ALTERNATIVE ACCESS TO 20-HYDROXYECDY-STEROID SIDE CHAIN BY MEANS OF SAMARIUM IODIDE-PROMOTED RADICAL ADDITION OF TETRAHYDROFURAN TO A 20-KETO STEROID

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Abstract – Samarium iodide-promoted radical addition of tetrahydrofuran to the 20-keto steroid afforded the adducts as a mixture of diastereomers at the 22-position in high yield. Both adducts were further converted into (20*R*,22*R*)-5α-cholestane-3β,20,22,25-tetraol.

Development of a methodology for the stereocontrolled construction of side chain is an important subject in the synthetic steroid chemistry because many steroids with a modified side chain exhibit interesting physiological activities. Recently we have disclosed the stereoselective synthesis of a various types of steroids, such as ecdysone[1] and 20-hydroxyecdysones,[2] brassinosteroids,[3] withanolides,[4] aragusterols,[5] and gerardiasterone.[6] As a continuing work on the synthesis of physiologically active steroids, we have investigated an alternative synthetic approach to the construction of 20-hydroxyecdysone side chain,[7] in which we planned to utilize samarium iodide-promoted radical addition of tetrahydrofuran, developed by Inanaga and co-workers,[8] into 20-keto steroid as a key reaction, since we noted in advance that the samarium iodide-promoted radical addition reaction into 20-keto group occurred from the less hindered side to provide the desired stereochemistry at the 20-position[5] and also that tetrahydrofuran is a suitable carbon unit with the oxygen function for

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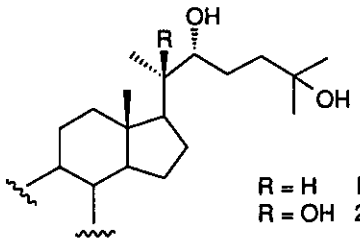
This paper is dedicated to Professor Koji Nakanishi on the occasion of his 75th birthday.

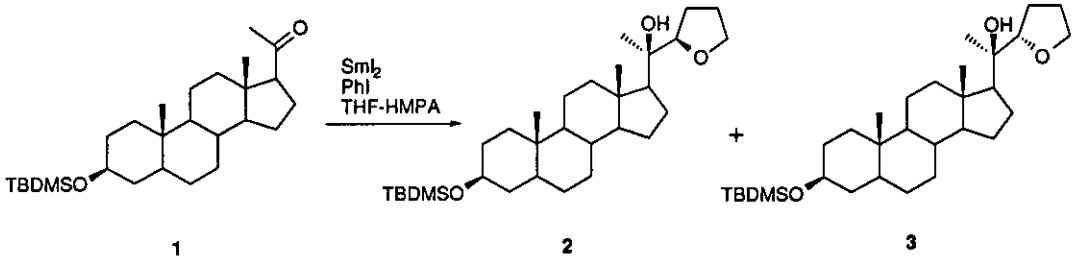


R = H Ecdysone (α-Ecdysone) type side chain
R = OH 20-Hydroxyecdysone (β-Ecdysone) type side chain

Figure 1.

the construction of steroidal side chain.[1]

Thus, samarium iodide-promoted radical addition of tetrahydrofuran into 5α-pregnan-20-one *tert*-butyldimethylsilyl ether (**1**) was carried out using iodobenzene in THF-HMPA at ambient temperature to give the adducts (**2** and **3**) in 46.3% and 47.4% yields, respectively. Although the stereochemistry at the 20-position of the adduct was assumed to be *R* on the basis of the previous results,[5] the stereoselectivity at the 22-position could not be observed in this addition reaction, unfortunately. The configurations at the 22-positions of both adduct were determined by their further conversion into the known steroids bearing 20-hydroxyecdysone-type side chain as follows.



