mg, 50%): mp 252-253 °C; UV λ_{max} nm (log ϵ) (EtOH) 347 (4.31), 283 (4.21); (EtOH-$AlCl_3$) 370 (4.39), 295 (4.24); (EtOH-NaOAc) 366 (4.22), 324 (4.07), 277 (4.25). The mother liquor was separated by preparative HPLC: **3e** (40 mg, 29%); **2e** (9 mg, 6%); **3f** (6 mg, 4%). Tetraacetate: mp 250-251 °C (from $CHCl_3$-MeOH); ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 3 × OAc), 2.41 (s, OAc), 3.86 (s, OMe), 6.58 (s, C_3-H), 7.00 (d, $C_{5'}$-H, J = 9 Hz), 7.41 (s, C_8-H), 7.49 (d, $C_{2'}$-H, J = 2.5 Hz), 7.66 (dd, $C_{6'}$-H, J = 2.5, 9 Hz). The isolation of **3e** from *Arnica viscosa* has been reported by Wolf et al.,[12] but its physical properties have not been reported.

Identification of the Demethylated Product from 4c. Acetate **4c** (1 g) was dissolved in 30% w/v anhydrous aluminum chloride in acetonitrile (20 mL) and heated at 70 °C for 48 h. The mixture was treated with dilute hydrochloric acid, and the product obtained was recrystallized from methanol to give **3c**.[2] The mother liquor was separated by preparative HPLC, and the following three demethylation products were obtained: 3',4',5,5',6,7-hexahydroxyflavone (**3i**)[10] (15 mg), 3',4',5,6,7-pentahydroxy-5'-methoxyflavone (**3h**) (34 mg) [mp 234-235 °C (from aqueous methanol); UV λ_{max} nm (log ϵ) (EtOH) 360 (4.31), 282 (4.13); (EtOH-$AlCl_3$) 383 (4.40), 301 (4.12); (EtOH-NaOAc) 400 sh (4.18), 375 (4.22); ^{1}H NMR (DMSO-d_6) δ 3.90 (s, OMe), 6.58 (s, C_8-H), 6.77 (s, C_3-H), 7.16 (2 H, s, $C_{2',6'}$-H), 12.82 (s, C_5-OH). Pentaacetate of **3h**: mp 284-286 °C (from $CHCl_3$-MeOH); ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 4 × OAc), 2.41 (s, OAc), 6.55 (s, C_3-H), 7.24 (2 H, s, $C_{2',6'}$-H), 7.45 (s, C_8-H)], and 4',5,6,7-tetrahydroxy-3',5'-dimethoxyflavone (**3g**) (65 mg) [mp 290-292 °C (from aqueous methanol); UV λ_{max} nm (log ϵ) (EtOH) 360 (4.31), 284 (4.16); (EtOH-$AlCl_3$) 379 (4.45), 303 (4.15); (EtOH-NaOAc) 403 (4.22), 377 (4.23), 321 (4.06); ^{1}H NMR (DMSO-d_6) δ 3.90 (s, 2 × OMe), 6.66 (s, C_8-H), 6.85 (s, C_3-H), 7.27 (2 H, s, $C_{2',6'}$-H), 12.81 (s, C_5-OH)]. Tetraacetate of **3g**: mp 259-261 °C (from $CHCl_3$-MeOH); ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 3 × OAc), 2.42 (s, OAc), 3.87 (s, 2 × OMe), 6.55 (s, C_3-H), 7.02 (2 H, s, $C_{2',6'}$-H), 7.46 (s, C_8-H).

Supplementary Material Available: Table III with analytical data for the new demethylated products **3e**, **3g**, and **3h** and their acetates (1 page). Ordering information is given on any current masthead page.

(12) Wolf, S. J.; Denford, K. E. *Biochem. Syst. Ecol.* **1984**, *12*, 183-188.

Regioselective Synthesis of Δ^6-, Δ^7-, and Δ^8-14α-Cyanosterol Derivatives: Versatile Precursors to 14α-Demethylase Inhibitors

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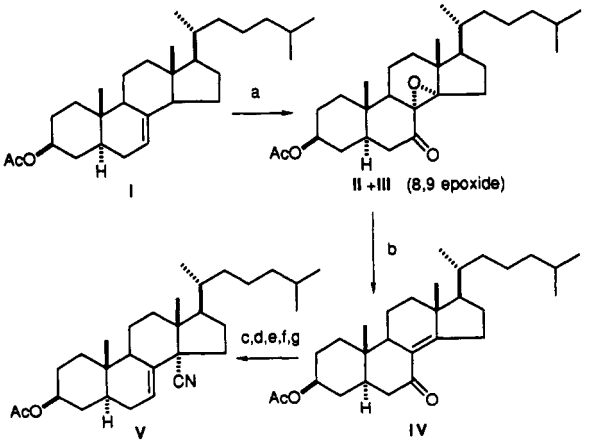
The efficient preparation of 3β-(benzoyloxy)-4,4-dimethyl-5α-cholest-8(14)-en-7-one (**4a**) and 3β-(benzyloxy)-5α-ergost-8(14)-en-7-one (**4b**) and their conversion to Δ^6-, Δ^7- or Δ^8-14α-functionalized sterols is reported. The alkylaluminum-mediated 1,4-addition of HCN (Nagata reaction) to enones **4a,b** is used to introduce the 14α substituent. Reduction of these conjugate addition products (**5a,b**) affords the 7α-hydroxysterols (**6a,b**). The dehydration of **6a** with Martin sulfurane reagent regioselectively produces the Δ^6-14α-cyanosterol **8**. Alternatively, mesylation of **6a** and elimination affords a mixture of Δ^7:Δ^6-sterols (3:1) from which the Δ^6-sterol is removed by selective ozonolytic degradation. The ozonolytic stability of the Δ^7-14α-cyanosterols is also exploited in the preparation of 14α-cyanosterols possessing modified side chains. Ozonolysis of 3β-(benzoyloxy)-5α-ergost-7,22-diene-14α-carbonitrile (**9b**) gave **18**, which is used to prepare compounds containing the "24 methenyl" (**21**) and "lanosterol" (**23**) side chains. The trapping of the intermediate aluminum enolate formed in the hydrocyanation of **4a** gives an 8β-bromosterol **13**. Dehydrobromination of **13** provides a novel regioselective synthesis of the difficult to prepare Δ^8-14α-functionalized sterol **14**.

Introduction

Lanosterol 14α-demethylase is the rate-limiting enzyme in the conversion of lanosterol to cholesterol in mammals and to ergosterol in fungi. Inhibitors of the fungal enzyme have proven utility in the treatment of both human and plant fungal disease.[1] Additionally, the inhibition of the mammalian enzyme has been suggested as a potential target for treatment of hypercholesterolemia.[2] As part of a program to prepare selective inhibitors of sterol 14α-demethylase, we required efficient and regiospecific syntheses of 14α-functionalized sterols which could serve as precursors to rationally designed substrate analogs. Because the side-chain structure and the position of nuclear unsaturation (Δ^7 and Δ^8 preferred) were known to be important variables for 14α-demethylase substrates,[3] we wanted a method which would accommodate the synthesis of Δ^6-, Δ^7-, and Δ^8-14α-functionalized sterols with various side chains. On the basis of the known biosynthetic pathways, the side chains which we considered of primary

Scheme I[a]



[a] (a) CrO_3; (b) chromatography, then treatment of **II** with Zn, HOAc; (c) Et_2AlCN; (d) $NaBH_4$; (e) MsCl, pyridine; (f) 2,4,6-collidine, Δ; (g) chromatography, $AgNO_3$ on silica.

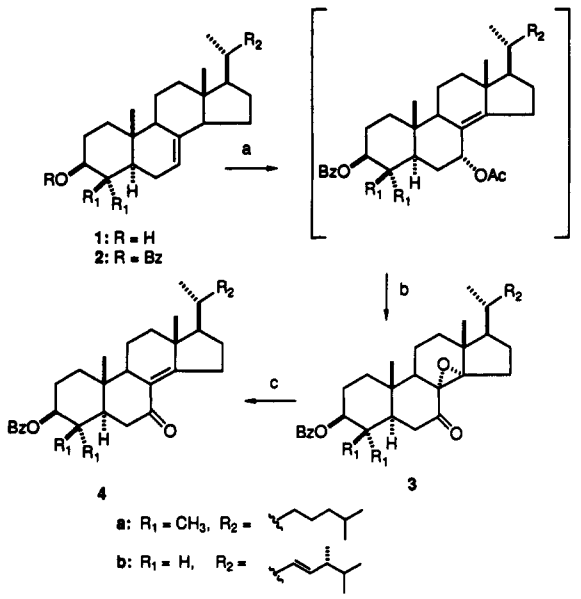
(1) Gravestock, M. B.; Ryley, J. F. *Ann. Rep. Med. Chem.* **1984**, *19*, 127.

(2) Miettinen, T. A. *J. Lipid Res.* **1988**, *29*, 43.

(3) (a) Aoyama, Y.; Yoshida, Y. *Biochem. Biophys. Res. Commun.* **1978**, *85*, 28. (b) Trzaskos, J. M.; Fischer, R. T.; Favata, M. F. *J. Biol. Chem.* **1986**, *261*, 16937. (c) Aoyama, Y.; Yoshida, Y.; Sonada, Y.; Sato, Y. *J. Biol. Chem.* **1987**, *262*, 1239. (d) Akhtar, M.; Alexander, K; Boar, R. B.; McGhie, J. F.; Barton, D. H. R. *Biochem. J.* **1978**, *169*, 449. (e) Aoyama, Y.; Yoshida, Y.; Sonada, Y.; Sato, Y. *Biochem. Biophys. Acta* **1991**, *1081*, 262.

