Summary

Some 2-ethoxalyl-4-en-3-one was treated with N-halo-succinimide in pyridine to give the corresponding 2α-halo-4-en-3-one in a good yield. Direct chlorination of testosterone acetate with sulfuryl chloride (1 mole) gave a small amount of 2α-chlorotestosterone acetate in dry benzene or dry ether, and with sulfuryl chloride (excess) gave mainly 2α,4-dichlorotestosterone acetate in dry benzene and mainly 2α,6β-dichlorotestosterone acetate in dry ether. These observations were confirmed by the syntheses of their related compounds through the unequivocal routes.

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170. Hiromu Mori: Studies on Steroidal Compounds. XII.*1 Stereochemistry of 1,4-Addition of Grignard Reagent for α,β-Unsaturated Steroidal Ketones. Grignard Reaction of 3β-Hydroxycholest-4-en-6-one.

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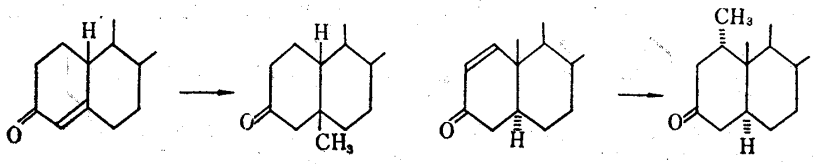
In the preceding papers, the Grignard reactions of 19-nor-3-oxo-4-ene (I) and 3-oxo-1-ene (II) steroids were described.[1,2] 1,4-Addition product was isolated in each case, when Grignard reaction was taken place in the presence of cuprous chloride: 5β-methyl-3-oxo (III) and 1α-methyl-3-oxo (IV) compound were obtained respectively as shown in Chart 1. The stereochemical course of the reaction was explained by stereochemical



I III II IV

Chart 1.

interaction. This paper describes further study of stereochemistry of Grignard reaction, in which the reaction of 3β-hydroxycholest-4-en-6-one (V) will be reported, and discussion will be made concerning the stereochemistry of 1,4-addition of Grignard reagent for α,β-unsaturated ketones.

When 3β-hydroxycholest-4-en-6-one (V)[3] was treated with methyl magnesium iodide in the presence of cuprous chloride or cupric acetate, there was obtained a new compound (VI), m.p. 175.5~177.5° with no characteristic absorption in ultraviolet spectrum.

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*1 H. Mori, J. Yamada: This Bulletin, **11**, 1418 (1963).
*2 1604 Shimosakunobe, Kawasaki-shi (森 弘).
1) H. Mori: This Bulletin, **10**, 382 (1962).
2) *Idem*: *Ibid.*, **10**, 386 (1962).
3) I. M. Heilbron, E. R. H. Jones, F. S. Spring: J. Chem. Soc., **1937**, 801.

The infrared spectrum of Ⅵ displayed six-membered carbonyl band (1716 cm^{-1}) and a hydroxyl band (3660 cm^{-1}). Mono acetate (Ⅶ), m.p. 145.5~146.5° was obtained on acetylation of Ⅵ with acetic anhydride in pyridine at room temperature. Ⅵ or its acetate (Ⅶ) was isomerized to the stable isomer, Ⅷ, m.p. 170~171.5°, or Ⅸ, m.p. 120~121.5° respectively on treatment with alkali or acid. Ⅸ was also obtained from Ⅷ by acetylation with acetic anhydride in pyridine.

In order to assign the structures of these compounds, an attempt to transform the carbonyl group in Ⅷ to methylene group by thioketal formation, followed by Raney nickel desulfuration was undertaken without success. The Huang-Minlon reduction of Ⅷ, however, gave 4β-methyl-5α-cholestan-3β-ol (X), the structure of which was easily