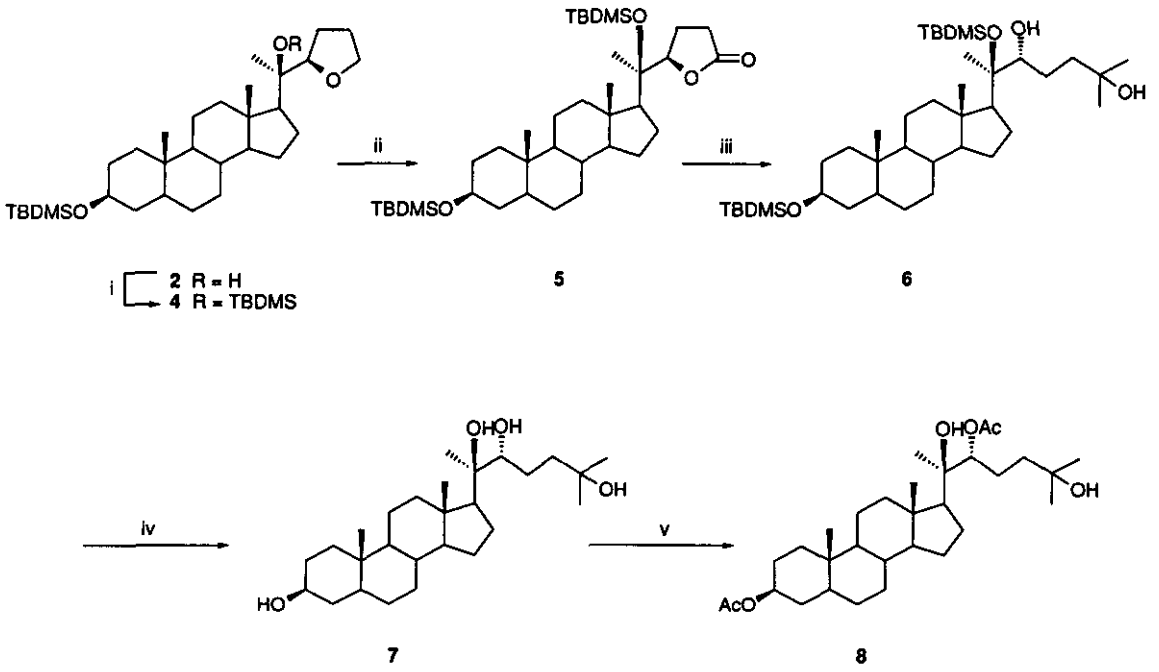
1 **2** **3**

Scheme 1.

After protection of the tertiary hydroxy group of the less polar adduct (**2**) with *tert*-butyldimethylsilyl triflate, the silyl ether (**4**) was subjected to the oxidation with ruthenium tetroxide[9] to give the γ-lactone (**5**) in 68.7% yield from **2**. Treatment of the γ-lactone (**5**) with an excess of methylmagnesium bromide at -78°C gave the desired compound (**6**) in 86.2% yield. Finally removal of the silyl groups with tetrabutylammonium fluoride, followed by acetylation of the resulting tetraol (**7**) with acetic anhydride afforded the known diacetate (**8**) having the natural 20-hydroxyecdysone-type side chain, in 98.0%

yield from **6**. The spectroscopic data of the diacetate (**8**) were identical with those reported.[10] Thus, the stereochemistries at the 20- and 22-positions of the less polar adduct (**2**) were unambiguously confirmed to be *R* and *R*, respectively.

The more polar adduct (**3**) was also transformed into the 20*R*, 22*S*-isomer (**13**) by adapting the essentially same procedure as for the synthesis of **8**, including the silylation of **3**, oxidation of the silyl