0022-3263/92/1957-3347$03.00/0

Scheme II[a]

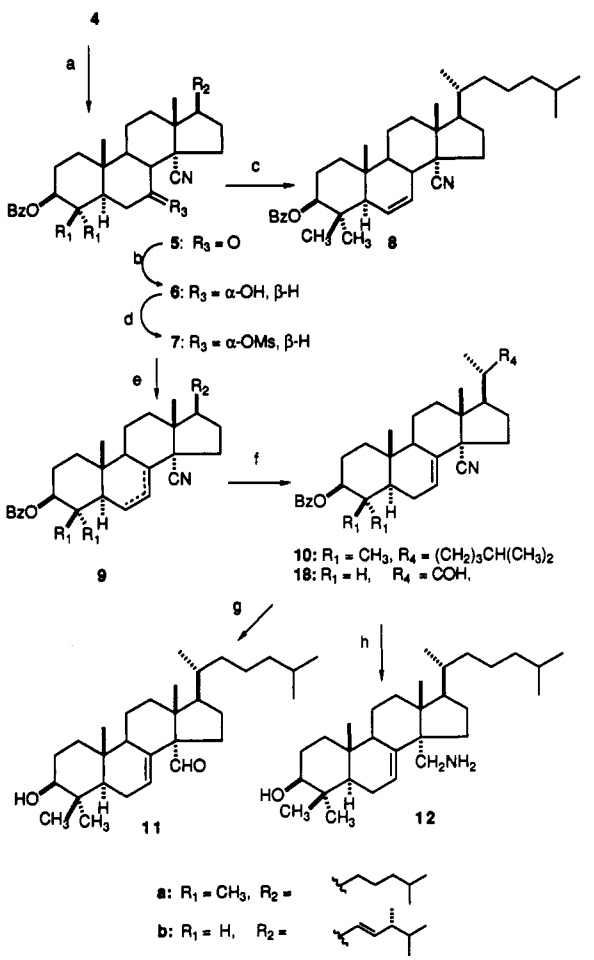


[a] (a) SeO_2, HOAc; (b) CrO_3; (c) Zn, HOAc.

interest were those present in lanosterol and dihydrolanosterol (substrate for both mammalian and fungal enzymes) and 24-methylenelanosterol (substrate for fungal enzyme).

After reviewing the literature,[4] we focused our attention on the work of Anastasia et al.[4a] (Scheme I), which describes the hydrocyanation, reduction, mesylation, and elimination of 3β-acetoxy-5α-cholest-8(14)-en-7-one (**IV**) to give 3β-acetoxy-5α-cholest-7-ene-14α-carbonitrile (**V**).[5] In addition to the versatility afforded by the nitrile functionality,[6] we felt that this approach would be particularly appealing if the corresponding Δ^7-14α-nitrile of ergosterol underwent selective ozonolysis at the Δ^{22} olefin, as this would allow for introduction of modified side chains. The limitations of the Anastasia procedure were (1) the need to separate 3β-acetoxy-8α,14α-epoxy-5α-cholest-7-one (**II**) from its 8,9 isomer (**III**) en route to enone **IV**, (2) the use of argentation chromatography to separate 3β-acetoxy-5α-cholest-7-ene (**V**) from its Δ^6 isomer, and (3) the inaccessibility of the Δ^8 isomer. Our efforts towards addressing these limitations and the application of this chemistry to the 4,4-dimethylcholesterol and ergosterol series is the subject of this report.

Scheme III[a]



[a] (a) Et_2AlCN; (b) $NaBH_4$; (c) $[C_6H_5C(CF_3)_2O]_2S(C_6H_5)_2$; (d) MsCl, pyridine; (e) 2,4,6-collidine, Δ; (f) O_3; (g) DIBAL-H, then H^+; (h) DIBAL-H, then $NaBH_4$.

Results and Discussion

The mixture of epoxy ketones **II** and **III** obtained by Anastasia results from the nonspecific oxidation of **I** by CrO_3. This problem was circumvented by applying the findings of Fieser and Ourisson, who showed that SeO_2 regiospecifically oxidizes Δ^7-sterols to $\Delta^{8(14)}$-7α-allylic acetates which, in turn, can be oxidized to 8α,14α-epoxy 7-ketones with CrO_3.[7] Accordingly, treatment of **2a** with SeO_2 in HOAc/toluene followed by addition of CrO_3 directly to the reaction mixture led to epoxy ketone **3a** (Scheme II). After partial purification, **3a** was reduced with zinc in HOAc to give pure enone **4a** in 38% overall yield from **2a** without recourse to chromatography. Treatment of the Δ^7 olefin derived from ergosterol (**2b**) under the same reaction conditions afforded **4b** in 43% overall yield.

Reaction of **4a** with Et_2AlCN followed by immediate reduction of the resulting product [cyano ketone **5a**] with $NaBH_4$ gave the 14α-cyano 7α-alcohol **6a** in good yield (Scheme III). The assignment of the configuration at C-7 in **6a** was based upon analysis of the ^1H NMR spectrum and upon analogy with similar results obtained in the cholesterol series.[4a] The proton at C-7 appeared as a tightly coupled multiplet (or broad singlet). Such a pattern is consistent only with a 7β-proton since a 7α-proton should appear as a broad multiplet resulting from the trans-diaxial

(4) (a) Anastasia, M.; Fiecchi, A.; Cighetti, G.; Galli, G. *J. Chem. Soc., Perkin Trans. 1* **1977**, 700. (b) Parish, E. J.; Schroepfer, G. J. Jr. *J. Lipid Res.* **1981**, *22*, 859. (c) Batten, P. L.; Bentley, T. J.; Boar, R. P.; Draper, R. W.; McGhie, J. F.; Barton, D. H. R. *J. Chem. Soc., Perkin Trans. 1* **1972**, 739. (d) Fried, J.; Brown, J. W.; Borkenhagen, L. *Ibid.* **1972**, 2499.

(5) (a) We also simultaneously investigated the alkylation of 3β-(benzyloxy)-4,4-dimethyl-5α-cholest-8(14)-en-15-one (Bossard, M. J.; Tomaszek, T. A.; Gallagher, T. F.; Metcalf, B. W.; Adams, J. L. *Biorg. Chem.* **1991**, *19*, 418). (b) Additional but unsuccessful approaches include: (1) the conjugate addition of organocuprates to IV (no reaction) and (2) the Ireland silylketene acetal Claisen rearrangement of the Δ8(14)-7α-allylic acetate **3b** (elimination to the diene was the only product observed). (c) Subsequent to the onset of our investigations a successful 2,3 Wittig rearrangement of the (trialkylstannyl)methyl ether of a $\Delta^{8(14)}$-7α-hydroxy sterol was reported (Eguchi, S.; Ebihara, K.; Morisake, M. *Chem. Pharm. Bull.* **1988**, *36*, 4638). (d) Recently a modification of the procedure of Fried et al.[4d] has been reported to afford a regiospecific route to lanost-7-ene-3β,32-diol (Frye, L. L.; Robinson, C. H. *J. Org. Chem.* **1990**, *55*, 1579).

(6) The nitrile moiety was considered to be an excellent synthon for the aminomethyl functionality and derivatives thereof, as well as a precursor to the corresponding aldehyde which, in turn, could be readily converted to a variety of potential 14α-demethylase inhibitors. For examples see: ref. 5d.

(7) Fieser, L. F.; Ourisson, G. *J. Am. Chem. Soc.* **1953**, *75*, 4404.

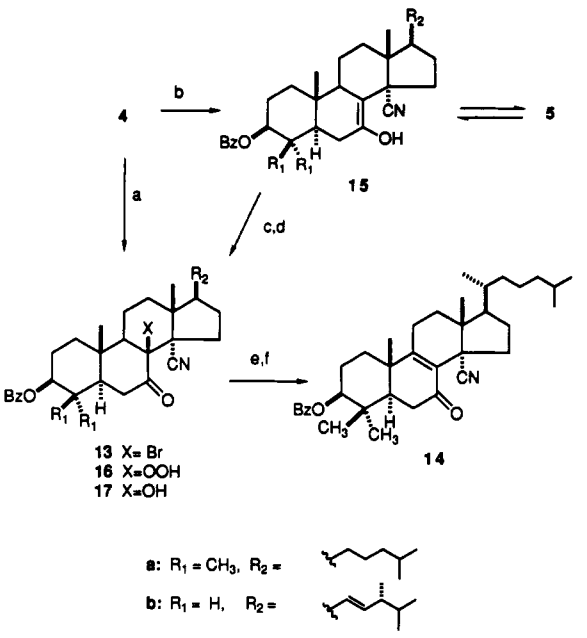
couplings with the β-protons at C-6 and C-8. Furthermore, in the cholesterol series, Anastasia found that treatment of the analogous 14α-cyano-7-keto derivative with $NaBH_4$ gave a 90% yield of the corresponding 7α-alcohol.[8]

Dehydration of **6a** with the Martin sulfurane reagent[9] led exclusively to the Δ^6 isomer **8**. Alternatively, elimination of the mesylate **7a** gave approximately a 2/1 mixture of the Δ^7 (**10**) and Δ^6 (**8**) isomers as estimated by high-field proton NMR. Elimination of mesylate **7b**, which was prepared using the same reaction conditions employed with **7a**, afforded approximately a 3/1 mixture of the Δ^7 and Δ^6 isomers **9b**, respectively, in 65% overall yield from **4b**. The exclusive formation of the Δ^6 isomer using Martin sulfurane reagent can be explained on the basis of the reported preference of this reagent to effect eliminations via an E2 mechanism. Since E2 eliminations in six-membered rings generally proceed through a trans-diaxial arrangement of the departing groups, dehydration of **6a** with Martin sulfurane reagent could only lead to loss of the 6β- or 8β-protons. Loss of the 6β-proton, however, is more favorable due to the less crowded environment around this proton. The 6β-proton is 1,3 diaxially disposed to a single methyl group compared to two such interactions for the 8β-proton. In contrast, the elimination of mesylates **7a** and **7b** in refluxing collidine most likely proceeds through a highly E1-like transition state with product distribution following Zaitsev's rule to give a preponderance of the more highly substituted olefins.

