H, d, $J = 6$ Hz, Me-21), 0.95 (3H, d, $J = 6$ Hz, Me-27), 1.12 (3H, s, Me-19), 1.97 (3H, s, OAc), 2.95 (1H, dd, $J = 14$, 5 Hz, H-26ax), 3.75 (1H, d, $J = 14$ Hz, H-26eq), 5.07 (2H, ABq, $J = 22$, 12, H-Bz), 5.25 (1H, m, H-16α), 5.64 (1H, bs, H-4), 7.30 (5H, bs, aromatic H); ^{13}C nmr see Table 1.

HYDROBORATION OF **11**.—The BF_3-etherate complex and THF were distilled under N_2, and the diglyme was purified (22) just before use. A solution of 1.5 g of **11** in 20 ml dry THF was put in contact with a stream of N_2 containing B_2H_6 generated separately according to Zweifel and Herbert (11); 27 ml of 1.0 M $NaBH_4$ in diglyme was added drop by drop to a solution of BF_3 complex (6.9 ml) in diglyme (6 ml). After the addition of $NaBH_4$ was complete, the generator was heated to 70° to complete the transference of B_2H_6. The organo-borane complex was treated with 20 ml 3 N NaOH and 20 ml of 30% H_2O_2 under stirring. The mixture was extracted with Et_2O. The organic phase was saturated with NaCl and extracted twice with 25 ml of Et_2O. The Et_2O layer was dried over anhydrous $MgSO_4$ and concentrated under vacuum. The residue (1.3 g) showed two substances on tlc with R_f 0.27 and 0.16. Separation was accomplished on Si gel using vacuum chromatography. C_6H_6-EtOAc (5:1) eluted **12** (510 mg): mp 144–146°; $[\alpha]^{25}D$ 16.4 ($c = 0.011$, MeOH). Calcd for $C_{37}H_{57}NO_5$, C 74.58, H 9.64, N 2.35; found C 74.43, H 9.62, N 2.36. Ir ν max cm^{-1} 3519, 1696, 1262, 1080; ^1H nmr (80 MHz, $CDCl_3$) δ 0.78 (3H, s, Me-18), 0.83 (3H, s, Me-19), 1.03 (3H, d, $J = 6$ Hz, Me-21), 1.14 (3H, d, $J = 6$ Hz, Me-27), 3.02 (1H, dd, $J = 14$, 5 Hz, H-26ax), 3.40 (1H, m, H-3α), 3.50 (1H, m, H-4α), 3.85 (1H, d, $J = 14$ Hz, H-26eq), 3.95 (1H, m, H-16), 5.10 (2H, ABq, $J = 22$, 12, H-Bz), 7.3 (5H, bs, aromatic H); ^{13}C nmr see Table 1. Increasing the polarity of the solvent to C_6H_6-EtOAc (2:1) yielded 435 mg of **16**: mp 103–104°; $[\alpha]^{25}D$ 27.0 ($c = 0.0133$, MeOH). Calcd for $C_{37}H_{55}NO_6 \cdot MeOH$, C 71.10, H 9.27, N 2.18; found C 70.86, H 8.91, N 2.19. Ir ν max cm^{-1} 3447, 1734, 1690, 1266, 1247, 1064; ^1H nmr (80 MHz, $CDCl_3$) δ 0.76 (3H, s, Me-18), 0.82 (3H, s, Me-19), 0.89 (3H, d, $J = 6$ Hz, Me-21), 0.98 (3H, d, $J = 6$ Hz, Me-27), 3.04 (1H, dd, $J = 14$, 5 Hz, H-26ax), 3.35 (1H, m, H-3α), 3.50 (1H, m, H-4α), 3.80 (1H, d, $J = 14$ Hz, H-26eq), 5.10 (2H, ABq, $J = 22$, 12 Hz, H-Bz), 5.25 (1H, m, H-16α), 7.3 (5H, bs, aromatic H); ^{13}C nmr see Table 1.

