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SYNTHESIS OF POTENTIAL ECDYSTEROID PRECURSORS FROM $\Delta^{7,22}$ STEROLS

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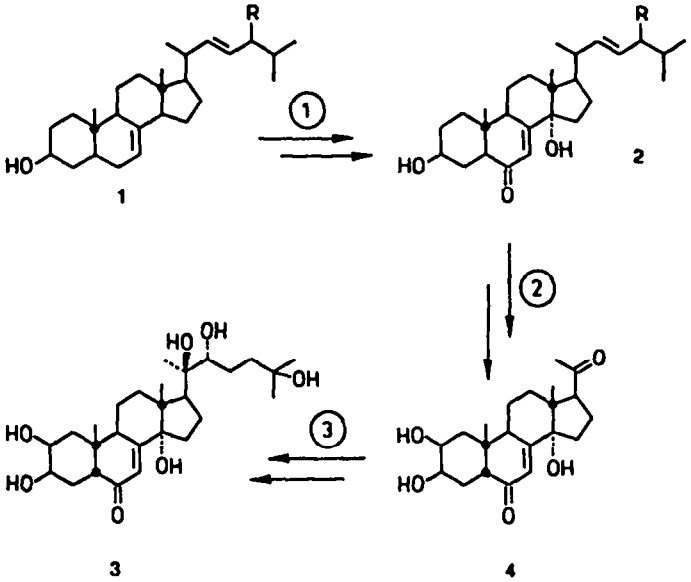
Abstract - Two routes for the conversion of 5α-cholest-7-ene-3β-ol (**11**) into **7**, which has the typical ecdysteroid substitution pattern in rings B, C, and D, have been developed. Making use of one of the methods, 5,6-dihydroergosterol (**31**) was converted into the **38**, possessing all the functionalities required for the synthesis of naturally occurring ecdysteroids.

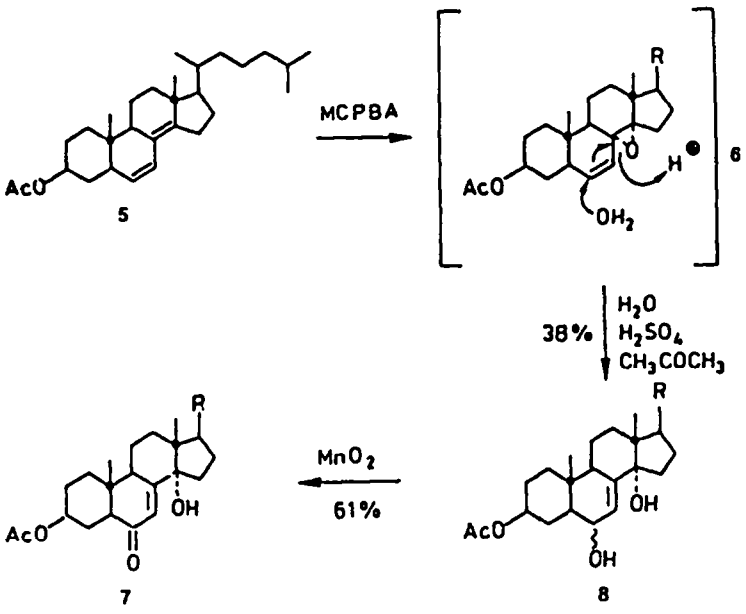
Introduction

Whereas Δ^5-sterols such as cholesterol, β-sitosterol, and campesterol play an important rôle as starting materials for the synthesis of biologically active steroids,[1,2] little efforts have been devoted to developing methods for the use of compounds of type **1** (R=H, CH_3, C_2H_5) as steroidal raw materials. Δ^7-sterols (examples of which are chondrillasterol[3] or spinasterol[3]) have been isolated from many sources (higher[4] and lower plants,[5] marine organisms[6]). Since the last three years we embarked on a project aimed at the synthesis of ecdysteroids such as 20-hydroxyecdysone (**3**) using the general sequence **1** → **2** → **4** → **3** (Scheme 1). We have already published a new method for the conversion of poststeron (**4**) into **3**.[7] Here we wish to outline the successful execution of part 1 of our synthetic plan (Scheme 1, **1** → **2**).

We based our investigations on work of Wada,[8] who has found that 5α-cholesta-6,8(14)-diene (**5**) on reaction with m-chloroperbenzoic acid gives the unsaturated epoxide **6**. Under acidic conditions **6** hydrolyses to provide the enediol **8**, which



Scheme 1



Scheme 2

on oxidation with manganese dioxide provides 7 with the typical ecdysteroid substitution pattern in rings B, C, and D (Scheme 2).

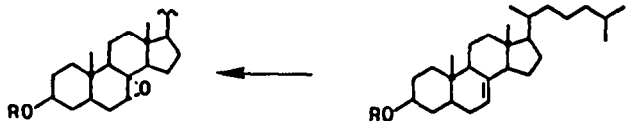
Conversion of 11 and 19 into 7.

The overall yield reported by Wada[8] for the formation of 7 starting from 5, was 23%. We found that the yield was considerably increased when after peracid oxidation the intermediate 6 was immediately oxidized with sodium dichromate in acetic acid. 7 was then obtained in an overall yield of 68%.

Dienes of type 5 are easily available by rearrangement of 5,7-dienes such as 19.[9,10] (Scheme 3). Combined with the oxidation methodology discussed above this constitutes an efficient access of ecdysteroid-like substituted compounds such as 7 using 5,7-dienes as starting materials.[11]

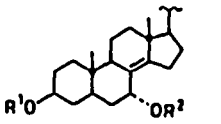
For Δ^7-sterols such as 11 the situation is more complicated. Allyl alcohol 14 which is prepared from 12 via selenium dioxide oxidation[12] or by acid-catalyzed rearrangement of epoxide 10 under carefully controlled conditions (Fieser performed the reaction in chloroform solution[13], we obtained best results with 0.01 molar p-toluenesulfonic acid in dimethoxyethane (DME): 76%) was shown to furnish exclusively the unwanted diene 16 on elimination with thionyl chloride.[12,14] On attempted conversion of 14 into the tosylate and the mesylate, respectively, we also isolated only 16.[15] The same result was obtained when acetate 15 was submitted to Trost's eliminination conditions[16] (heating of 15 with molybdenum hexacarbonyl to 110°C in toluene solution).