Rather than attempting to separate the isomers by argentation chromatography, as reported by Anastasia in the cholesterol series, we took advantage of the differences in the rate of reaction of the Δ^6 and Δ^7 double bonds with ozone. In the 4,4-dimethylcholesterol series, careful ozonolysis of **9a** led to selective destruction of the Δ^6 double bond, enabling facile isolation of the pure Δ^7-sterol **10** following flash chromatography in all overall yield of 48% from **6a**. In the ergosterol series, ozonolysis of **9b** led to selective cleavage of the side-chain olefin in only the Δ^7 isomer. As a result, isomerically pure **18** was readily isolated from the reaction mixture after flash chromatography in 62% yield. DIBAL-H reduction of **10** followed by an acidic workup led to the known 14α-formyl derivative **11**. Alternatively, $NaBH_4$ reduction of the intermediate imine gave the aminomethyl compound **12** in high yield. This two-step procedure was necessitated by the failure of either DIBAL-H or $LiAlH_4$ to effect the reduction of the nitrile directly to the amine.[10]

At the time we began this work there were no regioselective syntheses of Δ^8-14α-alkylsterols.[11] We felt that trapping of the enolate formed in the conjugate addition of diethylaluminum cyanide to enone **4a** with an appropriate electrophile[12] might offer an expeditious synthesis

Scheme IV[a]



[a] (a) Et_2AlCN, then Br_2; (b) Et_2AlCN; (c) O_2; (d) Zn, HOAc; (e) pyridine, Δ; (f) $SOCl_2$, pyridine.

of such sterols. All attempts to trap the enolate as a silyl enol ether or an enol acetate were unsuccessful, not reproducible, or proceeded in poor yield. However, the addition of bromine[13] to the hydrocyanation reaction mixture led directly to the 8β-bromo-14α-cyano-7-keto **13**, which upon heating in pyridine gave enone **14** in 30% yield from **4a** (Scheme IV).[14]

We have also serendipitously discovered an alternative method for the preparation of **14**. The key observation was made while investigating the lack of reproducibility of the hydrocyanation reaction. If the product of the hydrocyanation of **4b** was not either reduced immediately or rigorously excluded from oxygen, the major product (40%) obtained was the 8β-hydroperoxide **16b** (Scheme IV). Under similar conditions, hydrocyanation of **6a** gave **16a** but in much lower yield (10%). Because the autoxidations of ketones are known to proceed via the enol of the ketone, we suspected that the enols of **4a,b** which are the initial products of the hydrocyanation reaction might be undergoing an unusually slow tautomerization to the keto form. Support for this proposal was obtained from the analysis of the ^{13}C NMR spectra of the initial hydrocyanation products. If taken within 0.5 h of workup, the ^{13}C NMR spectrum ($CDCl_3$) of the crude product from the treatment of **4b** with Et_2AlCN showed approximately a 70:30 mixture of enol to ketone. Within the same time frame, the product resulting from the hydrocyanation of **4a** consisted of approximately a 40:60 mixture of enol to ketone.[15] Assuming that the enols react with molecular oxygen at similar rates, the higher yield of **16b** vs **16a** can be attributed to a difference in the rates of enol–keto

(8) Anastasia's assignment of the 7α-hydroxyl configuration was based upon similar analysis of the ^1H NMR spectrum, along with comparison of the ^1H NMR spectrum with that of 3β-acetoxy-7α-hydroxy-14α-methyl-5α-cholestane and the relative difficulty of acetylation.[4a]

(9) Arhart, R. J.; Martin, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 5003.

(10) Resistance of a related 14α-cyano sterol to direct reduction with aluminum hydrides has been recently noted (Cooper, A. B.; Wright, J. J.; Ganguly, A. K.; Desai, J.; Loebenberg, D.; Parmegiani, R.; Feingold, D. S.; Sud, I. J. *J. Chem. Soc., Chem. Commun.* **1989**, 898).

(11) In addition to our efforts,[5a] another regiospecific alkylation of 3β-(benzyloxy)-4,4-dimethyl-5α-cholest-8(14)-en-15-one has been reported (Magolda, R. L.; Chen, H.; Favata, Fisher, I. T.; M. F.; Gaylor, J. L.; Johnson, P. R.; Ko, S. S.; Shapiro, E.; Stam, S. H.; Traskos, J. M. *Abstracts of Papers*, 186th National Meeting of the American Chemical Society, New Orleans, LA, Fall 1987; American Chemical Society: Washington, DC, 1987; ORGN 186).

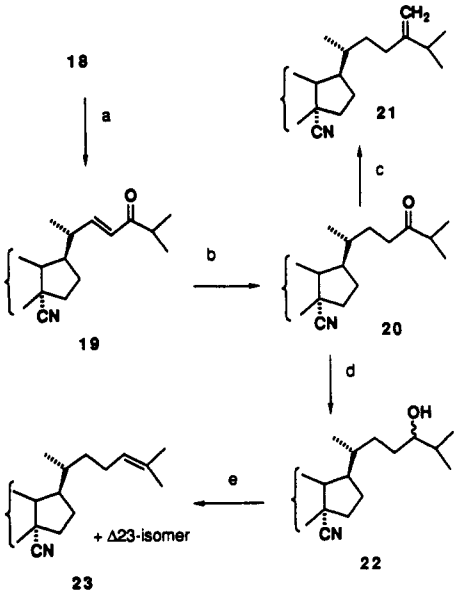
(12) (a) Tsuda, T.; Satomi, H.; Hayashi, T.; Saegusa, T. *J. Org. Chem.* **1987**, *52*, 439. (b) Utimoto, K.; Obayashi, M.; Shishiyama, Y; Inoue, M.; Nozaki, H. *Tetrahedron Lett.* **1980**, 3389. (c) Blanco, L.; Amice, P.; Conia, J. M. *Synthesis* **1976**, 194.

(13) Stotter, P. L.; Hill, K. A.; *J. Org. Chem.* **1973**, *38*, 2576.

(14) The dithioacetal of **14** could be prepared (BF_3-OEt_2, ethanedithiol, 24 h at rt); however, Raney nickel reduction led to a complex mixture. Due to the success of an alternative route to Δ^8-sterols,[5a] we did not pursue alternative deoxygenation procedures.

(15) Resonances appearing at δ 104 (C8) and δ 147 (C7), which were not present in the parent ketones, demonstrated the existence of the enol forms. Ratios were estimated on the basis of the relative heights of C-3 resonances [**5a** (81)/**15a** (82) and **5b** (73)/**15b** (74)] for enol and keto forms. The predominance of one form over the other was also qualitatively reinforced by the relative intensities of other assignable resonances.

Scheme V[a]



[a] (a) $LiCH_2C(O)CH(CH_3)_2$, then H^+; (b) H_2, Pd/C; (c) $LiCH_2Si(CH_3)_3$; (d) $NaBH_4$; (e) $[C_6H_5C(CF_3)_2O]_2S(C_6H_5)_2$.

tautomerization. Treatment of **16a** with zinc/HOAc gave the corresponding hydroxyl derivative **17a**. The downfield shift of approximately 0.2 ppm of the C-18 and C-19 proton resonances of **17a** is consistent with the expected β configuration at C-8.[16] Treatment of **17a** with $SOCl_2$/pyridine led to the same enone (**14**) which was obtained upon elimination of bromide **13**.

Our side-chain elaboration strategy was to prepare a single intermediate from which we could synthesize 14α-substituted sterol derivatives possessing either the "24-methenyl" or "lanosterol" side chains.[17] Ketone **20** was considered to be an appropriate intermediate since conversion of other 24-keto sterols to their corresponding 24-methenyl and $\Delta^{24(25)}$ derivatives had been reported.[18] Our only reservation about this approach was the inefficiency of existing procedures to effect the latter process. For example, in the lanosterol series, Sato and Sonoda[18b] treated the alcohol resulting from the $NaBH_4$ reduction of the 24-keto compound with $POCl_3$. They obtained a 3/1 mixture of the desired Δ^{24} and the 24-chloro derivatives, respectively. Purification of these compounds required reduction of the chloride with $LiAlH_4$ to give the corresponding methylene derivative which was then separated from the desired compound by argentation chromatography.

