Synthesis of Biomarkers in Fossil Fuels: C-23 and C-24 Diastereomers of (20*R*)-4,17β,23,24-Tetramethyl-18,19-dinorcholesta-1,3,5,7,9,11,13-heptaene[1]

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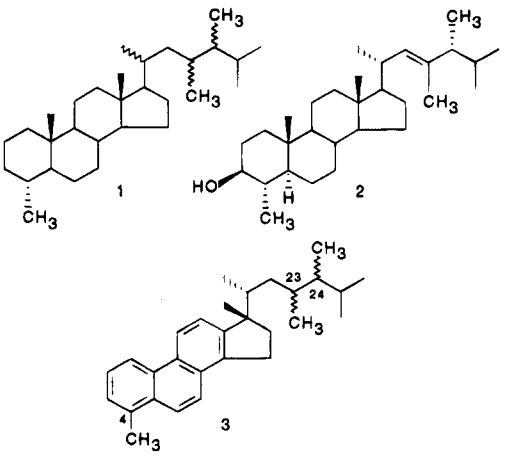
A synthesis of the C-23 and C-24 diastereomers of triaromatic dinosteroids useful as maturation biomarkers for marine-sourced petroleum was developed. Conversion of stigmasterol to (20*R*,22*E*,24*S*)-4-methyl-19-norstigmasta-1,3,5(10),22-tetraene, ozonolysis of the stigmasterol sidechain, sodium borohydride reduction, and sequential treatment with methanesulfonyl chloride and sodium iodide furnished (20*S*)-20-(iodomethyl)-4-methyl-19-norpregna-1,3,5(10)-triene. The alkylation of this iodide with methyl 3,4-dimethyl-2-pentenoate provided the C-23*R* and C-23*S* diastereomers of methyl (20*R*,23ζ)-4-methyl-24-methylene-19-norcholesta-1,3,5(10)-triene-23-carboxylate, reduction with lithium aluminum hydride, and separation gave (20*R*,23*R*)- and (20*R*,23*S*)-23-(hydroxymethyl)-4-methyl-24-methylene-19-norcholesta-1,3,5(10)-triene. The further reduction of the 24-methylene and the hydroxymethyl group in (20*R*,23*R*)-23-(hydroxymethyl)-4-methyl-24-methylene-19-norcholesta-1,3,5(10)-triene provided (20*R*,23*R*,24*R*)- and (20*R*,23*R*,24*S*)-4,23,24-trimethyl-19-norcholesta-1,3,5(10)-triene. In the same fashion, the reduction of the 24-methylene and the hydroxymethyl group in (20*R*,23*S*)-23-(hydroxymethyl)-4-methyl-24-methylene-19-norcholesta-1,3,5(10)-triene provided (20*R*,23*S*,24*R*)- and (20*R*,23*S*,24*S*)-4,23,24-trimethyl-19-norcholesta-1,3,5(10)-triene. A chloranil oxidation of each of these monoaromatic diastereomers to (20*R*)-4,17β,23,24-tetramethyl-18,19-dinorcholesta-1,3,5,7,9,11,13,15-octaene and a catalytic hydrogenation furnished the C-23 and C-24 diastereomers of the triaromatic biomarker, (20*R*)-4,17β,23,24-tetramethyl-18,19-dinorcholesta-1,3,5,7,9,11,13-heptaene.

The petroleum-derived dinosteranes[2] **1**, shown in Scheme 1, are interesting as "molecular fossils" or "biomarkers" because they derive from ancient sterol precursors having the unusual 4,23,24-trimethylation pattern. This pattern is characteristic of modern-day marine sterols such as dinosterol (**2**), a natural product isolated from unicellular algae called dinoflagellates.[3] The presence of dinosteranes **1** in petroleum implicates antediluvian dinoflagellates as organisms that contributed widely to petroleum source rock. Sterols are converted to sterene hydrocarbons (C_{27}–C_{30}) during early diagenesis, and these sterenes undergo either reduction to steranes like **1** or sequential aromatization of the C and then the AB rings as maturation progresses to give triaromatic steroids such as **3**.[4] It was of interest to synthesize the previously unknown triaromatic dinosteroids **3** in order to determine if they would be useful as biomarkers[4] for mature petroleum.

Scheme 1



Published routes[5,6] for the synthesis of triaromatic steroids rely on commercially available sterols as starting

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(1) This is paper 10 in the series: Synthesis of Biological Markers in Fossil Fuels. For paper 9 in this series, see: Stoilov, I.; Smith, S. L.; Watt, D. S.; Carlson, R. M. K.; Fago, F. J.; Moldowan, J. M. *Mag. Res. Chem.* **1994**, *32*, 101.

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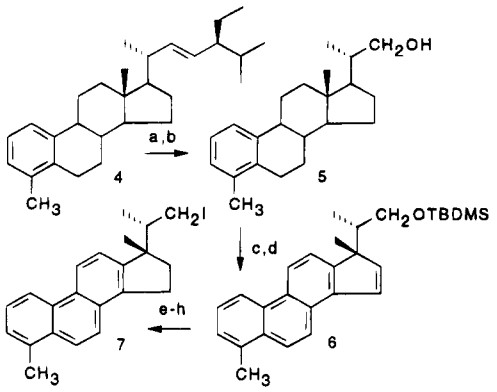
Scheme 2[a]



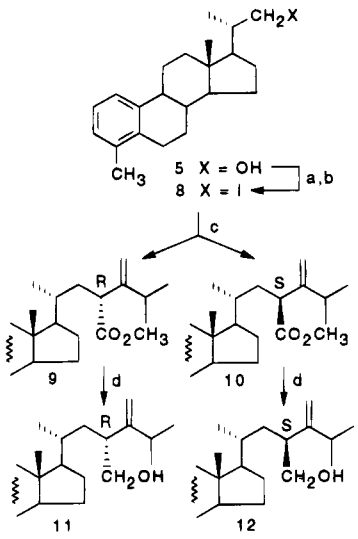
[a] a, O_3; b, $NaBH_4$; c, TBDMSCl, imidazole; d, chloranil, anisole, reflux; e, H_2, PtO_2; f, n-Bu_4NF; g, MsCl, Et_3N; h, NaI, acetone.

materials. In the absence of significant amounts of dinosterol (**2**) or a suitable sterol precursor having both the characteristic dinosterol side chain and a C-4 methyl group, an alternate approach was required for the synthesis of these triaromatic dinosteroids. We report a route in which a common sterol, stigmasterol, provided access to four diastereomers of the triaromatic dinosteroids **3**.