In order to bypass these difficulties, 11 was converted to 24 by a) oxidation with two equivalents of m-chloroperbenzoic acid to give 20,[17,18] b) acid-catalyzed rearrangement to give 23,[17,18] and c) acetylation. On reaction with tosylhydrazine 24 furnished two isomeric hydrazones 25 (rather sensitive compounds), the configurations of which were not determined.[19] In their reactivity towards methyl lithium (Shapiro reaction [20]) the two tosylhydrazones differed somewhat. One isomer reacted faster (24h at 20°C) and yielded diene 28 (the desired precursor of 7, vide supra) and its isomer 18 in a 4.5:1 ratio (combined yield: 76%). For the Shapiro reaction of the other hydrazone an elevated temperature had to be chosen

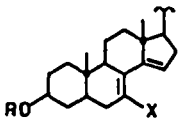


	R
11	H
12	Ac

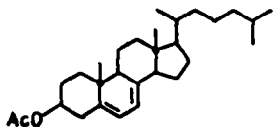
	R
9	H
10	Ac



	R^1	R^2
13	H	H
14	Ac	H
15	Ac	Ac



	R	X
16	Ac	H
17	Ac	$OPO(OEt)_2$
18	H	H



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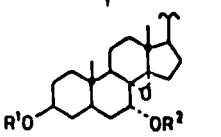
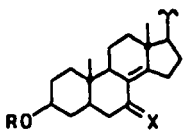
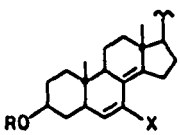


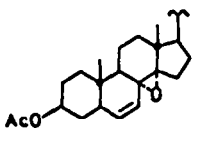
	R^1	R^2
20	H	H
21	Ac	H
22	Ac	Ms



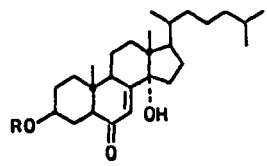
	R	X
23	H	O
24	Ac	O
25	Ac	N NHTS
26	H	2 H



