Synthesis of Zymosterol, Fecosterol, and Related Biosynthetic Sterol Intermediates[1,2]

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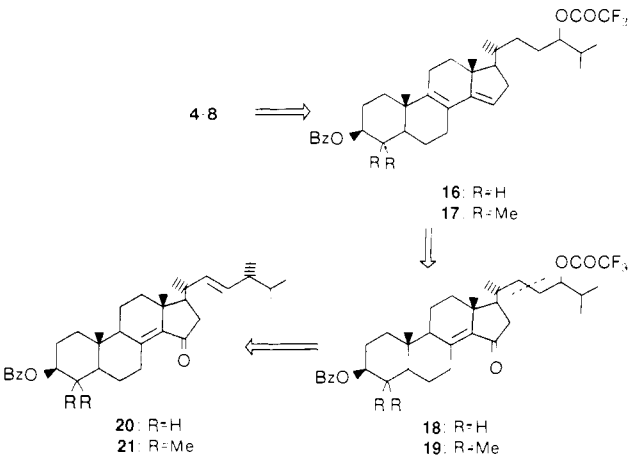
Abstract: The first syntheses of sterol biosynthetic intermediates zymosterol (**4**), 4,4-dimethylzymosterol (**5**), cholesta-8,14,24-trien-3β-ol (**6**), the 4,4-dimethyl analogue **7**, and fecosterol (**8**) are described in detail. Multigram quantities of key intermediates **16** and **17** were efficiently prepared from known enones **20** and **21** (eight steps, 35% overall yield). Novel entry into Δ^8-sterols was achieved through regiospecific hydroboration/deoxygenation of the 8,14-diene systems. Sterols containing Δ^{24}- or $\Delta^{24(28)}$-olefins were obtained from C24-hydroxy intermediates either via dehydration using bis[α,α-bis(trifluoromethyl)benzenemethanolato]diphenylsulfur in CH_2Cl_2 or via Swern oxidation/Wittig olefination, respectively. In this way, **16** and **17** were converted to the desired $\Delta^{8,24}$-, $\Delta^{8,14,24}$-, and $\Delta^{8,24(28)}$-sterols with high regiocontrol.

The elaborate cascades of fungal ergosterol (**1**) and mammalian cholesterol (**2**) biosynthesis via lanosterol (**3**) share a number of common enzymatic transformations and sterol intermediates.[4] Divergent transformations of sterol intermediates **4** ((3β,5α)-cholesta-8,24-dien-3-ol (zymosterol)), **5** (4,4-dimethylzymosterol), **6** ((3β,5α)-cholesta-8,14,24-trien-3-ol), and **7** (the 4,4-dimethyl analogue) mark the branch point in mammalian and fungal pathways[4e,f,h,5] (Figure 1). The fungal enzyme *S*-adenosylmethionine-Δ^{24}-methyl transferase (24-SMT) transfers a methyl group to C24 in sterol substrates **4**-**7**, generating C24,28-unsaturated products **8** ((3β,5α)-ergosta-8,24(28)-dien-3-ol (fecosterol)), **9** (4,4-dimethylfecosterol), and **10** and **11** ((3β,5α)-ergosta- and (3β,5α)-4,4-dimethylergosta-8,14,24(28)-trien-3-ols).[6] In mammalian cells a NADPH-dependent enzyme, Δ^{24}-sterol reductase, saturates the C24,25 bond in sterols **4**-**7**, affording dihydro intermediates **12** ((3β,5α)-cholest-8-en-3-ol (24,25-dihydrozymosterol)), **13** (the 4,4-dimethyl congener), and **14** and **15** ((3β,5α)-cholesta- and 4,4-dimethylcholesta-8,14-trien-3-ols).[7] Our current interest in designing novel steroid-based inhibitors of cholesterol (**1**) and ergosterol (**2**) biosynthesis necessitated the development of a general strategy for the construction of sterols **4**-**15**.[8]

Scheme I. Retrosynthetic Analysis for the Synthesis of Sterol Biosynthetic Intermediates **4**-**8**



Although zymosterol (**4**)[9] and fecosterol (**8**)[10] were first isolated in the late 1920s, the position of the nuclear double bond ($\Delta^{8,14}$ vs $\Delta^{9,11}$ vs Δ^8) in these sterols was debated for some 20 years. It was not until the elegant deductions of Barton and Cox[11] in 1949 that the correct C8,9 site of nuclear unsaturation was unequivocally established. Furthermore, the exceedingly low abundance of **6** and **7** in yeast and mammals has hindered efforts to isolate these sterols, although these have been postulated as biosynthetic intermediates.[12] Only recently has 4,4-dimethylcholesta-8,14,24-trien-3β-ol been isolated and the structure **7** proposed on the basis of the interpretation of ^{1}H NMR (100 MHz), mass spectra, and UV data.[12a,b] Characterization of 4,4-dimethylzymosterol (**5**) was reported in 1965.[13]

(1) In memory of Dr. Geoffrey I. Feutrill, Department of Chemistry, University of Melbourne, Australia. Deceased July 4, 1987.

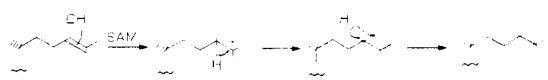
(2) (a) Presented in part at the 195th National Meeting of the American Chemical Society: Schmidt, S. J.; Dolle, R. E.; Kruse, L. I. *Abstracts of Papers*, 195th National Meeting of the American Chemical Society, New Orleans, LA; American Chemical Society: Washington, DC, 1987; ORGN 245. (b) Preliminary communication: Dolle, R. E.; Schmidt, S. J.; Kruse, L. I. *J. Chem. Soc., Chem. Commun.* **1988**, 19.

(3) Department of Medicinal Chemistry, Research and Development Division, Smith Kline & French Laboratories, Swedeland, PA 19479.

(4) (a) Benveniste, P. *Annu. Rev. Plant Physiol.* **1986**, *37*, 275. (b) Harrison, D. M. *Nat. Prod. Rep.* **1985**, *2*, 525. (c) Mercer, E. I. *Pestic. Sci.* **1984**, *15*, 133. (d) Schroepfer, G. J., Jr. *Annu. Rev. Biochem.* **1981**, *50*, 585. (e) Schroepfer, G. J., Jr. *Annu. Rev. Biochem.* **1982**, *51*, 555. (f) Frantz, I. D.; Schroepfer, G. J., Jr. *Annu. Rev. Biochem.* **1967**, *36*, 656. (g) Gaylor, J. L. In *Biosynthesis of Isoprenoid Compounds*; Porter, J. W., Spurgeon, S. L., Eds.; Wiley: New York, 1981; Vol. 1, p 482. (h) Parks, L. W. *CRC Crit. Rev. Microbiol.* **1978**, *6*, 301. (i) Akhtar, M.; Jones, C. *Tetrahedron* **1978**, *34*, 831.

(5) The 4α-methyl congeners are also intermediates in the biosynthesis of **1** and **2**.[4]

(6) This biotransformation may be viewed as a formal nucleophilic attack of the C24,25 olefin on the methyl group of *S*-adenosylmethionine (SAM), the mechanism of which involves carbonium ion intermediates. (a) Moore,



J. T.; Gaylor, J. L. *J. Biol. Chem.* **1970**, *245*, 4684. (b) Parks, L. W. In *Transmethylation*; Usdin, E., Borchardt, R., Creveling, C., Eds.; Elsevier: North Holland, 1979; pp 319-327.

(7) (a) Watkinson, I. A.; Wilton, D. C.; Rahimtula, A. D.; Akhtar, M. *Eur. J. Biochem.* **1971**, *23*, 1. (b) Greig, J. B.; Varma, K. R.; Caspi, E. *J. Am. Chem. Soc.* **1971**, *93*, 760. (c) Kienle, M. G.; Varma, K. R.; Mulheirn, J.; Yagen, B.; Caspi, E. *J. Am. Chem. Soc.* **1973**, *95*, 1996.

(8) For leading references regarding the inhibition of sterol biosynthesis, see: (a) Reference 4. (b) Sisler, H. D.; Ragsdale, N. N. *Symp. Br. Mycol. Soc.* **1983**, *9*, 257.

(9) (a) Smedley-Maclean, I. *Biochem. J.* **1928**, *22*, 22. (b) Wieland, H.; Asano, M. *Justus Liebigs Ann. Chem.* **1929**, *473*, 300. (c) Haussler, E. P.; Branchli, E. *Helv. Chim. Acta* **1929**, *12*, 187. (d) Wieland, H.; Gornhardt, L. *Justus Liebigs Ann. Chem.* **1947**, *557*, 248. (e) Wieland, H.; Rath, F.; Benend, W. *Justus Liebigs Ann. Chem.* **1941**, *548*, 19. (f) Heath-Brown, B.; Heilbron, I. M.; Jones, E. R. H. *J. Chem. Soc.* **1940**, 1482. (g) Zymosterol (**4**) has been isolated from bakers' yeast: Taylor, U. F.; Kisic, A.; Pascel, R. A., Jr.; Isumi, A.; Tsuda, M.; Schroepfer, G. J., Jr. *J. Lipid Res.* **1981**, *22*, 171.

(10) (a) Reference 8b. (b) Wieland, H.; Rath, F.; Hesse, H. *Justus Liebigs Ann. Chem.* **1941**, *548*, 34. (c) Barton, D. H. R. *J. Chem. Soc.* **1945**, 813. (d) Isolation of pure fecosterol was only recently described: Barton, D. H. R.; Kempe, U. M.; Widdowson, D. A. *J. Chem. Soc.* **1972**, 513.

