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Stereochemistry in the Hydrogenation of Steroidal (22*R*)- and (22*S*)-Δ^{24}-26,22-Lactones

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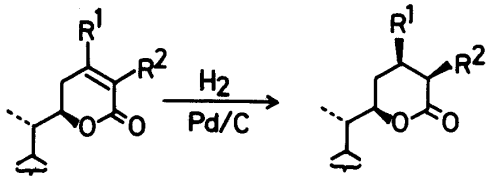
Catalytic hydrogenation of the (22*R*)-unsaturated lactone **8** and its (22*S*)-epimer **9** afforded stereoselectively the (22*R*,24*R*)-saturated lactone **10** and the (22*S*,24*S*)-isomer **11**, respectively. The C-24 stereochemistry of the hydrogenated products was determined by their conversion into 24-ethylcholesterols.

Keywords——stereoselective hydrogenation; steroidal lactone; sitosterol; clionasterol

We have recently completed the synthesis of several steroids which belong to the withanolide family.[2] In the course of construction of the side chain of withaferin A, it was found that catalytic hydrogenation of the unsaturated lactone (I) afforded the saturated lactone (II) as a single product[2d] (Chart 1). Similar stereoselectivity was independently



(22*R*)

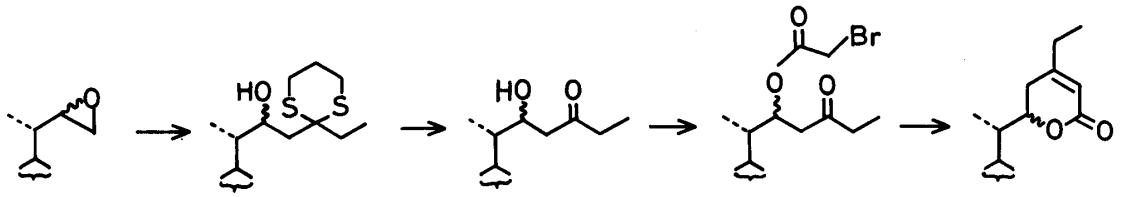
I: R^1=Me, R^2=H II: R^1=Me, R^2=H
III: R^1=Me, R^2=CH_2OAc IV: R^1=Me, R^2=Me

Chart 1

reported by Lavie and coworkers in the hydrogenation of a lactone (III), yielding (IV).[3] The high stereoselectivity for (22*R*)-compounds observed in those hydrogenations prompted us to investigate the stereochemical course of the hydrogenation of a (22*S*)-lactone and further to apply this stereoselective reaction to the synthesis of some natural steroids. This paper presents a detailed account of the hydrogenation of both epimers of the Δ^{24}-26,22-lactones **8** and **9**.

The unsaturated lactones **8** and **9** were prepared starting from the 22,23-epoxide (epimeric mixture at the C-22 position[4]) (Chart 2). Reaction of **1** with 2-ethyl-1,3-dithiane anion gave the 22-hydroxydithioketal, which was easily separated by column chromatography on silica gel into the more polar (22*R*)-alcohol **2** (21%) and the less polar (22*S*)-epimer **3** (44%). The stereochemistry at the C-22 position was established after conversion of these alcohols into the unsaturated lactones **8** and **9**. Treatment of **2** with mercuric oxide–boron trifluoride etherate gave the (22*R*)-22-hydroxy-24-one **4**. Acetylation of **4** with bromoacetyl bromide gave the 22-bromoacetate **6**. Arbusov reaction of **6** with triethyl phosphite followed

by intramolecular Wittig-Horner reaction[5] of the resulting diethylphosphonate gave the (22*R*)-Δ^{24}-lactone **8** (64% from **2**). The same sequence of reactions for the (22*S*)-isomer **3** gave the (22*S*)-Δ^{24}-lactone **9**, *via* the intermediates **5** and **7**. The C-22 configuration of **8** and **9** was



