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Preparation of Desmosterol from Fucosterol[1]

Toru Takeshita, Sachio Ishimoto,[2a] and Nobuo Ikekawa[2b]

Teijin Institute for Biomedical Research[2a] and Laboratory of Chemistry for Natural Products, Tokyo Institute of Technology[2b]

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Desmosteryl acetate, a useful key intermediate for synthesis of the metabolites of vitamin D_3, was synthesized from fucosterol by two routes; (1) 24, 28-epoxyfucosteryl acetate was treated with solid acids such as zeolite, silica-alumina and alumina-boria to give desmosteryl acetate in a yield of 16%—40%, (2) dehydration of 24-hydroxycholesteryl acetate, which was obtained by ozonolysis of fucosteryl acetate followed by reduction with sodium borohydride, with P_2O_5 in benzene afforded desmosteryl acetate in a yield of 85%.

Desmosterol (**4**) has proved to be a useful key intermediate of the metabolites of vitamin D_3, such as 25-hydroxyvitamin D_3,[3] 24,25-, 25, 26-[4] and 1α,25-dihydroxyvitamin D_3[5] and 1α,24,25-trihydroxyvitamin D_3.[6] In the earlier synthesis of desmosterol, the 24,25-double bond was introduced by a Wittig reaction[7] on a C24-aldehyde or by dehydration of 25-hydroxycholesterol.[8] Recently Dasgupta, *et al.*[9] reported new methods for the synthesis of desmosterol from 3β-hydroxybisnorcholenic acid and 3β-hydroxynorcholenic acid.

We have reported previously[10] that brief treatment of 24,28-epoxyfucosteryl acetate (**2**) which was easily led from fucosterol, an abundant sterol in brown marine algae, with Lewis acids such as BF_3-etherate, $SnCl_4$ and $AlCl_3$, gave desmosteryl acetate (**3**) by a fragmentation reaction in about 20—35% yield. In an attempt to increase the yield of **3**, the fragmentation reaction of the epoxide with solid acids was investigated (section A). An effective synthetic route for **3** from fucosteryl acetate (**1**) *via* 24-hydroxycholesteryl acetate (**6**) is also described (section B).

(A) Application of Solid Acids for the Fragmentation Reaction of Epoxide 2

We found that 24,28-epoxyfucosteryl acetate (**2**) was effectively converted to desmosteryl acetate (**4**) by solid acid such as zeolite,[11] alumina-boria, silica-gel and silica-alumina in anhydrous benzene with a simple technique. The reaction conditions and the yield of **3** are summarized in Table I. The highest yield (40%) was obtained by use of Mn-zeolite (Y).

1) This is Part 35 in the series of "Studies on Steroids". For Part 34 see N. Ikekawa and N. Koizumi, *J. Chromatog.*, **119**, 227 (1976).
2) Location: *a*) *Hino-shi, Tokyo*; *b*) *Ookayama, Meguro-ku, Tokyo.*
3) M. Morisaki, J. Rubio-Lightbourn and N. Ikekawa, *Chem. Pharm. Bull.* (Tokyo), **21**, 457 (1973).
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Table I. Reaction of Epoxide **2** with Solid Acids[a]

Solid acids	Weights of catalyst (mg)	Reaction time (hr)[b]	Yield of **3** (%)
Silica-Alumina[c]	300	1.5	24
Silica-gel[d]	450	4.0	16
η-Alumina-Boria[e]	700	6.0	27
Mn-Zeolite[f] (X)[g]	600	1.5	34
Mn-Zeolite (Y)[h]	400	2.0	40
Co-Zeolite (X)	700	3.5	28
Co-Zeolite (Y)	400	3.0	34
Zn-Zeolite (Y)	450	1.5	30
Ca-Zeolite (Y)	300	1.0	31
Mg-Zeolite (Y)	600	2.5	37
Ba-Zeolite (X)	700	5.0	28
Cu-Zeolite (X)	800	3.0	21