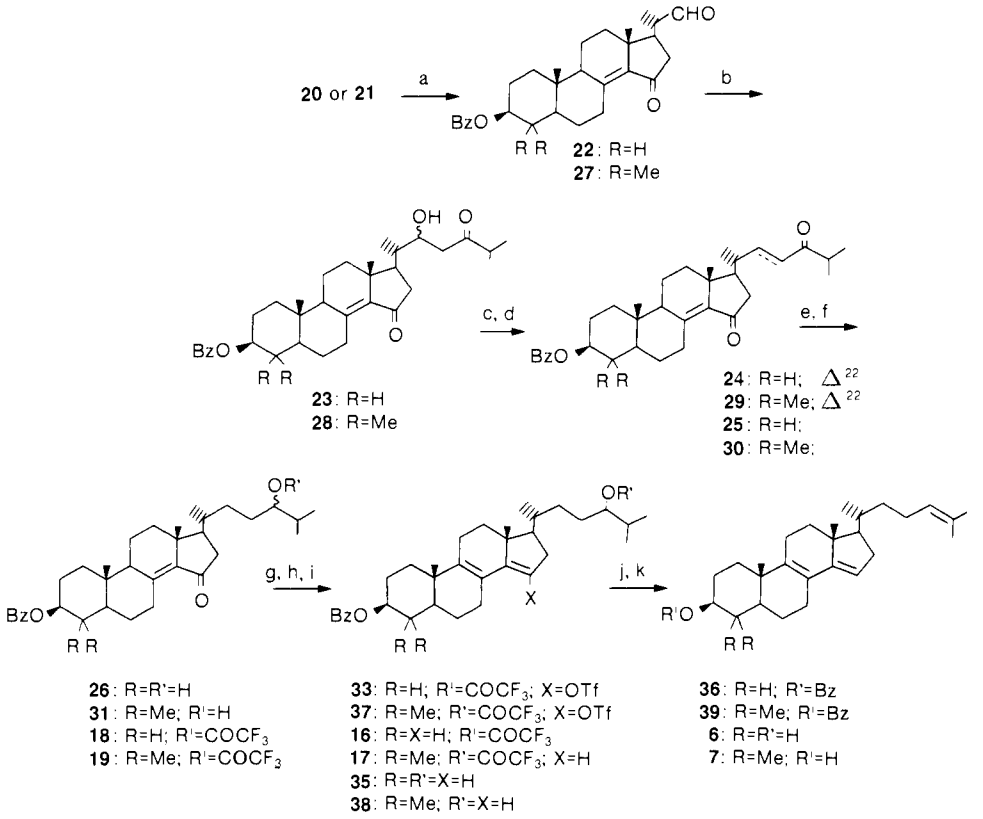
(11) Barton, D. H. R.; Cox, J. D. *J. Chem. Soc.* **1949**, 214.

(12) (a) Pierce, A. D., Jr.; Pierce, A. M.; Srinivasan, R.; Unrau, A. M.; Oehlschlager, A. C. *Biochim. Biophys. Acta* **1978**, *529*, 429. (b) Aoyama, Y.; Yoshida, Y. *Biochem. Biophys. Res. Commun.* **1978**, *85*, 29. (c) To our knowledge **6** has never been isolated or characterized. Ramsey and Fredericks (Ramsey, R. B.; Fredericks, M. *Biochem. Pharmacol.* **1977**, *26*, 1169), who described **6** as a capillary GC standard, have confirmed (personal communication) that the actual standard was (3β,5α)-cholesta-8(14)-en-3-ol and that the t_R reported for **6** represented an extrapolation from the cholesta-8(14)-en-3-ol.

(13) Ponsinet, G.; Ourisson, G. *Bull. Soc. Chim. Fr.* **1965**, 3682.

0002-7863/89/1511-0278$01.50/0

Scheme II. Synthesis of 3β-Hydroxy-5α-cholesta-8,14,22-triene (**6**) and the 4,4-Dimethyl Analogue **7**[a]



[a] Reagents and conditions: (a) O_3, Sudan III, CH_2Cl_2, −78 °C; (b) methyl isopropyl ketone, LDA (4 equiv each), THF, −78 °C; (c) *p*-TSA, $CHCl_3$, toluene (3:1), 70 °C; (d) 1 atm H_2, Lindlar cat., $CHCl_3$, toluene (3:1); (e) *t*-$BuNH_2$·BH_3, CH_2Cl_2, reflux; (f) $(CF_3CO)_2O$, pyr, DMAP (cat.), CH_2Cl_2, 0 °C; (g) $(CF_3SO_2)_2O$, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, 25 °C then reflux; (h) Bu_3N, HCOOH, $Pd(OAc)_2(Ph_3P)_2$ (cat.), DMF, 70 °C; (i) K_2CO_3, MeOH, 25 °C; 2 min; (j) Martin sulfurane, CH_2Cl_2, 0 °C; (k) i, 12 h.

Syntheses of the dihydrosterols **12**[14a] and **14**[14b,c] from 7-dehydrocholesterol (possessing the saturated cholesterol side chain) have been reported. To date, as noted in our previous paper,[2b] syntheses of **4–9** have not appeared. This is due to the absence of suitable methodology required for the regiocontrolled introduction of the salient *combination* of nuclear (Δ^8, $\Delta^{8,14}$) and side-chain (Δ^{24}, $\Delta^{24(28)}$) unsaturation present in these sterols.[15] The development of such methodology represents a long-standing problem in steroid chemistry.

Herein we detail the synthesis of zymosterol (**4**), 4,4-dimethylzymosterol (**5**), cholesta-8,14,24-trien-3β-ol (**6**), the 4,4-dimethyl analogue **7**, and fecosterol (**8**). This successful synthesis was realized by a novel entry into Δ^8-sterols through regiospecific hydroboration/deoxygenation of the 8,14-diene system. These dienes in turn were generated in high yield from C24-functionalized cholest-8(14)-en-15-ones via a novel formation and palladium-catalyzed reduction of intermediate dienol triflates.

Results and Discussion

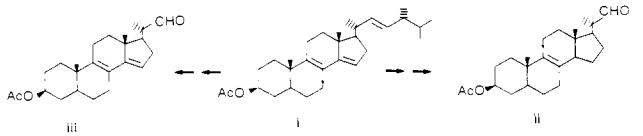
In designing a regioselective synthesis of **4–8**, a common intermediate was desired which would provide access to both the $\Delta^{8,14}$- and Δ^8-unsaturation present in these structures.[16] We have recently disclosed a highly regiocontrolled method for the late-stage introduction of 6,8(14)-, 7,14-, and 8,14-dienes into the steroid nucleus based on the regiospecific generation of dienoltriflates from appropriate enone precursors.[17a] By extending this methodology and anticipating sterol side-chain requirements, the following retrosynthetic analysis for sterols **4–8** became apparent (Scheme I).

Each of the desired sterols could be derived from 8,14-dienes **16** or **17** (differing only in substituent methyl groups at C4). Dehydration or oxidation/Wittig olefination of the latent C24 alcohol present in **16** and **17** was expected to provide the required

(14) (a) Anastasia, M.; Fiecchi, A.; Galli, G. *J. Org. Chem.* **1981**, *46*, 3421. (b) Dolle, R. E.; Schmidt, S. J.; Eggleston, D.; Kruse, L. I. *J. Org. Chem.*, **1988**, *53*, 1563–1566. (c) Fieser, M.; Rosen, W. E.; Fieser, L. F. *J. Am. Chem. Soc.* **1952**, *74*, 5397.

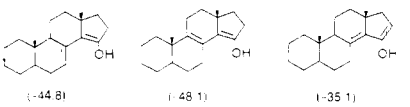
(15) Other methods for Δ^8-bond formation: (a) Hallsworth, A. S.; Henbest, H. B.; Wrigley, T. I. *J. chem. Soc.* **1957**, 1969. (b) Fryberg, M.; Oehlschlager, A. C.; Unrau, A. M. *J. Am. Chem. Soc.* **1973**, *95*, 5747. For other preparations of $\Delta^{8,14}$ sterols, see: (c) Andrieux, J.; Barton, D. H. R.; Patin, H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 359. (d) Barton, D. H. R.; Brooke, C. J. M. *J. Chem. Soc.* **1971**, 277. (e) Barton, D. H. R.; Davis, S. G.; Motherwell, W. B. *Synthesis* **1979**, 265. (f) Apfel, M. A. *J. Org. Chem.* **1979**, *44*, 643. For synthesis of Δ^{24} and $\Delta^{24(28)}$ sterols, see: (g) Rozen, S.; Hebel, D. *J. Org. Chem.* **1987**, *52*, 2588. (h) Reference c. (i) Sata, Y.; Sonoda, Y. *Chem. Pharm. Bull.* **1981**, *29*, 2604. (j) *Steroids* **1977**, *30*, 795. (k) Reference 10d.

(16) Our initial attempts at the construction of **4**, **6**, and **8** were based on efficient manipulation of ergosta-8,14-22-trien-3β-ol acetate[14b,15e] (ergosterol B_1 acetate) i. It was hoped that i would give ready access to aldehydes ii or



iii via a combination of selective 14,15 π bond reduction[11] and side-chain oxidation.[15b] Further elaboration of the intermediate aldehydes to **4**, **6**, or **8** was envisioned via standard methodology. However, due to the relative reactivities of the diene vs side-chain olefin toward electrophilic or oxidizing agents, this approach was unsuccessful.

(17) (a) Dolle, R. E.; Schmidt, S. J.; Kruse, L. I. *Tetrahedron Lett.* **1988**, 1581. (b) MNDO calculations for the ΔH_f (kcal/mol) of the following dienol substructures allow for a more precise comparison of the stability of these isomeric systems. The discernible stability trends support the experimental



results. The authors thank Dr. M. Saunders and Dr. A. Davis, Department of Computer Science, SK&F, The Frythe, for their assistance in obtaining these values.

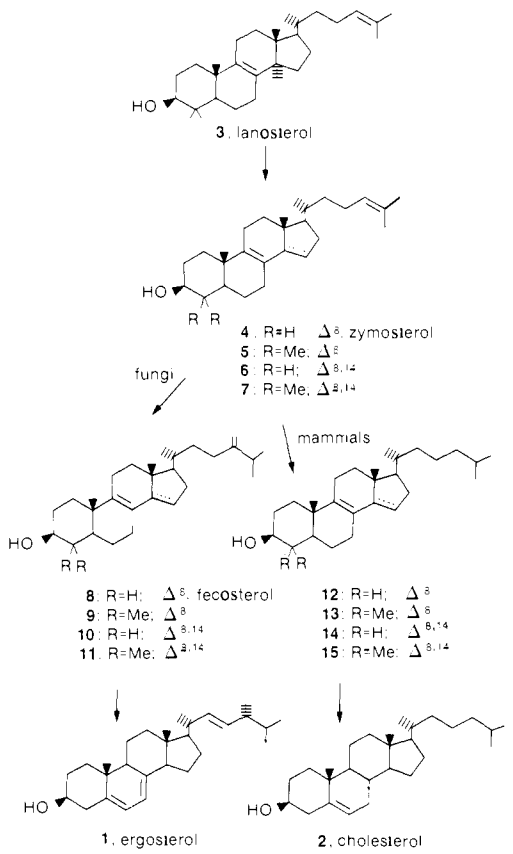
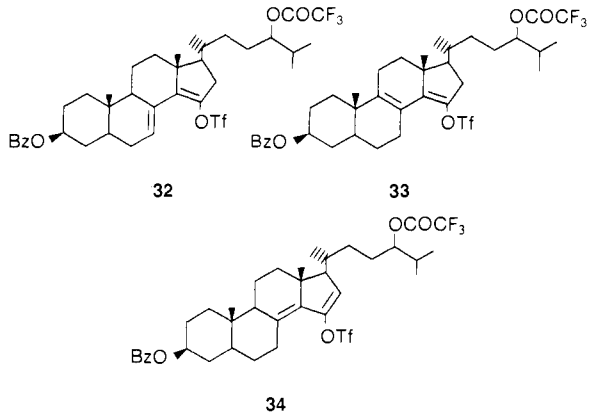


Figure 1. Salient fungal and mammalian sterol biosynthetic intermediates.