Our initial attempts to prepare **20** involved a benzoic acid catalyzed Wittig reaction of **18** with (isobutyrylmethylene)triphenylphosphorane.[18a] Although the reaction could be forced to completion after 18 h in refluxing toluene, analysis of the product (^1H NMR) revealed that epimerization at C-20 had occurred. In contrast, condensation of **18** with the lithium enolate of 3-methyl butanone[19] and the subsequent dehydration of the intermediate aldol gave enone **19** in 84% yield without any apparent epimerization (Scheme V). Hydrogenation of **19** in the presence of Pd/C afforded a nearly quantitative yield of epimerically pure ketone **20**. Conversion of **20** to the corresponding 24-methenyl derivative **21** was effected most efficiently (69%) using the Peterson olefination reaction.[20] Several attempts[21] were made to convert **20** regiospecifically to the trisubstituted olefin **23**. Our most successful result was obtained by reducing **20** with $NaBH_4$ to give the corresponding epimeric alcohols[22] (**22**) which upon treatment with Martin sulfurane reagent led in high yield to a 7/1 (GC) mixture of **23** and its Δ^{23} isomer, respectively.

In summary, we have presented methodology to regioselectively prepare 3β-(benzoyloxy)-4,4-dimethyl-5α-cholest-6-ene-14α-carbonitrile (**8**) and 3β-(benzoyloxy)-4,4-dimethyl-5α-cholest-7-ene-14α-carbonitrile (**10**) from a common intermediate, namely, 3β-(benzoyloxy)-7α-hydroxy-4,4-dimethyl-5α-cholestane-14α-carbonitrile (**6a**). The versatility of these compounds as precursors to 14α-demethylase inhibitors was demonstrated by the conversion of **10** to its corresponding 14α-formyl (**11**) and 14α-aminomethyl (**12**) derivatives. Adaptation of the methodology to the ergosterol series afforded access to 14α-cyano derivatives possessing the side chains found in lanosterol (**23**) and 24-methylenelanosterol (**21**). Noteworthy synthetic methodology developed and novel transformations observed include (1) the use of a one-pot sequential SeO_2/CrO_3 oxidation of olefins **2a** and **2b** to regiospecifically prepare epoxy ketones **3a** and **3b**, respectively, (2) regioselective dehydration of alcohol **6a** with Martin sulfurane reagent to afford only the 6-ene (**8**), (3) efficient preparation of side-chain precursor **18** and purification of **10** (from **8**) by utilizing the selective ozonolysis of Δ^6 and Δ^{22} olefins over Δ^7 double bonds in 14α-cyanosterols, (4) the use of a one-pot sequential DIBAL-H/$NaBH_4$ reduction of **10** to afford isomerically pure aminomethyl derivative **12**, (5) treatment of the aluminum enolate of **15a** with bromine to afford bromide **13** followed by dehydrohalogenation to afford the Δ^8-14α-cyanosterol **14**, and (6) observation of metastable enols **15a** and **15b** and isolation of the subsequent autoxidation products (hydroperoxides **16a** and **16b**, respectively). We have recently reported[5a] preparation and characterization of (3β,32*R*,*S*)-32-ethynyllanost-7-ene-3,32-diol from **11** as a mechanism-based inhibitor of 14α-demethylase, along with an alternative approach to Δ^8-14α-substituted sterol derivatives. Conversion of nitriles **10**, **21**, and **23** to a variety of 14α-demethylase inhibitors will be detailed in future publications.

Experimental Section

Melting points are uncorrected. IR spectra were recorded using KBr pellets. ^1H NMR spectra were recorded at 90, 250, 270, or 360 MHz. ^{13}C NMR spectra were recorded at 62.5 MHz. Unless otherwise noted, the NMR solvent was $CDCl_3$. Mass spectra were determined using the chemical ionization technique with methane as the carrier gas unless otherwise noted. THF was dried by distillation from either $LiAlH_4$ or sodium and benzophenone.

(16) Bhacca, N. S.; Williams, D. H.; *Applications of NMR Spectroscopy in Organic Chemistry*; Holden-Day: San Francisco, 1964; pp 13–40.

(17) Dolle et al. have recently reported their efforts to address the regiospecific preparation of similar Δ^{24} olefins (Dolle, R. E.; Schmidt, S. J.; Erhard, K. F.; Kruse, L. I. *J. Am. Chem. Soc.* **1989**, *111*, 278).

(18) (a) Sucrow, W.; Littmann, W.; Raduchel, B. *Chem. Ber.* **1977**, *110*, 1523. (b) Sato, Y.; Sonoda, Y. *Chem. Pharm. Bull.* **1981**, *29*, 2604.

(19) A similar aldol approach has been reported utilizing 3-methyl-3-(tetrahydropyranyloxy)but-2-one to prepare 24,25-dihydroxyprovitamin D_3 (Eyley, S. C.; Williams, D. H. *J. Chem. Soc. Perkin Trans. 1* **1976**, 727.)

(20) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780.

(21) Our first approach involved the palladium-catalyzed reduction of the thermodynamic enol triflate of **20**. While the reduction proceeded efficiently, regiospecific preparation of the thermodynamic enol triflate proved problematic. The method of Krafft and Holton (Krafft, M. R.; Holten, R. A. *Tetrahedron Lett.* **1983**, *24*, 1345) was not successful and treatment of **20** with Tf_2O and 2,6-di-*tert*-butyl-4-methylpyridine gave an inseparable mixture (~60/40) of Δ^{24} and Δ^{23} (*E* and *Z*) enol triflates, as evidenced by the Δ^{23} olefinic resonances at δ 5.28 (t) and 5.38 (dd) in the ^1H NMR spectrum.

(22) Treatment of **22** with $POCl_3$ in pyridine using the conditions of Sato and Sonoda[18b] gave approximately a 2/1 mixture of **23** and presumably the 24-chloro derivative (multiplet at δ 4.33 in the ^1H NMR) along with traces of the Δ^{23} isomer(s) (multiplet at δ 5.35).

Aldrich "gold label" toluene and CH_2Cl_2 were used if it was necessary for these solvents to be dry. $MgSO_4$ was used to dry organic solutions after aqueous workups. When air- or moisture-sensitive reagents were used, reactions were run under argon. Chromatography refers to purification by flash chromatography on E. Merck silica gel 60 (230–400 mesh). Capillary GC analyses were run on a Perkin-Elmer 8320 instrument using a Chrompack sil 5 CB column.

3β-(Benzoyloxy)-4,4-dimethyl-5α-cholest-7-ene (2a). Benzoyl chloride (167 mL, 200 g, 1.4 mol) was added dropwise to a solution of 4,4-dimethyl-5α-cholest-7-en-3β-ol[23] (**1a**) (150 g, 0.36 mol) in pyridine (3.3 L) at 0 °C. After being stirred at rt for 18h, the reaction mixture was poured into water, and the resulting precipitate was collected and washed successively with water, 1:1 MeOH/water, and cold MeOH. After drying in vacuo at 40 °C, **2a** was obtained as a white solid; yield 175 g (93%). An analytical sample was obtained by recrystallization from CH_2Cl_2/MeOH: mp 160–161 °C; ^1H NMR δ 0.53 (s, 3 H, 18-H), 0.85 (d, 3 H, 26- or 27-H, J = 1.2 Hz), 0.88 (d, 3 H, 26- or 27-H, J = 1.2 Hz), 0.92 (d, 3 H, 21-H, J = 6.2 Hz), 0.93 (s, 3 H), 0.95 (s, 3 H), 1.13 (s, 3 H), 4.78 (dd, 1 H, 3-H, $J_{2\beta,3}$ = 13 Hz, $J_{2\alpha,3}$ = 5 Hz), 4.70 (m, 1 H, H-7), 7.46 (t, 2 H, 3′- and 5′-H, J = 8.4 Hz), 7.74 (t, 1 H, 4′-H, J = 7.7 Hz), 8.05 (d, 2 H, 2′- and 6′-H, J = 7.0 Hz); IR 2950, 1715 cm^{-1}; MS, m/z (relative intensity) 519 (M^+ + H, 16), 518 (21), 517 (25), 503 (8), 397 (100). Anal. Calcd for $C_{36}H_{54}O_2 \cdot {}^1/_4H_2O$: C, 82.62; H, 10.50. Found: C, 82.52, H; 10.68.

3β-(Benzoyloxy)-4,4-dimethyl-8α,14α-epoxy-5α-cholestan-7-one (3a). SeO_2 (22 g, 0.20 mol) in 250 mL of water and 2 L of HOAc was added dropwise to a solution of **2a** (100 g, 0.19 mol) in toluene (2.7 L) and HOAc (2 L). The reaction mixture was stirred for 18 h at rt and was accompanied by a precipitation of red selenium. CrO_3 (60 g, 0.11 mol) dissolved in water (50 mL) was added dropwise. After being stirred for 3 h, the dark brown reaction mixture was filtered through a pad of silica gel. The filtrate was poured into water and extracted with ether. The layers were separated and the organic phase was concentrated. The dark-green residue was filtered through another pad of silica, eluting with CH_2Cl_2 to give a yellow filtrate. The solvent was evaporated and the residue triturated with methanol to give **3a** (60 g) as a faint yellow solid. Analytically pure material could be obtained by recrystallization from CH_2Cl_2/MeOH: mp 214–216 °C; ^1H NMR δ 0.85 (d, 3 H, 26- or 27-H, J = 0.8 Hz), 0.88 (d, 3 H, 26- or 27-H, J = 0.8 Hz), 0.91 (d, 3 H, 21-H, J = 6.2 Hz), 0.94 (s, 3 H, 18-H), 0.99 (s, 3 H, 19-H), 1.12 (s, 3 H, 4-CH_3), 1.22 (s, 3 H, 4′-CH_3), 4.82 (dd, 1 H, 3-H, $J_{2\beta,3}$ = 16 Hz, $J_{2\alpha,3}$ = 4 Hz), 7.45 (t, 2 H, 3′- and 5′-H, J = 6.9 Hz), 7.58 (t, 1 H, 4′-H, J = 7.5 Hz) 8.05 (d, 2 H, 2′- and 6′-H, J = 6.9 Hz); IR 2950, 1705 cm^{-1}; MS, m/z (relative intensity) 549 (M^+ + H, 75), 548 (12), 547 (27), 531 (66), 427 (100), 409 (75). Anal. Calcd for $C_{36}H_{52}O_4$: C, 78.79; H, 9.55. Found: C, 78.52; H, 9.68.

