[Chem. Pharm. Bull. 35(8)3467—3469(1987)]

Synthesis of 14α-Methylcholesterol

KYOKO TAKAHASHI, KEIKO USAMI, TAMAMI TAKAHASHI, TOMOKO OKADA and MASUO MORISAKI*

Kyoritsu College of Pharmacy, Shibakoen, Minato-ku, Tokyo 105, Japan

(Received January 23, 1987)

14α-Methylcholesterol was synthesized from lanosterol *via* 19 steps in 1—2% overall yield.

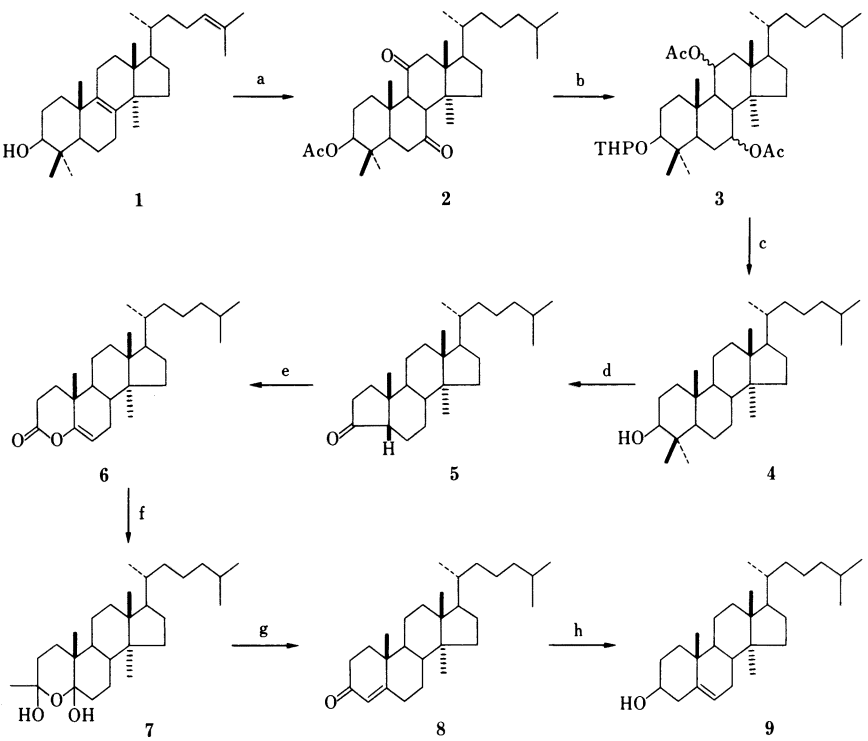
Keywords——14α-methylcholesterol; lanosterol; deacetoxylation; masked 1,5-diketone

For our investigation on sterol structure–function relationships,[1] we have required a sample of 14α-methylcholesterol. To our knowledge, this sterol (**9**) has never been prepared, although analogs such as 14α-methylcholestan-3β-ol,[2] 14α-methylcholest-4-en-3-one,[3] and 14α-methylcholest-7-en-3β-ol,[4] are known. Further, various 14α-methylated sterols were recently isolated from natural sources,[5] and have received considerable attention since they are potential intermediates in cholesterol biosynthesis. Several attempts to prepare 14α-methylestrone derivatives were also reported.[6] Here we describe the synthesis of 14α-methylcholesterol (**9**) from lanosterol (**1**) *via* 19 steps in 1—2% overall yield.