1 22*R* series **2** **4** **6** **8**
22*S* series **3** **5** **7** **9**

Chart 2. The Steroid Nuclei are in the 6β-Methoxy-3α,5-cyclo Form

determined based on the characteristic coupling pattern of the C-22 hydrogens; 4.40 ppm (dt, $J=13$ and 4 Hz) for **8** and 4.45 ppm (dd, $J=12.5$ and 4 Hz) for **9**.[6]

The unsaturated lactone **8** was hydrogenated over 10% Pd–C in dioxane to give the (22*R*,24*R*)-saturated lactone **10** quantitatively. The hydrogenation of the epimeric (22*S*)-unsaturated lactone **9** under the same conditions afforded the (22*S*,24*S*)-saturated lactone **11** quantitatively. In order to determine the direction of hydrogen attack on **8** and **9**, compounds **10** and **11** were converted into 24-ethylcholesterols (Chart 3), although the (24*R*)-stereochemistry of **10** was predicted from the aforementioned selectivity in the hydrogenation of the lactones (I) and (III).

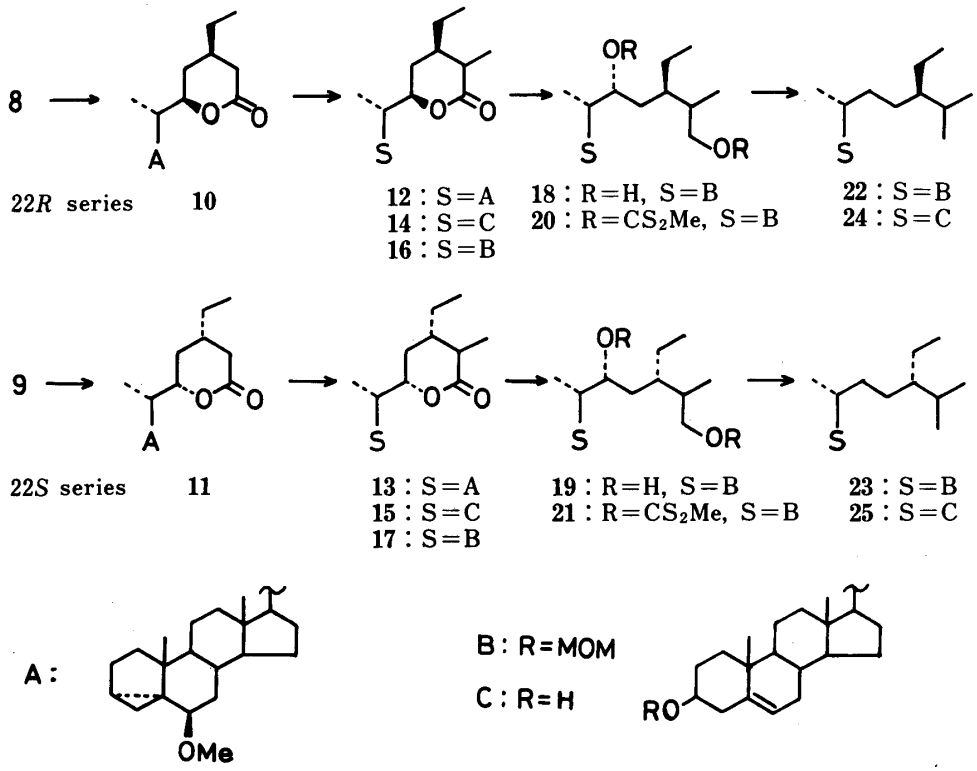
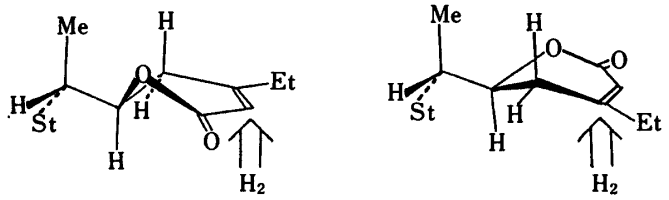


