A Convenient Synthesis of Cholesta-1,5,7-trien-3β-ol

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Synopsis. Cholesta-4,6-dien-3β-ol (**4**) was obtained selectively by the dehydrobromination of 7-bromocholesterol with a base in the presence of a catalytic amount of tetrabutylammonium bromide. The oxidation of **4** with 2,3-dichloro-5,6-dicyano-p-benzoquinone gave cholesta-1,4,6-trien-3-one (**7**). Treatment of **7** with isopropenyl acetate under acidic conditions afforded 3-acetoxy-1,3,5,7-cholestatetraene, which was reduced with calcium borohydride to yield cholesta-1,5,7-trien-3β-ol (**2**).

The synthesis of cholesta-5,7-diene-1α,3β-diol (**1**), the photoprecursor of the physiologically active 1α-hydroxyvitamin D_3, has been reported by many research groups.[1-13] Kaneko et al.[5] reported the synthesis of cholesta-1,5,7-trien-3β-ol (**2**), a key intermediate for the preparation of **1**, by the base-catalyzed rearrangement of cholesta-1,4,6-trien-3-one (**7**)[14,15] followed by the reduction of the formed cholesta-1,5,7-trien-3-one. This method is interesting and attractive, but generally gives a poor yield of **2**. Thus, it is desirable to prepare **2** in higher yield. In the present paper, an improved method for the preparation of cholesta-4,6-dien-3-one (**6**)[16] and its conversion to **2** are described.

Lappordt et al.[17] reported the selective synthesis of cholesta-4,6-dien-3-β-ol (**4**) through the dehydrobromination of 7-bromocholesterol (**3**) derivative[18,19] in the presence of a combination of a large excess of tetrabutylammonium bromide and 2,4,6-trimethylpyridine in tetrahydrofuran. In contrast to their results, we have found that at higher temperature, the dehydrobromination of **3** by a base proceeded smoothly in the presence of a catalytic amount of tetrabutylammonium bromide (Table 1).

The 4,6-dien-3-ol (**4**) was oxidized by various oxidizing agents to give the corresponding 4,6-dien-3-one (**6**) in 50—85% yields (Table 2). Treatment of **4** with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone[20,21] afforded **7** in one stage without isolation of **6**.

It is well-known that the steroidal 1,4-dienone and 1,4,6-trienone undergo rearangement to give the phenol derivatives under acidic conditions.[22,23] However it was found that the enol acetylation of the 1,4,6-trien-3-one (**7**) with isopropenyl acetate in the presence of p-toluenesulfonic acid successfully yielded 3-acetoxy-1,3,5,7-cholestatetraene (**8**)[12] in a fairly good yield. The tetraenyl acetate (**8**) was reduced with calcium borohydride to afford the 1,5,7-trien-3-ol (**2**)

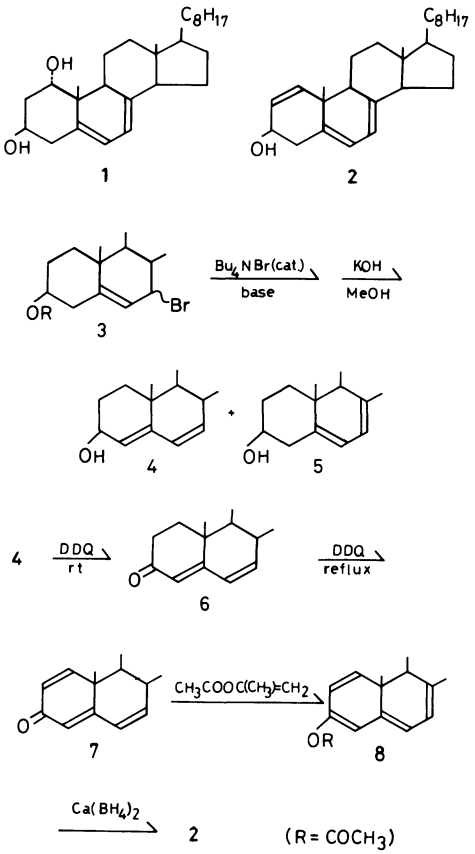

Table 1. Yields of Cholesta-4,6-dien-3β-ol (**4**) in the Dehydrobromination of 7-Bromocholesteryl Acetate (**3**)[1]

Bu_4NBr/**3**	Base	Temp °C	Time min	Yield[2] %	4/5[4]
0.1	2,4,6-Trimethylpyridine	100	20	60	7.4
0.1	2,4,6-Trimethylpyridine	125	10	62	6.8
0.1	2,4,6-Trimethylpyridine	65	70	18[3]	9.5
1.0	2,4,6-Trimethylpyridine	125	10	68	8.3
1.0	2-Methylquinoline	125	10	44	5.9

1) 7-Bromocholesteryl acetate was prepared by the reaction of cholesteryl acetate with *N*-bromosuccinimide and employed without further purification. 2) Isolated yield. 3) Tetrahydrofuran was used as a solvent. 4) The formation ratio was determined on the basis of UV spectra.