C24,25 and C24,28 unsaturation. The 8,14-diene intermediates **16** and **17** were available from enones **18** and **19**, which in turn have their origins (C22,23 disconnection) from known enones **20** and **21**.[18]

The large-scale preparation of **20** has been reported from these laboratories.[18] Ozonolysis (CH_2Cl_2, −78 °C) of 50-g portions of **20** in the presence of Sudan III[19a] provided aldehyde **22** in 75% isolated yield[19b] (Scheme II). Aldol condensation of **22** with the kinetic enolate of isopropyl methyl ketone furnished crystalline aldol adducts **23** in virtually quantitative yield.[20] Smooth dehydration of **23** to bis-enone **24** was observed upon treatment with *p*-toluenesulfonic acid and anhydrous $MgSO_4$. The side-chain olefin in crude **24** was selectively hydrogenated over Lindlar catalyst, furnishing keto enone **25**.[21,22] Chemoselective reduction of the C24 ketone using *tert*-butylamine–borane complex[23] (*t*-BAB) followed by rapid trifluoroacetylation gave trifluoroacetates **18** (via alcohols **26**).[24] Following flash chromatography, the overall yield of **18** from **22** was 80–85% (40–45% overall from **20**) and the sequence could be conveniently carried out on a 30–50-g scale without isolation of intermediates **23–25**. The sequence proved equally effective for the synthesis of the 4,4-dimethyl analogue **19** from **21** via analogous intermediates **27–31**.

The key transformation of enone **18** to 8,14-diene **16** was carried out by exposure of **18** to trifluoromethanesulfonic anhydride (Tf_2O, 1.2 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (*t*-DBMP, 1.5 equiv) in dry CH_2Cl_2 at 25 °C for 12 h and then at reflux temperature for 30 min.[25a,b] Of the three isomeric trienol triflates potentially generated in this reaction, **32**, **33**, and **34**, a single



product corresponding to the 8,14-dienol triflate **33** was obtained in quantitative yield. We have shown previously that the 8,14-dienol triflates are the thermodynamic products of this reaction, with the diene unit occupying the most stable arrangement in the steroid nucleus.[17a,b] An ^1H NMR (250 MHz) spectrum of crude **33** was free of vinyl resonances which otherwise would have been observed if **32** or **34** had been present. Final confirmation of the regiospecific generation of **33** resulted following palladium-catalyzed reduction[25b] of the trifluoromethanesulfonyl moiety (8 equiv of Bu_3N, 3 equiv of HCOOH, 0.1 equiv of $Pd(OAc)_2$, 0.2 equiv of Ph_3P, DMF, 70 °C, 30 min) which furnished diene **16** (95% yield from **18**).

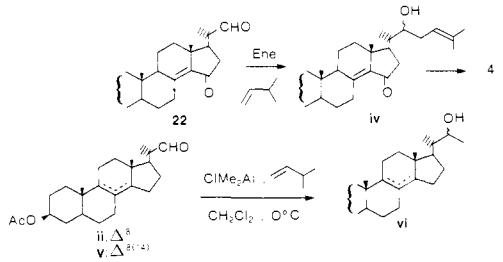
^{13}C NMR (GASPE) spectrum of **16** revealed three quaternary carbon resonances, 150.5, 140.4, and 123.3 ppm, and a single methine carbon resonance, 118.0 ppm, which are indicative of the 8,14-diene system. ^1H NMR also revealed a singlet, 5.4 ppm, corresponding to the C15 vinyl proton in **16**, with no other vinyl resonances detected. Alcohol **35** was subsequently obtained upon brief treatment of **16** with base (K_2CO_3, MeOH, 25 °C, 2 min; 100%). Completing the synthesis of **6** required dehydration of the C24 alcohol and debenzoylation.

Dehydration of a C24 side-chain alcohol should provide ready access to Δ^{24}-sterols; however a high-yield, reliable method to carry out this transformation has yet to be reported. Thus, whereas $POCl_3$ in pyridine has been reported to provide Δ^{24}-olefins from C24-alcohols,[15i,j] yields for unsaturated product range from 35 to 70%, and large amounts of C24-chloro and Δ^{23} byproducts are produced. Bis[α,α-bis(trifluoromethyl)benzenemethanolato]diphenylsulfur, the Martin sulfurane dehydrating agent (MSDA), has been reported to be a useful dehydrating agent for secondary and tertiary alcohols via carbocationic intermediates.[26] Treatment

(18) Dolle, R. E.; Kruse, L. I. *J. Org. Chem.* **1986**, *51*, 4047.

(19) (a) Veysoglu, T.; Mutscher, L.; Swayze, J. K. *Synthesis* **1980**, 807. (b) Use of the indicator consistently provided 75% yields of **22** and **27** and represents an improvement over our original procedure[18] for this sometimes capricious reaction.

(20) A Lewis-acid-catalyzed ene reaction (Snider, B. B.; Rudini, D. J.; Kirk, T. C.; Corodova, R. *J. Am. Chem. Soc.* **1982**, *104*, 555) followed by Barton-type deoxygenation (ref 32) was originally envisaged as a novel method for the elaboration of **22** → iv → → **4** or **6**. Unfortunately, the ene reaction



of **22** with 2-methylbut-1-ene failed to provide homoallylic alcohol iv under all conditions tried; steric hinderance of the aldehyde group may account for its poor reactivity. Similarly, the Me_2AlCl-catalyzed ene reaction of aldehyde ii or v afforded only methyl carbinols of the type vi.

(21) Reduction of the C8,14-olefin was never observed with this catalyst.

(22) Absence of epimerization at C20 following ozonolysis, aldol condensation, dehydrating, and Δ^{22}-hydrogenation, as determined by ^1H and ^{13}C NMR, is consistent with previous observations. See ref 18 and Eyley, S. C.; Williams, D. H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 727.

(23) We recommend the use of CH_2Cl_2 soluble *tert*-butylamine–borane complex (*t*-BAB) as a reducing agent for alcohol-insoluble aldehydes and ketones. Crawford, T. C.; Andrews, C. G. *Tetrahedron Lett.* **1980**, *21*, 693.

(24) The diastereomeric C24-alcohols could be resolved on TLC (silica, 2% EtOAC–CH_2Cl_2); however these were never separated.

(25) (a) Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85. (b) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1984**, 4281.

of **35** with MSDA (1.2 equiv) in dry CH_2Cl_2 at −20 °C for 1 min gave triene **36** in quantitative yield (capillary GC showed 97% $\Delta^{8,14,24}$-isomer and 3% $\Delta^{8,14,23}$-isomer). The sulfurane has been equally effective for the dehydration of other C24-OH containing sterol substrates in our laboratories[26c,d] and is the reagent of choice for the C24-OH to Δ^{24} conversion. Target sterol **6** was subsequently isolated following saponification of benzoate **36** (K_2CO_3, 3:1 MeOH–toluene). The 4,4-dimethyl analogue **7** was prepared from **19** via intermediates **37–39** in an identical fashion as in the case of **18** → **6**.

Synthetic sterols **6** and **7** exhibited physical and spectroscopic properties consistent with their structures.[12a,b,27] The ^1H NMR (250 MHz) and low-resolution mass spectra of synthetic **7** were in excellent agreement with those previously reported for this sterol,[12a,b] although the melting point for the synthetic acetate derivative was higher by some 15 °C (**7**: mp 139–140 °C; lit.[12a] mp 126–128.5 °C). Resonances for the C18, C19, C4α, and C4β methyl groups in synthetic **7** observed at 1.04, 0.81, 1.02, and 0.83 ppm, respectively, were identical with those recorded for the natural sterol.[12a] The mass spectral fragmentation patterns were also similar: *m/e* 410 (M^+), 393 ($M + H - H_2O$), 377 ($M^+ - H_2O - CH_3$) and 299 ($M^+ - C_8H_{15}$).[12b]

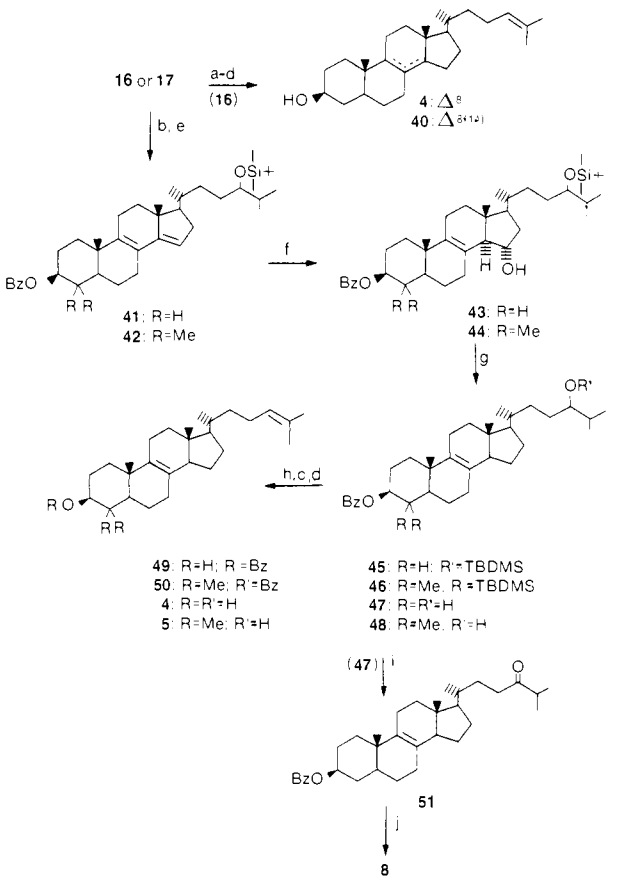
Synthesis of Sterols 4, 5, and 8. Zymosterol (**4**) was initially obtained as a 1:1 mixture with the $\Delta^{8(14)}$-isomer **40** following sequential hydrogenation, detrifluoroacetylation, dehydration, and saponification of intermediate **16** (Scheme III). Pure **4** (30%) and isomer **40** (32%) were isolated after careful reverse-phase HPLC (Zorbax, 1:1 CH_3CN–THF). The structure of **40** was assigned on the basis of ^{13}C NMR (C8, 128 ppm; C14, 142 ppm) while synthetic **4** showed physical and spectroscopic properties (^{13}C NMR: C8, 128 ppm; C9, 135 ppm) identical with that of the naturally occurring sterol.[27,28]