3β-(Benzoyloxy)-8α,14α-epoxy-5α-ergostan-7-one (3b) was prepared in a similar manner from 3β-(benzoyloxy)-5α-ergost-7-ene:[24] mp 149–151 °C; ^1H NMR δ 0.82 (d, 3 H, 26- or 27-H, J = 4.9 Hz), 0.84 (d, 3 H, 26- or 27-H, J = 4.9 Hz), 0.92 (d, 3 H, 21- or 28-H, J = 6.4 Hz), 0.97 (s, 3 H, 18-H), 1.03 (d, 3 H, 21- or 28-H, J = 6.4 Hz), 1.17 (s, 3 H, 19-H), 4.97 (m, 1 H, 3-H), 5.22 (m, 2 H, 22- and 23-H), 7.44 (t, 2 H, 3′- and 5′-H, J = 7.4 Hz), 7.56 (t, 1 H, 4′-H, J = 8.8 Hz), 8.02 (d, 2 H, 2′- and 6′-H, J = 8.3 Hz); IR 2950, 1710 cm^{-1}; MS, m/z (relative intensity) 533 (M^+ + H, 93), 531 (24), 517 (23), 515 (40), 411 (100), 393 (40), 389 (37), 339 (13), 287 (69). Anal. Calcd for $C_{35}H_{48}O_4$: C, 78.90; H, 9.08. Found: C, 78.49; H, 9.12.

3β-(Benzoyloxy)-4,4-dimethyl-5α-cholest-8(14)-en-7-one (4a). A mixture of **3a** (60 g, 0.11 mol), HOAc (1 L), and zinc dust (60 g, 0.92 mol) was heated at reflux for 3 h. The hot solution was filtered and concentrated to approximately 150 mL. After cooling to rt, chromatographically pure (5:1 hexane/EtOAc) **4a** crystallized from the HOAc solution. The white crystals were collected by filtration, washed with cold MeOH, and dried in vacuo; yield 40 g (38% from **2a**). A sample was recrystallized from CH_2Cl_2/MeOH for analytical purposes: mp 189–190 °C; ^1H NMR δ 0.85 (s, 3 H, 18-H), 0.86–0.93 (12 H), 0.95 (d, 3 H, 21-H, J = 6.5 Hz), 1.18 (s, 3 H), 4.81 (dd, 1 H, 3-H, $J_{2\beta,3}$ = 17 Hz, $J_{2\alpha,3}$ = 4 Hz), 7.45 (t, 2 H, 3′- and 5′-H, J = 6.4 Hz), 7.58 (t, 1 H, 4′-H, J = 7.7 Hz), 8.05 (d, 2 H, 2′- and 6′-H, J = 7.0 Hz); IR 2960, 1710, 1680, 1610 cm^{-1}; MS, m/z (relative intensity) 533 (M^+ + H, 49), 532 (8.4), 531 (13), 517 (6.3), 419 (9.5), 411 (100). Anal. Calcd for $C_{36}H_{52}O_3$: C, 81.15; H, 9.84. Found: C, 81.47; H, 9.78.

3β-(Benzoyloxy)-5α-ergost-8(14)-en-7-one (4b) was prepared in a similar manner from **3b**: yield (43% from **1b**); mp 156–157 °C; ^1H NMR δ 0.82 (d, 3 H, 26- or 27-H, J = 4.7 Hz), 0.85 (d, 3 H, 26- or 27-H, J = 4.7 Hz), 0.89 (s, 3 H, 18-H), 0.92 (d, 3 H, 21- or 28-H, J = 5.6 Hz), 0.93 (s, 3 H, 19-H), 1.06 (d, 3 H, 21- or 28-H, J = 6.6 Hz) 3.08 (m, 1 H), 4.99 (m, 1 H, 3-H), 5.23 (m, 2 H, 22- and 23-H), 7.43 (t, 2 H, 3′- and 5′-H, J = 7.0 Hz), 7.55 (t, 1 H, 4′-H, J = 7.5 Hz), 8.03 (d, 2 H, 2′- and 6′-H, J = 8.5 Hz); MS, m/z (relative intensity) 517 (M^+ + H, 63), 516 (27), 515 (21), 501 (9.3), 395 (100), 391 (33), 271 (50); IR 2970, 1720, 1675, 1595 cm^{-1}. Anal. Calcd for $C_{35}H_{48}O_3$: C, 81.35; H, 9.36. Found: C, 81.27; H, 9.34.

3β-(Benzoyloxy)-4,4-dimethyl-7-oxo-5α-cholestane-14α-carbonitrile (5a). A pure sample of **5a** could be obtained if instead of reducing the crude Et_2AlCN addition product (see the following experimental for **6a**) immediately with $NaBH_4$, it was first chromatographed (eluting successively with 3:1 and 5:1 CH_2Cl_2/hexanes followed by pure CH_2Cl_2) and then recrystallized from CH_2Cl_2/MeOH: mp >300 °C; ^1H NMR δ 0.79 (s, 3 H, 18-H), 0.85 (d, 3 H, 26- or 27-H, J = 1.4 Hz), 0.88 (d, 3 H, 26- or 27-H, J = 1.4 Hz), 0.92 (d, 3 H, 21-H, J = 6.5 Hz) 0.93 (s, 3 H), 1.08 (s, 3 H), 1.18 (s, 3 H), 4.73 (dd, 1 H, 3-H, $J_{2\beta,3}$ = 12 Hz, $J_{2\alpha,3}$ = 5 Hz), 7.44 (t, 2 H, 3′- and 5′-H, J = 7.0 Hz), 7.57 (t, 1 H, 4′-H, J = 7.7 Hz), 8.02 (d, 2 H, 2′- and 6′-H, J = 8.3 Hz); ^{13}C NMR δ 81 (3-C), 123 (quaternary phenyl), 128 (methine phenyl), 129 (methine phenyl), 131 (*C*N), 166 (O*C*OBz), 208 (7-C); IR 2950, 2220, 1705 cm^{-1}; MS, m/z (relative intensity) 560 (M^+ + H, 75), 544 (8.0), 533 (9.3), 438 (100), 419 (23), 411 (6.0). Anal. Calcd for $C_{37}H_{53}NO \cdot {}^1/_8H_2O$: C, 79.06; H, 9.55; N, 2.49. Found: C, 78.93; H, 9.60; N, 2.56.

3β-(Benzoyloxy)-7α-hydroxy-4,4-dimethyl-5α-cholestane-14α-carbonitrile (6a). Et_2AlCN (1.4 M in toluene, 12.4 mL, 17 mmol) was added to a solution of **4a** (5.0 g, 9.4 mmol) in toluene (75 mL) at 0 °C under Ar. After being stirred for 0.5 h at 0 °C, the reaction mixture was poured into 1 N NaOH and extracted with CH_2Cl_2. The layers were separated and the organic phase was washed with water and brine and dried. An equal volume of MeOH was added followed by $NaBH_4$ (0.75 g, 20 mmol). After being stirred for 0.5 h, the reaction mixture was poured into brine, the layers were separated, and the organic phase was dried. Concentration of the filtrate gave **6a** (4.5 g, 85%). An analytical sample of **6a** was obtained by recrystallization from CH_2Cl_2/MeOH: mp 270–271 °C; ^1H NMR δ 0.80 (s, 3 H, 18-H), 0.85 (d, 3 H, 26- or 27-H, J = 1.3 Hz), 0.88 (d, 3 H, 26- or 27-H, J = 1.3 Hz), 0.92 (d, 3 H, 21-H, J = 6.0 Hz), 0.94 (s, 3 h), 0.97 (s, 3 h), 1.03 (s, 3 h), 4.07 (M, 1 h, 7-H), 4.69 (dd, 1 H, 3-H, $J_{2\beta,3}$ = 16 Hz, $J_{2\alpha,3}$ = 5 Hz), 7.43 (t, 2 H, 3′- and 5′-H, J = 7.9 Hz), 7.55 (t, 1 H, 4′-H, J = 7.9 Hz), 8.02 (d, 2 H, 2′- and 6′-H, J = 7.9 Hz); IR 3505, 2950, 2230, 1710 cm^{-1}; MS, m/z (relative intensity) 562 (M^+ + H, 4.0), 560 (4.0), 544 (27), 517 (5.4), 422 (100), 395 (23). Anal. Calcd for $C_{37}H_{55}NO_3$: C, 79.10; H, 9.87; N, 2.49. Found: C, 78.93; H, 9.84; N, 2.41.