Table 2. Oxidation of Cholesta-4,6-dien-3β-ol (**4**) into Cholesta-4,6-dien-3-one (**6**) under Various Conditions

Oxidizing agent	Time / h	Solvent	Temp / °C	Yield[1] / %
DDQ[2]	20	Dioxane	rt[3]	85
DDQ	20	Toluene	rt	74
PDC[4]	6	Dichloro-methane	rt	75
PCC[5]	20	Dichloro-methane	rt	58
$Al(OPr^i)_3$-*p*-benzoquinone	20	Toluene	rt	72
$Al(OPr^i)_3$-*p*-benzoquinone	20	Toluene	110	70
RuO_2-$NaIO_4$	48	Trichloro-ethylene/ methanol/H_2O	rt	50

1) Isolated yield. 2) 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone. 3) Room temperature. 4) Pyridinium dichromate. 5) Pyridinium chlorochromate.

quantitatively. The 1,5,7-trien-3-ol (**2**) was converted to **1** by the method described in the literatures.[5,12-13]

Since cholesta-1,5,7-trien-3β-ol (**2**) is obtainable readily from cholesterol as described above, the present study provides a simple and efficient method for the preparation of 1α-hydroxyprovitamin D_3 (**1**).

Experimental

Melting points are uncorrected. UV spectra were taken on a Hitachi 320 spectrometer. Optical rotations were determined with JASCO DIP-4 polarimeter.

Cholesta-4,6-dien-3β-ol (4). A hexane solution of cholesteryl acetate (42.8 g), *N*-bromosuccinimide (21.0 g) and a catalytic amount of benzoyl peroxide was allowed to react under reflux for 40 min. The hexane solution was filtered to remove succinimide and the filtrate was evaporated to dryness under reduced pressure at below 40 °C. The residue was dissolved in butyl acetate (150 ml). Tetrabutylammonium bromide (3.2 g) and 2,4,6-trimethylpyridine (14.5 g) were added to the butyl acetate solution. The mixture was refluxed for 20 min. The solution was washed with dil. hydrochloric acid, water, dried over sodium sulfate and concentrated to a semi-crystalline residue under reduced pressure. To the residue, methanolic potassium hydroxide solution (KOH 6.2 g, methanol 200 ml) was added and the mixture was refluxed for 10 min. The methanol solution was allowed to stand overnight at room temperature. The crude cholesta-4,6-dien-3β-ol (**4**) was collected by filtration. The crude product was purified by silica-gel column chromatography (eluted with chloroform) to give **4**. 23.8 g (62%): Mp 116—117 °C (lit,[15] mp 119—120 °C); λ_{max} 239 nm (ε=25,000, EtOH).

Cholesta-4,6-dien-3-one (6). A typical procedure for the preparation of cholesta-4,6-dien-3-one (**6**) from cholesta-4,6-dien-3β-ol (**4**) is described in the following. A mixture of **4** (3.8 g) and 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) (2.9 g) in dioxane (20 ml) was allowed to react at room temperature for 18 h. After the formed hydroquinone was filtered off, the filtrate was condensed to dryness at reduced pressure. The residue was chromatographed on silica gel using hexane–ethyl acetate (9/1) as eluent. Crystallization from acetone gave cholesta-4,6-dien-3-one (**6**). 3.2 g (85%): Mp 81—82 °C (lit,[17] mp 80.5—81.5 °C); λ_{max} 284 nm (ε=28,700, EtOH).

Cholesta-1,4,6-trien-3-one (7). A dioxane solution containing the 4,6-dienol (**4**) (7.7 g) and DDQ (5.2 g) was treated with stirring at room temperature for 18 h. After the hydroquinone was removed by filtration, a further DDQ (4.4 g) was added to the filtrate. The dioxane solution was refluxed for 2 h. After filtration and removal of the solvent under reduced pressure, the resulting residue was chromatographed on silica gel. Elution with hexane–ethyl acetate (9/1) and crystallization from acetone gave the 1,4,6-trienone (**7**). 4.9 g (65%): Mp 89—90 °C (lit,[14] mp 82—83 °C; λ_{max} 300 nm (ε=13,400, EtOH).

Cholesta-1,5,7-trien-3β-ol (2). A mixture of the 1,4,6-trien-3-one (**7**) (38.0 g), *p*-toluenesulfonic acid (19.0 g) in butyl acetate (500 ml) and isopropenyl acetate (400 ml) was refluxed for 7 h. The butyl acetate solution was washed with water and dried over sodium sulfate. The solution was concentrated to dryness under reduced pressure. The residue was crystallized from acetone to give 3-acetoxy-1,3,5,7-cholestatetraene (**8**) as yellow needles. 27.0 g (64%): Mp 123—124 °C (lit,[12] mp 122—124 °C); $[\alpha]_D^{25}$ −507° (*c* 0.6, $CHCl_3$).

The ether solution of the tetraene (**8**) (15.0 g) was added dropwise at −10 °C to a stirred solution of calcium borohydride in ethanol–methanol (calcium chloride (30.0 g) in methanol (250 ml) and sodium borohydride (15.0 g) in ethanol (250 ml)).[5] The mixture was stirred at 0 °C for 3 h and standed overnight. After addition of 50% acetic acid to dissolve the resulted precipitate, the product was extracted with ether. The extract was washed with aq sodium hydrogencarbonate, water and dried over sodium sulfate. The ether was evaporated to dryness under reduced pressure and the residue was chromatographed on silica gel. The product, which was eluted with hexane–ethyl acetate (4/1) was crystallized from acetone to give **2**. 12.8 g (94%): Mp 126—127 °C (lit,[5] mp 128—129 °C); λ_{max} 282 nm (ε=10,900, EtOH).

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