Regiocontrolled entry into the Δ^8-sterols from the 8,14-diene system was ultimately solved by employing a two-step hydroboration/deoxygenation sequence. Schroepfer and co-workers have reported, in conjunction with their synthesis of steroid-based hypocholesterolemic agents, that cholesta-8,14-dien-3β-ol undergoes hydroboration with complete regio- and diastereofacial control to provide cholest-8-ene-3β,15α-diol in high yield.[29] Exchange of the trifluoroacetyl for the *tert*-butyldimethylsilyl protecting groups[30] (**16** or **17** → **41** or **42**) and hydroboration of the resulting silyl ethers using borane–dimethyl sulfide complex in THF furnished intermediate alcohols **43** or **44** (50%; 75% yield based on recovered **41** or **42**).[31a,b] Barton-type deoxygenation[32] (thiocarbonate formation then Bu_3SnH reduction) readily provided isomerically pure benzoates **45** or **46** (90%).[31c] Intermediates **45** and **46** were converted to zymosterol (**4**) and 4,4-dimethylzymosterol (**5**), respectively, via standard fluoride-mediated desilylation (3 equiv of Bu_4NF, 25 °C, 12 h), dehydration (1.2 equiv of MSDA), and saponification (**45**, **46** → **47**, **48** → **49**, **50** → **4**, **5**; 85% overall yield).

Fecosterol (**8**) was prepared in three steps from **45** (Scheme III) via desilylation, Swern oxidation, and Wittig olefination[10d] (**45** → **47** → **51** → **8**; 82% overall yield). Again, synthetic sterols **4**, **5**, and **8** displayed physical and spectroscopic properties consistent with those of the naturally occurring sterols.[27]

In summary, the first syntheses of sterol biosynthetic intermediates **4–8** have been successfully completed. Noteworthy synthetic methodologies developed here include (1) an efficient six-step conversion of the ergosterol to cholesterol side chain (e.g. **20** → **18**) containing an appropriately protected C24-hydroxy moiety, (2) regiospecific preparation of 8,14-dienes from 8-(14)-en-15-ones (**18**, **19** → **16**, **17**) via intermediate 8,14-dienol triflates, (3) regiocontrolled entry into Δ^8 from $\Delta^{8,14}$-dienes (**41** → **43**) via a hydroboration/deoxygenation sequence, and (4) the quantitative dehydration of C24-OH to yield Δ^{24}-sterols (**35** → **36**). Moreover, we have now confirmed by synthesis that the proposed structure for **6**, the terminal fungal biosynthetic sterol intermediate of C14 demethylation of lanosterol, as characterized by Oehlschlager[12b] is correct. It is also believed that synthetic **7** will be of value in establishing the existence of this mammalian sterol as a constituent of cells.

Scheme III. Synthesis of Zymosterol (**4**), 4,4-Dimethylzymosterol (**5**), and Fecosterol (**8**)[a]



[a] Reagents and conditions: (a) Lindlar cat., toluene; (b) K_2CO_3, MeOH, 25 °C, 2 min; (c) Martin sulfurane, CH_2Cl_2, 0 °C; (d) b, 12 h; (e) *t*-BDMSiCl, imidazole, DMF, 25 °C; (f) $BH_3{\cdot}SMe_2$, THF, 25 °C, then H_2O_2; (g) PhOC(S)Cl, pyr, DMAP (cat.) CH_2Cl_2, 25 °C, then Bu_3SnH, AIBN, toluene, 80 °C; (h) *n*-Bu_4NF, THF, 24 h; (i) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, (j) $Ph_3P^+CH_3Br^-$, KO-*t*-Am, toluene, 70 °C.

Experimental Section

General Methods. Ergosterol was purchased from Sigma Chemical Co. Potassium *tert*-amylate was purchased from Calvery Chemical Co., Calvery, PA. All capillary GC analyses were carried out on a Chrom-

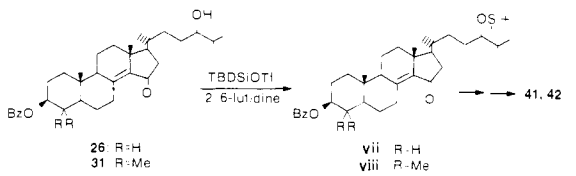
(26) (a) *Aldrichimica Acta* **1985**, *18*, 81. (b) Arhart, R. J.; Martin, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 5003. (c) Dolle, R. E.; Schmidt, S. J.; Kruse, L. I., unpublished results. (d) The trace amounts of the Δ^{23}-isomer can be readily removed by recrystallization.

(27) We thank Professor Oehlschlager, Department of Chemistry, Simon Fraser University, B.C., Canada for the ^1H NMR and mass spectrums of 7, as well as authentic samples of zymosterol (**4**) and fecosterol (**8**).

(28) ^{13}C NMR is a convenient and reliable method for assigning C8,9 vs C8,14 sites of unsaturation. Tsuda, M.; Parish, E. J.; Schroepfer, G. J., Jr. *J. Org. Chem.* **1979**, *44*, 1282.

(29) Parish, E. J.; Schroepfer, G. J., Jr. *Chem. Phys. Lipids* **1979**, *25*, 381.

(30) Direct silylation of alcohols **26** and **31** afford vii and viii in quantitative yield. Dienol triflate formation and then palladium-catalyzed reduction of these intermediates provide **41** and **42**, thus negating the need for **16** → **41** or **17** → **42** C24-protecting group exchange.



(31) (a) The remaining identified product was the corresponding diol. (b) Protonolysis of the borane intermediate with propionic acid afforded the rearranged $\Delta^{8(14)}$-isomer. (c) We have used this sequence to prepare 24,25-dihydrozymosterol (**12**) from (3β,5α)-cholesta-8,14-dien-3-ol benzoate.[2b]

(32) Robins, M. J.; Wilson, J. S. *J. Am. Chem. Soc.* **1982**, *103*, 932.

pack sil 5, 10 m × 0.24 mm column; flow rate, 1 mL/min H_2; oven temperature, 270 °C. All semipreparative HPLC was carried out on a Zorbax ODS column, 21.2 mm i.d. × 25 cm, with either 90:10 or 85:15 CH_3CN–THF as eluent and UV detection of sterols at 210 nm. High-resolution mass spectra (FAB) were determined at the Mass Spectrometer Resource facility in the SK&F Physical and Structural Chemistry Department (Philadelphia). Elemental analyses were also performed in this department.

(3β,5α,20S)-3-(Benzoyloxy)-15-oxopregn-8,14-ene-20-carboxaldehyde (22). A solution of ergostenone (**20**)[18] (50.0 g, 96.8 mmol) in CH_2Cl_2 (2.5 L) containing Sudan III (40 mL of a 0.05% CH_2Cl_2 solution) was cooled to −78 °C. Ozone was passed into the solution with stirring until the brilliant red color of the reaction began to fade to dull orange. Excess dimethyl sulfide (approximately 100 mL) was then added, and the solution was brought to room temperature.

The solution was concentrated in vacuo, and the residue was purified by flash chromatography (3% EtOAc–CH_2Cl_2) to give pure aldehyde **22** (33.1 g, 75%): mp 181–183 °C (lit.[18] mp 185–187 °C); R_f 0.46 (3% EtOAc–CH_2Cl_2); IR 3020, 2960, 2870, 1710, 1620, 1280 cm^{-1}; ^1H NMR δ 9.68 (d, 1 H, J = 3.5 Hz, CHO), 8.10 and 7.5 (m, 5 H, Ar), 5.05 (m, 1 H, H-3), 4.20 (d, 1 H, J = 16.0 Hz, H-7β), 2.80–0.80 (m, remaining H); mass spectrum, m/e 449 (M + H), 431, 391, 327. Anal. Calcd for $C_{29}H_{36}O_4$: C, 77.65; H, 8.09. Found: C, 77.38; H, 8.10.

(3β,5α,22R,S)-3-(Benzoyloxy)-22-hydroxycholest-8(14)-ene-15,24-dione (23). *n*-Butyllithium (90 mL of a 2.5 M hexane solution) was added to diisopropylamine (31.6 mL, 225 mmol) in THF (250 mL) at −78 °C. After 20 min, 3-methyl-2-butanone (24 mL, 223 mmol) in THF (50 mL) was added, and the colorless solution was then stirred for an additional 15 min. The resulting kinetic enolate was transferred rapidly via a cannula into a precooled (−78 °C) solution of aldehyde **22** (25 g, 55.8 mmol) in THF (150 mL). The stirred reaction was brought to 0 °C over a 1-h period and then poured into saturated aqueous NH_4Cl (400 mL). The solution was extracted with EtOAc (3 × 200 mL), and the combined extracts were further washed with 1 N aqueous HCl (2 × 200 mL), saturated $NaHCO_3$ (2 × 200 mL), water (200 mL), and brine (200 mL) and then dried ($MgSO_4$). The solution was filtered and concentrated (to ca. 200 mL) and then hexane (200 mL) was added and the solution was chilled to 0 °C. The white crystals of **23** which separated (25.2 g, 85%) were collected and dried (25 °C, 1.0 mm). The mother liquor was concentrated in vacuo to a thick oil which, following flash chromatography (30% EtOAc–CH_2Cl_2), gave additional aldol adduct **23** (3 g, 95% combined yield): mp 175–180 °C; R_f 0.15 (5% EtOAc–CH_2Cl_2); IR 3350, 2940, 1720, 1710, 1620, 1280 cm^{-1}; ^1H NMR δ 8.10 and 7.50 (m, 5 H, Ar), 5.05 (m, 1 H, H-3), 4.11 (m, 2 H, H-7β,22), 2.25–0.80 (m, remaining H): mass spectrum, m/e 535 (M + H), 517, 499, 449, 413, 395, 327, 309. Anal. Calcd for $C_{34}H_{46}O_5$: C, 76.40; H, 8.61. Found: C, 76.22; H, 8.65.