An initial goal was the synthesis of (20*S*)-20-(iodomethyl)-4,17β-dimethyl-18,19-dinorpregna-1,3,5,7,9,11,-13-heptaene (**7**) in Scheme 2 as a common *triaromatic* precursor to which different side chains could be attached. It was thought that the alkylation of this iodide with acyclic esters would provide access to various C-23 and C-24 diastereomers of **3** using a recently reported, stereoselective synthesis of dinosteroid side chains.[7,8] According to a published procedure,[6] stigmasterol was first converted to the monoaromatic steroid 4-methyl-19-norstigmasta-1,3,5(10),22-tetraene (**4**) in Scheme 2 as the starting material for this particular study. As shown in Scheme 2, the ozonolysis of **4** and reduction of the intermediate aldehyde with sodium borohydride provided the C-20*S* alcohol **5**. The protection of the alcohol **5** as the *tert*-butyldimethylsilyl ether and a subsequent chloranil oxidation[5d] secured the rearranged triaromatic Δ^{15}-olefin **6** in 30% yield in which the angular methyl group had migrated from the C-13β to the C-17β position. The catalytic hydrogenation of **6** with palladium on carbon led, contrary to literature reports,[5a] to reduction of both the Δ^{15}-olefin and the phenanthrene nucleus to a diaromatic steroid,[9] but the hydrogenation of **6** using Adams' catalyst led to the desired triaromatic steroid. Subsequent desilylation, mesylation, and a Finkelstein reaction provided the iodide **7**. Unfortunately, the alkylation of this *triaromatic* steroid iodide **7** with a saturated, acyclic ester, methyl (3*S*)-3,4-dimethyl-2-pentanoate,[8] failed presumably because of steric hindrance.

Unable to effect the alkylation of this sterically hindered *triaromatic* steroid iodide **7**, a less sterically demanding *monoaromatic* steroid iodide was sought. It was hoped that inverting the order for the construction of the side chain and the aromatization of the BC rings

Scheme 3[a]



[a] a, MsCl, Et_3N; b, NaI, acetone; c, LDA, methyl 3,4-dimethyl-2-pentenoate, HMPA, THF, −78 °C; d, $LiAlH_4$.

would provide a solution to this alkylation problem. The conversion of the alcohol **5** in Scheme 2 to a *monoaromatic* steroid iodide **8** in Scheme 3 provided a substrate that did not possess a sterically hindered, quaternary carbon at C-17. As shown in Scheme 3, the alkylation of **8** with an α,β-unsaturated ester, methyl 3,4-dimethyl-2-pentenoate,[8] provided a 1.2:1 mixture of the β,γ-unsaturated esters **9** and **10**.

The esters **9** and **10** were difficult to separate in significant quantities, but their reduction furnished the readily separable homoallylic alcohols **11** and **12** that were assigned the C-23*R* and C-23*S* stereochemistry, respectively, on the basis of ^{13}C NMR data. The ^{13}C NMR chemical shift for C-29 (*i.e.*, the hydroxymethyl group) in **11** (δ 63.7) and **12** (δ 66.4) was in agreement with values for (20*R*,23*R*)-5α-dinoster-24(28)-en-29-ol (δ 63.7) and (20*R*,23*S*)-5α-dinoster-24(28)-en-29-ol (δ 66.8).[8] These assignments were also in accord with a preference, albeit marginal in this particular case, for the C-23*R* diastereomer seen in similar alkylations with unsaturated esters.[8] Although this preference and the ^{13}C NMR data were consistent with the C-23*R* and C-23*S* stereochemical assignments in the homoallylic alcohols **11** and **12**, respectively, these attributions were regarded as tentative at this point in the synthesis. Additional supporting evidence was later secured by correlating the homoallylic alcohols **11** and **12** with saturated alcohols synthesized by another pathway (*vide infra*).

The homoallylic alcohols **11** and **12** served, nevertheless, as the key intermediates for the preparation of all four diastereomers of the triaromatic dinosteroids **3**. As shown in Scheme 4, the protection of the C-23R homoallylic alcohol **11** as the *tert*-butyldimethylsilyl ether **13** and a subsequent catalytic hydrogenation[8] provided the saturated *threo*- and *erythro-tert*-butyldimethylsilyl ethers **14** and **15** in a 1.4:1 ratio, respectively. Chromatographic separation of **14** and **15** and individual deprotection afforded the saturated alcohols **16** and **17**, respectively. The preparation of the *tert*-butyldimethylsilyl ethers in this series facilitated the separation of diastereomers. It was also interesting that the presence of the aromatic A ring in **14** and **15** relative to their saturated counterparts, the *tert*-butyldimethyl silyl ethers of (20*R*,23*R*)- and (20*R*,23*S*)-5α-dinoster-24(28)-en-29-ol,[8] diminished the