	R	X
5	Ac	H
27	Ac	$OPO(OEt)_2$
28	H	H



6

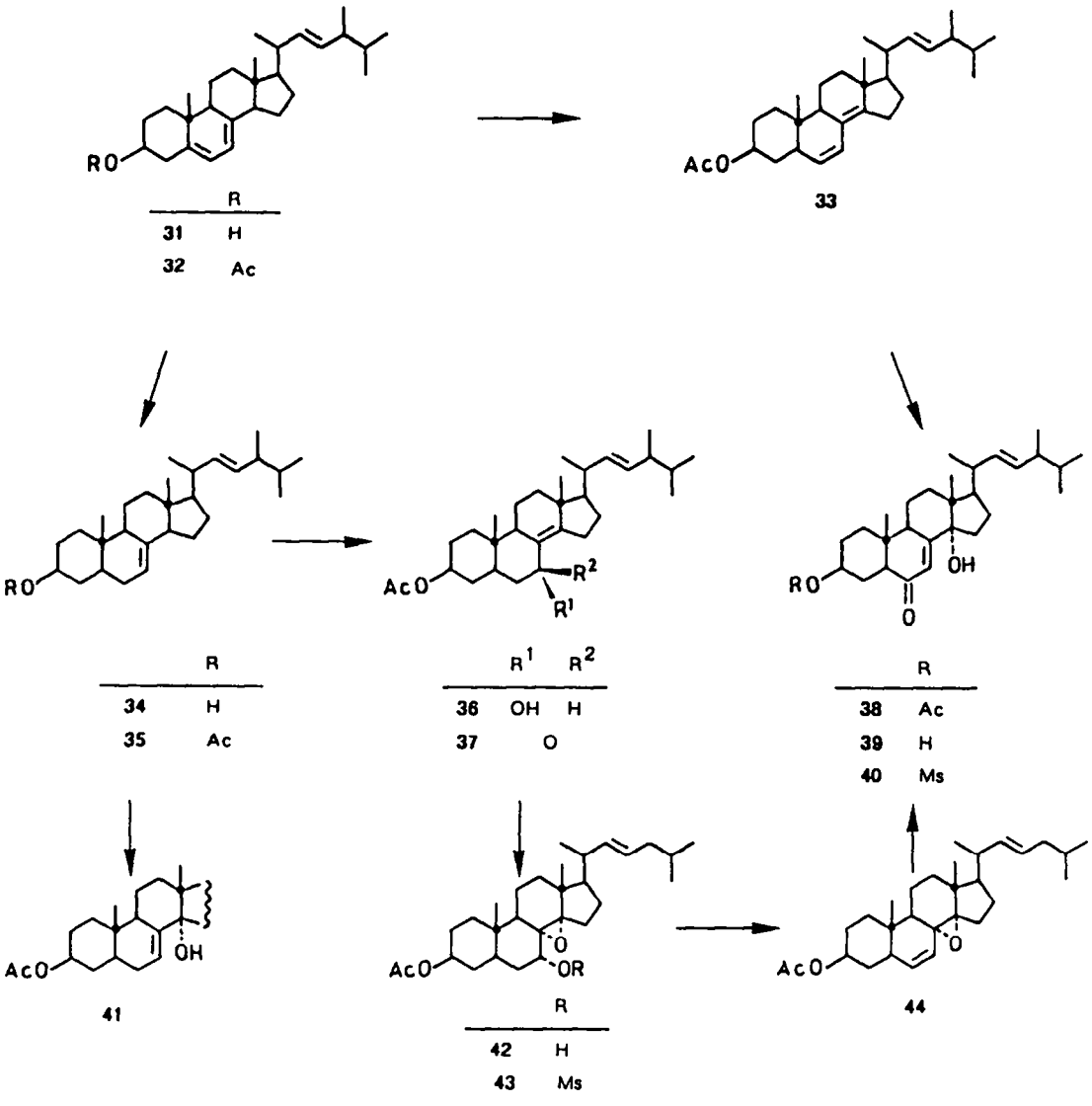


	R
7	Ac
29	H
30	Ms

Scheme 3

(20h at 40°C). In this case, **28** and **18** were formed in a 1.6:1 ratio. It should be pointed out that diene **28** could not be obtained from **24** by using of the Ireland method.[21] Treatment of **24** with a) lithium diisopropylamide and b) diethyl chlorophosphate furnished dienol phosphate **17** rather than **27**. Reduction of **17** with lithium in ethylamine led to the formation of **26** (75%).

In a different set of experiments **12** was oxidized with m-chloroperbenzoic acid (2 equivalents) according to Fieser and Djerassi[17,18] providing **21**. Mesylation followed by elimination (by heating of **22** in diazabicyclononane) gave **6** which was directly oxidized with sodium dichromate in acetic acid whereby the final product **7** was obtained in 85% yield.



Scheme 4

In conclusion: We have developed two routes from a Δ^7-sterol to **7**. The first sequence (**11** → **20** → **23** → **24** → **25** → **28** → **5** → **7**) comprises eight steps with an overall yield of 18%.[22] In a second, much more practical five-step route (**11** → **12** → **21** → **6** → **7**) an overall yield of 40% was achieved.

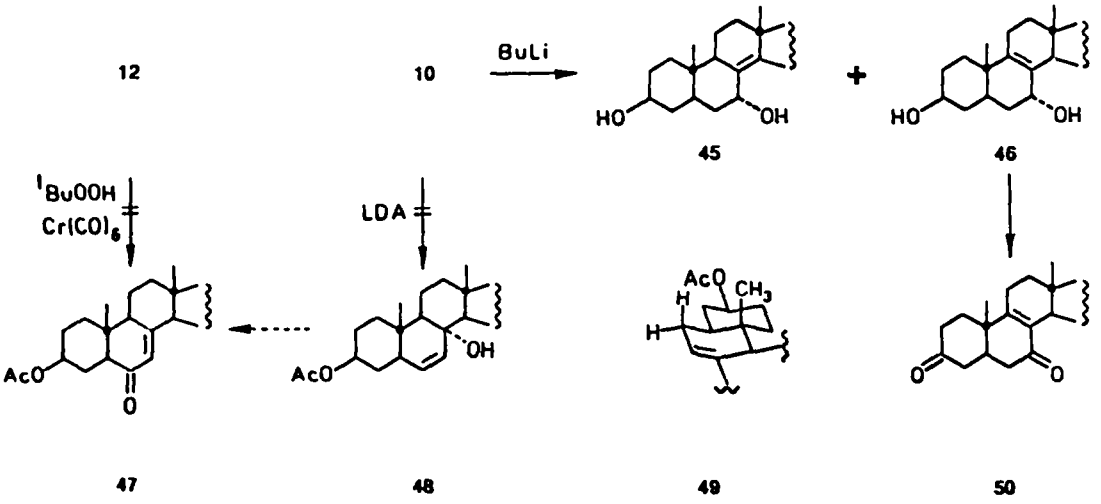
Conversion of 31 and 34 into 39

As a model for 7,22-dienic sterols, dihydroergosterol[23,24] was chosen. The Fieser-Djerassi oxidation[17,18] of **35** to give **42** (49% yield) had to be performed under carefully selected conditions otherwise the side-chain double bond reacted as well.[25] **42** was also obtained from **35** by a) selenium dioxide oxidation[26] to furnish a 3:1 mixture of **36** and a compound which we presume to be **41**, since it slowly rearranged into **36**, and b) oxidation of **36** with pyridinium dichromate (PDC), which led to **42** along with **37**. **42** was converted to **44** by a) mesylation and b) elimination, essentially as described above. Finally, oxidation with sodium dichromate in acetic acid provided **38**. **38** was also prepared from **32** by a) double bond isomerization, b) m-chloroperbenzoic acid oxidation, and c) oxidation with sodium dichromate in acetic acid, as described for the conversion of **19** into **7**.

From **38** and **7**, the corresponding mesylates **40** and **30**, respectively, have been prepared by acetate hydrolysis and mesylation. **30** and **40** have a functionality in ring A which is well-suited for the introduction of the ecdysteroid 2,3-diol system by elimination and hydroxylation.[27]

Addendum

At the outset of our work we intended to make use of Pearson's allylic oxidation method.[28] However, all attempts to prepare **47** by oxidation of **12** with t-butylhydroperoxide/chromium hexacarbonyl failed.[29] We believe that 6β-H, which has to be abstracted in the oxidation process[30], is for sterical reasons not accessible (see Scheme 5, formula **49**). We also tried to rearrange epoxide **10** into allyl alcohol **48**[31] which we hoped to oxidize to **45** with pyridinium chlorochromate.[32] Again, all attempts met with no success. We were unable to rearrange **10** with lithium diisopropylamide, and the reaction of **10** with butyllithium furnished allyl alcohols **45** and **46** which are of little use in the present context.