(3β,5α-22E)-3-(Benzoyloxy)cholesta-8(14),22-diene-15,24-dione (24). A solution of benzoate **23** (30 g, 56.2 mmol) in 3:1 toluene–$CHCl_3$ (600 mL) containing *p*-toluenesulfonic acid (1.0 g) and anhydrous $MgSO_4$ (20 g) was heated to 70 °C for 3 h. The reaction was filtered, diluted with ether (400 mL), washed with saturated aqueous $NaHCO_3$ (2 × 200 mL), water (200 mL), and brine (200 mL), and then dried ($MgSO_4$). Removal of the solvents in vacuo gave essentially pure bis-enone **24** (28.3 g, 98%). A sample was recrystallized (ether–hexane): mp 155–156 °C; R_f 0.35 (5% EtOAc–CH_2Cl_2); $[\alpha]^{25}_D$ +92° (c 1.0, $CHCl_3$); IR 2960, 2880, 1720, 1710, 1670, 1620, 1280 cm^{-1}; ^1H NMR δ 8.10 and 7.50 (m, 5 H, Ar), 6.81 (dd, 1 H, J = 15.0 and 9.0 Hz, H-22), 6.22 (d, 1 H, J = 15.0 Hz, H-23), 5.10 (m, 1 H, H-3), 4.10 (m, 1 H, H-7β), 2.80 (m, 1 H, H25), 1.18 (d, 6 H each, J = 2.0 Hz, CH_3-26,27), 1.09 (d, 3 H, J = 2.5 Hz, CH_3-20), 1.01 (s, 3 H, CH_3-19), 0.77 (s, 3 H, CH_3-18), 2.50–0.90 (m, remaining H); ^{13}C NMR δ 206.4, 203.8, 166.0, 151.0, 150.3, 139.6, 132.7, 130.8, 129.5, 128.2, 126.9, 73.7, 50.8, 50.1, 43.9, 38.9, 38.6, 19.9, 19.1, 18.4, 18.3, 12.9; mass spectrum, m/e 517 (M + H), 395, 377, 269. Anal. Calcd for $C_{34}H_{44}O_4$: C, 79.03; H, 8.58. Found: C, 79.11; H, 8.83.

(3β,5α)-3-(Benzoyloxy)cholest-8(14)-ene-15,24-dione (25). Lindlar catalyst (2.0 g, Aldrich) was added to a solution of crude bis-enone **24** (28.3 g, 56.8 mmol) in 3:1 toluene–$CHCl_3$ (250 mL). The mixture was stirred under ambient H_2 pressure for 12 h and then filtered. The solvents were removed in vacuo to furnish essentially pure diketone **25** (28.4 g, 100%). A sample was recrystallized (EtOAc–hexane). For **25**: mp 177–178 °C; R_f 0.35 (5% EtOAc–CH_2Cl_2); $[\alpha]^{25}_D$ +100.0° (c 1.0, $CHCl_3$); IR 2960, 2880, 1720, 1630, 1260 cm^{-1}; ^1H NMR δ 8.10 and 7.50 (m, 5 H, Ar), 4.95 (m, 1 H, H-3), 4.15 (m, 1 H, H-7β), 0.76 (s, 3 H, CH_3-18), 2.55–0.80 (m, remaining H); ^{13}C NMR δ 214.5, 207.3, 165.9, 150.2, 140.2, 132.7, 130.7, 129.5, 128.2, 73.7, 50.8, 50.7, 43.9, 40.8, 34.0, 18.9, 18.8, 18.3, 18.2, 12.8; mass spectrum, m/e 519 (M + H), 397, 379, 315. Anal. Calcd for $C_{34}H_{46}O_4$: C, 78.72; H, 8.94. Found: C, 78.74; H, 9.30.

(3β,5α,24R,S)-3-(Benzoyloxy)-24-(trifluoroacetoxy)cholest-8(14)-en-15-one (18). A solution of crude diketone **25** (28.4 g, 56.8 mmol) in CH_2Cl_2 (300 mL) was treated with *tert*-butylamine–borane complex (4.0 g, 46.5 mmol). The solution was heated at reflux for 1 h and cooled to 0 °C, and 1 N aqueous HCl (200 mL) was then added. The two-phase solution was stirred for 1 h at 0 °C (H_2 evolution). The CH_2Cl_2 phase was removed and was washed with 1 N aqueous HCl (100 mL), water (100 mL), saturated aqueous $NaHCO_3$ (2 × 100 mL), and brine (100 mL) and then dried ($MgSO_4$). Removal of the solvent in vacuo afforded crude enone alcohol **26** (29 g, 100%), which was used directly. Compound **26**: R_f 0.25 (8% EtOAc–CH_2Cl_2); ^1H NMR δ 8.10 and 7.50 (m, 5 H, Ar), 5.05 (m, 1 H, H-3), 4.20 (m, 1 H, 7β-H), 3.30 (br s, 1 H, H-24), 2.55–0.80 (m, remaining H).

Crude enone alcohol **26** was redissolved in CH_2Cl_2 (300 mL) and cooled to 0 °C. Pyridine (15 mL, 184 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (6.6 g, 55.2 mmol) were then added followed by the dropwise (10 min) addition of trifluoroacetic anhydride (11.9 mL, 85.2 mmol). The reaction mixture was stirred for 2 min and then washed with water (100 mL), 1 N aqueous HCl (3 × 100 mL), saturated aqueous $NaHCO_3$ (100 mL), water (100 mL), and brine (100 mL) and then dried ($MgSO_4$). Removal of solvent in vacuo gave a residue which, following flash chromatography (70% CH_2Cl_2 in petroleum ether), afforded trifluoroacetate **18** (32.3 g, 92%): foam; R_f 0.35 (5% EtOAc–CH_2Cl_2); IR 2960, 2880, 1785, 1720, 1620, 1210 cm^{-1}; ^1H NMR δ 8.10 and 7.50 (m, 5 H, Ar), 4.95 (m, 2 H, H-3,24), 4.20 (m, 1 H, H-7β), 2.55–0.80 (remaining H); mass spectrum, m/e 617 (M + H), 503, 495, 467, 453, 391, 381, 269, 251; high-resolution FAB mass spectrum, calcd for $C_{36}H_{47}O_5F_3$ 616.3381, found 616.3382.

(3β,5α,20S)-3-(Benzoyloxy)-4,4-dimethyl-15-oxopregn-8,14-ene-20-carboxaldehyde (27). Ozonolysis of enone **21** (30 g, 55.1 mmol) was carried out as described for the preparation of **22**, to give enone aldehyde **27** (19.4 g, 74%). A small sample was recrystallized (ether–hexane). **27**: mp 148–149 °C; R_f 0.51 (3% EtOAc–CH_2Cl_2); IR 2960, 1710, 1630, 1260 cm^{-1}; ^1H NMR δ 9.70 (d, 1 H, J = 3.5 Hz, CHO), 8.10 and 7.50 (m, 5 H, Ar), 4.90 (m, 1 H, H-3), 4.20 (d, 1 H, J = 16.0 Hz, H-7β), 2.80–0.80 (m, remaining H); mass spectrum, m/e 477 (M + H), 459, 449, 391, 355, 327. Anal. Calcd for $C_{31}H_{40}O_4 \cdot {}^1/_2H_2O$: C, 76.70; H, 8.45. Found: C, 76.42; H, 8.45.

(3β,5α,24R,S)-3-(Benzoyloxy)-4,4-dimethyl-24-(trifluoroacetoxy)-cholest-8(14)-en-15-one (19). Aldol condensation, dehydration, hydrogenation, reduction, and trifluoroacetylation of aldehyde **27** (15 g, 31.5 mmol) was carried out as for the preparation of the desmethyl analgoue **18**, without purification of intermediates **28–31** to yield **19** (17.4 g, 86%): mp 143–145 °C; R_f 0.40 (5% EtOAc–CH_2Cl_2); IR 2980, 1785, 1720, 1280 cm^{-1}; ^1H NMR δ 8.10 and 7.50 (m, 5 H, Ar), 4.81 (m, 2 H, H-3,24), 4.20 (m, 1 H, H-7β), 2.55–0.80 (remaining H); mass spectrum, m/e 645 (M + H), 531, 523, 409. Anal. Calcd for $C_{38}H_{51}O_5F_3$: C, 70.78; H, 7.97. Found: C, 70.78; H, 7.98.

(3β,5α,24R,S)-Cholesta-8,14-diene-3,15,24-triol 3-Benzoate 24-Trifluoromethanesulfonate (33). A solution of enone **18** (25 g, 40.6 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (DBMP, 13.3 g, 64.9 mmol) in CH_2Cl_2 (250 mL) at 0 °C was treated with trifluoromethanesulfonic anhydride (9.6 mL, 56.8 mmol). The reaction mixture was stirred overnight at ambient temperature and then heated at reflux for 30 min. The reaction mixture was cooled to 0 °C and diluted with hexane (800 mL). The precipitated pyridinium triflate salt was removed by filtration, and the solvents were removed in vacuo.

The residue so obtained was purified by flash chromatography (50% CH_2Cl_2–petroleum ether) to remove excess DBMP to give dienol triflate **33** (29.1 g, 96%): mp 90 °C dec; R_f 0.45 (5% EtOAc–petroleum ether); IR 2960, 1785, 1720, 1630, 1280 cm^{-1}; ^1H NMR 8.10 and 7.50 (m, 5 H, Ar), 5.05 (m, 2 H, H-3,24), 2.55–0.80 (m, remaining H); mass spectrum, m/e 748 (M + H), 627, 615, 601, 493. Anal. Calcd for $C_{37}H_{46}O_7F_6S$: C, 59.61; H, 6.06. Found: C, 59.41; H, 6.09.

(3β,5α,24R,S)-Cholesta-8,14-diene-3,24-diol 3-Benzoate 24-Trifluoroacetate (16). Palladium acetate (450 mg, 2.0 mmol) and triphenylphosphine (1.05 g, 4.0 mmol) were added to a solution of dienol triflate **33** (27.0 g, 36.1 mmol) in DMF (105 mL). Following the addition of tributylamine (37.5 mL, 156.1 mmol) and then formic acid (3.75 mL of a 98% solution), the reaction was warmed to 70 °C for 30 min.