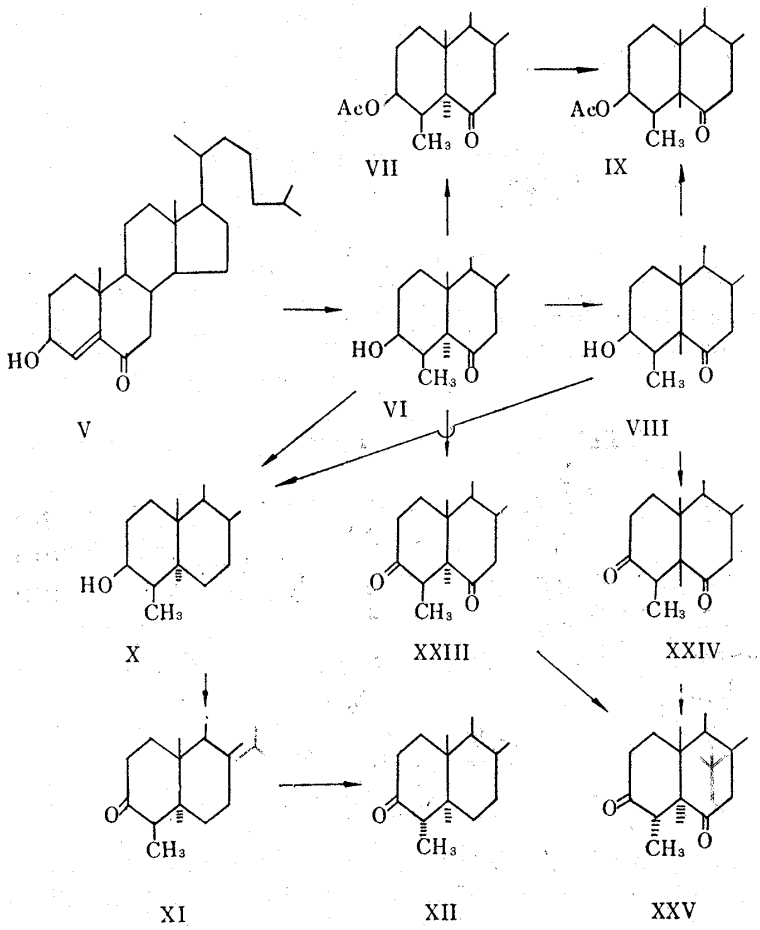


Chart 2.

shown by the oxidation of X with chromium trioxide in acetone to known 4β-methyl-5α-cholestan-3-one (Ⅺ).[4] The treatment of Ⅺ with acid gave the stable isomer, 4α-methyl-5α-cholestan-3-one(Ⅻ).[4] These observations indicate that the Grignard reaction of V gave undoubtedly 4β-methyl-6-oxo compound by 1,4-addition of the Grignard reagent to α,β-unsaturated oxo function, and isomerization of Ⅵ to Ⅷ (or Ⅶ to Ⅸ) was concerned with A/B ring juncture. The configuration of C-5 in Ⅷ would be considered as α from observation described above, but this assignment was proved to be questionable, because the Huang-Minlon reduction of the unstable isomer (Ⅵ) gave also 4β-methyl-5α-cholestan-3β-ol (X).

4) Y. Mazur, F. Sondheimer : J. Am. Chem. Soc., 80, 5220 (1958).

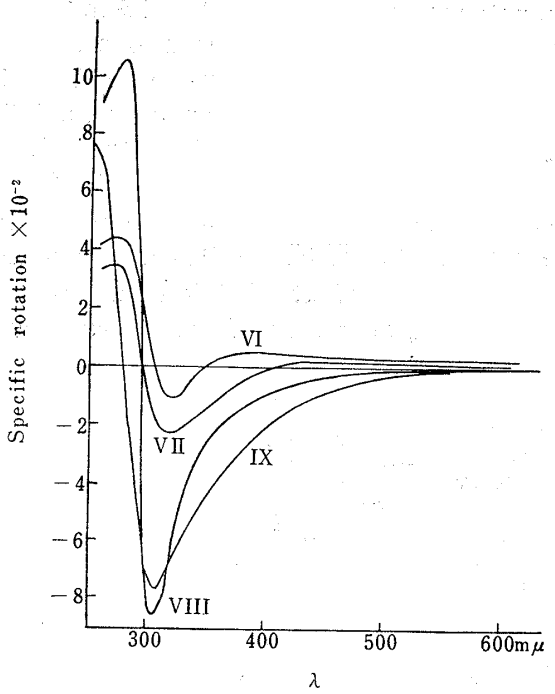


Fig. 1. Rotatory Dispersion Curves of Ⅵ, Ⅶ, Ⅷ, and Ⅸ (ethanol)