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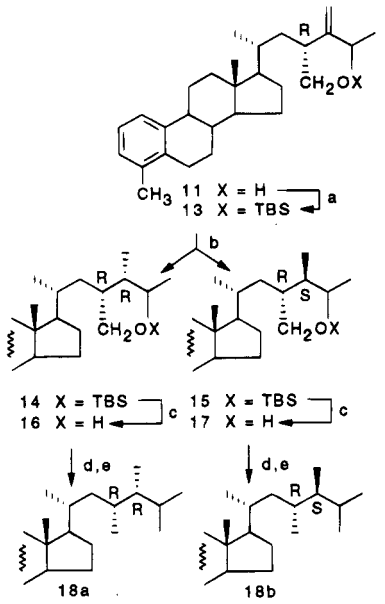
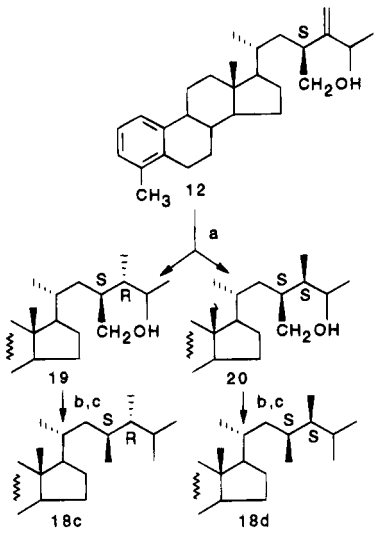
(9) For a related reduction using lithium in ammonia, see: Riolo, J.; Ludwig, B.; Albrecht, P. *Tetrahedron Lett.* **1985**, *26*, 2697.

Scheme 4[a]



[a] a, TBSOTf, 2,6-lutidine; b, H_2, PtO_2; c, $(n\text{-}C_4H_9)_4NF$; d, MsCl, Et_3N; e, $LiAlH_4$.

Scheme 5[a]



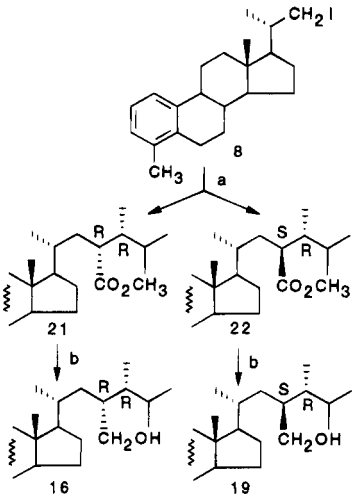
[a] a, H_2, PtO_2; b, MsCl, Et_3N; c, $LiAlH_4$.

level of diastereoselection seen previously in the reduction of the $\Delta^{24(28)}$-olefin.[8] Conversion of the saturated alcohols **16** and **17** to the corresponding mesylates and reduction of each mesylate secured the monoaromatic dinosteroids **18a** and **18b**, respectively.

As shown in Scheme 5, the direct hydrogenation of the C-23S homoallylic alcohol **12** afforded the saturated alcohols **19** and **20** that were separable by HPLC. There was no particular advantage, as in the previous case, in the preparation of the *tert*-butyldimethylsilyl ethers. Conversion of the alcohols **19** and **20** to the corresponding mesylates and further reduction secured the monoaromatic dinosteroids **18c** and **18d**, respectively, and completed the synthesis of all four C-23 and C-24 diastereomers of **18a–d**.

Before completing the synthesis of the triaromatic dinosteroids **3**, the issue of stereochemistry at C-23 in the homoallylic alcohols **11** and **12** was investigated in more detail. The homoallylic alcohols **11** and **12** were

Scheme 6[a]

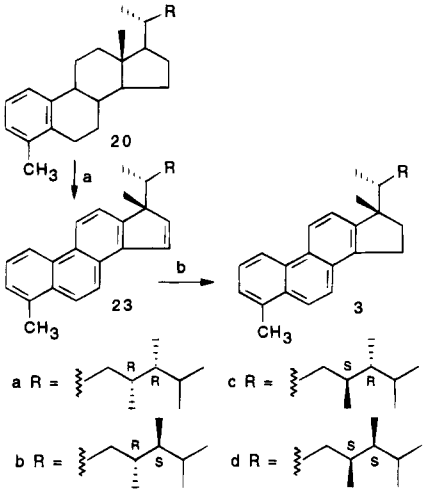


[a] a, LDA, methyl (3*S*)-3,4-dimetylpentanoate, HMPA, THF, −78 °C; b, $LiAlH_4$.

tentatively assigned the C23*R* and C-23*S* stereochemistry on the basis of ^{13}C NMR data. In order to obtain additional evidence to corroborate these assignments, the alkylation of the steroid iodide **8** with a saturated ester, methyl (3*S*)-3,4-dimethylpentanoate,[8] was investigated as shown in Scheme 6. The selection of methyl (3*S*)-3,4-dimethylpentanoate guaranteed that the steroid ester products would possess the C-24*R* stereochemistry. As expected, the alkylation shown in Scheme 6 furnished the esters **21** and **22** in good yield, unfortunately as an inseparable mixture of C-23 diastereomers. GC analysis, however, displayed two diastereomers in a 1.7 to 1 ratio, and the major isomer, based on prior work,[8] was expected to be the *erythro* isomer methyl (20*R*,23*S*,24*R*)-4,24-dimethyl-19-norcholesta-1,3,5(10)-triene-23−carboxylate (**22**). That is, the alkylation was expected to furnish the ester **22** having the C-23*S* configuration as the major product.

To confirm this point, the mixture of esters **21** and **22** was reduced with lithium aluminum hydride in order to obtain the separable alcohols **16** and **19**, respectively. The minor alcohol **16** would possess the 23*R*,24*R* configuration, and the major alcohol **19** would possess the 23*S*,-24*R* configuration. Indeed, the 23*R*,24*R* and 23*S*,24*R* stereochemical assignments for **16** and **19**, respectively, were consistent with the ^1H and ^{13}C chemical shift data for the hydroxymethyl group of the alcohols **16** (δ 3.66, 62.8) and **19** (δ 3.54, 64.1) in comparison with related sterols, (20*R*,23*R*,24*R*)-5α-dinosteran-29-ol (δ 3.64, 62.8) and (20*R*,23*S*,24*R*)-5α-dinosteran-29-ol (δ 3.52, 65.6).[8] The structure of the latter compound, (20*R*,23*S*,24*R*)-5α-dinosteran-29-ol, was secured by an X-ray crystallographic determination, and, thus, correlating the monoaromatic alcohols **16** and **19** with these saturated alcohols provided confidence in the stereochemical assignments. Since the major alcohol **19** in Scheme 6 possessed the 23*S*,24*R* configuration and since this alcohol was identical to the alcohol **19** produced by the route in Scheme 5, the homoallylic alcohol **12** possessed the C-23*S* configuration. In the same fashion, since the minor alcohol **16** in Scheme 6 possessed the 23*R*,24*R* configuration and was identical to the alcohol **16** produced by the route in Scheme 4, the homoallylic alcohol **11** possessed the C-23*R* stereochemistry. At this point, confident that the stereochemical issue with respect to the C-23 configuration

Scheme 7[a]



[a] a, chloranil, anisole, reflux; b, H_2, PtO_2.

in homoallylic alcohols **11** and **12** was resolved, we proceeded to complete the synthesis of the C-23 and C-24 diastereomers of the triaromatic dinosteroids **3**.