The black mixture was concentrated in vacuo to a thick dark oil and then diluted with water (300 mL) and extracted with 10% CH_2Cl_2–ether (3 × 50 mL). The combined extracts were washed with 1 N aqueous HCl (3 × 100 mL), saturated aqueous $NaHCO_3$ (100 mL), water (5 × 100 mL), and brine (100 mL) and dried ($MgSO_4$). Removal of the solvents in vacuo and flash chromatography (50% CH_2Cl_2–petroleum ether) gave diene **16** (21.2 g, 98%): foam; R_f 0.47 (5% EtOAc–petroleum ether); IR 2960, 2880, 1785, 1720, 1280, 1220 cm^{-1}; ^1H NMR δ 8.10 and 7.50 (m, 5 H, Ar), 5.40 (s, 1 H, H-15), 4.95 (m, 2 H, H-3,24), 2.55–0.70

(m, remaining H); ^{13}C NMR δ 166.0, 150.9, 140.5, 132.6, 130.8, 129.4, 128.2, 123.2, 117.2; mass spectrum, *m/e* 600 (M^+), 487, 479, 463, 375, 253. Anal. Calcd for $C_{36}H_{47}O_4F_3$: C, 72.06; H, 7.83. Found: C, 72.08; H, 7.97.

(3β,5α,24*R*,*S*)-4,4-Dimethylcholesta-8,14-diene-3,24-diol 3-Benzoate 24-Trifluoroacetate (17). Enone **19** (10 g, 15.5 mmol) was converted to intermediate dienol triflate **37** and then to diene **17** (9.1 g, 94%) as described for the desmethyl diene: foam; R_f 0.54 (5% EtOAc–petroleum ether); IR 2960, 1785, 1720, 1280 cm^{-1}; ^{1}H NMR δ 8.10 and 7.50 (m, 5 H, Ar), 5.40 (s, 1 H, H-15), 4.85 (m, 2 H, H-3,24), 2.55–0.70 (m, remaining H); mass spectrum, *m/e* 628 (M^+), 515, 507, 403, 393, 226. Anal. Calcd for $C_{38}H_{51}O_4F_3$: C, 72.61; H, 8.12. Found: C, 72.93; H, 8.15.

(3β,5α)-Cholesta-8,14,24-trien-3-ol Benzoate (36) and the 4,4-Dimethyl Analogue (39). Trifluoroacetate **16** (2 g, 3.3 mmol) was dissolved in 1:1 CH_2Cl_2–methanol (20 mL) and powdered anhydrous K_2CO_3 (500 mg) was added in one portion. The heterogeneous reaction mixture was stirred for 5 min at 25 °C and then diluted with water (100 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The extracts were combined and washed with 1 N aqueous HCl (2 × 20 mL), water (2 × 20 mL), and brine (20 mL) and then dried ($MgSO_4$). Evaporation of solvents in vacuo gave essentially pure alcohol **35** (1.7 g, 100%), which was used without further purification: foam; R_f 0.3 (3% EtOAc–CH_2Cl_2); ^{1}H NMR 8.10 and 7.50 (m, 5 H, Ar), 5.10 (m, 1 H, H-3), 3.42 (m, 1 H, H-24), 2.55–0.80 (m, remaining H).

The crude alcohol was azeotroped with dry toluene (3 × 15 mL) and dissolved in CH_2Cl_2 (10 mL). Bis[α,α-bis(trifluoromethyl)benzenemethanolato]diphenylsulfur (3.3 g, 4.5 mmol) was then added to the cooled (−20 °C) solution. After stirring for 15 min at 0 °C, the solvent was removed in vacuo and the residue was purified by flash chromatography (70% CH_2Cl_2–petroleum ether) to give a mixture of trienes **36** (97%) and the $\Delta^{8,14,23}$-isomer (3%; capillary GC). Two recrystallizations (EtOAc–hexane) of this material afforded pure **36** (1.4 g, 87%): mp 124–5 °C; R_f 0.90 (5% EtOAc–petroleum ether); IR 2960, 1720, 1270 cm^{-1}; ^{1}H NMR 8.10 and 7.50 (m, 5 H, Ar), 5.40 (s, 1 H, H-15), 5.11 (m, 2 H, H-3, 24), 2.55–0.80 (m, remaining H); mass spectrum, *m/e* 487 (M + H), 471, 375, 365. Anal. Calcd for $C_{34}H_{46}O_2$: C, 83.90; H, 9.53. Found: C, 83.57; H, 9.52.

The 4,4-dimethyl analogue **39** was prepared from **17** as described above (88%): mp 130–132 °C; R_f 0.95 (5% EtOAc–petroleum ether); IR 2960, 1720, 1450, 1280 cm^{-1}; ^{1}H NMR δ 8.10 and 7.50 (m, 5 H, Ar), 5.45 (s, 1 H, (m, remaining H); mass spectrum, *m/e* 513 (M − H), 499, 393. Anal. Calcd for $C_{36}H_{50}O_2 \cdot {}^1/_2H_2O$: C, 82.40; H, 9.80. Found: C, 82.68; H, 9.88.

(3β,5α)-Cholesta-8,14,24-trien-3-ol (6) and (3β,5α)-4,4-Dimethylcholesta-8,14,24-trien-3-ol (7). Benzoate **36** (1 g, 2.1 mmol) was dissolved in 2:1 toluene–methanol (10 mL) at 25 °C and NaOMe (8 mL of 1 M methanol solution) was then added. The reaction was stirred for 12 h, concentrated to one-third the original volume, diluted with water (40 mL), and extracted with EtOAc (3 × 10 mL). The extracts were combined and washed sequentially with 1 N aqueous HCl (2 × 10 mL), water (2 × 10 mL), and brine (10 mL) and then dried ($MgSO_4$). The solvents were removed in vacuo, and the resulting residue was purified by flash chromatography (10% EtOAc–CH_2Cl_2) to provide analytically pure trienol **6** (762 mg, 95%): mp 114–115 °C; R_f 0.25 (15% EtOAc–petroleum ether); $[\alpha]^{25}_D$ +12.5° (*c* 0.8, $CHCl_3$); IR 3350, 2960, 1640, 1270 cm^{-1}; ^{1}H NMR δ 5.35 (s, 1 H, H-15), 5.10 (t, 1 H, *J* = 7.0 Hz, H-24), 3.62 (m, 1 H, H-3), 1.68 and 1.60 (s, 3 H, CH_3-26,27), 0.99 (s, 3 H, CH_3-18), 0.95 (d, 3 H, *J* = 6.2 Hz, CH_3-20), 0.81 (s, 3 H, CH_3-19), 2.40–0.80 (m, remaining H); ^{13}C NMR δ 151.0, 140.8, 130.9, 125.1, 123.1, 117.4, 70.9, 57.1, 45.0, 40.9, 38.3, 18.8, 18.4, 17.6, 15.7; mass spectrum, *m/e* 383 (M + H), 365, 271. Anal. Calcd for $C_{27}H_{42}O$: C, 84.75; H, 11.06. Found: C, 84.36; H, 11.08.

The dimethyl analogue **7** was prepared by saponification of benzoate **39** using NaOMe/MeOH as described above (96%): mp 119–121 °C; R_f 0.30 (5% EtOAc–petroleum ether); $[\alpha]^{25}_D$ −17.2° (*c* 1.0, $CHCl_3$); IR 3350, 2960, 1640, 1450, 1360, 1240 cm^{-1}; ^{1}H NMR δ 5.35 (s, 1 H, H-15), 5.10 (t, 1 H, *J* = 7.0 Hz, H-24), 3.25 (dd, 1 H, *J* = 4.6 and 11.5 Hz, H-3), 1.67 and 1.61 (singlets, 3 H each, CH_3-26,27), 1.04 (s, 3 H, CH_3-18), 1.02 (s, 3 H, CH_3-4α), 0.96 (d, 3 H, *J* = 6.5 Hz, CH_3-20), 0.83 (s, 3 H, C-4β), 0.81 (s, 3 H, CH_3-19), 2.40–0.80 (m, remaining H); ^{13}C NMR δ 151.1, 141.8, 130.9, 125.2, 122.9, 117.3, 78.8, 57.3, 50.5, 45.1, 39.1, 37.8, 20.5, 18.8, 17.6, 15.7, 15.4; mass spectrum, *m/e* 409 (M − H), 393, 377, 299. Anal. Calcd for $C_{29}H_{46}O$: C, 84.81; H, 11.29. Found: C, 84.83; H, 11.45.

The acetate of **7** was prepared in the standard fashion: mp 139–140 °C (lit.[12a] mp 126–128.5 °C); ^{1}H NMR δ 5.35 (s, 1 H, H-15), 5.10 (t, 1 H, *J* = 7.0 Hz, H-24), 4.45 (m, 1 H, H-3), 2.03 (s, 3 H, $OCOCH_3$), 1.68 and 1.60 (s, 3 H each, CH_3-26,27), 1.09 (s, 3 H, CH_3-18), 0.96 (s, 9 H, CH_3-4α,4β,20), 0.81 (s, 3 H, CH_3-19).

(3β,5α)-Cholesta-8,24-dien-3-ol (4) and (3β,5α)-Cholesta-8(14),24-dien-3-ol (40). Lindlar catalyst (100 mg, Aldrich) was added to a solution of **16** (1.1 g, 1.6 mmol) in toluene (40 mL). The mixture was stirred under ambient H_2 pressure for 12 h and then filtered. Removal of the solvent in vacuo gave a white crystalline residue (1.1 g, 100%) which was shown by ^{13}C NMR to be a 1:1 mixture of Δ^8- and $\Delta^{8(14)}$-isomers: ^{13}C NMR δ 142.5 (C14, $\Delta^{8(14)}$), 135.0 (C9, Δ^8), 128.2 (C8, Δ^8), 126.1 (C8, $\Delta^{8(14)}$).[28] Subsequent detrifluoroacetylation (K_2CO_3, MeOH), dehydration (Martin sulfurane), and saponification (NaOMe, MeOH) as described for the synthesis of intermediates **38** and **6** gave pure zymosterol **4** (640 mg, 22%) and the 8(14),22-diene isomer **40** (785 mg, 27%), following reverse phase HPLC (9:1 CH_3CN–THF). For **4**: mp 109–110 C (lit.[9g] mp 110–111 °C); R_f 0.21 (5% EtOAc–petroleum ether); retention time 13.2 min (HPLC, 9:1 CH_3CN–THF; flow rate 2.0 mL/min); $[\alpha]^{25}_D$ +50° (*c* 0.45, $CHCl_3$) [lit.[9g] $[\alpha]^{25}_D$ +52° (*c* 1.0, $CHCl_3$)]; IR 3350, 2980, 2860, 1420 cm^{-1}; ^{1}H NMR δ 5.10 (t, 1 H, *J* = 7.0 Hz, H-24), 3.60 (m, 1 H, H-3), 1.68 and 1.60 (s, 3 H each, CH_3-26,27), 0.61 (s, 3 H, CH_3-18), 2.40–0.80 (m, remaining H); ^{13}C NMR δ 135.1, 130.8, 128.3, 125.2, 71.2, 54.9, 51.9, 42.2, 40.8, 38.4, 37.0, 18.6, 17.8, 17.6, 17.2; mass spectrum, *m/e* 383 (M − H), 367, 273; high-resolution FAB mass spectrum calcd for $C_{27}H_{44}O$ 384.3401, found 384.3390.