Chart 3

Treatment of **10** with lithium diisopropylamide (LDA) and methyl iodide gave the methylated compound **12** in 82% yield.[7] The *i*-ether protecting group of **12** was transformed into the methoxymethyl ether (MOM) **16** in 79% yield *via* the alcohol **14**, then **16** was reduced

with lithium aluminum hydride ($LiAlH_4$) to give the 22,26-diol **18**. An attempt to remove the hydroxy group *via* the corresponding 22,26-ditosylate or dimesylate by treatment with $LiAlH_4$ was not successful because of the exclusive formation of the olefinic compound.[8] However, tributyltin hydride reduction[9] of the dixanthate ester **20**, which was obtained by treatment of **18** with sodium hydride, carbon disulfide and methyl iodide in 78% yield (from **16**), gave the ether **22**. Removal of the protecting group furnished the (24*R*)-24-ethylcholesterol (sitosterol) (**24**), mp 137—139 °C, in 48% yield (2 steps). A parallel experiment starting from the (22*S*)-lactone **11** afforded, *via* the intermediates **13**, **15**, **17**, **19**, **21** and **23**, the (24*S*)-24-ethylcholesterol (clionasterol) (**25**), mp 142—144 °C. The structure and stereochemical homogeneity of **24** and **25** were established by proton nuclear magnetic resonance (^{1}H-NMR) (360 MHz) comparison with authentic samples.[10] Signals due to the C-24 epimer were not observed in either case.

It is therefore concluded that the hydrogenated compound **10** has (24*R*) stereochemistry, while **11** has (24*S*). It follows that the hydrogen attack takes place from the direction depicted in Chart 4. It has become clear that the stereochemical course of the hydrogen attack depends



8 (22*R*) 9 (22*S*)

Chart 4

on the configuration at the C-22 position, and that the stereochemical environment due to the C-17 and C-20 chiral centers does not play an important role. From a synthetic point of view the present hydrogenation approach provides a new methodology for a stereoselective introduction of a C-24 and/or C-25 stereocenter on a steroid side chain.[11]

Experimental

Melting points were determined on a hot-stage microscope and are uncorrected. Infrared (IR) spectra were taken with a Hitachi model 260-10 spectrometer. ^{1}H-NMR spectra were recorded on a Hitachi R-24A (60 MHz), JEOL PS-100 (100 MHz), or Nicolet NT-360 (360 MHz) spectrometer in $CDCl_3$ solution with tetramethylsilane as an internal reference. The ^{1}H-NMR data for the cyclopropane protons of the 6β-methoxy-3α,5-cyclo form (δ: 0.3—0.7, m, 4-H_2) are not given. Mass spectra (MS) were taken with a Shimadzu LKB-9000S or GCMS 9020 DF spectrometer. Column chromatography was performed with Kieselgel 60 (70-230 mesh, E. Merck). Kieselgel 60 F_{254} (0.25 mm thickness, E. Merck) was used for analytical thin layer chromatography (TLC). Compounds reported herein were obtained as oils, unless otherwise stated, and were homogeneous on TLC. Ether refers to diethyl ether, THF to tetrahydrofuran.

The Dithiane Adducts 2 and 3——*n*-Buthyllithium (5 ml, 1.6 mmol solution in hexane) was added to a solution of 2-ethyl-1,3-dithiane (0.82 ml) in dry THF (20 ml) under argon at −78 °C. A solution of **1** (980 mg) in THF (15 ml) was then added dropwise to the resulting dithiane anion, and the mixture was stirred at −78 °C for 30 min. Extractive (ether) work-up gave a crude dithiane adduct, which was chromatographed on silica gel (solvent, ethyl acetate–hexane (1 : 9)) to give the less polar (22*S*)-22-hydroxy compound **3** (609 mg, 44%), ^{1}H-NMR δ: 0.72 (s, 3H, 18-CH_3), 1.02 (s, 3H, 19-CH_3), 1.02 (d, 3H, J=7 Hz, 21-CH_3), 1.12 (t, 3H, J=7 Hz, 26-CH_3), 2.65—2.94 (m, 6H, $S(CH_2)_3S$), 3.29 (s, 3H, OCH_3), 4.02 (t, 1H, J=7 Hz, 22-H), and the more polar (22*R*)-epimer **2** (294 mg, 21%), ^{1}H-NMR δ: 0.75 (s, 3H, 18-CH_3), 1.03 (s, 3H, 19-CH_3), 1.03 (d, 3H, J=7 Hz, 21-CH_3), 2.65—3.00 (m, 6H, $S(CH_2)_3S$), 3.29 (s, 3H, OCH_3), 4.02 (t, 1H, J=7 Hz, 22-H).