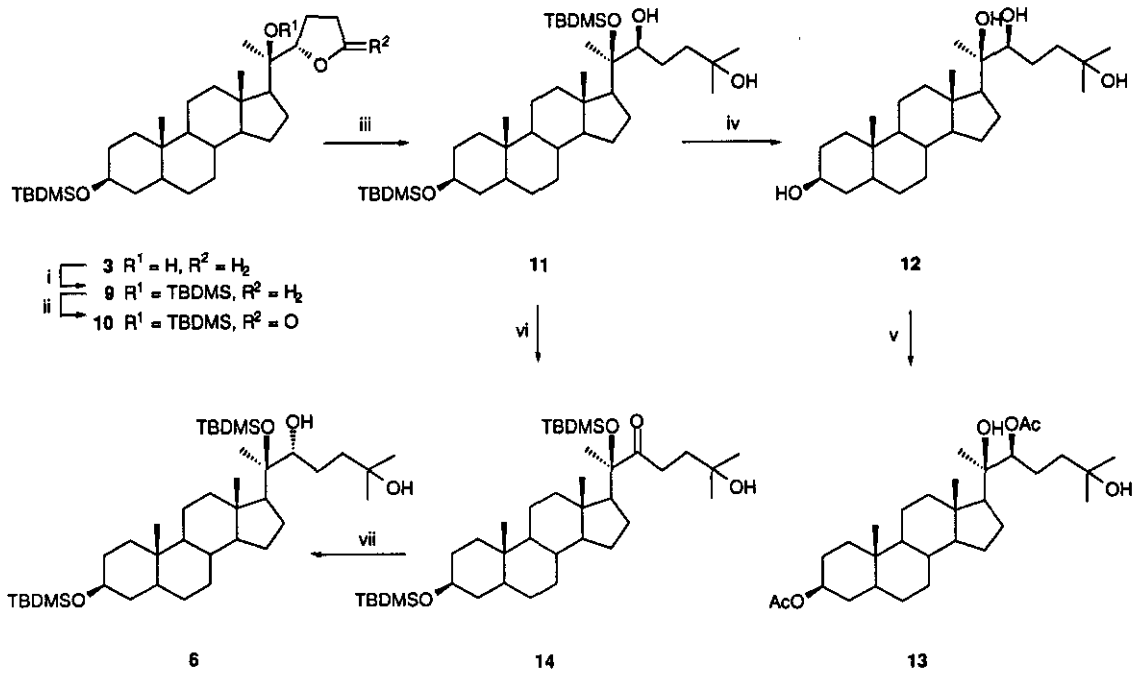


Scheme 2. *Reactions and conditions*: i, TBDMSOTf, 2,6-lutidine, CH_2Cl_2, rt; ii, RuO_2, $NaIO_4$, CCl_4-MeCN-H_2O, rt; iii, MeMgBr, THF, -78°C; iv, TBAF, THF, rt; v, Ac_2O, pyridine, rt.

ether (**9**) into the γ-lactone (**10**), methylation of **10** with methylmagnesium bromide, desilylation of the disilyl ether (**11**), and the acetylation of the resulting tetraol (**12**). In order to synthesize 20-hydroxyecdysone-type side chain from the stereoisomeric adduct (**3**), the inversion of the configuration at the 22-position was required during the above transformation. Thus, the compound (**11**) was oxidized with pyridinium chlorochromate to give the ketone (**14**), which on reduction with lithium tri-*tert*-butoxyaluminum hydride[11] afforded the desired compound (**6**).

Thus, we disclose a simple synthetic procedure for the construction of the 20-hydroxyecdysone-type

side chain by employing samarium iodide-promoted radical addition of tetrahydrofuran into 5α-pregnan-20-one derivative as a key step, where both stereoisomeric adducts could be converted into the desired compound.



Scheme 3. *Reactions and conditions*: i, TBDMSOTf, 2,6-lutidine, CH_2Cl_2, rt; ii, RuO_2, $NaIO_4$, CCl_4-MeCN-H_2O, rt; iii, MeMgBr, THF, -78°C; iv, TBAF, THF, rt; v, Ac_2O, pyridine, rt; vi, PCC, CH_2Cl_2, rt; vii, $LiAlH(^tBuO)_3$, THF, -78°C.

EXPERIMENTAL SECTION

IR spectra were recorded on a Hitachi 260-10 spectophotometer. ^{1}H-NMR spectra were obtained for solution in CDCl3 on a JEOL GSX-270 instrument, and chemical shifts are reported on the δ-scale from internal TMS. MS spectra were measured with a JEOL JMS D-300 spectrometer. Optical rotations were taken with a JASCO DIP-360 polarimeter.