The aromatization of the BC rings in the monoaromatic dinosteroids **18a-d** with chloranil[5b] proceeded in modest yield to give the triaromatic Δ^{15}-olefins **23a–d**, respectively, as shown in Scheme 7. The individual catalytic hydrogenation of **23a–d** over platinum oxide removed the extraneous Δ^{15}-olefin and provided the desired triaromatic dinosteroid biomarkers **3a–d**. The synthetic triaromatic dinosteroids **3a–d** were used to identify the same compounds in petroleum by GC-MS coelution experiments that will be reported in due course.

Experimental Section

(20*S*)-20-(Hydroxymethyl)-4-methyl-19-norpregna-1,3,5-(10)-triene (5). A solution of 3.15 g (8.04 mmol) of **4** in 200 mL of CH_2Cl_2 at −78 °C was exposed to a stream of ozone for 1.25 h at rate of 1 L/min. To this solution was added 13.2 mL (179 mmol, 22.3 equiv) of dimethyl sulfide. The solution was stirred for several minutes, and a solution of 820 mg (21.7 mmol, 2.7 equiv) of $NaBH_4$ in 75 mL of methanol was added. The mixture was warmed slowly to 25 °C and stirred for 30 min. The solvent was evaporated, and the residue was extracted with EtOAc. This extract was washed successively with water and brine and dried over anhydrous $MgSO_4$. The crude product was chromatographed on silica gel using 1:10 EtOAc–hexane to give 1.81 g (72%) of **5** as a white solid. A sample was recrystallized from 1:3 hexane-EtOAc: mp 125–127 °C; IR (KBr) 3260, 2936, 2868, 2849, 1582, 1471, 1455, 1442, 1380, 1332, 1046, 997, 775, 736 cm^{-1}. Anal. Calcd for $C_{22}H_{32}O$: C, 84.56; H 10.32. Found: C, 84.74; H, 10.36.

(20*S*)-20-(Iodomethyl)-4-methyl-19-norpregna-1,3,5(10)-triene (8). To a solution of 1.58 g (5.06 mmol) of **5** in 100 mL of CH_2Cl_2 at −40 °C under a N_2 atmosphere was added 2.13 mL (15.2 mmol, 3 equiv) of triethylamine followed by 0.5 mL (6.57 mmol, 1.3 equiv) of distilled methanesulfonyl chloride. The mixture was warmed to 25 °C and stirred for 10 min. This solution was poured into cold water and extracted with CH_2Cl_2. The organic layer was washed successively with water and brine and dried over anhydrous $MgSO_4$. The crude product was chromatographed on silica gel with 1:10 EtOAc–hexane to give 1.90 g (98%) of (20*S*)-20-([methanesulfonyloxy]-methyl)-4-methyl-19-norpregna-1,3,5(10)-triene as a white solid. A portion of this material was recrystallized from 1:10 EtOAc–hexane to obtain an analytical sample: mp 127–128 °C; IR (KBr) 3026, 2994, 2966, 2932, 2858, 1470, 1456, 1443, 1350, 1179, 954, 842, 829, 783, 740, 535, 482 cm^{-1}. Anal. Calcd for $C_{23}H_{34}O_3S$: C, 70.73; H, 8.77. Found: C, 70.67; H, 8.79. A solution of 1.99 g (5.08 mmol) of the mesylate and 7.6 g (50.8 mmol) of sodium iodide in 75 mL of acetone was refluxed under a N_2 atmosphere for 7 h. The mixture was concentrated under reduced pressure and diluted with EtOAc. The solution was washed successively with water and brine and dried over anhydrous $MgSO_4$. The crude product was chromatographed on silica gel using hexane to give 1.98 g (92%) of **8** as white solid: mp 125–126 °C; IR (KBr) 2909, 2859, 1580, 1468, 1378, 784, 740 cm^{-1}. Anal. Calcd for $C_{22}H_{31}I$: C, 62.56; H, 7.40. Found: C, 62.44; H, 7.45.

Methyl (20*R*,23*R*)-4-Methyl-24-methylene-19-norcholesta-1,3,5(10)-triene-23-carboxylate (9) and Methyl (20*R*,-23*S*)-4-Methyl-24-methylene-19-norcholesta-1,3,5(10)-triene-23-carboxylate (10). To a solution of 15.4 mL of 0.86 M (13.2 mmol, 4.5 equiv) of LDA in THF at −78 °C under an Ar atmosphere was added 1.5 mL (8.78 mmol, 3 equiv) of methyl 3, 4-dimethyl-2-pentenoate.[8] The solution was stirred for *ca.* 30 min. To this solution was added a solution of 1.24 g (2.93 mmol) of **8** in 8 mL of THF and 1.5 mL (8.78 mmol, 3 equiv) of anhydrous HMPA. The solution was stirred for 15 min, diluted with hexane, and extracted with ether. The organic layer was washed successively with water and brine and dried over anhydrous $MgSO_4$. The product was chromatographed on silica gel using 1:50 EtOAc–hexane to give 1.03 g (81%) of a mixture of **9** and **10**. A small portion of this mixture was subjected to medium pressure chromatography on silica gel using 1:100 EtOAc–hexane to give pure samples of **9** and **10** having the following physical and spectral data. For the (20*R*,23*R*)-diastereomer **9**: mp 84–85 °C; IR (KBr) 2933, 1734, 1646, 1472, 1436, 1167 cm^{-1}. Anal. Calcd for $C_{30}H_{44}O_2$: C, 82.52; H, 10.16. Found: C, 82.42; H, 10.20. For the (20*R*,-23*S*)-diastereomer **10**: mp 62–63 °C; IR (KBr) 2939, 1741, 1637, 1457, 1379, 1285, 1160 cm^{-1}. Anal. Calcd for $C_{30}H_{44}O_2$: C, 82.52; H, 10.16. Found: C, 82.54; H, 10.18.