(22*R*)-22-Hydroxy-6β-methoxy-27-nor-3α,5-cyclo-5α-cholestan-24-one (4)——A solution of **2** (245 mg) in THF (1 ml) was added to a mixture of HgO (211 mg) and BF_3-etherate (0.1 ml) in THF (12 ml)–H_2O (12 ml) and the mixture was stirred at room temperature for 45 min. After filtration, the filtrate was washed with aqueous $NaHCO_3$. Drying and evaporation of the organic phase gave **4** (231 mg, no purification). ^{1}H-NMR δ: 0.72 (s, 3H, 18-CH_3), 0.91 (d, 3H, J=7 Hz, 21-CH_3), 1.00 (s, 3H, 19-CH_3), 1.05 (t, 3H, J=7 Hz, 26-CH_3), 2.21—2.56 (m, 4H, 23-H_2 and 25-H_2),

2.72 (m, 1H, 6-H), 2.80 (br, 1H, 22-OH), 3.28 (s, 3H, OCH_3), 4.09 (br, 1H, 22-H).

(22*S*)-22-Hydroxy-6β-methoxy-27-nor-3α,5-cyclo-5α-cholestan-24-one (5)——Treatment of **3** (568 mg) in the same manner as described for **2** gave **5** (470 mg, 98%). ^{1}H-NMR δ: 0.70 (s, 3H, 18-CH_3), 1.01 (d, 3H, J=7 Hz, 21-CH_3), 1.01 (s, 3H, 19-CH_3), 2.26—2.60 (m, 5H, 22-OH, 23-H_2 and 25-H_2), 2.72 (m, 1H, 6-H), 3.29 (s, 3H, OCH_3), 3.98—4.25 (m, 1H, 22-H). Compound **5** was less polar than the epimer **4** on TLC (solvent, ethyl acetate–hexane (1 : 5)).

(22*R*)-6β-Methoxy-27-nor-3α,5-cyclo-5α-stigmast-24-en-26,22-lactone (8)——Bromoacetyl bromide (0.11 ml) was added to a solution of **4** (231 mg) in dry ether (15 ml) and dry pyridine (1.3 ml) at 0 °C under argon. The mixture was stirred for 30 min, and extractive (ether) work-up gave **6** (251 mg, no purification). ^{1}H-NMR δ: 0.71 (s, 3H, 18-CH_3), 0.96 (d, 3H, J=7 Hz, 21-CH_3), 1.00 (s, 3H, 19-CH_3), 1.01 (t, 3H, J=7 Hz, 26-CH_3), 2.18—2.98 (m, 6H, 6-H, 22-OH, 23-H_2 and 25-H_2), 3.29 (s, 3H, OCH_3), 3.84 (s, 2H, CH_2Br), 5.21—5.55 (m, 1H, 22-H).

A solution of **6** (251 mg) in triethyl phosphite (1.6 ml) was heated at 100—110 °C for 40 min, and then excess triethyl phosphite was removed under reduced pressure to give an oil. A mixture of the oil and sodium hydride (20 mg, 60% in mineral oil) in THF (10 ml) was stirred initially at 0 °C and then at room temperature for 10 min. Extractive (ether) work-up gave a crude product, which was chromatographed on silica gel (solvent, ethyl acetate–hexane (1 : 9)) to afford **8** as a solid (136 mg, 64% from **2**). ^{1}H-NMR δ: 0.76 (s, 3H, 18-CH_3), 1.03 (d, 3H, J=7 Hz, 21-CH_3), 1.04 (s, 3H, 19-CH_3), 1.13 (t, 3H, J=7 Hz, 29-CH_3), 2.76 (m, 1H, 6-H), 3.33 (s, 3H, OCH_3), 4.40 (dt, 1H, J=13, 4 Hz, 22-H), 5.75 (br s, 1H, 25-H). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700. MS *m/z*: 440 (M^+), 425, 408, 385 (base peak), 125.