Lanosterol (**1**), through a conventional four step sequence[7] (catalytic hydrogenation, acetylation, chromic acid oxidation, reduction with zinc/acetic acid) was converted to the 7,11-diketone (**2**) in 59% yield. We avoided the hazardous Wolff–Kishner reduction to remove the 7,11-oxygen function of **2**[8] and instead, deacetoxylation of the 7,11-diacetate (**3**) was performed. Thus the latter, derived from **2** by successive saponification, tetrahydropyranyl ether formation, $LiAlH_4$ reduction and acetylation with acetic anhydride/pyridine in the presence of 4-dimethylaminopyridine, was subjected to reaction with sodium in hexamethylphosphoric triamide/*tert*-butanol.[9] Subsequent acid treatment afforded lanostanol (**4**) in 61% overall yield from **2**. Transformation of **4** into the enol lactone (**6**) *via* the A-nor-ketone (**5**), was effected essentially by the reported method (see Chart 1)[3a] in 18% yield. Grignard reaction of **6** with methyl magnesium iodide[10] gave the masked 1,5-diketone (**7**) in 75% yield. The latter had neither carbonyl absorption (infrared (IR) and carbon-13 nuclear magnetic resonance (^{13}C-NMR)) nor an olefinic bond (^{1}H- and ^{13}C-NMR), and was much more polar than the starting enol lactone (**6**) on thin layer chromatography (TLC). Other NMR signals as well as the mass spectral peak at *m/z* 416 (M-18) strongly suggested the dihemiacetal structure (**7**), although its stereochemistry remained undetermined. Alkaline treatment of **7** gave the 3-oxo-4-ene (**8**).[3] Enol acetylation of **8** with isopropenyl acetate/*p*-toluenesulfonic acid,[11] followed by reduction with $NaBH_4$ furnished 14α-methylcholesterol (**9**, 42%), together with its 3-epimer (4%). The spectroscopic data of **9** unequivocally established the structure.

Experimental

Melting points were determined on a hot plate microscope and are uncorrected. Thin layer and column chromatography were carried out with Kieselgel $60F_{254}$ plates (Merck, 0.25 mm thick) and Kieselgel 60 (Merck, 70—230 mesh), respectively. ^{1}H-NMR and ^{13}C-NMR were recorded in $CDCl_3$ solution with a JEOL JNM-GX 270 at 270 MHz and at 67.8 MHz, respectively. Mass spectra (MS) were recorded on a JEOL JMS-DX303 with a direct-inlet



(a) i, H_2/Pd–C/AcOEt; ii, Ac_2O/pyr.; iii, CrO_3/AcOH; iv, Zn/AcOH.
(b) i, KOH/MeOH; ii, dihydropyran/ Amberlyst 15/CH_2Cl_2; iii, $LiAlH_4$/THF; iv) Ac_2O/DMAP/pyr.
(c) i, Na/HMPA/*tert*-BuOH; ii, d. HCl/MeOH–CH_2Cl_2.
(d) i, PCl_5/*n*-hexane; ii, O_3/CH_2Cl_2 and then Zn/AcOH; iii, KOH/MeOH.
(e) i, CF_3COOOH/CH_2Cl_2; ii, Jones oxid.; iii, Ac_2O/$HClO_4$. (f) CH_3MgI/Et_2O–C_6H_6. (g) NaOH/MeOH.
(h) i, $CH_2=C(OAc)Me$/*p*-TsOH; ii, $NaBH_4$/MeOH–THF.

Chart 1

system. Usual work-up refers to dilution with brine, extraction with CH_2Cl_2, drying ($MgSO_4$) and solvent evaporation under vacuum.

Lanostanol (4)——3β-Acetoxylanostane-7,11-dione (**2**, 230 mg)[7] was refluxed with 5% KOH–methanol (15 ml) for 20 min. Usual work-up gave the 3β-ol and this was stirred in a mixture of dihydropyran (150 mg), Amberlyst 15 (Rohm and Haas, 150 mg) and CH_2Cl_2 (8 ml) at room temperature for 5 h.[12] Filtration and solvent evaporation gave the tetrahydropyranyl (THP) ether as an oil, which was stirred with $LiAlH_4$ (150 mg) in dry tetrahydrofuran (10 ml) at room temperature overnight. The crude 7,11-diol obtained by usual work-up was allowed to stand in a mixture of acetic anhydride (1.5 ml), pyridine (6 ml) and 4-dimethylaminopyridine (150 mg) at room temperature for 5 h. Work-up as usual gave a yellow paste, which was chromatographed on silica gel with *n*-hexane–ethyl acetate (50 : 1) to give the 7,11-diacetate (**3**). This was dissolved in a mixture of dry *tert*-butanol (1.2 ml) and dry ethyl ether (1.5 ml), and added slowly (to maintain the deep blue color due to the radical anion) through a syringe to a stirred mixture of sodium (0.7 g), dry hexamethylphosphoric triamide (7 ml) and dry ethyl ether (5 ml) at room temperature under argon. Stirring was continued for 4 h and the mixture was worked up as usual. The crude product was allowed to stand in a mixture of conc. HCl (50 μl), methanol (2.5 ml) and CH_2Cl_2 (2.0 ml) at room temperature for 2 h. Usual work-up followed by column chromatography with *n*-hexane–ethyl acetate (40 : 1) gave lanostanol (**4**, 120 mg, 61% from **2**), mp 175—177 °C (needles from methanol, lit.[3b] 175—176 °C). MS *m/z*: 430 (M^+).