Scheme 5

EXPERIMENTAL

General

All O_2- or moisture-sensitive reactions were performed in oven-dried glassware under a positive pressure of argon. Sensitive liquids and solutions were transferred by syringe and were introduced into the reaction flask through rubber septa. Usual work-up means partitioning the reaction mixture between water and an organic solvent (given in paranthesis), drying the combined organic solutions over Na_2SO_4 and removal of the solvent by distillation in vacuo at 40°C, using a rotatory evaporator. The instrumentation used was: ^1H NMR: WP-80 (Bruker); AM-400 (Bruker); ^{13}C NMR: AM-400 (Bruker); IR: Perkin Elmer 257; MS: MAT-731 and MAT-CH-5 (Finnigan); HPLC: High-pressure chromatography using pump system model 6000 (Waters Associates Inc.), UV-detector LC-3 (Pye Unicam), stainless steel columns 25.0 cm x 0.4 cm (analytical) or 25.0 cm x 2 cm (preparative), stationary phase and eluent are given in parenthesis; MPLC: Medium-pressure chromatography using 31.0 cm x 2.5 cm glass tubes, silica gel Grace (50 µm), Duramat pump (CFG); Thomachrom UV detector (Reichelt).

7α,8-Epoxy-5α,8α-cholestan-3β-yl acetate (10).

10 was prepared from **12** [24] using the procedure of Fieser et al. [13]: yield 75%.- M.p. 95-96°C (from methanol, lit., [13] 96-97°C).- IR (CCl_4): 1740 cm^{-1}(CO).- ^1H NMR (80 MHz, $CDCl_3$): δ = 0.74 (s, CH_3-18), 0.84 (s, CH_3-19), 2.02 (s, OAc), 3.30 (m, $W_{1/2}$=5 Hz, 7-H), 4.45-4.85 (m, 3-H) .- $C_{29}H_{48}O_3$ (444.6), MS: m/z (%) = 444 (28, M^+), 426 (24), 411 (8), 366 (9), 351 (11) 313 (29), 120 (100)

5α-Cholest-8(14)-ene-3β,7α-diol 3-acetate (14).[33]

To a solution of **10** (1.0 g, 2.25 mmol) in DME (25 ml) a 0.01 m solution of p-toluenesulfonic acid in diethylether (0.6 ml) was added. The mixture was stirred at 25°C for 2 h. The acid was then neutralized by addition of solid K_2CO_3 Filtration, solvent evaporation and LC (hexanes-ethyl acetate-NEt_3 7:1:0.01) gave **14** (720 mg, 72%) and **16** (180 mg, 18%).- M.p. 113-115°C (from methanol).- IR (CCl_4): 3600, 3450 (OH), 1725 cm^{-1} (CO).- ^1H NMR (80 MHz, $CDCl_3$): δ = 0.71 (s, CH_3-18), 0.87 (s, CH_3-19), 2.02 (s, OAc), 4.53 (m, $W_{1/2}$=6 Hz, 7-H), 4.50-4.90 (m, 3-H).- $C_{29}H_{48}O_3$ (444.6), MS: m/z (%) = 444 (100, M^+), 426 (24), 351 (13), 331 (13), 313 (42), 290 (45).

Reaction of 15 with molybdenum hexacarbonyl.

To a solution of **15** (18 mg, 0.04 mmol, prepared from **5** as described by Fieser [12]) O,N-bistrimethylsilylacetamide (0.01 ml) was added. The mixture was stirred at 110°C (sealed reaction flask) for 15 min. After cooling to 25°C, molybdenum hexacarbonyl (2 mg, 0.008 mmol) was added. The mixture was stirred at 110°C for 16 h. Filtration through silica gel (0.5 g, hexanes-ethyl acetate 10:1) and solvent evaporation gave **16**.- M.p. 84-86°C (from methanol, lit., [34] 85-86°C). When the reaction was performed at 80°C , **15** was recovered.

8,14-Epoxy-5α,8α-cholestan-3β,7α-diol (20).

To a solution of **10** (2.0 g, 5.2 mmol) in CH_2Cl_2 (50 ml) at 25°C MCPBA (2.5 g, 15.0 mmol) was added in small portions. The mixture was kept at 4-6°C for 160 h. After solvent evaporation the residue was redissolved in diethylether (50 ml). Usual work-up and MPLC (hexanes-ethyl acetate 3:2) furnished **20** (1.4 g, 66%) along with small amounts of the corresponding 8,9-epoxide (0.3 g, 16%).- M.p. 186-187°C (from ethanol, lit.,[12] 186-187°C).- IR ($CHCl_3$): 3600-3300 cm^{-1} (OH).- ^1H NMR (80 MHz, $CDCl_3$): δ = 0.80-1.00 (CH_3 signals), 2.20-2.40 (m, OH), 3.35-3.80 (m, 3-H), 3.52 ($W_{1/2}$=6 Hz, 7-H).- $C_{27}H_{46}O_3$ (418.6), MS: m/z (%) = 418 (40, M^+), 403 (26), 400 (6), 385 (7), 369 (9), 305 (37), 287 (60), 269 (29), 107 (100).

3β-Acetoxy-5α-cholest-8(14)-en-7-one (24).

A solution of **20** (1.9 g, 4.5 mmol) in ethanol (70 ml) and conc. HCl (3.5 ml) was refluxed for 2 h. Water (100 ml) was added and the mixture was cooled to 0°C. A crystalline fraction was obtained by filtration and the filtrate was extracted with diethylether and the ethereal solution was combined with the crystalline product (dissolved in 100 ml of ether), washed with saturated aq. $NaHCO_3$ and water and dried over Na_2SO_4. After solvent evaporation the residue was acetylated (pyridine (20 ml), acetic anhydride (6 ml), 16 h at 20°C). Evaporation to dryness (after addition of toluene) and MPLC (hexanes-ethyl acetate 3:2) furnished **24** (1.5 g, 75%) along with small amounts of the corresponding 8(14)-en-15-one isomer.[17] M.p. 140-142°C (from ethanol, lit.,[17] 141-142°C).- IR ($CHCl_3$): 1720, 1665 cm^{-1}.- ^1H NMR (80 MHz, $CDCl_3$): δ = 0.81 (s, CH_3-18), 0.91 (s, CH_3-19), 2.01 (s, OAc), 4.45-4.95 (3-H).- $C_{29}H_{46}O_3$ (442.4), MS: m/z (%) = 442 (M^+, 100), 357 (65), 329 (29), 276 (59).