That the assignment of A/B ring juncture of Ⅷ as *trans* is not the case was shown on the basis of following observations. i) Ⅵ was precipitated from 95% ethanol solution as digitonide, when a solution of digitonin in 95% ethanol was added. On the other hand, no insoluble digitonide of Ⅷ was formed on similar treatment. This suggests that A/B ring juncture of Ⅵ and Ⅷ are *trans* and *cis*, respectively.[5] ii) Optical rotatory dispersion curves of Ⅵ, Ⅶ, Ⅷ, and Ⅸ are shown in Fig. 1. The curves for Ⅷ and Ⅸ are negative single Cotton effect curves similar as those observed in 3β-hydroxy-5α-cholestan-6-one (XIII) or 3β-hydroxy-5β-cholestan-6-one (XIV).[6] The curves for Ⅵ and Ⅶ should be considered as unusual curves comparing with those for XIII and XIV because of their unusual low amplitude. This fact can be explained naturally by the consideration derived from the assignment described

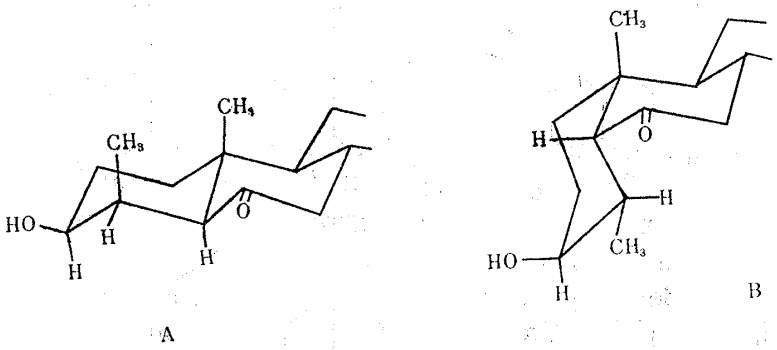


Chart 3.

above. The conformations of A/B *trans* and *cis* 3β-hydroxy-4β-methyl-6-ones are shown as A and B in Chart 3. In conformation A, there is a strong 1,3-diaxial methyl-methyl interaction between 4β-methyl and 10β-methyl group, while such a strong interaction is not observed in A/B *cis* series. If unusual curves are considered to be observed in A/B *trans* series, the distortion of ring A or B on account of the strong interaction (1,3-diaxial interaction) will cause the unusual curves.[7] On the other hand, if the opposite

5) It has been shown that only 3β-hydroxy-5α compound is precipitated as digitonide among four isomers of 3-hydroxy saturated compounds (3α,5α; 3α,5β; 3β,5α; 3β,5β). R. N. Jones, F. Herling: J. Org. Chem., **19**, 1252 (1954).

6) C. Djerassi, W. Closson: J. Am. Chem. Soc., **78**, 3761 (1956).

7) Optical rotatory despersion curve of 4,4-dimethyl-5α-cholestan-3-one is known to be an unusual one, and this fact is considered to be due to the distortion of ring A and B. On the other hand, optical rotatory dispersion curves of 4β- or 2β-methyl-5α-cholestan-3-one are possitive Cotton effect curves usually observed in A/B *trans*-3-oxo steroids. (C. Djerassi, O. Halpern, V. Halpern, B. Riniker: J. Am. Chem. Soc., **80**, 4001 (1958)). Thus it should be considered that the influence of 1,3-diaxial 4β-methyl-10β methyl interaction on the conformation is not so serious for 3-oxo Octant diagram, but very serious for 6-oxo diagram.