4-Oxa-3β,14α-dimethylcholestan-3ξ,5ξ-diol (7)——The enol lactone (**6**, 1.25 g) prepared from lanostanol (**4**) according to the literature,[3a] was dissolved in a 1 : 1 mixture (62 ml) of dry ethyl ether and dry benzene. To this stirred solution was added a methyl magnesium iodide solution (8.6 ml), which was prepared from magnesium (243 mg), methyl iodide (2.3 g) and dry ethyl ether (10 ml). Thirty min later, the mixture was worked up to give yellow amorphous material (1.3 g). A part (200 mg) of this material was chromatographed with *n*-hexane–ethyl acetate (30 : 1)—(5 : 1) to give the dihemiacetal (**7**, 150 mg), mp 163—165 °C (needles from methanol). ^{1}H-NMR δ: 0.73 (3H,

s, 13-Me), 0.84—0.89 (12H, m, 14-Me, 20-Me, 25-Me_2), 0.98 (3H, s, 10-Me), 1.28 (3H, s, 3-Me). MS *m/z*: 416 (M-18), 398, 380.

14α-Methylcholesterol (9)——The crude dihemiacetal (**7**, 1.15 g) was refluxed with a mixture of 10% NaOH (9.5 ml) and methanol (100 ml) for 2 h. Usual work-up gave the 3-oxo-4-ene (**8**),[3] which was then refluxed with a mixture of isopropenyl acetate (8.6 ml), *p*-toluenesulfonic acid (150 mg) and dry benzene (50 ml) under nitrogen for 5 h. Usual work-up gave the 3,5-dienol acetate. ^{1}H-NMR δ: 0.82 and 0.83 (each 3H, s, 13- and 14-Me), 0.86 (6H, d, J=6.5 Hz, 25-Me_2), 0.89 (3H, d, J=6.5 Hz, 20-Me), 1.03 (3H, s, 10-Me), 2.13 (3H, s, acetyl), 5.40 (1H, br s, 6-H), 5.68 (1H, s, 4-H), and this was stirred with $NaBH_4$ (2 g) in tetrahydrofuran (20 ml). Methanol (30 ml) was then added very slowly; a vigorous reaction occurred, resulting in solvent refluxing. After being stirred for 1 h, the mixture was worked up as usual and the crude product was chromatographed with *n*-hexane–ethyl acetate (50 : 1)—(10 : 1) to give the recovered enol acetate (384 mg), 14α-methylcholest-5-en-3α-ol (46 mg), mp 135—137 °C (needles from methanol). ^{1}H-NMR δ: 0.81 and 0.84 (each 3H, s, 13- and 14-Me), 0.87 (6H, d, J=6.5 Hz, 25-Me_2), 0.89 (3H, d, J=6.5 Hz, 20-Me), 4.0 (1H, m, 3-H), 5.4 (1H, m, 6-H), and 14α-methylcholest-5-en-3β-ol (**9**, 480 mg), mp 155—157 °C (needles from methanol). MS *m/z*: 400 (M^+), 395 (M-15), 392 (M-18). ^{1}H-NMR δ: 0.81 and 0.83 (each 3H, s, 13- and 14-Me), 0.87 (6H, d, J=6.5 Hz, 25-Me_2), 0.88 (3H, d, J=6.5 Hz, 20-Me), 1.05 (3H, s, 10-Me), 3.5 (1H, m, 3-H), 5.37 (1H, m, 6-H). ^{13}C-NMR δ: 37.3 (C1), 31.7 (C2), 71.7 (C3), 42.4 (C4), 140.2 (C5), 122.1 (C6), 32.0 (C7), 36.2 (C8), 43.1 (C9), 37.4 (C10), 20.1 (C11), 33.9 (C12), 45.2; 47.5 (C13; C14), 27.0 (C15), 28.0 (C16), 51.2 (C17), 14.2; 16.8 (C18; C32), 19.1 (C19), 35.5 (C20), 18.7 (C21), 36.6 (C22), 24.1 (C23), 39.5 (C24), 28.0 (C25), 22.6; 22.8 (C26; C27). Recycling of the recovered enol acetate afforded further 14α-methylcholesterol (**9**). Total yield of **9**: 445 mg (42% from **7**).

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