3β-Acetoxy-5α-cholesta-7,14-dien-7-yl diethyl phosphate (17).

To a LDA solution [35] (0.33 mmol in THF (1 ml)) at -78°C a solution of **24** (80 mg, 0.18 mmol) in dry THF (3.3 ml) was added. After being allowed to warm to ambient temperature the mixture was stirred for 1.5 h. Diethyl chlorophosphate (173 mg, 1.0 mmol) was added and the mixture was stirred for 1 h at 20°C . Usual work-up (diethylether) and MPLC (hexanes-ethyl acetate 3:1) gave **17** (45 mg, 43%) and recovered **24** (15mg, 19%).- IR (CCl_4): 1725 (CO), 1625 cm^{-1} (C=C).- ^1H NMR (400 MHz, $CDCl_3$): δ = 0.69 (s, CH_3-18), 0.84 (d, J=6 Hz, CH_3-26, CH_3-27), 0.86 (s, CH_3-19), 0.92 (d, J=6 Hz, CH_3-21), 1.32 (m, $C\underline{H}_3$-CH_2-O), 2.01 (s, OAc), 2.16 (m, 1 H), 2.52-2.62 and 2.75-2.86 (2 m' s, CH_2-6), 4.12 (m, CH_3-$C\underline{H}_2$-O), 4.67-4.77 (m, 3-H), 5.18 (m, 15-H).- $C_{33}H_{55}O_6P$ (578.7), MS: m/z (%) = 578 (85, M^+), 563 (5), 518 (8), 465 (10), 440 (9), 424 (70), 380 (25), 364 (100), 349 (39), 339 (27), 311 (57), 251 (81).

Reduction of 17.

17 was prepared from **24** (100 mg. 0.23 mmol) as described above. To the crude reaction mixture at -78°C tert. butanol (0,07 ml) was added. This mixture was introduced dropwise at -60°C into a solution of lithium (14 mg, 2,0 mmol) in ethylamine (2 ml). After being stirred for 1 h at -60°C the mixture was allowed to warm to ambient temperature and was quenched with 1:1 THF/water. Evaporation of ethylamine, usual work-up (diethylether) and LC (hexanes-ethyl acetate 5:1) furnished 5α-cholest-7-en-3β-ol (**26**)(30 mg, 35%).- M.p. 117-119°C (from ethanol, lit.,[36] 119-119.5°C).

3β-Acetoxy-5α-cholest-8(14)-en-7-one-(p-toluene-sulfonylhydrazone) (25), two stereoisomers.

A mixture of **24** (400 mg, 0.9 mmol), p-toluene-sulfonylhydrazine (310 mg, 1.6 mmol), CH_2Cl_2 (10 ml), and conc. HCl (3 drops) was stirred at 40°C (sealed reaction flask) for 5 h. After being cooled to ambient temperature to the mixture was added solid K_2CO_3. Filtration, solvent evaporation, and MPLC (hexanes-ethyl acetate 6:1) gave the unpolar hydrazone (300 mg, 55 %) and then the polar isomer (230 mg, 42%).

Unpolar isomer: M.p. 129-132°C (from diisobutylether).- IR ($CHCl_3$): 3300, 3200 (NH), 1720 (CO), 1600 cm^{-1} (C=C).- ^1H NMR (80 MHz, $CDCl_3$): δ = 0.78 (s, CH_3-18), 0.90 (s, CH_3-19), 2.02 (s, OAc), 2.43 (s, Ar-CH_3), 4.35-4.85 (m, 3-H), 7.30 and 7.77 (Ar-H).- CD (ethanol): λ_{max} (ε) = 275 (+4.10), 269 (+3.56), 249 (-3.33), 232 (+2.50), 209 (-15.77), 197 nm (+35.10).- $C_{36}H_{54}N_2O_4S$ (610.8), MS: m/z (%) = 610 (0.4, M^+), 454 (45), 453.3455 (100, Calc for $C_{29}H_{45}N_2O_2$: 453.3481), 452 (75), 437 (8), 426 (8), 314 (25).

Polar isomer: IR ($CHCl_3$): 3300, 3200 (NH), 1720 (CO), 1600 cm^{-1} (C=C).- ^1H NMR (80 MHz, $CDCl_3$): δ = 0.72 (s, CH_3-18), 0.84 (s, CH_3-19), 2.03 (s, OAc), 2.43

(s, Ar-CH_3), 4.40-4.90 (m, 3-H), 7.30 and 7.85 (Ar-H).- CD (ethanol): λ_{max} (ϵ) = 275 (+11.62) 270 (+11.70), 218 (-8.02), 198 nm (+7.37).- $C_{36}H_{54}N_2O_4S$ (610.8) MS: m/z (%) = 454 (47), 453.3446 (100, Calc for $C_{29}H_{45}N_2O_2$: 453.3481), 452 (72), 437 (8), 426 (12), 314 (25).

Shapiro reaction of **25**.

a) unpolar isomer: To a solution of **25** (unpolar isomer, 50 mg, 0.082 mmol) in dry diethylether (2 ml) a 1.6 M solution of methyllithium in diethylether (0.26 ml, 0.41 mmol) was added and the mixture was stirred for 24 h at 20°C. After addition of water (2 ml) and usual work-up (diethylether) LC (hexanes-ethyl acetate 5:1) gave a mixture of **18** and **28** [37] 24 mg, 76%; ratio 1:4.5 (from the intensities of the olefinic proton signals (80 MHz)).

b) polar isomer: Using the above procedure from **25** (polar isomer) a 1.6:1 mixture of **28** and **18** was obtained in 72 % yield.

8,14-Epoxy-5α,8α-cholestan-3β,7α-diol 3-acetate 7-mesylate (**22**).