(22*S*)-6β-Methoxy-27-nor-3α,5-cyclo-5α-stigmast-24-en-26,22-lactone (9)——Treatment of **5** (482 mg) in the same manner as described for **4** gave **7** (466 mg, no purification). ^{1}H-NMR δ: 0.69 (s, 3H, 18-CH_3), 0.69 (d, 3H, J=7 Hz, 21-CH_3), 1.00 (s, 3H, 19-CH_3), 1.03 (t, 3H, J=6 Hz, 26-CH_3), 2.16—2.86 (m, 6H, 6-H, 22-OH, 23-H_2, and 25-H_2), 3.29 (s, 3H, OCH_3), 3.75 (s, 2H, CH_2Br), 5.36 (t, 1H, J=7 Hz, 22-H). Compound **7** was less polar than the epimer **6** on TLC (solvent, ethyl acetate–hexane (1 : 5)).

The bromoacetate **7** was converted into the crystalline unsaturated lactone **9** (246 mg, 50% from **3**). ^{1}H-NMR δ: 0.76 (s, 3H, 18-CH_3), 1.05 (s, 3H, 19-CH_3), 1.06 (d, 3H, J=6 Hz, 21-CH_3), 1.12 (t, 3H, J=7 Hz, 29-CH_3), 2.78 (m, 1H, 6-H), 3.34 (s, 3H, OCH_3), 4.45 (dd, 1H, J=12.5, 4 Hz, 22-H), 5.57 (br s, 1H, 25-H). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700. MS *m/z*: 440 (M^+), 425, 408, 385, 125 (base peak). Compound **9** was less polar than the epimer **8** on TLC (solvent, ethyl acetate–hexane (1 : 3)).

Catalytic Hydrogenation of 8 and 9——A mixture of **8** (123 mg), $NaHCO_3$ (37 mg) and 10% Pd–C (30 mg) in dioxane (6 ml) was stirred under a hydrogen atmosphere for 3 h. Extractive (ether) work-up gave **10** (122 mg, 99%). ^{1}H-NMR δ: 0.76 (s, 3H, 18-CH_3), 0.94 (d, 3H, J=6 Hz, 21-CH_3), 0.95 (t, 3H, J=7 Hz, 29-CH_3), 1.04 (s, 3H, 19-CH_3), 2.78 (br s, 1H, 6-H), 3.33 (s, 3H, OCH_3), 4.34 (dt, 1H, J=13, 4 Hz, 22-H). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730. MS *m/z*: 442 (M^+), 427, 410 (base peak), 395, 387, 291.

Similar hydrogenation of **9** (215 mg) gave **11** (214 mg, 99%). ^{1}H-NMR δ: 0.74 (s, 3H, 18-CH_3), 0.94 (t, 3H, J=7 Hz, 29-CH_3), 0.99 (d, 3H, J=6 Hz, 21-CH_3), 1.04 (s, 3H, 19-CH_3), 2.78 (br s, 1H, 6-H), 3.33 (s, 3H, OCH_3), 4.38 (dd, 1H, J=12, 3.5 Hz, 22-H). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730. The MS was the same as that of **10**.