Diene **40**: mp 104–105 °C; R_f 0.21 (5% EtOAc–petroleum ether); retention time 12.9 min (HPLC, 9:1 CH_3CN–THF; flow rate 2.0 mL/min); $[\alpha]^{25}_D$ +18° (*c* 0.6, $CHCl_3$); IR 3350, 2940, 2880, 1450, 1380, 1150 cm^{-1}; ^{1}H NMR δ 5.11 (t, 1 H, *J* = 7.0 Hz, H-24), 3.61 (m, 1 H, H-3), 1.68 and 1.60 (s, 3 H each, CH_3-26,27), 0.68 (s, 3 H, CH_3-18), 2.4–0.7 (m, remaining H); ^{13}C NMR δ 142.6, 130.9, 126.3, 125.1, 25.7, 18.9, 18.3, 17.6, 12.8; mass spectrum, *m/e* 385 (M^+), 367, 273. Anal. Calcd for $C_{27}H_{44}O$: C, 84.31; H, 11.53. Found: C, 84.46; H, 11.43.

(3β,5α,24*R*,*S*)-24-[(*tert*-Butyldimethylsilyl)oxy]cholesta-8,14-dien-3-ol Benzoate (41) and the 4,4-Dimethyl Analogue (42). Selective saponification of the 24-trifluoroacetyl protecting group in diene **16** (2 g, 3.3 mmol) was conducted with K_2CO_3 in methanol as described for the preparation of intermediate **38**. Crude alcohol 36 so obtained (quantitative yield) was azeotropically dried with toluene (3 × 10 mL) and dissolved in CH_2Cl_2 (10 mL). 2,6-Lutidine (0.60 mL, 5.0 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.84 mL, 3.5 mmol) were then added to the cooled (0 °C) solution. The reaction mixture was stirred for 2 min and then diluted with ether (90 mL) and sequentially washed with 1 N aqueous HCl (2 × 15 mL), saturated aqueous $NaHCO_3$ (2 × 15 mL), water (15 mL), and brine (15 mL) and then dried ($MgSO_4$). Removal of the solvents in vacuo and purification by flash chromatography (50% CH_2Cl_2–petroleum ether) gave silyl ether **41** (2.0 g, 98%): mp 67–69 °C; R_f 0.95 (CH_2Cl_2); IR 2960, 2880, 1720, 1280 cm^{-1}; ^{1}H NMR δ 8.10 and 7.50 (m, 5 H, Ar), 5.40 (s, 1 H, H-15), 4.95 (m, 1 H, H-3), 3.40 (m, 1 H, H-24), 0.01 (m, 6 H, $SiCH_3$), 2.55–0.80 (m, remaining H); mass spectrum, *m/e* 617 (M − H), 603, 561, 497, 487, 431, 365; high-resolution FAB mass spectrum calcd for $C_{40}H_{62}O_3Si$ 618.4450, found 618.4470.

The 4,4-dimethyl analogue **42** was prepared (98%) from diene **17** as described above. Compound **42**: foam, R_f 0.42 (50% CH_2Cl_2–petroleum ether); IR 2930, 2855, 1720, 1250 cm^{-1}; ^{1}H NMR δ 8.10 and 7.50 (m, 5 H, Ar), 5.40 (s, 1 H, H-15), 4.75 (m, 1 H, H-3), 3.40 (m, 1 H, H-24), 0.001 (m, 6 H, $SiCH_3$), 2.40–0.80 (m, remaining H); mass spectrum, *m/e* 648 (M + H), 515, 499, 257. Anal. Calcd for $C_{42}H_{66}SiO_3$: C, 77.96; H, 10.28. Found: C, 77.70; H, 10.14.

(3β,5α,15α,24*R*,*S*)-24-[(*tert*-Butyldimethylsilyl)oxy]-cholest-8-ene-3,15-diol 3-Benzoate (43). A solution of diene **41** (2.0 g, 3.2 mmol) in THF (30 mL) was cooled to 0 °C. Borane–dimethyl sulfide complex (0.6 mL of a 10 M THF solution) was added and the reaction was stirred at room temperature for 2 h. The solution was recooled (0 °C) and water (1 mL) was cautiously added, followed by the addition of 3 N aqueous NaOH (1 mL) and 30% aqueous H_2O_2 (1 mL). After stirring at 0 °C for 1 h, the solution was diluted with water and extracted with ether (3 × 50 mL). The ether extracts were combined and washed with water (3 × 40 mL) and brine (40 mL) and dried ($MgSO_4$). Evaporation of the solvents in vacuo and purification of the residue by flash chromatography (2% EtOAc–CH_2Cl_2) gave recovered **41** (600 mg, 30%) and alcohol **43** (1.1 g, 50%, 70% yield based on recovered diene): foam; R_f 0.41 (C-H_2Cl_2); IR 3350, 2960, 2880, 1720, 1280 cm^{-1}; ^{1}H NMR δ 8.10 and 7.50 (m, 5 H, Ar), 4.95 (m, 1 H, H-3), 4.10 (m, 1 H, H-15), 3.38 (br s, 1 H, H-24), 0.01 (m, 6 H, $SiCH_3$), 2.40–0.80 (m, remaining H); mass spectrum, *m/e* 635 (M − H), 619, 603, 579, 561, 515, 497, 487, 383, 365; high-resolution FAB mass spectrum calcd for $C_{40}H_{64}O_4Si$ 636.4570, found 636.4571.

(3β,5α,24*R*,*S*)-24-[(*tert*-Butyldimethylsilyl)oxy]cholest-8-en-3-ol Benzoate (45) and the 4,4-Dimethyl Analogue (46). Phenyl chlorothionocarbonate (0.45 mL, 2.6 mmol) was added to a cooled (0 °C) solution of alcohol **43** (1.46 g, 2.3 mmol) containing pyridine (5 mL) and

4-(*N*,*N*-dimethylamino)pyridine (61 mg, 0.15 mmol). The reaction was stirred for 12 h then and poured onto ice and ether (40 mL). The organic phase was washed with saturated $CuSO_4$ (6 × 10 mL), water (10 mL), 1 N aqueous NaOH (3 × 10 mL), water (10 mL), and brine (10 mL) and then dried ($MgSO_4$). The solvents were removed in vacuo to give the crude thiocarbonate (100% yield), which was used directly.

The above thiocarbonate was azeotroped with toluene (3 × 10 mL) and dissolved in toluene (8 mL). The solution was degassed with argon, treated with tributyltin hydride (0.87 mL, 3.0 mmol) and AIBN (20 mg), and heated to 90 °C. After 20 min the reaction was cooled and concentrated in vacuo. Purification of the residual dark oil by flash chromatography (40% CH_2Cl_2–petroleum ether) gave the Δ^8-olefin **45** (1.48 g, 92%): foam; R_f 0.48 (50%, CH_2Cl_2–petroleum ether); IR 2960, 2880, 1720, 1430, 1240 cm^{-1}; ^1H NMR δ 8.10 and 7.50 (m, 5 H, Ar), 4.95 (m, 1 H, H-3), 3.35 (br s, 1 H, H-24), 0.01 (m, 6 H, $SiCH_3$), 2.40–0.80 (m, remaining H); mass spectrum, *m/e* 619 (M − H), 605, 563, 499, 489, 367; high-resolution FAB mass spectrum calcd for $C_{40}H_{64}O_3Si$ 620.4640, found 620.4630.

The 4,4-dimethyl analogue **46** was prepared from diene **42** (2 g, 3.1 mmol) by conversion to Δ^8-olefin **46** (843 mg, 42%) via hydroboration and deoxygenation as described for the desmethyl analogue. For **46**: foam; R_f 0.61 (50% CH_2Cl_2–petroleum ether); IR 2960, 2880, 1720 cm^{-1}; ^1H NMR δ 8.10 and 7.50 (m, 5 H, Ar), 4.75 (m, 1 H, H-3), 3.45 (m, 1 H, H-24), 0.01 (m, 6 H, $SiCH_3$), 2.40–0.80 (m, remaining H); mass spectrum, *m/e* 645 (M + H), 512, 495, 255.

Anal. Calcd for $C_{42}H_{68}O_3Si \cdot {}^1/_2H_2O$: C, 76.59; H, 10.33. Found: C, 76.28; H, 10.24.

(3β,5α,24*R*,*S*)-Cholest-8-ene-3,24-diol 3-Benzoate (47). Silyl ether **45** (1 g, 1.6 mmol) was dissolved in a THF solution containing tetra-*n*-butylammonium fluoride (8 mL of 1 M THF solution). After stirring at ambient temperature for 12 h, the reaction mixture was diluted with ether (50 mL). The ether solution was washed with water (5 × 15 mL) and brine (15 mL) and then dried ($MgSO_4$). Removal of the solvents in vacuo and purification of the residue by flash chromatography (CH_2Cl_2) furnished alcohol **47** (807 mg, 99%): foam; R_f 0.21 (CH_2Cl_2); IR 3350, 2940, 2880, 1720, 1260 cm^{-1}; ^1H NMR δ 8.10 and 7.50 (m, 5 H, Ar), 4.95 (m, 1 H, H-3), 3.45 (m, 1 H, H-24), 2.40–0.80 (m, remaining H); mass spectrum, *m/e* 505 (M − H), 489, 463, 385, 367, 255; high-resolution FAB mass spectrum calcd for $C_{34}H_{50}O_3$ 506.3730, found 506.3760.