To a solution of **21** (350 mg, 0.76 mmol) in dry pyridine (6 ml) methanesulfonyl chloride (0.43 ml, 0.43 mmol) was added. The mixture was stirred at 40°C for 16 h. Solvent evaporation (by codistillation with toluene) and LC (hexanes-ethyl acetate 6:1) gave **22** (335 mg, 87%).- M.p. (dec.) 111-112°C (from hexanes/ethylacetate).- IR (CCl_4): 1735 (CO), 1360, 1170 cm^{-1} (SO_2).- ^1H NMR (80 MHz, $CDCl_3$): δ = 0.80-1.00 (CH_3 signals), 2.02 (s, OAc), 3.10 (s, SO_2CH_3), 4.50-4.90 (m, 3-H, 7-H).- MS: m/z (%) = 442 (15), 424 (26), 409 (50), 349 (19), 327 (12), 311 (40), 301 (29), 43 (100).- (Found: C, 66.80; H, 9.33; $C_{30}H_{50}O_6S$ (538.8) requires C, 66.87; H, 9.35).

8,14-Epoxy-5α,8α-cholest-6-en-3β-yl acetate (**6**).

A solution of **22** (514 mg, 0.96 mmol) in DBN (7.5 ml) was stirred at 80°C for 38 h. Usual work-up (diethylether) and MPLC (hexanes-ethyl acetate-NEt_3 9:1:0.05) gave **6** (312 mg, 75%).- M.p. 91-92°C/115-120°C (from hexanes-CH_2Cl_2).- IR (CCl_4): 1735 (CO), 1620 cm^{-1} (C=C).- ^1H NMR (80 MHz, $CDCl_3$): δ = 0.80-1.00 (CH_3 signals), 2.02 (s, OAc), 4.50-4.90 (m, 3-H), 5.22 (6-H), and 5.60 (7-H, AB-part of an ABX-system, $J_{7,6}$=9 Hz, $J_{6,5}$=3 Hz, $J_{7,5}$=2 Hz).- MS: m/z (%) = 442 (4, M^+), 424 (4), 382 (11), 364 (5), 349 (9), 329 (100).- (Found: C, 78.70; H, 10.50; $C_{29}H_{46}O_3$ (442.6) requires C, 78.68; H, 10.47).

3β-Acetoxy-14-hydroxy-5α-cholest-7-en-6-one (**7**).

a) From **5**: A solution of **5** (207 mg, 0.49 mmol) and MCPBA (110 mg, 0.55 mmol) in diethylether (15 ml) was kept at 4-6°C for 24 h. Then a solution of sodium dichromate (160mg, 0.61 mmol) in 96 % acetic acid (4 ml) was added and the mixture was stirred at 20°C for 15 min. Usual work-up (diethylether) and LC (hexanes-ethyl acetate 3:1) gave **20** (152 mg, 68 %).- M.p. 185-186°C (from methanol, lit.,[8] 186-187°C).

b) From **6** : To a solution of **6** (50 mg, 0.11 mmol) in diethylether (5 ml) at 20°C a solution of sodium dichromate (40 mg, 0.15 mmol) in 96 % acetic acid (1 ml) was added. The mixture was stirred at 20°C for 30 min and then diluted with diethylether (15 ml). Usual work-up and LC (hexanes-ethyl acetate 5:2) gave **7** (43 mg, 83 %).

14-Hydroxy-3β-mesyloxy-5α-cholest-7-en-6-one (**30**).

To a solution of **29** (49 mg, 0.12 mmol, prepared from **7** as described in ref. [11]) in dry pyridine (2 ml), methanesulfonyl chloride (0.02 ml, 0.2 mmol) was added and the mixture was stirred at 25°C for 3 h. Usual work-up (diethylether) and LC (hexanes-ethyl acetate 5:2) gave **30** (42 mg, 69 %).- M.p. 157-159°C (from hexanes-ethyl acetate).- IR ($CHCl_3$): 3590 (OH), 1670 (unsat. CO), 1365, 1170 cm^{-1} (SO_2).- ^1H NMR (80 MHz, $CDCl_3$): δ = 0.79 (s, CH_3-18), 0.89 (s, CH_3-19), 3.02 (s, SO_2CH_3),

4.40-4.85 (m, 3-H), 5.90 (d, J=2 Hz, 7-H).- MS: m/z (%) = 494.3064 (2, M^+, Calc for $C_{28}H_{46}O_3S$: 494.3066), 476 (25), 461 (32), 398 (18), 380 (38), 365 (89), 363 (100), 349 (20), 326 (20), 267 (64).

Selenium dioxide oxidation of 35.

To a solution of **35** (150 mg, 0.33 mmol, prepared from ergosterol **31** by hydrogenation using Wilkinson's catalyst to give **34** and subsequent acetylation [38]) in dioxane (6 ml) a solution of SeO_2 (39 mg, 0.33 mmol) in 1:9 water-dioxane (6 ml) was added. The mixture was stirred under reflux for 10 min and after cooling it was poured into ice water. Usual work-up (diethylether) gave a crude product which was redissolved in diethylether (25 ml) and filtered. Solvent evaporation and LC (hexanes-diethylether, gradient 3:1 - 0:100) gave **36** (85 mg, 55%) and **41** (16 mg, 10%).

5α-Ergosta-8(14),22-diene-3β,7α-diol 3-acetate (36).

M.p. 129-131°C (from pentane, lit., [39] 125-126°C).- IR (CCl_4): 3600, 3550-3350 (OH), 1730 cm^{-1} (CO).- ^1H NMR (80 MHz, $CDCl_3$): δ = 0.65-1.00 (CH_3 signals), 2.00 (s, OAc), 4.47 (m, $W_{1/2}$=6 Hz, 7-H), 4.50-4.85 (m, 3-H), 5.12-5.25 (m, 22-H, 23-H).- MS: m/z (%) = 456.3597 (100, M^+, Calc for $C_{30}H_{48}O_3$: 456.3603), 438 (9), 423 (4), 395 (2), 331 (32), 313 (14), 312 (15), 302 (8), 253 (16).