(20*R*,22*R*)-3β-*tert*-Butyldimethylsiloxy-20-hydroxy-22,25-epoxy-25-homo-5α-cholane (**2**) and (20*R*, 22*S*)-3β-*tert*-Butyldimethylsiloxy-20-hydroxy-22,25-epoxy-25-homo-5α-cholane (**3**)

To a stirred suspension of samarium metal (6.6 g, 44 mmol) in dry THF (104 mL) was added a solution of 1,2-diiodoethane (11.7 g, 42 mmol) in dry THF (52 mL) under argon at ambient temperature and the solution was stirred for 30 min. After addition of HMPA (52 mL), the resulting solution was stirred for a further 15 min. To this mixture were added a solution of 5α-pregnan-20-one derivative (**1**) (3.0 g, 6.9 mmol) in THF (15 mL) and iodobenzene (3.9 mL, 35 mmol). After stirring for 5 min, the solution was treated with saturated sodium hydrogen carbonate solution, an excess of ether and Celite. Insoluble materials were filtered off, and the filtrate was extracted with ethyl acetate. The extract was washed with water and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (9:1 v/v) afforded the less polar adduct (**2**) (1.62 g, 46.3%) as colorless plates; mp 182-185°C (ether-MeOH); IR ($CHCl_3$) 3500 and 2930 cm^{-1}; NMR ($CDCl_3$) δ 0.05 (6H, s, 2×SiMe), 0.80 (3H, s, 18-Me), 0.82 (3H, s, 19-Me), 0.88 (9H, s, Si-Bu), 1.17 (3H, s, 21-Me), 3.45-3.62 (1H, m, 3-H), 3.57-3.81 (3H, m, 22-H and 25-H_2); MS *m/z* $C_{31}H_{54}O_2Si$ requires: 486.3891 (M^+-H_2O). Found: 486.3888 (M^+-H_2O); Anal. Calcd for $C_{31}H_{56}O_3Si$: C, 73.75; H, 11.18. Found: C, 73.60; H, 11.23. $[\alpha]_D$ +3.69° (c=1.1, $CHCl_3$). Further elution with the same solvent system afforded the more polar adduct (**3**) (1.66 g, 47.4%) as colorless plates; mp 191-195°C (ether-MeOH); IR ($CHCl_3$) 3500 and 2930 cm^{-1}; NMR ($CDCl_3$) δ 0.05 (6H, s, 2×SiMe), 0.79 (3H, s, 18-Me), 0.80 (3H, s, 19-Me), 0.88 (9H, s, Si-Bu), 1.26 (3H, s, 21-Me), 3.45-3.62 (1H, m, 3-H), 3.63-3.82 (3H, m, 22-H and 25-H_2); MS *m/z* $C_{31}H_{54}O_2Si$ requires: 486.3891 (M^+-H_2O). Found: 486.3888 (M^+-H_2O); Anal. Calcd for $C_{31}H_{56}O_3Si$: C, 73.75; H, 11.18. Found: C, 73.56; H, 11.14. $[\alpha]_D$ -0.21° (c=1.3, $CHCl_3$).

(20*R*,22*R*)-3β, 20-Di-*tert*-butyldimethylsiloxy-22,25-epoxy-25-homo-5α-cholane (**4**)

A solution of 20-hydroxy compound (**2**) (0.36 g, 0.7 mmol), 2,6-lutidine (0.5 mL, 4.3 mmol), and TBDMSOTf (0.49 mL, 2.1 mmol) in dry dichloromethane (13 mL) was stirred for 12 h under argon and then treated with brine. The solution was extracted with ethyl acetate and the extract was washed with water and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (20:1 v/v) afforded silyl ether (**4**) (0.44 g, 100%) as colorless plates; mp 190-195°C (ether-MeOH); IR ($CHCl_3$) 2930 cm^{-1}; NMR ($CDCl_3$) δ 0.05 (6H, s, 2×SiMe), 0.07 (3H, s, SiMe), 0.09 (3H, s, SiMe), 0.78 (3H, s, 18-Me), 0.86 (9H, s, Si-Bu), 0.87 (3H, s, 19-Me), 0.88 (9H, s, Si-Bu), 1.22 (3H, s, 21-Me), 3.45-3.85 (4H, m, 3-H, 22-H

and CH_2O); MS *m/z* $C_{33}H_{61}O_3Si_2$ requires: 561.4159 (M^+-C_4H_9). Found: 561.4159 (M^+-C_4H_9); Anal. Calcd for $C_{37}H_{70}O_3Si_2$: C, 71.78; H, 11.40. Found: C, 71.69; H, 11.40. $[\alpha]_D$ +5.73° (c=0.4, $CHCl_3$).