(20*R*,23*R*)-23-(Hydroxymethyl)-4-methyl-24-methylene-19-norcholesta-1,3,5(10)-triene (11) and (20*R*,23*S*)-23-(Hydroxymethyl)-4-methyl-24-methylene-19-norcholesta-1,3,5(10)-triene (12). To a solution of 798 mg (1.83 mmol) of a mixture of **9** and **10** in 20 mL of anhydrous THF at 25 °C under an Ar atmosphere was added 208 mg (5.48 mmol, 3 equiv) of lithium aluminum hydride. The solution was stirred for 1 h. The reaction was successively diluted with EtOAc and water, and the mixture was extracted with EtOAc. The combined extracts were washed successively with 1 N HCl solution, water, and brine and dried over anhydrous $MgSO_4$. The product was chromatographed on silica gel using 1:10 EtOAc–hexane to give 303 mg (41%) of **11** and 300 mg (40%) of **12** having the following physical and spectral data. For the (20*R*,23*R*) diastereomer **11**: mp 100–102 °C; IR (KBr) 3490, 2935, 1452, 1379, 1031, 887, 778, 738 cm^{-1}. Anal. Calcd for $C_{29}H_{44}0$: C 85.23; H, 10.85. Found: C, 85.15; H 10.87. For the (20*R*,23*S*) diastereomer **12**: mp 110–112 °C; IR (KBr) 3294, 2936, 2865, 1638, 1462, 1379, 1044, 891, 778, 737 cm^{-1}. Anal. Calcd for $C_{29}H_{44}O$: C, 85.23; H, 10.85. Found: C, 85.02; H, 10.84.

(20*R*,23*R*)-23-([(*tert*-Butyldimethylsilyl)oxy]methyl)-4-methyl-24-methylene-19-norcholesta-1,3,5(10)-triene (13). To a solution of 250 mg (0.61 mmol) of **11** in 0.6 mL of CH_2Cl_2 at 25 °C under a N_2 atmosphere was added 180 μL (1.53 mmol, 2.5 equiv) of 2,6-lutidine. To this solution at 0 °C was added 210 μL (0.92 mmol, 1.5 equiv) of *tert*-butyldimethylsilyl triflate. The mixture was stirred at 25 °C for 0.5 h and was quenched with water. The solution was diluted with CH_2Cl_2, washed with brine, and dried over anhydrous $MgSO_4$. The product was chromatographed on silica gel using hexane to give 300 mg of **13** (94%) as white solid. A portion of this material was recrystallized from hexane–ethanol: mp 109–111 °C; IR (KBr) 2936, 1465, 1251, 1102, 843, 775 cm^{-1}. Anal. Calcd for $C_{35}H_{58}$-OSi: C, 80.39; H, 11.18. Found: C, 80.17; H, 11.12.

(20*R*,23*R*,24*R*)-23-([(*tert*-Butyldimethylsilyl)oxy]methyl)-4,24-dimethyl-19-norcholesta-1,3,5(10)-triene (14) and (20*R*,23*R*,24*S*)-23-([(*tert*-Butyldimethylsilyl)oxy]methyl)-4,24-dimethyl-19-norcholesta-1,3,5(10)-triene (15). A mixture of 120 mg (0.23 mmol) of **13** and 13 mg (0.06 mmol) of platinum oxide in 10 mL of hexane was hydrogenated at 60 psi for 1.5 h. The mixture was filtered through Celite. The

filtrate was concentrated and chromatographed on silica gel using hexane to give 75 mg (63%) of **14** and 39 mg (32%) of **15**. These samples were independently recrystallized from ethanol-hexane and had following physical and spectral data. For the (20*R*,23*R*,24*R*)-diastereomer **14**: mp 94–96 °C; IR (KBr) 2933, 2860, 1587, 1467, 1380, 1252, 1080, 836, 772 cm^{-1}. Anal. Calcd for $C_{35}H_{60}OSi$: C, 80.08; H, 11.52. Found: C, 79.99; H, 11.49. For the (20*R*,23*R*,24*S*) diastereomer **15**: mp 140–142 °C; IR (KBr) 2939, 2866, 1593, 1465, 1385, 1252, 1094, 839, 773 cm^{-1}. Anal. Calcd for $C_{35}H_{60}OSi$: C, 80.08; H, 11.52. Found: C, 79.94; H, 11.50.

(20*R*,23*R*,24*R*)-23-(Hydroxymethyl)-4,24-dimethyl-19-norcholesta-1,3,5(10)-triene (16). To a solution of 45 mg (0.086 mmol) of **14** in 2 mL of anhydrous THF under an Ar atmosphere at 25 °C was added 0.5 mL (0.52 mmol, 6 equiv) of a 1 M solution of tetra-*n*-butylammonium fluoride in THF. The mixture was stirred for 24 h. The solution was diluted with water and extracted with ether. The organic layer was washed successively with water and brine and dried over anhydrous $MgSO_4$. The product was chromatographed on silica gel using 1:5 EtOAc–hexane to afford 34 mg (96%) of **16** as a white solid: mp 110–112 °C; IR (KBr) 3387, 2939, 2867, 1584, 1465, 1379, 1034, 777, 737 cm^{-1}; exact mass calcd for $C_{29}H_{46}O$ 410.3549, found 410.3546.