Conversion of 10 into Sitosterol (24)——A solution of **10** (100 mg) in dry THF (1.4 ml) was added to lithium diisopropylamide (LDA, prepared from diisopropylamine (0.14 ml) and *n*-butyllithium (0.66 ml)) in THF (1.0 ml) at −78 °C. After being stirred for 1 h, the reaction mixture was gradually warmed to room temperature. Extractive (ether) work-up and chromatographic separation (solvent, hexane–ethyl acetate (7 : 3)) gave **12** (83 mg, 82%). ^{1}H-NMR δ: 0.76 (s, 3H, 18-CH_3), 0.98 (t, 3H, J=7 Hz, 29-CH_3), 0.99 (d, 3H, J=7 Hz, 21-CH_3), 1.04 (s, 3H, 19-CH_3), 1.32 (d, 3H, J=7 Hz, 27-CH_3), 2.76 (br s, 1H, 6-H), 3.34 (s, 3H, OCH_3), 4.30 (dt, J=12, 4 Hz, 22-H). MS *m/z*: 456 (M^+).

A mixture of **12** (50 mg), zinc acetate (30 mg), and acetic acid (10 ml) was refluxed for 1 h. Extractive (ether) work-up gave a solid, which was treated with 5% KOH–MeOH (2 ml) at reflux for 0.5 h. Extractive (ether) work-up afforded a crude product which was chromatographed on silica gel (solvent, hexane–ethyl acetate (7 : 3)) to give **14** (43 mg, 88%). ^{1}H-NMR δ: 0.69 (s, 3H, 18-CH_3), 0.91 (d, 3H, J=6 Hz, 21-CH_3), 0.98 (s, 3H, 19-CH_3), 1.29 (d, 3H, J=6 Hz, 27-CH_3), 3.19—3.74 (m, 1H, 3-H), 4.08—4.43 (m, 1H, 22-H), 5.12—5.36 (m, 1H, 6-H).

N,N-Diethylcyclohexylamine (40 μl) and chloromethyl methyl ether (15 μl) were added to a solution of **14** (43 mg) in dioxane (1.5 ml) and then the mixture was stirred at 60 °C for 2 h. After cooling, extractive (ether) work-up gave **16** (42 mg, 90%, no purification) as an oil. ^{1}H-NMR δ: 0.69 (s, 3H, 18-CH_3), 0.91 (d, 3H, J=6 Hz, 21-CH_3), 0.98 (s, 3H, 19-CH_3), 1.30 (d, 3H, J=6 Hz, 27-CH_3), 3.32 (s, 3H, OCH_3), 4.10—4.49 (m, 1H, 22-H), 4.63 (s, 2H, OCH_2O), 5.13—5.38 (m, 1H, 6-H).

$LiAlH_4$ (16 mg) was added to a solution of **16** (40 mg) in dry ether (2 ml) at 0 °C and the resulting mixture was stirred for 1 h. Extractive (ether) work-up gave **18** (25 mg, no purification). ^{1}H-NMR δ: 0.70 (s, 3H, 18-CH_3), 0.92 (d, 3H, J=7 Hz, 21-CH_3), 1.00 (s, 3H, 19-CH_3), 1.30 (d, 3H, J=6 Hz, 27-CH_3), 3.36 (s, 3H, OCH_3), 3.58 (d, 2H, J=5 Hz, 26-H_2), 3.25—3.60 (m, 2H, 3-H and 22-H), 4.65 (s, 2H, OCH_2O), 5.18—5.42 (m, 1H, 6-H).

A solution of **18** in dry THF (0.5 ml) and imidazole (1 mg) was added to a suspension of sodium hydride (67 mg) in dry THF (0.8 ml) at room temperature. The reaction mixture was refluxed for 3.5 h, then allowed to cool. Carbon

disulfide (46 μl) was added to the reaction mixture at room temperature and the resulting solution was refluxed for 1 h. Methyl iodide (0.15 ml) was added and the reaction mixture was gradually cooled to room temperature. Extractive (ether) work-up gave **20** (35 mg, 78% for 2 steps). ^{1}H-NMR δ: 0.66 (s, 3H, 18-CH_3), 0.95 (d, 3H, J=6 Hz, 21-CH_3), 1.00 (s, 3H, 19-CH_3), 1.25 (d, 3H, J=6 Hz, 27-CH_3), 2.52 (s, 3H, 26-OCS_2Me), 2.72 (s, 3H, 22-OCS_2Me), 3.32 (s, 3H, OCH_3), 4.35—4.58 (m, 1H), 4.65 (s, 2H, OCH_2O), 5.21—5.38 (m, 1H, 6-H).