SELECTIVE ACETYLATION OF **12**.—A solution containing 400 mg of **12** in 3.0 ml of pyridine at 2° was reacted with Ac_2O for 15 min. Cold H_2O was added, and the precipitate was washed with H_2O, dried at 45°, dissolved in toluene, and taken to dryness under vacuum. A mixture (360 mg) of three products was obtained which was separated using vacuum chromatography over Si gel. C_6H_{14}-EtOAc (10:1) eluted **13** as a gum: $[\alpha]^{25}D$ 20.7 ($c=0.015$, MeOH). Calcd for $C_{41}H_{61}NO_7$, C 72.44, H 9.04, N 2.06; found C 72.17, H 9.29, N 2.18. Ir ν max cm^{-1} 1742, 1697, 1250; ^1H nmr (80 MHz, $CDCl_3$) δ 0.76 (3H, s, Me-18), 0.84 (3H, s, Me-19), 0.98 (3H, d, $J=6$ Hz, Me-21), 1.15 (3H, d, $J=6$ Hz, Me-27), 1.98 (3H, s, OAc), 3.05 (1H, dd, $J=14$, 5 Hz, H-26ax), 3.78 (1H, d, $J=14$ Hz, H-26eq), 3.97 (1H, m, H-16α), 4.79 (1H, m, H-4α), 4.90 (1H, m, H-3α), 5.09 (2H, ABq, $J=22$, 12, H-Bz), 7.3 (5H, bs, aromatic H); ^{13}C nmr see Table 1. Increasing the polarity of the solvent yielded **14** (120 mg, R_f 0.66) as a gum. Calcd for $C_{39}H_{59}NO_6$, C 73.43, H 9.32, N 2.20; found C 73.65, H 9.20, N 2.07. Ir ν max cm^{-1} 3452, 1734, 1697, 1250; ^1H nmr (80 MHz, $CDCl_3$) δ 0.75 (3H, s, Me-18), 0.84 (3H, s, Me-19), 1.02 (3H, d, $J=6$ Hz, Me-21), 1.18 (3H, d, $J=6$ Hz, Me-27), 2.00 (3H, s, OAc), 3.05 (1H, dd, $J=14$, 5, H-26ax), 3.50 (1H, m, H-4α), 3.80 (1H, d, $J=14$ Hz, H-26eq), 3.95 (1H, m, H-16α), 4.70 (1H, m, H-3α), 5.10 (2H, ABq, $J=23$, 13, H-Bz), 7.3 (5H, bs, aromatic H); ^{13}C nmr see Table 1. Finally, **15** was obtained, which could not be induced to crystallize. Calcd for $C_{39}H_{59}NO_6$, C 73.46, H 9.33, N 2.20; found C 73.55, H 9.47, N 2.15. Ir ν max cm^{-1} 3450, 1734, 1695, 1248; ^1H nmr (80 MHz, $CDCl_3$) δ 0.75 (3H, s, Me-18), 0.83 (3H, s, Me-19), 1.01 (3H, d, $J=6$ Hz, Me-21), 1.19 (3H, d, $J=6$ Hz, Me-27), 2.05 (3H, s, OAc), 3.05 (1H, dd, $J=14$, 5, H-26ax), 3.40 (1H, m, H-3α), 3.75 (1H, d, $J=14$ Hz, H-26eq), 3.95 (1H, m, H-16α), 4.70 (1H, m, H-4α), 5.10 (2H, ABq, $J=23$, 13 Hz, H-Bz), 7.30 (5H, bs, aromatic H); ^{13}C nmr see Table 1.