assignment is made, the unusual curves can not be explained stereochemically. iii) If the stable isomer (Ⅷ) is considered to be A/B *cis* isomer, the fact that the Huang-Minlon reductions of Ⅵ and Ⅷ gave the same compound (X) must be considered as follows. The equilibrium mixture (Ⅵ⟷Ⅷ) is rapidly produced, only one isomer, 3β-hydroxy-4β-methyl-5α-cholestan-6-one (Ⅵ) was transformed to the hydrazone (XV), and the formation of hydrazone of another isomer, 3β-hydroxy-4β-methyl-5β-cholestan-6-one (Ⅷ) was blocked by stereochemical factor. It is generally accepted that rate determining step of hydrazone formation is the addition of hydrazine to ketone $\left(C{=}O \rightarrow C\langle^{OH}_{NHNH_2}\right)$.[8] In the case of A/B *trans* isomer (conformation A in Chrat 3), if hydrazine attacks from rear

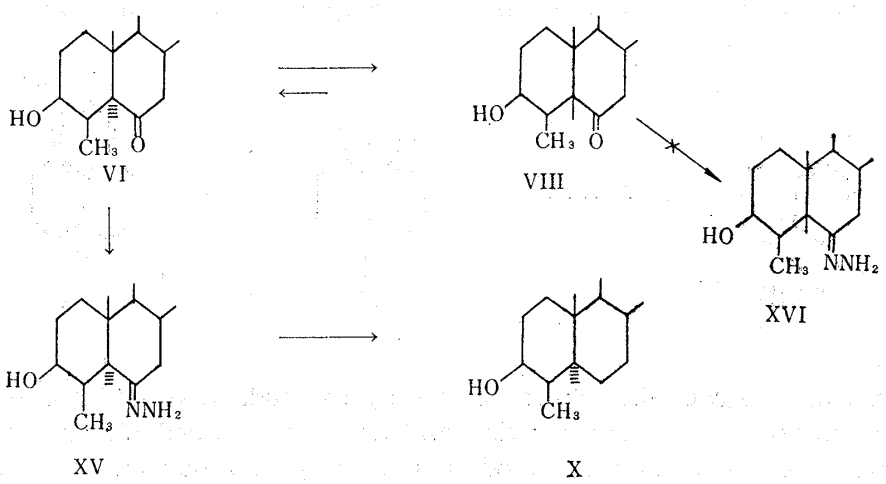
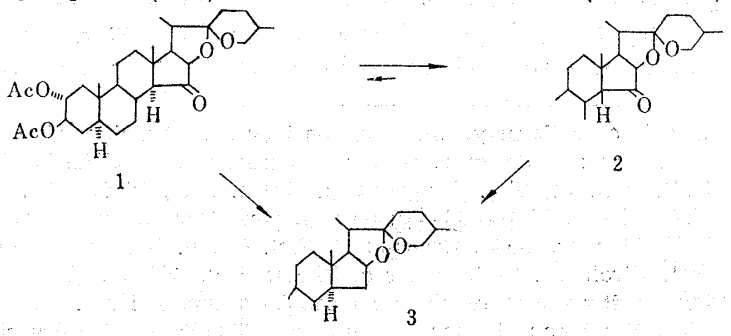


Chart 4.

side of the steroid, no serious interaction is observed, and the attack of the reagent was probably preceded from this direction. On the other hand, in the case of another isomer (conformation B in Chart 3), both rear side and front side attack of the reagent are seriously interacted by 10β-methyl and 4β-methyl group, respectively. Thus the behaviour of Huang-Minlon reduction under consideration can be smoothly explained stereochemically.[9] iv) In order to elucidate the difference of hinderance of C-6 oxo group between Ⅵ and Ⅷ, the Grignard reactions (methyl magnesium iodide, at room temperature) of Ⅵ and Ⅷ were undertaken. In the case of Ⅷ, the starting material was recovered completely. On the other hand, the same reaction of Ⅵ gave an oily substance, the infrared spectrum of which showed that there was obtained an addition product, but isolation in crystalline state was unsuccessful. From this experiment, it became clear that oxo group in Ⅷ is highly sterically hindered.