(20*R*,22*R*)-3β, 20-Di-*tert*-butyldimethylsiloxy-25-homo-5α-cholano-25,22-lactone (**5**)

To a stirred suspension of ruthenium dioxide (0.06 g, 0.4 mmol) in carbon tetrachloride (18 mL), acetonitrile (18 mL) and water (27 mL) was added sodium periodate (1.2 g, 5.8 mmol) at ambient temperature. The silyl ether (**4**) (0.9 g, 1.5 mmol) was then added to the solution and the resulting mixture was stirred for 2 h at the same temperature. The mixture was extracted with chloroform and the extract was treated with saturated sodium hydrogen carbonate solution and brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (5:1 v/v) afforded the γ-lactone (**5**) (0.63 g, 68.7%) as colorless needles; mp 210-212°C (ether-MeOH); IR ($CHCl_3$) 2930 and 1780 cm^{-1}; NMR ($CDCl_3$) δ 0.05 (6H, s, 2×SiMe), 0.14 (3H, s, SiMe), 0.17 (3H, s, SiMe), 0.79 (3H, s, 18-Me), 0.84 (3H, s, 19-Me), 0.87 (9H, s, Si-Bu), 0.88 (9H, s, Si-Bu), 1.28 (3H, s, 21-Me), 2.25-2.48 (2H, m, CH_2CO_2), 3.45-3.62 (1H, m, 3-H), 4.35 (1H, dd, J=6.9 and 9.7 Hz, 22-H); MS *m/z* $C_{33}H_{59}O_4Si_2$ requires: 575.3950 (M^+-C_4H_9). Found: 575.3945 (M^+-C_4H_9); Anal. Calcd for $C_{37}H_{68}O_4Si_2$: C, 70.19; H, 10.83. Found: C, 70.29; H, 10.82. $[\alpha]_D$ -2.05° (c=0.5, $CHCl_3$).

(20*R*,22*R*)-3β, 20-Di-*tert*-butyldimethylsiloxy-5α-cholestane-22,25-diol (**6**)

To a stirred solution of the γ-lactone (**5**) (0.53 g, 0.8 mmol) in dry THF (31 mL) was added 3.0M solution of methylmagnesium bromide in ether (2.8 mL, 8.4 mmol) at -78°C under argon and the resulting solution was stirred at the same temperature for 2 h. The mixture was treated with saturated ammonium chloride solution and extracted with ethyl acetate. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (4:1 v/v) afforded the compound (**6**) (0.48 g, 86.2%) as colorless plates; mp 177-179°C (AcOEt-benzene); IR ($CHCl_3$) 3400 and 2930 cm^{-1}; NMR ($CDCl_3$) δ 0.05 (6H, s, 2×SiMe), 0.13 (3H, s, SiMe), 0.14 (3H, s, SiMe), 0.78 (6H, s, 18-Me and 19-Me), 0.88 (9H, s, Si-Bu), 0.89 (9H, s, Si-Bu), 1.23 (6H, s, 26 and 27-Me), 1.31 (3H, s, 21-Me), 3.30-3.42 (1H, m, 22-H), 3.46-3.62 (1H, m, 3-H); MS *m/z* $C_{35}H_{67}O_4Si_2$ requires: 607.4577 (M^+-C_4H_9).

Found: 607.4583 (M^+-C_4H_9); Anal. Calcd for $C_{39}H_{76}O_4Si_2$: C, 70.42; H, 11.52. Found: C, 70.65; H, 11.49. $[\alpha]_D$ +16.78° (c=0.9, $CHCl_3$).

(20*R*,22*R*)-3β, 22-Diacetoxy-5α-cholestane-20,25-diol (**8**)

To a stirred solution of the silyl ether (**6**) (0.37 g, 0.56 mmol) in THF (15 mL) was added a solution of tetrabutylammonium fluoride in THF (1.7 mL) and the resulting solution was stirred at ambient temperature for 12 h. The mixture was treated with brine and extracted with chloroform-methenol (5:1, v/v). The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the tetraol (**7**), which without further purification, was used to the next reaction. A solution of the tetraol (**7**) in pyridine (8 mL) and acetic anhydride (4 mL) was allowed to stand at rt for 12 h, and then extracted with ethyl acetate. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (1:2 v/v) afforded the diacetate (**8**) (0.3 g, 98.0%) as colorless plates; mp 168-170°C (AcOEt-MeOH); IR ($CHCl_3$) 3460, 2930, 1730 and 1720 cm^{-1}; NMR ($CDCl_3$) δ 0.82 (3H, s, 19-Me), 0.85 (3H, s, 18-Me), 1.21 and 1.23 (each 3H, each s, 26 and 27-Me), 1.26 (3H, s, 21-Me), 2.02 and 2.10 (each 3H, each s, 2×OAc), 4.60-4.76 (1H, m, 3-H), 4.76-4.88 (1H, m, 22-H); MS *m/z* $C_{29}H_{46}O_3$ requires: 442.3658 (M^+-H_2O-AcOH). Found: 442.3655 (M^+-H_2O-AcOH) ; These spectral data were identical with those reported.