SELECTIVE ACETYLATION OF **16**.—Acetylation was performed in a manner similar to the acetylation of **12**. The mixture of acetates was separated by vacuum chromatography on Si gel using C_6H_{14}/EtOAc. Compound **17** eluted first, $[\alpha]^{25}D$ 13.6 ($c=0.006$, MeOH). Calcd for $C_{41}H_{59}NO_8$, C 70.97, H 8.57, N 2.02; found C 70.85, H 8.40, N 1.90. Ir ν max cm^{-1} 1734, 1695, 1250; ^1H nmr (80 MHz, $CDCl_3$) δ 0.76 (3H, s, Me-18), 0.86 (3H, s, Me-19), 0.89 (3H, d, $J=6$ Hz, Me-21), 0.98 (3H, d, $J=6$ Hz, Me-27), 1.95 (3H, s, OAc), 2.00 (3H, s, OAc), 3.00 (1H, dd, $J=14$, 5 Hz, H-26ax), 3.76 (1H, d, $J=14$ Hz, H-26eq), 4.70 (1H, m, H-3α), 4.85 (1H, m, H-4α), 5.10 (2H, ABq, $J=23$, 13 Hz, H-Bz), 5.25 (1H, m, H-16), 7.3 (5H, bs, aromatic H); ^{13}C nmr see Table 1. Increasing the polarity of the solvent eluted **18**. Calcd for $C_{39}H_{57}NO_7$, C 71.86, H 8.81, N 2.15; found C 71.64, H 8.72, N 2.04. Ir ν max cm^{-1} 1735, 1694, 1245; ^1H nmr (80 MHz, $CDCl_3$) δ 0.76 (3H, s, Me-18), 0.80 (3H, s, Me-19), 0.90 (3H, d, $J=6$ Hz, Me-21), 0.93 (3H, d, $J=6$ Hz, Me-27), 1.95 (3H, s, O-Ac), 2.05 (3H, s, O-Ac), 3.00 (1H, dd, $J=14$, 5 Hz, H-26ax), 3.42 (1H, m, H-4α), 3.78 (1H, d, $J=14$ Hz, H-26eq), 4.6 (1H, m, H-3α), 5.10 (2H, ABq, $J=23$, 13 Hz, H-Bz), 5.25 (1H, m, H-16α), 7.3 (5H, bs, aromatic H); ^{13}C nmr see Table 1. Finally **19** was eluted: ir ν max cm^{-1} 3447, 1737, 1695, 1242; ^1H nmr (80 MHz, $CDCl_3$) δ 0.75 (3H, s, Me-18), 0.85 (3H, s, Me-19), 0.90 (3H, d, $J=6$ Hz, Me-21), 0.95 (3H, d, $J=6$ Hz, Me-27), 1.99 (3H, s, OAc), 2.06 (3H, s, OAc), 2.98 (1H, dd, $J=14$, 5 Hz, H-26ax), 3.37 (1H, m, H-3α), 3.75 (1H, d, $J=14$ Hz, H-26eq), 4.80 (1H, m, H-4α), 5.10 (2H, ABq, $J=23$, 13 Hz, H-Bz), 5.25 (1H, m, H-16α), 7.3 (5H, aromatic H); ^{13}C nmr see Table 1.

(22*S*,25*R*)-3β-ACETOXY-16β-ETHOXY-22,26-*N*-Cbz-EPIMINO-5α-CHOLESTAN-4-ONE [**20**].—To a cold solution of **14** (80 mg) in Me_2CO, Jones reagent was added drop by drop to slight excess. The reaction mixture was left at room temperature for 1 h. After addition of MeOH and H_2O, the mixture was extracted with $CHCl_3$. The organic phase was dried over anhydrous Na_2SO_4 and taken to dryness under vacuum. Purification by vacuum chromatography over Si gel yielded 52 mg of **20**: mp 110–112°; $[\alpha]^{25}D$ 0.6 ($c=0.017$, MeOH). Calcd for $C_{39}H_{57}NO_6$, C 73.66, H 9.04, N 2.20; found C 73.49, H 9.08, N 2.35. Ir ν max cm^{-1} 1749, 1733, 1696, 1236; ^1H nmr (80 MHz, $CDCl_3$) δ 0.72 (3H, s, Me-18), 0.78 (3H, s, Me-19), 0.88 (3H, d, $J=6$ Hz, Me-21), 1.01 (3H, d, $J=6$ Hz, Me-27), 2.05 (3H, s, OAc), 3.01 (1H, dd, $J=14$, 5 Hz, H-26ax), 3.75 (1H, d, $J=14$ Hz, H-26eq), 3.95 (1H, m, H-16α), 4.95 (1H, m, H-3α), 5.10 (2H, ABq, $J=23$, 13 Hz, H-Bz), 7.3 (5H, bs, aromatic H); ^{13}C nmr see Table 1.

(22*S*,25*R*)-4β-ACETOXY-16β-ETHOXY-22,26-*N*-Cbz-EPIMINO-5-CHOLESTAN-3-ONE [**24**].—Compound **15** (50 mg) was oxidized with Jones reagent in a similar manner to that described for **14** to yield 35 mg of **24**: ir ν max cm^{-1} 1749, 1733, 1696, 1238; ^1H nmr (80 MHz, $CDCl_3$) δ 0.72 (3H, s, Me-18), 0.76 (3H, s, Me-19), 0.90 (3H, d, $J=7$ Hz), 1.03 (3H, d, $J=7$ Hz), 2.09 (3H, s, OAc), 3.04 (1H, dd, $J=14$, 5 Hz, H-26ax), 3.76 (1H, d, $J=14$ Hz, H-26eq), 3.95 (1H, m, H-16α), 5.05 (1H, m, H-4α), 5.10 (2H, ABq, $J=23$, 13 Hz, H-Bz), 7.30 (5H, bs, aromatic H); ^{13}C nmr see Table 1.