5α-Ergosta-7,22-diene-3β,14α-diol 3-acetate (41).

M.p. 198-200°C (from diethylether/pentane).[40]- IR (CCl_4): 3600, 3550-3400 (OH), 1730 cm^{-1} (CO).- ^1H NMR (80 MHz, $CDCl_3$): δ = 0.55-1.23 (CH_3 signals), 2.00 (s, OAc), 4.50-4.85 (m, 3-H), 5.11-5.25 (m, 7-H, 22-H, 23-H).- MS: m/z (%) = 456.3598 (50, M^+, Calc for $C_{30}H_{48}O_3$: 456.3603), 438 (28), 423 (4), 331 (16), 313 (14), 311 (8), 302 (100), 253 (32).

8,14-Epoxy-5α,8α-ergost-22-ene-3β,7α-diol 3-acetate (42).

a) From **36**: A solution of **36** (624.9 mg, 1.37 mmol) and pyridinium dichromate (747 mg, 1.99 mmol) in CH_2Cl_2 (60 ml) was stirred at 20°C for 7 h. Filtration through silica gel (elution with CH_2Cl_2 and ethyl acetate), solvent evaporation and LC (hexanes - ethyl acetate 7:1) gave **37** (292.3 mg, 28%) and **42** (339.1 mg, 41%).- M.p. 122-124°C (from methanol).- IR (CCl_4): 3575 (OH), 1730 cm^{-1} (CO).- ^1H NMR (80 MHz, $CDCl_3$): δ = 0.80-1.07 (CH_3 signals), 2.02 (s, OAc), 2.29 (m, OH), 3.56 (m, $W_{1/2}$=5 Hz, 7-H), 4.55-5.00 (m, 3-H), 5.15-5.32 (m, 22-H, 23-H).- MS m/z (%) = 472 (22, M^+), 457 (14), 379 (7), 356 (8), 347 (20), 329 (59), 311 (29), 269 (18), 251 (27), 236 (35), 107 (100).-(Found: C, 76.30; H, 10.18; $C_{30}H_{48}O_4$ (427.7) requires C, 76.23; H, 10.24).

b) From **35**: To a solution of **35** (20.0 mg, 0.044 mmol) in diethylether (1 ml) at -78°C a solution of MCPBA (13 mg, 0.064 mmol) in diethylether (0.5 ml) was added. The mixture was stirred at -78°C for 4 h and was then kept at -18°C for 44 h and at 4-6°C for 10 d. Usual work-up (diethylether) and LC (hexanes-ethyl acetate 5:1) gave **42** (9.7 mg, 47 %).

3β-Acetoxy-5α-ergosta-8(14),22-dien-7-one (37).

M.p. 149-151°C (from methanol).- IR (CCl_4): 1730, 1675 (CO), 1590 cm^{-1} (C=C).- ^1H NMR (80 MHz, $CDCl_3$): δ = 0.80-1.00 (CH_3 signals), 2.03 (OAc), 4.50-5.00 (3-H), 5.15-5.31 (22-H and 23-H).- MS: m/z (%) = 454 (M^+, 72), 439 (20), 411 (7), 355 (18), 328 (100), 315 (18), 304 (14), 301 (11), 276 (15).- (Found: C, 79.19; H, 10.14; $C_{30}H_{46}O_3$ (454.7) requires C, 79.25; H, 10.20).

8,14-Epoxy-5α,8α-ergost-22-ene-3β,7α-diol 3-acetate 7-mesylate (43).

43 was prepared from **42** as described for **22** yield: 87%.- M.p. (dec.) 128°C (from

hexanes-CH_2Cl_2).- IR (CCl_4): 1730 (CO), 1360, 1170 cm^{-1} (SO_2).- ^1H NMR (80 MHz, $CDCl_3$): δ = 0.80-1.06 (CH_3 signals), 2.03 (s, OAc), 3.12 (s, SO_2CH_3), 4.61 (m, $W_{1/2}$=5 Hz, 7-H), 4.50-4.90 (m, 3-H), 5.17-5.31 (m, 22-H, 23-H).- MS: m/z (%) = 550 (2, M^+), 454 (22), 439 (9), 436 (7), 425 (11), 411 (16), 383 (15), 337 (21), 329 (55), 328 (39), 311 (17), 107 (100).- (Found: C, 67.67; H, 9.04; $C_{31}H_{50}O_6S$ (550.8) requires C, 67.60; H, 9.15).

8,14-Epoxy-5α,8α-ergosta-6,22-dien-3β-yl acetate (44).

44 was prepared from **43** as described for **6** (44 h at 80°C): yield 72% .- M.p. 134-136°C (from methanol).- IR (CCl_4): 1730 cm^{-1} (CO).- ^1H NMR (80 MHz, $CDCl_3$): δ = 0.80-1.07 (CH_3 signals), 2.04 (s, OAc), 4.56-5.00 (m, 3-H), 5.13-5.37 (m, 6-H, 22-H, 23-H), 5.63 (A-part of an ABX-system, J_{AB} =10 Hz, J_{AX}=1.8 Hz, 7-H).- MS: m/z (%) = 454(1, M^+), 436 (4), 394 (6), 376 (4), 361 (7), 329 (100), 311 (10), 269 (9), 251 (36), 235 (23), 175 (45), 107 (88).- (Found: C, 79.18; H, 10.25; $C_{30}H_{46}O_3$ (454.7) requires C, 79.25; H, 10.20).