(20*R*,23*R*,24*S*)-23-(Hydroxymethyl)-4,24-dimethyl-19 norcholesta-1,3,5(10)-triene (17). The procedure described for the preparation of **16** was repeated using 24 mg (0.046 mmol) of **15** in 1 mL of THF and 0.27 mL (0.27 mmol, 6 equiv) of a 1 M solution of tetra-*n*-butyl ammonium fluoride in THF to afford, after chromatography on silica gel using 1:10 EtOAc–hexane, 16 mg (89%) of **17**: mp 154–155 °C; IR (KBr) 3359, 2938, 2866, 1585, 1466, 1379, 1044, 777, 738, 581 cm^{-1}; exact mass calcd for $C_{29}H_{46}O$ 410.3549, found 410.3548.

(20*R*,23*R*,24*R*)-4,23,24-Trimethyl-19-norcholesta-1,3,5-(10)-triene (18a). To a solution of 31 mg (0.075 mmol) of **16** in 1 mL of CH_2Cl_2 was added 32 μL (0.22 mmol, 2.9 equiv) of triethylamine. This solution was cooled to 0 °C. To this solution was added 11 μL (0.15 mmol, 2 equiv) of distilled methanesulfonyl chloride dropwise. The solution was stirred for 1 h and poured into cold water. This solution was extracted with CH_2Cl_2, washed successively with water and brine, and dried over anhydrous $MgSO_4$. The product was chromatographed on silica gel using 1:5 EtOAc–hexane to give 34 mg (96%) of (20*R*,23*R*,24*R*)-23-([methanesulfonyloxy]methyl)-4,-24-dimethyl-19-norcholesta-1,3,5(10)-triene as a white solid: mp 97–99 °C; IR (KBr) 2937, 2868, 1654, 1458, 1346, 1176, 978, 950, 909 cm^{-1}. To a stirred solution of 28 mg (0.05 mmol) of the mesylate in 0.5 mL of anhydrous THF under a N_2 atmosphere was added 22 mg (0.57 mmol, 10 equiv) of $LiAlH_4$. The solution was refluxed for 5 h and quenched with 5 mL of EtOAc. The pH was adjusted to 6 using 1 M HCl solution. This solution was extracted with EtOAc, washed successively with water and brine, and dried over anhydrous $MgSO_4$. The product was chromatographed on silica gel using hexane to give 23 mg (100%) of **18a**. This material was recrystallized from hexane-ethanol: mp 126–127 °C; IR (KBr) 2962, 2937, 2870, 1472, 1380, 778, 738 cm^{-1}; exact mass calcd for $C_{29}H_{46}$ 394.3600, found 394.3604.

(20*R*,23*R*,24*S*)-4,23,24-Trimethyl-19-norcholesta-1,3,5-(10)-triene (18b). The procedure described for the preparation of **18a** was repeated using 16 mg (0.039 mmol) of **17**, 16 μL (0.12 mmol, 3 equiv) of triethylamine, and 6 μL (0.08 mmol, 2 equiv) of distilled methanesulfonyl chloride in 1 mL of CH_2Cl_2 to afford, after chromatography on silica gel using 1:5 EtOAc–hexane, 17 mg (89%) of (20*R*,23*R*,24*S*)-23-([methanesulfonyloxy]methyl)-4,24-dimethyl-19-norcholesta-1,3,5(10)-triene: mp 118–120 °C; IR (KBr) 2941, 2869, 1472, 1353, 1176, 948, 828, 778, 738, 530 cm^{-1}; exact mass calcd for $C_{30}H_{48}O_3S$ 488.3324, found 488.3319. The procedure described for the preparation of **18a** was repeated using 17 mg (0.035 mmol) of this mesylate and 13 mg (0.35 mmol, 40 equiv) of $LiAlH_4$ in 0.5 mL of THF to afford, after chromatography on silica gel using hexane, 13 mg (97%) of **18b**: mp 120–121 °C; IR (KBr) 2962, 2933, 2866, 1458, 1380, 777, 737, 508 cm^{-1}; exact mass calcd for $C_{29}H_{46}$ 394.3600, found 394.3593.

(20*R*,23*S*,24*R*)-23-(Hydroxymethyl)-4,24-dimethyl-19-norcholesta-1,3,5(10)-triene (19) and (20*R*,23*S*,24*S*)-23-(Hydroxymethyl)-4,24-dimethyl-19-norcholesta-1,3,5(10)-triene (20). A solution of 109 mg (0.266 mmol) of **12** and 14 mg (0.06 mmol, 0.225 equiv) of platinum oxide in 5 mL of 1:3 benzene–hexane was hydrogenated at 60 psi for 2 h. The solution was filtered through Celite and chromatographed on silica gel using 1:5 EtOAc–hexane to give 108 mg (99%) of a 1.6:1 mixture of **19** and **20**. The mixture was separated by HPLC on Beckman C_{18} reversed phase column using 5:7:88 water–EtOAc–MeOH to give pure samples of **19** and **20**. The (20*R*,23*S*,24*R*) diastereomer **19** had the following physical and spectral data: mp 126–128 °C; IR (KBr) 3335, 2937, 2867, 1457, 1379, 1052, 777, 378, 591 cm^{-1}; exact mass calcd for $C_{29}H_{46}O$ 410.3549, found 410.3529. The (20*R*,23*S*,24*S*) diastereomer **20** had the following physical and spectral data: mp 143–145 °C; IR (KBr) 3243, 2960, 2865, 1458, 1379, 1043, 778, 738, 668 cm^{-1}; exact mass calcd for $C_{29}H_{46}O$ 410.3549, found 410.3536.