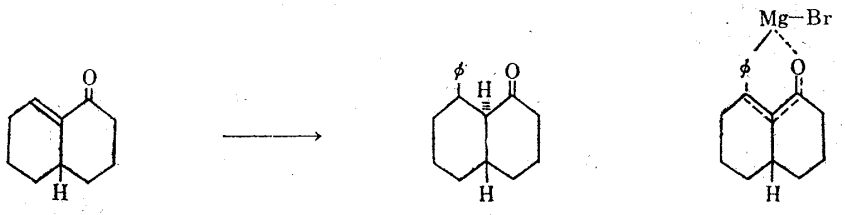
8) J. Hine: "Physical Organic Chemistry," p. 246 (1956), McGraw-Hill Book Co., Inc. (New York).

9) Similar observations concerning sapogenins having oxygen function at C-15 have been made by C. Djerassi, T. T. Grossnickle, L. B. High (J. Am. Chem. Soc., 78, 3166 (1956)). Digitogenone diacetate (1) is isomerized to thermodynamically stable isomer (2) by treatment with alkali. Both the Huang-Minlon reduction of digitogenone diacetate (1) and its C-14 isomer (2) gave the same 15-deoxo compound, gitogenin (3), the C-14 configuration of which is the same as that for thermodynamically unstable isomer, digitogenin (3).



All observations described above indicate that VI, 1,4-addition product must be formulated as 3β-hydroxy-4β-methyl-5α-cholestan-6-one, and the related compounds, VII, VIII, and IX as shown in Chart 2. It is to be noted that 1,3-diaxial 4β-methyl; 10β-methyl interaction inverts the stability order of A/B ring juncture. Generally A/B *trans* compound in decaline system is kinetically more stable than A/B *cis* compound;[10] in fact, Henbest and Wrigley[11] found that 5β-cholestan-6-one is isomerized into kinetically stable isomer, 5α-cholestan-6-one, on treatment with alumina. In contrast, A/B *cis* compound is more stable in 4β-methyl-6-oxo series.

Recently House and Thompson found that 1,4-addition of Grignard reagent to 3,4,4*a*, 5,6,7-hexahydro-1(2*H*)-naphthalenone (XVIII) gives 8-phenyloctahydro-1(2*H*)-naphthalenone (XIX), in which the configuration of phenyl group is β and ring juncture is *trans* as



XVIII XIX XX

Chart 5.

shown in Chart 5.[12] From this observation they conclude that 1,4-addition of Grignard reagent is comparable to Michael reaction and does not proceed *via* six-membered cyclic transition state (XX). It should be noted that alkyl group introduced newly is axially oriented both in their experiment and also in our case. The hypothesis, that a Grignard reagent attacks from axial direction in which case orbital overlap in the transition state is more favorable, became more acceptable. Moreover, we believe that all examples of 1,4-addition for steroidal α,β-unsaturated ketones can be explained by this concept.

Five types of example in 1,4-addition for steroidal α,β-unsaturated ketones can be seen from literature except our experiment. The most classic example is that for 16-en-20-ones.[13] Since a methyl group is introduced in five-membered D-ring (16α), discussion can not be made from this concept.*3 Discussion can be made for the other four examples as follows.

i) 4-En-3-ones. The 1,4-addition for 4-en-3-ones affords 5β-methyl-3-ones.[1,14] It should be noted that 5α- and 5β-methyl group are both axially oriented for ring A and the double bond in the starting material exists in A-ring. Thus attack of the reagent should occur from less-hindered β-side.[15]

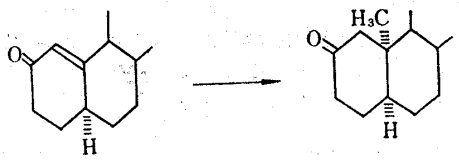
ii) 5α-1-En-3-ones. From the concept, 1α-methyl-5α-3-ones should be the product predicted. In fact, this compounds are obtained almost stereospecifically.[2]

iii) 5β-1-En-3-ones. Recently, Wechter[16] has described the Grignard reaction of 5β-1-en-3-ones, in which 1β-methyl-5β-3-ones are obtained as 1,4-addition products. Here again, a methyl group introduced by the reaction is axially oriented.

*3 In this case, it may, only, be considered that Grignard reagent attacks from less hindered rear side.