(20*R*,22*S*)-3β, 20-Di-*tert*-butyldimethylsiloxy-22,25-epoxy-25-homo-5α-cholane (**9**)

The silyl ether (**9**) (0.33 g, 92.8%) was synthesized from **3** (0.29 g) by the same procedure as for the preparation of the silyl ether (**4**), as colorless plates; mp 96-99°C (ether-MeOH); IR ($CHCl_3$) 2930 cm^{-1}; NMR ($CDCl_3$) δ 0.05 (6H, s, 2×SiMe), 0.09 (3H, s, 2×SiMe), 0.74 (3H, s, 18-Me), 0.78 (3H, s, 19-Me), 0.86 (9H, s, Si-Bu), 0.88 (9H, s, Si-Bu), 1.36 (3H, s, 21-Me), 3.45-3.87 (4H, m, 3-H, 22-H and CH_2O); MS *m/z* $C_{33}H_{61}O_3Si_2$ requires: 561.4159 (M^+-C_4H_9). Found: 561.4166 (M^+-C_4H_9); Anal. Calcd for $C_{37}H_{70}O_3Si_2$: C, 71.78; H, 11.40. Found: C, 71.88; H, 11.43. $[\alpha]_D$ +1.84° (c=1.1, $CHCl_3$).

(20*R*,22*S*)-3β, 20-Di-*tert*-butyldimethylsiloxy-25-homo-5α-cholano-25,22-lactone (**10**)

The lactone (**10**) (0.56 g, 68.5%) was synthesized from **9** (0.8 g) by the same procedure as for the preparation of the lactone (**5**), as colorless needles; mp 182-186°C (ether-MeOH); IR ($CHCl_3$) 2930

and 1789 cm^{-1}; NMR ($CDCl_3$) δ 0.05 (6H, s, 2×SiMe), 0.11 (6H, s, 2×SiMe), 0.74 (3H, s, 18-Me), 0.79 (3H, s, 19-Me), 0.86 (9H, s, Si-Bu), 0.88 (9H, s, Si-Bu), 1.41 (3H, s, 21-Me), 2.43-2.57 (2H, m, CH_2CO_2), 3.42-3.62 (1H, m, 3-H), 4.41 (1H, t, J=7.5 Hz, 22-H); MS *m/z* $C_{33}H_{59}O_4Si_2$ requires: 575.3950 (M^+-C_4H_9). Found: 575.3950 (M^+-C_4H_9); Anal. Calcd for $C_{37}H_{68}O_4Si_2$: C, 70.19; H, 10.83. Found: C, 70.53; H, 10.82. $[\alpha]_D$ +5.73° (c=1.4, $CHCl_3$).

(20*R*,22*S*)-3β, 20-Di-*tert*-butyldimethylsiloxy-5α-cholestane-22,25-diol (**11**)

The diol (**11**) (0.33 g, 87.2%) was synthesized from **10** (0.36 g) by the same procedure as for the preparation of the diol (**6**), as colorless plates; mp 126-130°C (AcOEt-benzene); IR ($CHCl_3$) 3420 and 2930 cm^{-1}; NMR ($CDCl_3$) δ 0.05 (6H, s, 2×SiMe), 0.16 (6H, s, 2×SiMe), 0.78 (3H, s, 18-Me), 0.81 (3H, s, 19-Me), 0.88 (9H, s, Si-Bu), 0.91 (9H, s, Si-Bu), 1.24 (6H, s, 26 and 27-Me), 1.56 (3H, s, 21-Me), 3.22-3.31 (1H, m, 22-H), 3.45-3.62 (1H, m, 3-H); MS *m/z* $C_{35}H_{67}O_4Si_2$ requires: 607.4577 (M^+-C_4H_9). Found: 607.4561 (M^+-C_4H_9); Anal. Calcd for $C_{39}H_{76}O_4Si_2$: C, 70.42; H, 11.52. Found: C, 70.13; H, 11.44. $[\alpha]_D$ -2.48° (c=0.9, $CHCl_3$).