a) Sixty mg of the epoxide in 2 ml of benzene was used in each reaction. Reaction temperature was 18° except for Silica-gel, 50°.
b) Reactions were followed by GLC and TLC.
c) Product of Nikkikagaku Co., Ltd., N-631-H.
d) Product of Nikkaseiko Co., Ltd.
e) Content of boria is 15% by weight.
f) Various types of metal zeolite were prepared by treating Na-zeolite (X) or Na-zeolite (Y) with aqueous 1N metal chloride solutions. X-Type of zeolite was activated at 350° and Y-type was activated at 280—300°.[11]
g) Zeolite (X) is a product of Tetsukosha, F-9.
h) Zeolite (Y) is a product of Union Carbide, SK-40.

The same by-products, as in the Lewis acid treatment,[10] 24-acetylcholesteryl acetate (**7**) (37%) and 24-formyl-24-methylcholesteryl acetate (**8**) (13%) were obtained. The yield of **3** may be depend upon the factors such as the acid strength and the activity of the surface of the catalysts.

(B) Synthesis of Desmosterol Acetate *via* Ozonolysis of Fucosteryl Acetate

The ozonolysis of fucosterol or its derivatives has been reported by several research groups.[12] In their methods the yields of 24-oxo compounds are not satisfactory for synthetic purpose.[13] We have searched for the reaction conditions of ozonolysis of **1**, so that 24,28-double bond of **1** was selectively ozonized. The best yield was obtained when **1** was treated with ozone-oxygen stream of 11.8—17.2 g $(O_3)/m^3(O_2)$ in CH_2Cl_2 at −78°. The ketone **5** thus obtained was directly converted to **6** by treatment with $NaBH_4$ in methanol in a yield of 73% from **1**. Dehydration of **6** with P_2O_5 in benzene preferentially afforded **3** in 85% yield with negligible amounts of 23-dehydrocholesteryl acetate (**10**).

Table II. Dehydration Reaction of 24-Hydroxycholesteryl Acetate (**6**)[a]

Catalyst (mg)	Solvent (ml)	Temp. (°C)	Time	Yield (%) Desmosterol (3)	Yield (%) 24-Cl Comp. (9)
P_2O_5 (160)	benzene (10)	5—10	20 min	85	—
P_2O_5 (200)	CH_2Cl_2 (10)	5—10	20 min	74	—
$POCl_3$ (0.5 ml)	pyridine (5)	20	3.5 hr	57	33
$SOCl_2$ (0.5 ml)	pyridine (5)	20	3.0 hr	58	29

a) Two hundred mg of **6** was used in each reaction.

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13) Recently an improved method of ozonolysis to 24-oxo compound was reported by Y.M. Sheikh and C. Djerassi, *Tetrahedron*, **30**, 4095 (1974).

Other dehydrating reagents such as $SOCl_2$ and $POCl_3$ gave inferior results obtaining **3** in a yield of 55—60% with a concomitant formation of 24-chlorocholesteryl acetate (**9**). The results of the dehydration reactions are summarized in Table II. Thus, ozonolysis of fucosteryl acetate followed by $NaBH_4$ reduction and P_2O_5 dehydration may be a most practical route to desmosteryl acetate.