3β-(Benzoyloxy)-4,4-dimethyl-7α-[(methylsulfonyl)oxy]-5α-cholestane-14α-carbonitrile (7a). A sample of pure **7a** could be obtained by recrystallizing the crude mesylate (see the following experimental for **10**) from CH_2Cl_2/MeOH: mp 220–221 °C; ^1H NMR δ 0.79 (s, 3 H, 18-H), 0.85 (d, 3 H, 26- or 27-H, J = 1.6 Hz), 0.88 (d, 3 H, 26- or 27-H, J = 1.6 Hz), 0.91 (d, 3 H, 21-H, J = 6.8 Hz), 0.93 (s, 3 H), 0.96 (s, 3 H), 1.04 (s, 3 H), 4.04 (m, 1 H, 7-H), 4.78 (dd, 1 H, 3-H, $J_{2\beta,3}$ = 13 Hz, $J_{2\alpha,3}$ = 5 Hz), 7.42 (t, 2 H, 3′- and 5′-H, J = 7.6 Hz), 7.54 (t, 1 H, 4′-H, J = 7.6 Hz), 8.01 (d, 2 H, 2′- and 6′-H, J = 6.9 Hz); IR 2950, 2230, 1710 cm^{-1}; MS m/z (relative intensity) 638 (M^+ – H, 6.2), 544 (7.1), 517 (8.9), 422 (100), 395 (64). Anal. Calcd for $C_{38}H_{57}NO_5S$: C, 71.32; H, 8.88; N, 2.19; S, 5.01. Found: C, 71.36; H, 8.88; N, 2.26; S, 4.98.

3β-(Benzoyloxy)-4,4-dimethyl-5α-cholest-6-ene-14α-carbonitrile (8). Martin sulfurane dehydrating reagent, bis[α,α-bis(trifluoromethyl)benzenemethanolato]diphenylsulfur (0.24 g, 0.36 mmol), in CH_2Cl_2 (2.5 mL) was added to a solution of **6a**

(23) Gautschi, F.; Block, K. *J. Biol. Chem.* **1958**, *233*, 1343.
(24) Tadros, W.; Boulos, A. L. *Helv. Chim. Acta* **1975**, *58*, 668.

(0.10 g, 0.18 mmol) in CH_2Cl_2 (2.5 mL) at −78 °C. After being warmed to rt, the solution was stirred for 6 h. The solvent was removed, the residue was triturated with MeOH, and **8** was obtained as a white solid; yield 0.080 g (82%). Analytically pure compound could be obtained by recrystallization from CH_2Cl_2/MeOH: mp 232–233 °C; ^1H NMR δ 4.80 (dd, 1 H, 3-H, $J_{2\beta,3}$ = 13 Hz, $J_{2\alpha,3}$ = 5 Hz), 5.77 (AB, 2 H, $\Delta\delta$ = 0.29 ppm, J_{AB} = 11 Hz, 6- and 7-H), 7.47 (t, 2 H, 3′- and 5′-H, J = 6.9 Hz), 7.59 (t, 1 H, 4′-H, J = 6.2 Hz), 8.04 (d, 2 H, 2′- and 6′-H, J = 6.9 Hz); IR 2940, 2230, 1710 cm^{-1}; MS, m/z (relative intensity) 544 (M^+ + H, 13), 517 (9), 440 (4), 422 (100), 406 (7), 395 (21). Anal. Calcd for $C_{37}H_{53}NO_2 \cdot H_2O$: C, 79.10; H, 9.86; N, 2.49. Found: C, 78.97; H, 9.47; N, 2.30.

3β-(Benzoyloxy)-5α-ergost-7-ene-14α-carbonitrile (9b). A mixture of the Δ^6 and Δ^7 isomers was prepared from **4b** in 65% overall yield, using essentially the same procedures as in the experimental for **10**: mp 165–168 °C; IR 2970, 2230, 1720 cm^{-1}; MS, m/z (relative intensity) 528 (M^+ + H, 68), 526 (29), 501 (28), 406 (100), 379 (65), 255 (59). Pure Δ^7 isomer could be obtained by chromatographing the mixture on silver nitrate impregnated (20%) silica gel eluting successively with 20:1 and 10:1 hexanes/EtOAc: mp 173–175 °C; ^1H NMR δ 0.65 (s, 3 H, 18-H), 0.81 (d, 3 H, 26- or 27-H, J = 3.6 Hz), 0.83 (d, 3 H, 26- or 27-H, J = 3.6 Hz), 0.87 (s, 3 H, m, 19-H), 0.91 (d, 3 H, 21- or 28-H, J = 4.6 Hz), 1.03 (d, 3 H, 21- or 28-H, J = 4.6 Hz), 4.94 (m, 3 H, 3-H), 5.22 (m, 2 H, 22- and 23-H), 5.51 (m, 1 H, 7-H), 7.42 (t, 2 H, 3′- and 5′-H, J = 7.2 Hz), 7.52 (t, 1 H, 4′-H, J = 7.2 Hz), 8.02 (d, 2 H, 2′- and 6′-H, J = 6.5 Hz); HRMS (EI) for $C_{36}H_{49}NO_2$, calcd 527.3752, found 527.3763.

3β-(Benzoyloxy)-4,4-dimethyl-5α-cholest-7-ene-14α-carbonitrile (10). Methanesulfonyl chloride (2.0 mL, 1.4 g, 12 mmol) was added to a solution of **6a** (4.5 g, 8.0 mmol) in pyridine (100 mL) at 0 °C. The reaction mixture was allowed to warm to rt and after 3 h at this temperature poured into water. The resulting mixture was extracted with 4:1 Et_2O/CH_2Cl_2. The layers were separated and the organic phase was extracted with brine and dried. The solvent was evaporated and the crude mesylate **7a** was dissolved in collidine (150 mL) and heated to reflux for 18 h. After being cooled to rt, the collidine solution was poured into water and extracted with 4:1 Et_2O/CH_2Cl_2, the organic extract was washed three times with 2 N HCl, saturated aqueous $NaHCO_3$, and brine, and dried, and the solvent was evaporated. The residue was dissolved in CH_2Cl_2 (200 mL) and the solution cooled to −78 °C. Ozone was bubbled through at −78 °C until a faint blue color persisted. Argon was bubbled through the solution to remove excess ozone. Excess Me_2S was added and the solution was allowed to warm to rt over a period of 2 h. The solvent was concentrated and the residue chromatographed eluting successively with 25:1 and 10:1 hexanes/EtOAc. Fractions containing only **10** were combined and the solvent was evaporated to afford a white solid; yield 2.1 g (48% from **6a**). A sample was recrystallized from CH_2Cl_2/MeOH: mp 175–176 °C; ^1H NMR δ 0.64 (s, 3 H, 18-H), 0.86 (d, 3 H, 26- or 27-H, J = 1.5 Hz), 0.88 (d, 3 H, 26- or 27-H, J = 1.5 Hz), 0.94 (s, 3 H), 0.95 (d, 3 H, 21-H, J = 6.4 Hz), 0.97 (s, 3 H), 1.14 (s, 3 H), 4.78 (dd, 1 H, 3-H, $J_{2\beta,3}$ = 17 Hz, $J_{2\alpha,3}$ = 5 Hz), 5.08 (m, 1 H, 7-H), 7.44 (t, 2 H, 3′- and 5′-H, J = 8.3 Hz), 7.54 (t, 1 H, 4′-H, J = 7.0 Hz), 8.03 (d, 2 H, 2′- and 6′-H, J = 7.0 Hz); MS, m/z (relative intensity) 544 (M^+ + H, 9), 542 (7), 517 (51), 458 (19), 422 (48), 395 (100); HRMS (EI) for $C_{37}H_{53}NO_2$, calcd 543.4072, found 543.4063.

3β-Hydroxylanost-7-en-30-al (11). DIBAL-H (1.5 M in toluene, 15 mL, 22.5 mmol) was added to a solution of **10** (3.7 g, 6.8 mmol) in toluene (175 mL) at −10 °C. The reaction mixture was stirred at −10 °C for 0.5 h. EtOAc (15 mL) was added and the solution was allowed to warm to rt and kept at this temperature for 0.5 h. Then 1 N H_2SO_4 was added and the two-phase system was heated at reflux for 0.5 h. After cooling to rt, the layers were separated and the organic phase was washed with water and brine and dried. The solution was concentrated and the residue was recrystallized from CH_2Cl_2/MeOH to afford **11** as a white solid: yield 1.6 g (53%); mp 123–124 °C (lit.[25] mp 119–120 °C); ^1H NMR δ 0.73 (s, 3 H, 18-H), 3.23 (dd, 1 H, $J_{2\beta,3}$ = 11 Hz, $J_{2\alpha,3}$ = 6 Hz, 3-H), 5.42 (m, 1 H, 7-H) 9.59 (s, 1 H, 30-H); IR 3290, 2965, 2940, 2880, 1715, 1440, 1390, 1370, 1030 cm^{-1}; MS, m/z (relative intensity) 443 (M^+ + H, 40), 441 (39), 425 (100), 413 (47), 407 (20), 397 (43).