(20*R*,22*S*)-3β, 22-Diacetoxy-5α-cholestane-20,25-diol (**13**)

The diacetate (**13**) (0.16 g, 93.0%) was synthesized from **11** (0.22 g), *via* the tetraol (**12**) by the same procedure as for the preparation of the diacetate (**8**), as colorless plates; mp 146-149°C (AcOEt-MeOH); IR ($CHCl_3$) 3460, 2930, 1730 and 1720 cm^{-1}; NMR ($CDCl_3$) δ 0.82 (3H, s, 19-Me), 0.83 (3H, s, 18-Me), 1.21 and 1.22 (each 3H, each s, 26 and 27-Me), 1.26 (3H, s, 21-Me), 2.01 and 2.02 (each 3H, each s, 2×OAc), 4.60-4.76 (1H, m, 3-H), 4.76-4.86 (1H, m, 22-H); MS *m/z* $C_{29}H_{46}O_3$ requires: 442.3658 (M^+-H_2O-AcOH). Found: 442.3678 (M^+-H_2O-AcOH); Anal. Calcd for $C_{31}H_{52}O_6$: C, 71.55; H, 10.07. Found: C, 71.25; H, 9.83. $[\alpha]_D$ -10.11° (c=0.2, $CHCl_3$).

(20*R*)-3β, 20-Di-*tert*-butyldimethylsiloxy-20-oxo-5α-cholestan-25-ol (**14**)

To a stirred suspension of pyridinium chlorochromate (0.1 g, 0.45 mmol) and Celite (0.1 g) in dry dichloromethane (8 mL) was added a solution of the diol (**11**) (0.1 g, 0.15 mmol) in dichloromethane (2 mL) at rt under argon and the resulting mixture was stirred for 4 h at the same temperature. After addition of an excess of ether, the mixture was filtered to remove the insoluble material and the filtrate was concentrated to leave a residue, which was subjected to column chromatography on silica gel.

Elution with hexane-ethyl acetate (4:1 v/v) afforded the ketone (**14**) (0.09 g, 92.1%) as colorless plates; mp 82-92°C (AcOEt-benzene); IR ($CHCl_3$) 3440, 2930 and 1720 cm^{-1}; NMR ($CDCl_3$) δ 0.05 (6H, s, 2×SiMe), 0.07 (3H, s, SiMe), 0.11 (3H, s, SiMe), 0.78 (3H, s, 18-Me), 0.82 (3H, s, 19-Me), 0.88 (9H, s, Si-Bu), 0.93 (9H, s, Si-Bu), 1.22 (6H, s, 26 and 27-Me), 1.51 (3H, s, 21-Me), 2.52-2.78 (2H, m, 23-H_2), 3.45-3.63 (1H, m, 3-H); MS *m/z* $C_{35}H_{63}O_3Si_2$ requires: 587.4313 (M^+-C_4H_9-H_2O). Found: 587.4307 (M^+-C_4H_9-H_2O). $[\alpha]_D$ -6.14° (c=0.5, $CHCl_3$).

Reduction of the Ketone (**14**) to the Diol (**6**)

To a stirred solution of lithium tri-*tert*-butoxyaluminum hydride (0.08 g, 0.3 mmol) in dry THF (4 mL) was added a solution of the ketone (**14**) (0.05 g, 0.08 mmol) in THF (1 mL) at -78°C under argon and the resulting mixture was stirred for further 8 h at the same temperature. 10% Sodium hydroxide solution was added to the mixture at 0°C and the insoluble material was removed off by filtration. The filtrate was concentrated to give a residue, which was purified by column chromatography on silica gel. Elution with hexane-ethyl acetate (4:1 v/v) afforded the diol (**6**) (0.03 g, 61.7%) as a major product, identical with the authentic sample, together with the diastereoisomer (**11**) (0.005 g, 10.3%).

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