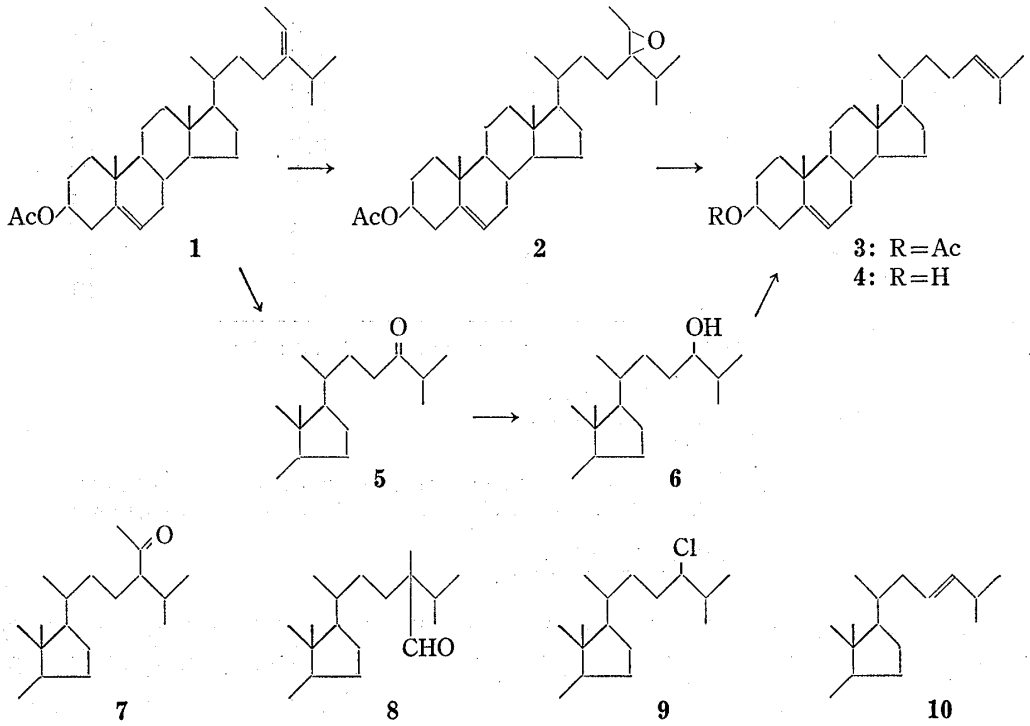

Chart 1

Experimental

Melting points were determined on a hot stage microscope and are uncorrected. Nuclear magnetic resonance (NMR) spectra were determined by a Varian EM360 or a JEOL SP/PFT-100 spectrometer in deuteriochloroform with tetramethylsilane as an internal standard. Mass spectra were recorded on a Shimadzu LKB-9000 GC-MS system. Optical rotation were determined with a JEOL DIP-SL model. Gas–liquid chromatography (GLC) analysis were performed on a Shimadzu GC-5APF gas chromatograph with a flame ionization detector. Column chromatography was effected with silica gel (Wakogel C-200).

Reaction of 24,28-Epoxyfucosteryl Acetate (2) with Solid Acid——To a solution of 24,28-epoxyfucosteryl acetate (60 mg) in 2 ml of dry benzene was added Mn-zeolite (Y) (400 mg) and the mixture was stirred at 18° for 2 hr. Mn-zeolite was filtered off and the filtrate was evaporated to dryness. The residue was applied on a column of silica gel (1 g). The fraction eluted with benzene–hexane (1: 4) gave 21.8 mg of desmosteryl acetate (**3**), mp 93—94°, $[\alpha]_D^{19}$ −42.7° (c=0.48, $CHCl_3$). It was identical in respect to NMR and mass spectra with an authentic specimen. The fraction eluted with benzene–hexane (1: 1) gave 7.8 mg of 24-formyl-24-methylcholesteryl acetate (**8**), mp 128—130° (from acetone), identified by comparison with the authentic sample.[10] The fraction eluted with benzene–hexane (3: 1) gave 22.2 mg of 24-acetylcholesteryl acetate (**7**),[10] mp 130—133° (from acetone).

A similar product ratio of **3**, **7**, and **8** was obtained with other solid acids (Table I).

24-Oxocholesteryl Acetate (5)——A stream of ozone (concentration of ozone, 11.8 g/m^3 (O_2)) was gently passed through a solution of fucosteryl acetate (10 g) in methylenechloride (300 ml) at −78° for 80 min. After ozonization, acetic acid (500 ml) and zinc dust (25 g) were added to the solution and the mixture was stirred vigorously for 1 hr at 45°. Zinc dust and zinc acetate were removed by filtration. The filtrate was then diluted with water and extracted with methylene chloride. The methylene chloride layer was washed with 6% $NaHCO_3$ and then with water and dried over Na_2SO_4. The solvent was evaporated and the crude product was chromatographed on silica gel. The fraction eluted with benzene–hexane (2: 1) gave 7.4 g of 24-oxochloesteryl acetate (**5**),[12b] mp 130—132°.