(22*S*,25*R*)-3β,16β-DIACETOXY-22,26-*N*-Cbz-EPIMINO-5α-CHOLESTAN-4-ONE [**21**].—A cold Me_2CO solution of **18** (60 mg) was treated with Jones reagent, yielding, after vacuum chromatography, 47 mg of **21**: mp 72–75°, $[\alpha]^{25}D$ 1.5 ($c=0.0135$), MeOH); ir ν max cm^{-1} 1733, 1693, 1240; ^1H nmr (80 MHz, $CDCl_3$) δ 0.72 (3H, s, Me-18), 0.78 (3H, s, Me-19), 0.91 (3H, d, $J=7$ Hz, Me-21), 0.96

(3H, d, J = 7 Hz, Me-27), 1.96 (3H, s, OAc), 2.12 (3H, s, OAc), 2.99 (1H, dd, J = 14, 5 Hz, H-26ax), 3.75 (1H, d, J = 14 Hz, H-26eq), 5.10 (2H, ABq, J = 23, 13 Hz, H-Bz), 5.23 (1H, m, H-16α), 7.30 (5H, bs, aromatic H); ^{13}C nmr see Table 1.

(22*S*,25*R*)-3β-HYDROXY-16β-ETHOXY-(22,26)-*N*-Cbz-EPIMINO-5α-CHOLESTAN-4-ONE [**22**].—To a solution of 30 mg of **20** in MeOH, a few drops of 5% aqueous K_2CO_3 was added, and the mixture was left overnight at room temperature. Tlc [Si gel plate, C_6H_{14}-EtOAc (1:1)] showed that the 3β-*O*-acetate **20**, R_f 0.85, had disappeared and that a new spot with R_f 0.22 was present. The solution was made alkaline and extracted with $CHCl_3$. The organic layer was dried over anhydrous Na_2SO_4 and the solvent evaporated to dryness. The residue was crystallized from MeOH yielding 22 mg of **22**: mp 138–142°. Calcd for $C_{37}H_{55}NO_5$, C 74.83, H 9.34, N 2.36; found C 75.12, H 9.47, N 2.28. Ir ν max cm^{-1} 1710, 1694; ^{1}H nmr (80 MHz, $CDCl_3$) δ 0.73 (3H, s, Me-18), 0.70 (3H, s, Me-19), 0.87 (3H, d, J = 6 Hz, Me-21), 1.00 (3H, d, J = 6 Hz, Me-27), 3.01 (1H, dd, J = 14, 5 Hz, H-26ax), 3.75 (1H, d, J = 14 Hz, H-26eq), 3.95 (1H, m, H-16α), 4.10 (1H, t, J = 10 Hz, H-3α), 5.10 (2H, ABq, J = 22, 12 Hz, H-Bz), 7.3 (5H, bs, aromatic H); ^{13}C nmr see Table 1.

(22*S*,25*R*)-3β-HYDROXY-16β-ACETOXY-22,26-*N*-Cbz-5α-EPIMINO-CHOLESTAN-4-ONE [**23**].—In a similar manner, 30 mg of **21** was hydrolyzed to yield 23 mg of **23**: mp 151–155°, R_f 0.15 on a Si gel plate [solvent C_6H_{14}-EtOAc (1:1)]. Calcd for $C_{37}H_{53}NO_6$, C 73.11, H 8.79, N 2.30; found C 73.28, H 8.91, N 2.23. Ir ν max cm^{-1} 1735, 1710, 1695, 1245; ^{1}H nmr (80 MHz, $CDCl_3$) δ 0.72 (3H, s, Me-18), 0.69 (3H, s,m Me-19), 0.91 (3H, d, J = 6 Hz, Me-21), 0.97 (3H, d, J = 6 Hz, Me-27), 2.10 (3H, s OAc), 3.00 (1H, dd, J = 14, 5 Hz, H-26ax), 3.75 (1H, d, J = 14 Hz, H-26eq), 4.12 (1H, t, J = 10 Hz, H-3α), 5.10 (2H, ABq, J = 22, 12 Hz, H-Bz), 5.24 (1H, m, H-16α), 7.3 (5H, bs, aromatic H); ^{13}C nmr see Table 1.

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