(20*R*,23*S*,24*R*)-4,23,24-Trimethyl-19-norcholesta-1,3,5-(10)-triene (18c). The procedure described for preparation of **18a** was repeated using 16 mg (0.037 mmol) of **19**, 15 μL (0.109 mmol, 3 equiv) of triethylamine, and 6 μL (0.073 mmol, 2 equiv) of distilled methanesulfonyl chloride in 0.5 mL of anhydrous CH_2Cl_2 to afford, after chromatography on silica gel using 1:5 EtOAc–hexane, 16 mg (90%) of (20R,23S,24R)-23–([methanesulfonyloxy]methyl)-4,24-dimethyl-19-norcholesta-1,3,5(10)-triene: mp 109–111 °C; IR (KBr) 2937, 2865, 1586, 1468, 1354, 1253, 1177, 943, 832, 778, 738, 530 cm^{-1}; exact mass calcd for $C_{30}H_{48}O_3S$ 488.3324, found 488.3340. The procedure described for the preparation of **18a** was repeated using 14 mg (0.029 mmol) of this mesylate and 11 mg (0.28 mmol, 40 equiv) of $LiAlH_4$ in 0.5 mL of THF to afford, after chromatography on silica gel using hexane, 11 mg (97%) of **18c**: mp 92–93 °C; IR (KBr) 2934, 2867, 1694, 1652, 1516, 1461, 1378, 766, 736, 583 cm^{-1}; exact mass calcd for $C_{29}H_{46}$ 394.3600, found 394.3601.

(20*R*,23*S*,24*S*)-4,23,24-Trimethyl-19-norcholesta-1,3,5-(10)-triene (18d). The procedure described for the preparation of **18a** was repeated using 25 mg (0.06 mmol) of **20**, 26 μL (0.18 mmol, 3 equiv) of triethylamine, and 10 μL (0.12 mmol, 2 equiv) of distilled methanesulfonyl chloride in 0.6 mL of anhydrous CH_2Cl_2 to afford, after chromatography on silica gel using 1:5 EtOAc–hexane, 26 mg (88%) of (20*R*,23*S*,24*S*)-23-([methanesulfonyloxy]methyl)-4,24-dimethyl-19-norcholesta-1,3,5(10)-triene: mp 138–140 °C; IR (KBr) 2939, 2867, 1590, 1468, 1347, 1173, 945, 828, 778, 738, 526 cm^{-1}; exact mass calcd for $C_{30}H_{48}0_3S$ 488.3324, found 488.3324. The procedure described for preparation of **18a** was repeated using 25 mg (0.05 mmol) of this mesylate and 19 mg (0.5 mmol, 10 equiv) of $LiAlH_4$ in 0.5 mL of THF to afford, after chromatography on silica gel using hexane, 19 mg (94%) of **18d**: mp 132–133 °C; IR (KBr) 2962, 2922, 2867, 1694, 1650, 1555, 1538, 1511, 1456, 1377, 772, 733, 589 cm^{-1}; exact mass calcd for $C_{29}H_{46}$ 394.3600, found 394.3608.

Methyl (20*R*,23ζ,24*R*)-4,24-Dimethyl-19-norcholesta-1,3,5(10)-triene-23-carboxylate (21 and 22). To a solution of 2.65 mL of 1.26 M (3.33 mmol, 4.5 equiv) LDA in anhydrous THF under a N_2 atmosphere at −78 °C was added 320 mg (2.22 mmol, 3 equiv) of methyl (3S)-3,4-dimethylpentanoate.[8] The solution was stirred for *ca.* 30 min. To this solution was added a solution of 312 mg (0.739 mmol) of **8** in 2.2 mL of THF and 380 μL (2.22 mmol, 3 equiv) of anhydrous HMPA. The solution was stirred at −78 °C for 1 h, −30 °C for 2 h, and 0 °C for 1 h. The mixture was diluted with hexane, washed successively with water and brine, and dried over anhydrous $MgSO_4$. The product was purified by medium pressure chromatography on silica gel using 1:50 EtOAc–hexane to give 242 mg of an oil that still contained about 5–10% of byproducts of methyl (3*S*)-3, 4-dimethylpentanoate self-condensation. A portion of the partially purified product was again chromatographed on silica gel on a medium pressure column using 1:100 EtOAc–hexane in order to obtain a pure mixture of esters epimeric at C-23: exact mass calcd for $C_{30}H_{46}O_2$ 438.3498, found 438.3504. A GC analysis (SE-30 fused silica capillary column; 15 m; 270–290 °C; rate 1 °C/

min) of this mixture displayed a 1:7:1 ratio of **22** and **21**. The stereochemistry was assigned as described in the text.

(20*R*,23*S*,24*R*)-23-(Hydroxymethyl)-4,24-dimethyl-19-norcholesta-1,3,5(10)-triene (19) and (20*R*,23*R*,24*R*)-23-(Hydroxymethyl)-4,24-dimethyl-19-norcholesta-1,3,5(10)-triene (16) from Esters 21 and 22. To a solution of 115 mg (0.27 mmol) of a mixture of **21** and **22** in 2 mL of anhydrous THF was added 102 mg (2.69 mmol, 10 equiv) of lithium aluminum hydride. The mixture was stirred at 25 °C for 1 h. The reaction was quenched with EtOAc and water. The pH was adjusted to 6 with 1 N HCl solution, and the solution was extracted with EtOAc. The combined extracts were washed successively with water and brine and dried over anhydrous $MgSO_4$. The product was chromatographed on silica gel (medium pressure apparatus) using 1:10 EtOAc–hexane to afford 30 mg (27%) of **19**, 11 mg (10%) of **16**, and 46 mg of a mixture of **19** and **16**. The samples of **16** and **19** were identical to those reported earlier in this paper.

(20*R*,23*R*,24*R*)-4,17β,23,24-Tetramethyl-18,19-dinorcholesta-1,3,5,7,9,11,13,15-octaene (23a). The procedure described for the preparation of **23c** was repeated using 23 mg (0.058 mmol) of **18a** and 96 mg (0.40 mmol) of chloranil in 0.5 mL of anisole to afford, after refluxing for a total of 24 h, a filtration through a 12-cm alumina column, and chromatography on preparative silica gel plate (three developments) using hexane, 10 mg (45%) of **23a**. A portion of this material was recrystallized from hexane-ethanol: mp 144–145 °C; IR (KBr) 2963, 2863, 1662, 1448, 1381, 777 cm^{-1}; exact mass calcd for $C_{29}H_{36}$ 384.2817, found 384.2825.