3β-Acetoxy-14-hydroxy-5α-ergosta-7,22-dien-6-one (38).

a) From **33**: **33** (prepared from **32** as described by Laubach et al. [9]) was oxidized to give **38** as described for **7** : yield 48% .- M.p. 194-195°C (from methanol).- IR ($CHCl_3$): 3600-3300 (OH), 1720 (CO), 1670 cm^{-1} (unsat. CO).- ^1H NMR (80 MHz, $CDCl_3$): δ = 0.68 (s, CH_3-18), 0.78-1.05 (CH_3 signals), 2.02 (s, OAc), 4.45-4.95 (m, 3-H), 5.13-5.28 (m, 22-H, 23-H), 5.89 (d, J=2.8 Hz, 7-H).- MS: m/z (%) = 470 (1, M^+), 452 (2), 437 (5), 410 (100), 367 (8), 328 (12), 318 (11), 276 (49), 257 (50), 229 (39), 216 (65), 215 (41).- (Found: C, 76.43; H, 9.92; $C_{30}H_{46}O_4$ (470.7) requires C,76.55; H, 9.85).

b) From **44**: **44** was oxidized with sodium dichromate to give **38** as described for the formation of **7** from **6**. The reaction was performed only in a 1 mg scale. TLC (hexanes-ethyl acetate 1:3) indicated the formation of a single product identical with **38** prepared from **33**.

3β,14-Dihydroxy-5α-ergosta-7,22-dien-6-one (39).

A mixture of **38** (290 mg, 0.62 mmol) in THF (15 ml) and 2.5 % K_2CO_3 in 1:1 methanol-water (20 ml) was stirred for 24 h at 25°C. The mixture was diluted with water, and methanol and THF were evaporated. Then usual work-up (diethylether) and LC (hexanes-ethyl acetate 1:2) gave **39** (198 mg, 75 %).- M.p. 219-222°C (from methanol).- IR ($CHCl_3$): 3600, 3550-3300 (OH), 1665 cm^{-1} (unsat. CO).- ^1H NMR (80 MHz, $CDCl_3$): δ = 0.71 (s, CH_3-18), 0.80-1.05 (CH_3 signals), 3.40-3.85 (m, 3-H), 5.18-5.32 (m, 22-H, 23-H), 5.91 (d, J=2.7 Hz, 7-H).- MS: m/z (%) = 430 (12), 429 (22), 428 (11, M^+), 396 (10), 395 (11), 367 (6), 285 (15), 276 (48), 275 (33), 235 (98), 234 (100).- (Found: C, 78.33; H, 10.41; $C_{28}H_{44}O_3$ (428.7) requires C, 78.46; H, 10.35).

14-Hydroxy-3β-mesyloxy-5α-ergosta-7,22-dien-6-one (40).

39 was mesylated to furnish **40** as described for **30** : yield 78% .- M.p. 195-196°C (from hexanes-CH_2Cl_2).- IR ($CHCl_3$): 3580-3300 (OH), 1665 (unsat. CO), 1350, 1170 cm^{-1} (SO_2).- ^1H NMR (80 MHz, $CDCl_3$): δ = 0.70 (s, CH_3-18), 0.80-1.06 (CH_3 signals), 3.04 (s, SO_2CH_3), 4.45-4.90 (3-H), 5.15-5.32 (m, 22-H, 23-H), 5,92 (d, J=2.7 Hz, 7-H).- MS: m/z (%) = 506.3068 (2, M^+, Calc for $C_{29}H_{46}O_5S$: 506.3066), 488 (11), 473 (14), 411 (17), 410 (23), 392 (32), 377 (38), 362 (51), 267 (47), 266 (56), 257 (28), 251 (34), 216 (44), 69 (100).

Reaction of **10** with butyllithium.

To a solution of **10** (200 mg, 0.46 mmol) in THF (5 ml) and HMPA (0.56 ml) at 0°C 1.6 M BuLi in hexane (2 ml, 3.2 mmol) was added, and the mixture was stirred at 20°C for 70 h. Usual work-up (diethylether) and MPLC (hexanes - ethyl acetate - methanol 10:10:0.75, then 10:10:1) furnished 5α-cholest-8(14)-ene-3β,7α-diol (**45**)

(65 mg, 35%, m.p. 154-156°C (from methanol - water), lit.,[12] 157-158°C, spectroscopic results in agreement with the published data [42]), and **46** (71 mg, 38%).

5α-Cholest-8-ene-3β,7α-diol (46).

M.p. 133-135°C (from methanol - water).- IR ($CHCl_3$): 3600, 3500-3300 cm^{-1} (OH).- ^1H NMR (80 MHz, $CDCl_3$): δ = 0.60 (s, CH_3-18), 0.80-1.00 (CH_3 signals), 3.45-3.90 (3-H), 4.02 (m, $W_{1/2}$=6 Hz, 7-H).- MS: m/z (%) = 402 (M^+, 0.5), 384 (100), 369 (22), 351 (14), 271 (20).- (Found: C, 80.36; H, 11.55; $C_{27}H_{46}O_2$ (402.6) requires C, 80.54; H, 11.52).

5α-Cholest-8-ene-3,7-dione (50).

A solution of **46** (40 mg, 0.1 mmol) and pyridinium dichromate (76 mg, 0.2 mmol) in CH_2Cl_2 (2 ml) was stirred at 20°C for 48 h. Filtration through silica gel (elution with CH_2Cl_2), solvent evaporation, and MPLC (hexanes - ethyl acetate 5:1) furnished **50** (32 mg, 82%).- M.p. 197-200°C (from methanol).- IR (CCl_4): 1720, 1670 cm^{-1} (CO).- ^1H NMR (80 MHz, $CDCl_3$): δ = 0.61 (s, CH_3-18), 0.80-1.00 (CH_3 signals), 1.32 (s, CH_3-19).- MS: m/z (%) = 398.3176 (69, M^+, Calc for $C_{27}H_{42}O_2$: 398.3185), 383 (14), 313 (4), 285 (44), 274 (16), 258 (26), 243 (39), 230 (62), 121 (100).

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