24-Hydroxycholesteryl Acetate (6)——24-Oxocholesteryl acetate (6 g) was treated with $NaBH_4$ (5.5 g) in MeOH (1.6 liter) at room temperature for 1 hr. Acetic acid (50 ml) was added and the mixture was extracted with ether, washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a white amorphous

powder, which was purified by silica gel column using benzene as an elution solvent to afford 5.8 g of 24-hydroxycholesteryl acetate (6),[14] mp 124—125°, identified by comparison with the authentic sample.

Reaction of 24-Hydroxycholesteryl Acetate (6) with P_2O_5——To a stirred suspension of P_2O_5 (160 mg) in 10 ml of dry benzene, **6** (200 mg) was added dropwise under ice-cooling. After stirring for 20 min at 7,° the reaction mixture was extracted with ether, washed with saturated $NaHCO_3$ solution and then with brine. Evaporation of the solvent afforded a slight yellow amorphous powder (198 mg), which was purified by column chromatography on silica gel. The fraction eluted with benzene–hexane (1: 4) gave 163 mg of desmosteryl acetate (**3**), mp 93—94.5.

The GLC analysis of the crude product using 1.5% OV-1 on Chromosorb WHP, 150 cm × 3 mm i.d. at 270°, demonstrated that 23-dehydrocholesteryl acetate (**10**) (3%) and **6** (4%) were contained in the reaction product. The retention times of **10**, **3** and **6** were 3.2, 3.6 and 6.0 min, respectively. 23-Dehydrocholesteryl acetate was identified in respect to the retention time of GLC and mass spectrum obtained by GC-MS system with an authentic sample.[15]

Reaction of 24-Hydroxycholesteryl Acetate (6) with $POCl_3$——In a solution of **6** (200 mg) in pyridine (5 ml), phosphorus oxychloride (0.5 ml) was added and the mixture was stirred for 3.5 hr at 20°. The solution was poured into ice-water and extracted with ether. The ether solution was washed with 1N HCl and then with brine. Evaporation of the solvent afforded a slight yellow amorphous powder (200 mg) which was purified by column chromatography. The fraction eluted with benzene–hexane (1: 4) gave desmosteryl acetate (109 mg) and the fraction eluted with benzene–hexane (1.5: 4) gave 24-chlorocholesteryl acetate (**9**) (69 mg), Mass Spectrum *m/e*: 404 (M^+-AcOH), 402, 351, 255, 253, 213; NMR δ, 0.68 (3H, s, 18-Me), 1.02 (3H, s, 19-Me), 2.02 (3H, s, Ac), 3.75 (1H, m, 24-H), 4.60 (1H, m, 3-H), 5.37 (1H, m, 6-H).

The GLC analysis of the crude product indicated that a small amount (2%) of 23-dehydrocholesteryl acetate (**10**) was contained in the reaction product. The yield of **3** and **9** in Table II were calculated from the chromatogram. The column conditions were same as above description. The retention time of **9** was 7.0 min.

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Halogenation Reaction of Bis(acetylacetonato)nickel(II) and -cobalt(II) Chelate

Koji Yamakawa and Hajime Kaneoya

Faculty of Pharmaceutical Sciences, Science University of Tokyo[1]

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Introduction of chlorine, bromine, and iodine atom into the ring of labile bivalent metal acetylacetonates, bis(acetylacetonato)nickel (II) and -cobalt(II) chelates, is effected by N-halosuccinimide in carbon tetrachloride. Infrared and ultraviolet spectra of halogenated metal(II)-acetylacetonate chelate derivatives were measured. The masses of substituent at the central carbon atom of these metal(II)-acetylacetonates affected the frequencies of C=O and C=C stretching bands.

The introduction of substituents at the central carbon atom of the trivalent metal-acetylacetonate ring, such as cobalt(III), chromium(III), and rhodium(III), *etc.*, by electrophilic

1) Location: *Ichigaya-funagawara-machi, Shinjuku-ku, Tokyo, 162, Japan.*