(20*R*,23*R*,24*S*)-4,17β,23,24-Tetramethyl-18,19-dinorcholesta-1,3,5,7,9,11,13,15-octaene (23b). The procedure described for the preparation of **23c** was repeated using 25 mg (0.063 mmol) of **18b** and 104 mg (0.42 mmol, 6.6 equiv) of chloranil in 0.5 mL of anisole to afford, after refluxing for a total of 24 h and chromatography on a preparative silica gel plate using pentane, 14 mg (57%) of **23b**: mp 130–131 °C; IR (KBr) 2959, 2876, 1461, 1380, 825, 776, 746, 722, 585 cm^{-1}; exact mass calcd for $C_{29}H_{36}$ 384.2817, found 384.2821.

(20*R*,23*S*,24*R*)-4,17β,23,24-Tetramethyl-18,19-dinorcholesta-1,3,5,7,9,11,13,15-octaene (23c). A solution of 40 mg (0.101 mmol) of **18c** and 55 mg (0.224 mmol, 2.2 equiv) of chloranil in 5 mL of anisole was refluxed for 3 h. To this solution was added an additional 111 mg (0.451 mmol, 4.5 equiv) of chloranil, and the solution was refluxed for an additional 16 h. The mixture was filtered through alumina, and the product was chromatographed on silica gel using hexane to give 18 mg (46%) of **23c**: mp 147–149 °C; IR (KBr) 2959, 2870, 1455, 1375, 1190, 822, 777, 746, 539 cm^{-1}; exact mass calcd for $C_{29}H_{36}$ 384.2817, found 384.2825.

(20*R*,23*S*,24*S*)-4,17β,23,24-Tetramethyl-18,19-dinorcholesta-1,3,5,7,9,11,13,15-octaene (23d). The procedure described for the preparation of **23c** was repeated using 36 mg (0.09 mmol) of **18d** and 150 mg (0.61 mmol, 6.9 equiv) of chloranil in 3 mL of anisole to afford, after refluxing a total of 19 h, a filtration through a 12-cm alumina column, and chromatography on silica gel using hexane, 18 mg (54%) of **23d**: mp 161–163 °C; IR (KBr) 2960, 2875, 1596, 1459, 1379, 1294, 1190, 1126, 1029, 822, 772, 744, 719, 538 cm^{-1}; exact mass calcd for $C_{29}H_{36}$ 384.2817, found 384.2812.

(20*R*,23*R*,24*R*)-4,17β,23,24-Tetramethyl-18,19-dinorcholesta-1,3,5,7,9,11,13-heptaene (3a). The procedure described for the preparation of **3c** was repeated using 9 mg (0.023 mmol) of **23a** and 5 mg (0.022 mmol) of platinum oxide in 2 mL of hexane to afford, after chromatography on an analytical silica gel plate using hexane, 9 mg (100%) of **3a**: mp 133–134 °C; IR (KBr) 2960, 2872, 1654, 1618, 1458, 1380, 819, 795, 768, 592 cm^{-1}; exact mass calcd for $C_{29}H_{38}$, 386.2974, found 386.2980.

(20*R*,23*R*,24*S*)-4,17β,23,24-Tetramethyl-18,19-dinorcholesta-1,3,5,7,9,11,13-heptaene (3b). The procedure described for the preparation of **3c** was repeated using 14 mg (0.036 mmol) of **23b** and 6 mg (0.026 mmol) of platinum oxide in 1 mL of hexane to afford, after chromatography on an analytical silica gel TLC plate using pentane, 14 mg (100%) of **3b**. The product was recrystallized using 1:5 hexane-ethanol: mp 121–122 °C; IR (KBr) 2960, 2869, 1595, 1459, 1379, 816, 795, 767, 594 cm^{-1}; exact mass calcd for $C_{29}H_{38}$ 386.2974, found 386.2962.

(20*R*,23*S*,24*R*)-4,17β,23,24-Tetramethyl-18,19-dinorcholesta-1,3,5,7,9,11,13-heptaene (3c). A solution of 28 mg (0.072 mmol) of **23c** and 12 mg (0.05 mmol) of platinum oxide in 4 mL of hexane was hydrogenated at 60 psi for 2 h. The mixture was filtered through Celite. The product was chromatographed on an analytical silica gel plate using pentane to give 27 mg (97%) of **3c**. The product was recrystallized using 5:1 ethanol-hexane: mp 144–146 °C; IR (KBr) 2956, 2871, 1458, 1375, 1089, 818, 794, 768, 539 cm^{-1}; exact mass calcd for $C_{29}H_{38}$ 386.2974, found 386.2970.

(20*R*,23*S*,24*S*)-4,17β,23,24-Tetramethyl-18,19-dinorcholesta-1,3,5,7,9,11,13-heptaene (3d). The procedure described for the preparation of **3c** was repeated using 40 mg (0.104 mmol) of **23d** and 17 mg (0.075 mmol) of platinum oxide in 5 mL of hexane to afford, after chromatography on silica gel using hexane, 40 mg (100%) of **3d**: mp 154–155 °C; IR (KBr) 2954, 2873, 1594, 1460, 1379, 1296, 1125, 1033, 818, 801, 768, 541 cm^{-1}; exact mass calcd for $C_{29}H_{38}$ 386.2974, found 386.2965.

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Supplementary Material Available: Experimental details for the preparation of all compounds, and ^1H and ^{13}C NMR data for **5**, **8**–**17**, **18a**–**d**, **19**, **20**, **21** and **22**, **23a**–**d**, **3a**–**d**, and copies of ^1H and ^{13}C NMR spectra of **3a**–**d**, **16**, **17**, **18a**–**d**, **19**, **20**, **23a**–**d** (51 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal and can be ordered from the ACS; see any current masthead page for ordering information.