30-Aminolanost-7-en-3β-ol (12). DIBAL-H (1.5 M in toluene, 0.49 mL, 0.74 mmol) was added to a solution of **10** (0.13 g, 0.23 mmol) in toluene at −10 °C. The solution was stirred at this temperature for 0.5 h. $NaBH_4$ (0.052 g, 1.4 mmol) was added followed by the dropwise addition of MeOH (10 mL). After being stirred at rt for 0.5 h, the reaction mixture was poured into 1 N sodium potassium tartrate and extracted with 4:1 Et_2O/CH_2Cl_2. The phases were separated and the organic phase was washed with brine and dried and the solution concentrated. The residue was triturated with Et_2O to afford **12** (0.080 g, 74%) as a white solid. A sample was further purified for analytical purposes by chromatography eluting with 90:10:1 $CHCl_3$/MeOH/NH_4OH followed by recrystallization from 2-propanol: mp 167–168 °C; ^1H NMR δ 0.72 (s, 3 H, 18-H), 2.54 (AB, 2 H, $\Delta\delta$ = 0.48 ppm, 30-H, J_{AB} = 14 Hz), 3.26 (t, 1 H, 3-H, $J_{3,4}$ = 10 Hz) 5.21 (m, 1 H, 7-H); MS, m/z (relative intensity) 444 (M^+ + H, 24), 442 (31), 426 (37), 413 (73), 409 (45), 397 (100), 395 (44). Anal. Calcd for $C_{30}H_{53}NO \cdot {}^1/_4\, H_2O$: C, 80.38; H, 12.03; N, 3.12. Found: C, 80.35; H, 12.28; N, 3.00.

3β-(Benzoyloxy)-8β-bromo-4,4-dimethyl-7-oxo-5α-cholestane-14α-carbonitrile (13). Et_2AlCN (1.4 M in toluene, 1.2 mL, 1.7 mmol) was added to a solution of **4a** (0.30 g, 0.55 mmol) in toluene (15 mL) at 0 °C. After stirring for 0.5 h, bromine was added dropwise until a faint red color persisted. The reaction mixture was poured into 1 N NaOH and extracted with 4:1 Et_2O/CH_2Cl_2. The layers were separated and the organic phase was washed with brine, dried, and concentrated. The residue was chromatographed eluting with 10:1 hexanes/EtOAc and **13** was obtained as a white solid; yield 0.15 g (43%). A sample was recrystallized from CH_2Cl_2/MeOH: mp 220 °C dec; ^1H NMR δ 0.86 (d, 3 H, 26- or 27-H, J = 1.6 Hz) 0.88 (d, 3 H, 26- or 27-H, J = 1.6 Hz), 0.91 (d, 3 H, 21-H, J = 6.3 Hz) 0.96 (s, 3 H), 1.07 (s, 3 H), 1.19 (s, 3 H), 1.29 (s, 3 H), 4.76 (dd, 1 H, 3-H, $J_{2\beta,3}$ = 16 Hz, $J_{2\alpha,3}$ = 5 Hz), 7.45 (t, 2 H, 3′- and 5′-H, J = 7.0 Hz), 7.59 (t, 1 H, 4′-H, J = 7.7 Hz), 8.03 (d, 2 H, 2′- and 6′-H, J = 7.7 Hz); ^{13}C NMR δ 73 (8-C), 81 (3-C), 123 (quaternary phenyl), 128 (methine phenyl), 129 (methine phenyl), 131 (CN), 133 (methine phenyl), 167 (OCOBz), 199 (7-C); IR 2960, 2220, 1720 cm^{-1}; MS, m/z (relative intensity) 558 (M^+ + H, 24), 558 (37), 516 (59), 436 (100).

3β-(Benzoyloxy)-4,4-dimethyl-7-oxo-5α-cholest-8-ene-14α-carbonitrile (14). A solution of **13** (0.15 g, 0.24 mmol) in pyridine was heated at reflux for 3 h. The solution was evaporated, the residue was chromatographed eluting with CH_2Cl_2, and **14** was obtained as a white solid; yield 0.10 g (75%). Analytically pure material was obtained by recrystallizing a sample from CH_2Cl_2/MeOH: mp 269–270 °C; ^1H NMR δ 0.69 (s, 3 H, 18-H), 0.85–0.90 (6 H), 0.97 (d, 3 H, 21-H, J = 6.7 Hz), 0.98 (s, 3 H), 1.13 (s, 3 H), 1.28 (s, 3 H), 4.77 (dd, 1 H, 3-H, $J_{2\beta,3}$ = 12 Hz, $J_{2\alpha,3}$ = 4 Hz), 7.45 (t, 2 H, 3′- and 5′-H, J = 7.7 Hz), 7.58 (t, 1 H, 4′-H, J = 7.0 Hz), 8.05 (d, 2 H, 2′- and 6′-H, J = 7.7 Hz); ^{13}C NMR δ 81 (3-C), 123 (quaternary phenyl), 129 (methine phenyl), 130 (methine phenyl), 131 (9-C or CN), 131.5 (9-C or CN), 133 (methine phenyl), 167 (OCOBz or 8-C), 169 (OCOBz or 8-C), 196 (7-C); IR 2930, 2220, 1710, 1680 cm^{-1}; MS, m/z (relative intensity) 558 (M^+ + H, 72), 542 (8), 531 (100), 436 (77), 417 (12), 409 (23). Anal. Calcd for $C_{37}H_{51}NO_3$: C, 79.67; H, 9.22; N, 2.51. Found: C, 79.48; H, 9.35; N, 2.44.

3β-(Benzoyloxy)-8β-hydroperoxy-7-oxo-5α-ergostane-14α-carbonitrile (16b). Et_2AlCN (2.7 mL, 3.9 mmol) was added to a solution of **4b** (1.0 g, 1.9 mmol) in toluene (10 mL) at 0 °C. After being stirred for 0.5 h at 0 °C, the reaction mixture was poured into 1 N NaOH. After aqueous workup, the residue was dissolved in CH_2Cl_2 and stirred vigorously overnight exposed to the atmosphere. The solvent was evaporated and the crude product subjected to chromatography eluting successively with 25:1 and 5:1 hexanes/EtOAc to afford **16b** (0.50 g, 46%) as a white solid. A sample was recrystallized from CH_2Cl_2/MeOH: mp 197–198 °C; ^1H NMR δ 0.82 (d, 3 H, 26- or 27-H, J = 4.0 Hz), 0.84 (d, 3 H, 26- or 27-H, J = 4.0 Hz), 0.87 (s, 3 H, 18-H), 0.92 (s, 3 H, 19-H), 0.93 (d, 3 H, 21- or 28-H, J = 5.6 Hz), 4.97 (m, 1 H, 3-H), 5.25 (m, 2 H, 22- and 23-H), 7.41 (t, 2 H, 3′- and 5′-H, J = 6.9 Hz), 7.52 (t, 1 H, 4′-H, J = 7.6 Hz), 8.02 (d, 2 H, 2′- and 6′-H, J = 6.9

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Hz); MS, m/z (relative intensity) 576 ($M^+ + H$, 23), 560 (43), 558 (32), 544 (47), 542 (29), 533 (100), 515 (43), 454 (100), 436 (48), 420 (57), 408 (67). Anal. Calcd for $C_{36}H_{49}NO_5$: C, 75.10; H, 8.58; N, 2.43. Found: C, 75.08, H, 8.72, N, 2.32.

3β-(Benzoyloxy)-8β-hydroperoxy-4,4-dimethyl-7-oxo-5α-cholestane-14α-carbonitrile (16a) was prepared from **4a** in the same manner in 18% yield: mp 184–185 °C; ^1H NMR δ 0.85 (d, 3 H, 26- or 27-H, J = 1.6 Hz), 0.88 (d, 3 H, 26- or 27-H, J = 1.6 Hz), 0.92 (d, 3 H, 21-H, J = 6.8 Hz), 0.93 (s, 3 H, 18-H), 1.09 (s, 3 H), 1.15 (s, 3 H), 1.19 (s, 3 H), 4.75 (dd, 1 H, 3-H, $J_{2\beta,3}$ = 12 Hz, $J_{2\alpha,3}$ = 6 Hz), 7.42 (t, 2 H, 3′- and 5′-H, J = 6.2 Hz), 7.58 (t, 1 H, 4′-H, J = 6.9 Hz), 8.02 (d, 2 H, 2′- and 6′-H, J = 6.9 Hz); MS (NH_4), m/z (relative intensity) 609 ($M^+ + NH_4$, 18), 593 (100), 581 (33), 577 (28), 565 (85), 563 (41), 424 (43).

3β-(Benzoyloxy)-8β-hydroxy-4,4-dimethyl-7-oxo-5α-cholestane-14α-carbonitrile (17a). Zinc dust (0.10 g) was added to a solution of **16a** (0.10 g, 0.087 mmol) in HOAc (2 mL) and CH_2Cl_2 (1 mL). The reaction mixture was stirred at rt for 24 h. The zinc was removed by filtration through Celite, and the solvent was evaporated to give a quantitative yield of **17a** as a white solid. A sample was recrystallized from CH_2Cl_2/MeOH: mp 292–293 °C; ^1H NMR δ 0.85 (d, 3 H, 26- or 27-H, J = 1.6 Hz) 0.88 (d, 3 H, 26- or 27-H, J = 1.6 Hz), 0.92 (d, 3 H, 21-H, J = 6.7 Hz), 0.95 (s, 3 H, 18-H), 1.07 (s, 6 H), 1.22 (s, 3 H), 4.73 (dd, 1 H, 3-H, $J_{2\beta,3}$ = 11 Hz, $J_{2\alpha,3}$ = 5 Hz), 7.45 (t, 2 H, 3′- and 5′-H, J = 7.0 Hz), 7.57 (t, 1 H, 4′-H, J = 7.0 Hz), 8.02 (d, 2 H, 2′- and 6′-H, J = 6.4 Hz); MS, m/z (relative intensity) 576 ($M^+ + H$, 100), 574 (31), 560 (22), 558 (13), 454 (82), 436 (55), 426 (29), 411 (16). A portion of **17a** (0.80 g, 0.14 mmol) was dissolved in pyridine (2 mL) and $SOCl_2$ (0.049 mL, 0.66 mmol) was added at rt. After being heated to 60 °C for 2 h, the reaction mixture was poured into water and extracted with Et_2O and the organic phased was evaporated. The residue was triturated with MeOH to afford pure **14** (0.40 g, 51%), which gave an ^1H NMR spectrum indistinguishable from material obtained from **13**.