The dixanthate ester **20** (31 mg) in dry toluene (1 ml) was added dropwise to a refluxing solution of (n-Bu)$_3$SnH (0.5 ml) in dry toluene (1 ml) and the mixture was stirred at reflux for 3 h, then cooled and filtered through a short column of silica gel. Concentration of the filtrate gave **22**, which was treated with 2 N HCl (0.2 ml) in THF (1 ml) at room temperature for 1 h. Extractive (ether) work-up gave a solid product which was chromatographed on silica gel (solvent, hexane–ethyl acetate (7:3)) to afford crystalline **24** (3 mg, 48% for 2 steps). An analytical sample was obtained by recrystallization from methanol, mp 137—139 °C. ^{1}H-NMR (recorded for the chromatographed sample) δ: 0.680 (s, 3H, 18-CH_3), 0.814 (d, 3H, J=7 Hz, 27-CH_3), 0.834 (d, 3H, J=7.5 Hz, 26-CH_3), 0.845 (t, 3H, J=7.5 Hz, 29-CH_3), 0.921 (d, 3H, J=6.6 Hz, 21-CH_3), 1.01 (s, 3H, 19-CH_3), 3.53 (m, 1H, 3-H), 5.36 (m, 1H, 6-H). MS m/z: 414 (M^+).[10]

Conversion of 11 into Clionasterol (25)——Compound **11** was converted into **25** as described for **10**. Methylation of **11** (58 mg) gave **13**. ^{1}H-NMR δ: 0.74 (s, 3H, 18-CH_3), 0.98 (d, 3H, J=6 Hz, 21-CH_3), 0.99 (t, 3H, J=6 Hz, 29-CH_3), 1.04 (s, 3H, 19-CH_3), 1.30 (d, 3H, J=7 Hz, 27-CH_3), 2.77 (br s, 1H, 6-H), 3.35 (s, 3H, OCH_3), 4.35 (br d, 1H, J=10 Hz, 22-H). MS m/z: 456 (M^+). Deprotection of **13** gave **15** (47 mg, 81% for 2 steps). ^{1}H-NMR δ: 0.67 (s, 3H, 18-CH_3), 0.99 (s, 3H, 19-CH_3), 1.30 (d, 3H, J=6 Hz, 27-CH_3), 3.21—3.66 (m, 1H, 3-H), 4.15—4.45 (m, 1H, 22-H), 5.15—5.39 (m, 1H, 6-H). Protection of **15** gave **17** (45 mg, 89%). ^{1}H-NMR δ: 0.67 (s, 3H, 18-CH_3), 0.99 (s, 3H, 19-CH_3), 1.29 (d, 3H, J=7 Hz, 27-CH_3), 3.15—3.69 (m, 1H, 3-H), 3.31 (s, 3H, OCH_3), 4.13—4.52 (m, 1H, 22-H), 4.60 (s, 2H, OCH_2O), 5.16—5.36 (m, 1H, 6-H).

Reduction of **17** (45 mg) with $LiAlH_4$ gave **19** (47 mg). ^{1}H-NMR δ: 0.68 (s, 3H, 18-CH_3), 0.90 (d, 3H, J=7 Hz, 21-CH_3), 1.00 (s, 3H, 19-CH_3), 1.45 (br s, 3H), 3.34 (s, 3H, OCH_3), 3.53 (d, 2H, J=6 Hz, 26-H_2), 3.16—3.70 (m, 2H, 3-H and 22-H), 4.66 (s, 2H, OCH_2O), 5.21—5.44 (m, 1H, 6-H).