(3β,5α)-Cholesta-8,24-dien-3-ol Benzoate (49) and the 4,4-Dimethyl Analogue (50). A solution of alcohol **47** (500 mg, 0.98 mmol) in CH_2Cl_2 (5 mL) was cooled to −20 °C and Martin sulfurane (1.1 g, 1.5 mmol) was then added in one portion. The reaction was stirred for 15 min at 0 °C, and then the solvents were removed in vacuo. Purification of the residue by flash chromatography (50% CH_2Cl_2–petroleum ether) afforded benzoate **49** (97%) containing some Δ^{23}-isomer (3%, capillary GC). Two recrystallizations (ether–hexane) of this material gave pure zymosterol benzoate (**49**) (419 mg, 87%): mp 125–127 °C (lit.[10d] mp 126–128 °C); R_f 0.90 (5% EtOAc–petroleum ether); $[\alpha]^{25}_D$ +45° (*c* 1.0, $CHCl_3$) [lit.[10d] $[\alpha]^{27}_D$ +44.8°]; IR 3060, 2940, 2880, 1720, 1240 cm^{-1}; ^1H NMR δ 8.10 and 7.50 (m, 5 H, Ar), 5.05 (m, 2 H, H-3, 24), 2.55–0.80 (m, remaining H); mass spectrum, *m/e* 489 (M + H), 471, 375. Anal. Calcd for $C_{34}H_{48}O_2$: C, 83.60; H, 9.83. Found: C, 83.92; H, 9.80.

4,4-Dimethylzymosterol benzoate (**50**) was prepared by desilylation of intermediate **46** (500 mg, 0.78 mmol) to give **48**. Dehydration with Martin sulfurane as described above for **47** provided benzoate **50** (350 mg, 87%): mp 131–132 °C (lit. mp 126–128 °C); R_f 0.95 (5% EtOAc–petroleum ether); $[\alpha]^{25}_D$ +36° (*c* 1.0, $CHCl_3$) [lit.[13] $[\alpha]^{25}_D$ +19°]; IR 2980, 2860, 1720, 1420, 1220 cm^{-1}; ^1H NMR δ 8.10 and 7.50 (m, 5 H, Ar), 5.21 (t, 1 H, *J* = 3.0 Hz, H-24), 4.80 (m, 1 H, H-3), 2.50–0.80 (m, remaining H); mass spectrum, *m/e* 517 (M + H), 501, 395. Anal. Calcd for $C_{36}H_{52}O_2$: C, 83.72; H, 10.07. Found: C, 83.70; H, 10.09.

Zymosterol (4) and 4,4-Dimethylzymosterol (5). A solution of zymosterol benzoate (**49**) (200 mg, 0.41 mmol) in CH_2Cl_2 (1 mL) was treated with Dibal (1 mL of a 1 M solution in hexane) at 0 °C. The reaction was stirred for 15 min, and methanol (0.2 mL) and EtOAc (10 mL) were added sequentially. The solution was washed with saturated aqueous sodium potassium tartrate (3 × 2 mL), water (2 mL) and brine (2 mL) and then dried ($MgSO_4$). Removal of the solvents in vacuo and purification of the residue by flash chromatography (15% EtOAc–CH_2Cl_2) gave zymosterol (**4**) (141 mg, 90%). This material exhibited physical and spectroscopic properties identical with those of **4** which had been prepared previously via the hydrogenation of intermediate diene **16**.

4,4-Dimethylzymosterol (**5**) was prepared by reduction of the benzoate protecting group in diene **50** using Dibal as described above (84%): mp 128–129 °C (lit.[13] mp 124–127 °C); R_f 0.42 (15% EtOAc–CH_2Cl_2); $[\alpha]^{25}_D$ +19° (*c* 0.5, $CHCl_3$ (lit.[13] $[\alpha]^{25}_D$ +12°); IR 3350, 2980, 2880, 1240 cm^{-1}; ^1H-NMR δ 5.21 (t, 1 H, *J* = 3.0 Hz, H-24), 3.30 (m, 1 H, H-3), 2.55–0.80 (m, remaining H); mass spectrum, *m/e* 413 (M + H), 394, 301.

Anal. Calcd for $C_{29}H_{48}O$: C, 84.46; H, 11.65. Found: C, 84.18; H, 11.61.

(3β,5α)-3-(Benzoyloxy)ergost-8-en-24-one (51). A solution of alcohol **47** (500 mg, 0.98 mmol) in CH_2Cl_2 (1 mL) was added to a cold solution (−78 °C) of DMSO (0.15 mL, 2 mmol) and oxalyl chloride (0.065 mL, 0.74 mmol) in CH_2Cl_2 (4 mL). The reaction was stirred for 5 min at −78 °C and triethylamine (0.40 mL, 3.9 mmol) was then added. The reaction mixture was warmed to 25 °C and then washed with water (2 × 1 mL) and brine (1 mL) and then dried ($MgSO_4$). Removal of solvents in vacuo and purification of the residue by flash chromatography (CH_2Cl_2) furnished ketone **51** (438 mg, 88%): mp 164–165 °C (lit.[10d] mp 152–156 °C); R_f 0.38 (CH_2Cl_2; $[\alpha]^{25}_D$ +47° (*c* 1.0, $CHCl_3$) [lit.[10d] $[\alpha]^{25}_D$ +50.0° (*c* 0.48, $CHCl_3$)]; IR 3060, 2940, 1720, 1710, 1280 cm^{-1}; ^1H NMR δ 8.10 and 7.50 (m, 5 H, Ar), 4.85 (m, 1 H, H-3), 2.40–0.80 (m, remaining H); mass spectrum, *m/e* 505 (M + H), 487, 383, 255. Anal. Calcd for $C_{34}H_{48}O_3$: C, 80.91; H, 9.51. Found: C, 81.27; H, 9.49.

(3β,5α)-Ergosta-8,24(28)-dien-3-ol (8). Methyltriphenylphosphonium bromide (1.43 g, 4 mmol) was suspended in toluene (10 mL) and potassium *tert*-amylate (4 mL of a 1 M solution in *tert*-amyl alcohol) was added and the solution warmed to 70 °C for 40 min. A solution of ketone **51** (504 mg, 1.0 mmol) in toluene (2 mL) was then added and the reaction was stirred at 70 °C for 4 h. The reaction was cooled and chromatographed (CH_2Cl_2 then 20% EtOAc–CH_2Cl_2) to give crude **8**. Analytically pure fecosterol (298 mg, 75%) was obtained following reverse-phase HPLC (CH_3CN–THF): mp 130–132 °C (lit.[10d] mp 133–136°, sealed tube); R_f 0.65 (2.5% EtOAc–CH_2Cl_2); retention time 8.3 min (85:15 CHCN–THF; flow rate 2.0 mL/min); $[\alpha]^{25}_D$ +51° (*c* 0.43, $CHCl_3$) [lit.[10d] $[\alpha]^{24}_D$ +46.6 (*c* 0.79, $CHCl_3$)]; IR 3350, 2960, 1270 cm^{-1}; ^1H NMR δ 4.71 and 4.66 (br s, 2 H, H-28), 3.61 (m, 1 H, H-3), 1.04 (d, 6 H, *J* = 7.0 Hz, CH_3-26,27), 1.01 (d, 3 H, *J* = 7.0 Hz, CH_3-21), 0.95 (s, 3 H, CH_3-19), 0.62 (s, 3 H, CH_3-18), 2.40–0.70 (m, remaining H); ^{13}C NMR δ 156.9, 135.1, 128.3, 105.9, 22.0, 21.9, 18.8, 17.8, 11.3; mass spectrum, *m/e* 397 (M − H), 381, 355, 273. Anal. Calcd for $C_{28}H_{46}O$: C, 84.36; H, 11.63. Found: C, 83.97; H, 11.71.

Registry No. 4, 128-33-6; **5**, 7448-02-4; **6**, 64284-65-7; **7**, 64284-64-6; **7** (acetate), 117438-78-5; **8**, 516-86-9; **16** (isomer 1), 117438-79-6; **16**-(isomer 1, Δ^8), 117438-80-9; **16** (isomer 1, $\Delta^{8(14)}$), 117438-81-0; **16** (isomer 2), 117438-82-1; **16** (isomer 2, Δ^8), 117438-83-2; **16** (isomer 2, $\Delta^{8(14)}$), 117438-84-3; **17** (isomer 1), 117438-85-4; **17** (isomer 2), 117438-86-5; **18** (isomer 1), 117438-87-6; **18** (isomer 2), 117438-88-7; **19** (isomer 1), 117438-89-8; **19** (isomer 2), 117438-90-1; **20**, 36071-76-8; **21**, 103751-19-5; **22**, 117151-64-1; **23** (isomer 1), 117556-81-7; **23** (isomer 2), 117556-82-8; **24**, 117160-80-2; **25**, 117151-69-6; **26** (isomer 1), 117438-91-2; **26** (isomer 2), 117438-92-3; **27**, 117438-93-4; **28** (isomer 1), 117438-94-5; **28** (isomer 2), 117438-95-6; **29**, 117438-96-7; **30**, 117438-97-8; **31** (isomer 1), 117438-98-9; **31** (isomer 2), 117438-99-0; **33** (isomer 1), 117439-00-6; **33** (isomer 2), 117439-01-7; **35** (isomer 1), 117439-02-8; **35** (isomer 2), 117439-03-9; **36**, 117439-04-0; **36** ($\Delta^{8,14,23}$-isomer), 117439-05-1; **37** (isomer 1), 117439-06-2; **37** (isomer 2), 117439-07-3; **39**, 117439-08-4; **40**, 117556-83-9; **41** (isomer 1), 117556-84-0; **41** (isomer 2), 117556-85-1; **42** (isomer 1), 117439-09-5; **42** (isomer 2), 117439-10-8; **43** (isomer 1), 117439-11-9; **43** (isomer 1, crude thiocarbonate), 117439-12-0; **43** (isomer 2), 117604-43-0; **43** (isomer 2, crude thiocarbonate), 117439-13-1; **44**, 117439-14-2; **44** (isomer 2), 117439-15-3; **45** (isomer 1), 117556-86-2; **45** (isomer 2), 117556-87-3; **46** (isomer 1), 117439-16-4; **46** (isomer 2), 117439-17-5; **47** (isomer 1), 117556-88-4; **47** (isomer 2), 117556-89-5; **48** (isomer 1), 117439-18-6; **48** (isomer 2), 117439-19-7; **49**, 117168-33-9; **50**, 7408-47-1; **51**, 36099-90-8; $(CF_3CO)_2O$, 407-25-0; $(CF_3SO_2)_2O$, 358-23-6; PhOC(S)Cl, 1005-56-7; $Ph_3P^+CH_3Br^-$, 1779-49-3; 3-methyl-2-butanone, 563-80-4; *tert*-butyldimethylsilyl trifluoromethanesulfonate, 69739-34-0.