3β-(Benzoyloxy)-22-oxo-23,24-dinor-5α-chol-7-ene-14α-carbonitrile (18). Ozone was bubbled through a solution of **9b** (5.0 g, 9.5 mmol) in CH_2Cl_2 (300 mL) at −78 °C until a faint blue color persisted. Argon was bubbled through to remove excess ozone and excess dimethyl sulfide was added. The solution was warmed to rt and stirred for 3 h. The solvent was evaporated and the residue was chromatographed eluting with 50:1 CH_2Cl_2/EtOAc to yield **18** (2.7 g, 62%) as a white solid: mp 214–216 °C; ^1H NMR δ 0.70 (s, 3 H, 18-H), 0.89 (s, 3 H, 19-H), 1.19 (d, 3 H, 21-H, J = 6.6 Hz), 4.95 (m, 1 H, 19-H), 5.54 (m, 1 H, 7-H), 7.43 (t, 2 H, 3′- and 5′-H, J = 7.3 Hz), 7.55 (t, 1 H, 4′-H, J = 7.3 Hz), 8.04 (d, 2 H, 2′- and 6′-H, J = 6.6 Hz), 9.57 (d, 1 H, C*H*O, J = 2.9 Hz); IR 2970, 2240, 1730, 1720 cm^{-1}; MS, m/z (relative intensity) 460 ($M^+ + H$, 57), 458 (25), 433 (88), 415 (11), 403 (44), 338 (100), 311 (83).

3β-(Benzoyloxy)-24-oxo-5α-cholesta-7,22-diene-14α-carbonitrile (19). 3-Methylbutanone (0.86 mL, 0.69 g, 8.6 mmol) was added to a solution of LDA (8.6 mmol) in THF (40 mL) at −78 °C. After 15 min of stirring at −78 °C, a solution of **18** (2.0 g, 4.3 mmol) in THF (40 mL) was added dropwise. Stirring was continued for an additional 5 min. The reaction mixture was poured into saturated NH_4Cl and extracted with Et_2O, and the extract was concentrated. The residue was dissolved in toluene (100 mL), p-toluenesulfonic acid (200 mg) was added, and the solution was heated at reflux for 0.5 h. The reaction was cooled to rt and washed with water and the solvent was evaporated. The residue was recrystallized from CH_2Cl_2/MeOH to give pure **19**: yield 1.9 g (84%); mp 208–209 °C; ^1H NMR δ 0.68 (s, 3 H, 18-H), 0.86 (s, 3 H, 19-H), 1.09 (d, 6 H, 26- and 27-H, J = 4.6 Hz), 1.13 (d, 3 H, 21-H, J = 4.6 Hz), 4.93 (m, 1 H, 3-H), 5.51 (m, 1 H, 7-H), 6.08 (d, 1 H, 23-H), 6.70 (dd, 1 H, 22-H, $J_{22,23}$ = 18 Hz, $J_{22,20}$ = 8 Hz) 7.42 (t, 2 H, 3′- and 5′-H, J = 7.2 Hz), 7.53 (t, 1 H, 4′-H, J = 8.1 Hz), 8.01 (d, 2 H, 2′- and 6′-H, J = 7.2 Hz); IR 2980, 2240, 1720, 1700, 1635 cm^{-1}; MS, m/z (relative intensity) 528 ($M^+ + H$, 28), 501 (27), 406 (85), 379 (33), 308 (60), 281 (100). Anal. Calcd for $C_{35}H_{45}NO_5 \cdot {}^1/_4H_2O$: C, 78.98; H, 8.61; N, 2.63. Found: C, 78.75; H, 8.88; N, 2.90.

3β-(Benzoyloxy)-24-oxo-5α-cholest-7-ene-14α-carbonitrile (20). 10% Palladium on carbon (10%) (0.20 g) was added to a solution of **19** (1.9 g, 3.6 mmol) in EtOAc (200 mL) and the reaction mixture was stirred for 3 h under an atmosphere of hydrogen at rt. The catalyst was removed by filtration through Celite. Removal of the solvent afforded **20** as a white solid; yield 1.8 g (95%). A sample was recrystallized from MeOH: mp 177–179 °C; ^1H NMR δ 0.66 (s, 3 H, 18-H), 0.88 (s, 3 H, 19-H), 0.95 (d, 1 H, 21-H, J = 7.4 Hz), 1.10 (d, 6 H, 26- and 27-H, J = 8.6 Hz), 4.91 (m, 1 H, 3-H), 5.53 (m, 3 H, 7-H), 7.43 (t, 2 H, 3′- and 5′-H, J = 9.1 Hz), 7.56 (t, 2 H, 4′-H, J = 8.6 Hz), 8.04 (d, 1 H, 2′- and 6′-H, J = 8.5 Hz); IR 2970, 2230, 1715 cm^{-1}; MS, m/z (relative intensity) 530 ($M^+ + H$, 8), 528 (8), 503 (85), 408 (85), 381 (100).

3α-Hydroxy-5α-ergosta-7,24(28)-diene-14α-carbonitrile (21). [(Trimethylsilyl)methyl]lithium (1 M, 11.2 mL, 11.2 mmol) was added to a solution of **20** (1.8 g, 3.4 mmol) in THF (50 mL) at −78 °C. The reaction was stirred for 15 min at −78 °C and then poured into saturated NH_4Cl and extracted with Et_2O. The solvent was removed and the residue was chromatographed eluting successively with 3:1 and 2:1 hexanes/EtOAc. The β-silanol was dissolved in THF (50 mL) and 2 N HCl (2 mL) was added. The mixture was stirred at rt for 3 h, the solvent was removed, and the residue was recrystallized from MeOH to give **21** as a white solid: yield 1.0 g (69%); mp 144–146 °C; ^1H NMR δ 0.65 (s, 3 H, 18-H), 0.81 (s, 3 H, 19-H), 0.98 (d, 3 H, 21-H, J = 7.0 Hz), 1.02 (d, 3 H, 26- or 27-H, J = 1.2 Hz), 1.05 (d, 3 H, 26 or 27-H, J = 1.2 Hz), 3.62 (m, 1 H, 3-H), 4.66 (s, 1 H, =C*H*$_2$), 4.73 (s, 1 H, =C*H*$_2$) 5.51 (m, 1 H, 7-H); ^{13}C NMR δ 72 (3-C), 107 (28-C), 124 (7-C), 125 (*C*N), 136 (8-C), 157 (24-C); IR 3370, 2980, 2240, 1650 cm^{-1}; MS, m/z (relative intensity) 424 ($M^+ + H$, 68), 406 (100), 397 (60), 271 (100). Anal. Calcd for $C_{29}H_{45}NO \cdot {}^1/_2H_2O$: C, 80.50; H, 10.72; N, 3.24. Found: C, 80.11; H, 10.84; N, 3.19.

3β-(Benzoyloxy)-5α-cholesta-7,24-diene-14α-carbonitrile (23). $NaBH_4$ (0.034 g, 0.090 mmol) was added to a solution of **20** (0.24 g, 0.45 mmol) in 1:1 CH_2Cl_2/MeOH (10 mL). After stirring for 15 min, the solvents were evaporated, and the residue partitioned between 4:1 Et_2O/CH_2Cl_2 and water. The layers were separated and the organic phase was washed with brine and dried. The solvent was removed, the residue was dissolved in CH_2Cl_2 (10 mL) and cooled to −78 °C, and a solution of Martin sulfurane reagent (0.60 g, 0.90 mmol) in CH_2Cl_2 (5 mL) was added. After 15 min at −78 °C, the reaction was allowed to warm to rt over a period of 0.5 h. The solvent was evaporated and the residue was triturated with MeOH to afford a white solid; yield 0.20 g (87%). This material was homogeneous by TLC (5:1 hexanes/EtOAc); however, capillary GC analysis indicated a 7/1 mixture of two components. ^1H NMR revealed that the components were the Δ^{24} and Δ^{23} isomers, respectively [δ 0.64 (s, 3 H, 18-H), 0.87 (s, 3 H, 19-H), 0.97 (d, 3 H, 21-H, J = 7.0 Hz), 1.58 (s, 3 H, 26- or 27-H, J = 1.2 Hz), 1.67 (s, 3 H, 26- or 27-H, J = 1.2 Hz), 4.96 (m, 1 H, 3-H), 5.52 (m, 1 H, 7-H), 7.42 (t, 2 H, 3′- and 5′-H, J = 7.5 Hz), 7.53 (t, 1 H, 4′-H, J = 7.0 Hz), 8.01 (d, 2 H, 2′- and 6′-H, J = 8.0 Hz); a multiplet at 5.35 could also be observed resulting from the ~14% Δ^{23} isomer(s) present]. Recrystallization from 2-propanol had no significant effect on isomer ratios (GC): mp 181–183 °C; MS, m/z (relative intensity) 514 ($M^+ + H$, 11), 512 (8), 487 (27), 392 (92), 375 (100), 365 (71), 253 (65), HRMS (EI) for $C_{35}H_{47}NO_2$, calcd 513.3595, found 513.3607.

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