The diol **19** (29 mg) was transformed into **21** (27 mg). ^{1}H-NMR δ: 0.72 (s, 3H, 18-CH_3), 0.93 (d, 3H, J=6 Hz, 21-CH_3), 1.01 (s, 3H, 19-CH_3), 1.01 (t, 3H, J=6 Hz, 27-CH_3), 2.52 (s, 3H, 26-OCS_2CH_3), 2.74 (s, 3H, 22-OCS_2CH_3), 3.36 (s, 3H, OCH_3), 3.08—3.70 (m, 1H, 3-H), 4.65 (s, 2H, OCH_2O), 5.16—5.39 (m, 1H, 6-H).

Compound **21** (29 mg) was transformed, *via* **23**, into crystalline **25** (3 mg, 52%), mp 142—144 °C. ^{1}H-NMR (recorded for the chromatographed sample) δ: 0.680 (s, 3H, 18-CH_3), 0.812 (d, 3H, J=7 Hz, 27-CH_3), 0.831 (d, 3H, J=7.0 Hz, 26-CH_3), 0.855 (t, 3H, J=7.4 Hz, 29-CH_3), 0.926 (d, 3H, J=6.5 Hz, 21-CH_3), 1.010 (s, 3H, 19-CH_3), 3.53 (m, 1H, 3-H), 5.36 (m, 1H, 6-H). MS m/z: 414 (M^+).[10]

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References and Notes

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2) *a*) K. Gamoh, M. Hirayama, and N. Ikekawa, *J. Chem. Soc., Perkin Trans. 1*, **1984**, 449; *b*) M. Hirayama, K. Gamoh, and N. Ikekawa, *Tetrahedron Lett.*, **23**, 4725 (1982); *c*) *Idem, J. Am. Chem. Soc.*, **104**, 3735 (1982); *d*) *Idem, Chem. Lett.*, **1982**, 491.
3) D. Lavie, I. Kirson, E. Glotter, and G. Snatzke, *Tetrahedron*, **26**, 2221 (1970).
4) The epoxide **1** was prepared by oxidation of 6β-methoxy-24-nor-3α,5-cyclo-5α-chol-22-ene with *m*-chloroperbenzoic acid and the mixture was used without separation. For a stereoselective approach to the two epimers, see: M. Ishiguro, H. Saito, A. Sakamoto, and N. Ikekawa, *Chem. Pharm. Bull.*, **26**, 3715 (1978).
5) G. R. Weihe and T. C. McMorris, *J. Org. Chem.*, **43**, 3942 (1978).
6) D. Lavie, E. Glotter, and Y. Shvo, *J. Chem. Soc.*, **1965**, 7517; A. Kajikawa, M. Morisaki, and N. Ikekawa, *Tetrahedron Lett.*, **1975**, 4135; M. Ishiguro, M. Hirayama, H. Saito, A. Kajikawa, and N. Ikekawa, *Heterocycles*, **15**, 823 (1981).
7) The alkylated product **12** (also **13**) appeared to be a single stereoisomer at the C-25 position, judging from the ^{1}H-NMR spectrum and TLC behavior: deprotonation (LDA) of **12** followed by quenching with H_2O afforded the starting material and its C-25-epimer, which are separable on TLC.
8) The ^{1}H-NMR spectrum of the crude product showed the formation of $\Delta^{20(22)}$- and Δ^{22}-compounds, see: K. Bannai, S. Ishizuka, T. Naruchi, and Y. Hashimoto, *J. Steroid Biochem.*, **10**, 411 (1979).
9) D. H. R. Barton and W. B. Motherwell, *Pure Appl. Chem.*, **53**, 15 (1981).
10) M. W. Khalil, D. R. Idler, and G. M. Patterson, *Lipids*, **15**, 69 (1980); Y. Fujimoto, M. Kimura, F. A. Khalifa, and N. Ikekawa, *Chem. Pharm. Bull.*, **32**, 4372 (1984).
11) Y. Fujimoto, H. Iwadate, N. Ikekawa, T. Kihira, and T. Hoshita, *J. Chem. Soc., Perkin Trans. 1*, **1985**, 2701.