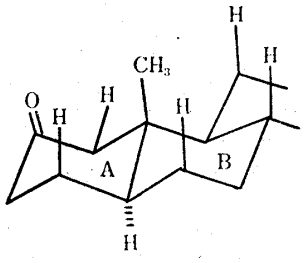
10) W. Klyne : "Progress in Stereochemistry, I," p. 47 (1954), Butterwoth Scientific Publications (London).
11) H. B. Henbest, T. I. Wrigley : J. Chem. Soc., **1957**, 4596.
12) H. O. House, H. W. Thompson : J. Org. Chem., **28**, 360 (1963).
13) R. E. Marker, H. M. Crooks : J. Am. Chem. Soc., **64**, 1280 (1942).
14) A. J. Birch, M. Smith : Proc. Chem. Soc., 356 (1962).
15) Concerning the stereochemical consideration, see ref. 1).
16) W. J. Wechter : J. Org. Chem., **29**, 163 (1964). He described in the original paper that the configuration of the methyl group of the product is α, but according to his private communication, the configuration of the 1-methyl group described in his paper should be revised to 1β-methyl.

iv) 1(10)-En-2-one. The reaction of 1(10)-en-2-one (XXI) has been described by Torigoe and Fishman[17] who obtained 10α-methyl-2-one (XXII) as 1,4-addition product. Both 10α- and 10β-methyl group are axially oriented for A-ring, in which the double bond of the starting material has existed (see Chart 7). This case is resemble to the case i), and the less hindered side attack should occur. It is easy to show that α-side is less hindered from models shown in Chart 7. In conformation C, main interactions for the 10-methyl group are three 1,3-diaxial methyl-hydrogen and one 1,2-methyl-hydrogen interactions, while in D, two 1,3-diaxial methyl-hydrogen*4 and two 1,2-methyl-hydrogen interactions. As interactions for conformation D are smaller than those for C, the product predicted from the concept is 10α-methyl compound and this agrees with the experimental result.

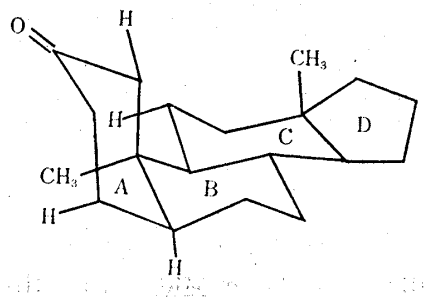


XXI XXII

Chart 6.



C



D

Chart 7.

From these considerations, it may be concluded that the configuration of a newly introduced alkyl group on an 1,4-addition reaction of a Grignard reagent to α,β-unsaturated ketone is predicted to be axial, and if both configurations are axial for the ring in which the double bond has existed, the product can be predicted only from stereochemical interactions.

The oxidations of VI and VII with chromium trioxide in acetone afforded the corresponding 3,6-diones, XXIII and XXIV, respectively. Both XXIII and XXIV were isomerized into the same diketone. As the most stable isomer must be considered to be 4α-methyl-5α-compound, the diketone can be formulated as 4α-methyl-5α-cholestane-3,6-dione. Similar observation has been made on the compounds derived from santonin by Tahara.[18] Fieser[19] has described that 4-methylcholest-4-ene-3,6-dione, which is obtained from cholest-4-ene-3,6-dione by the reaction with diazomethane followed by heating, is transformed into saturated compounds by reduction with zinc dust in acetic acid. He isolated two isomers of 4-methylcholestane-3,6-dione, m.p. 190° and 124°, but no assignment of the configurations of these compounds at C-4 and C-5 was given. From the comparison of melting points and optical rotations, Fieser's diketones, m.p. 190° and 124° are considered to be the same as XXIV and XXV, respectively.

Experimental*5

3β-Hydroxy-4β-methyl-5α-cholestan-6-one (VI). a) By Cu_2Cl_2 Catalized Reaction——Finely powdered

*4 The interaction between 10α-methyl and 11α-hydrogen is shown as an 1,3-diaxial interaction, because the interatomic distance between these groups is the same as that for 1,3-diaxial relationship.

*5 All optical rotations were measured in $CHCl_3$, and all melting points were uncorrected.

17) M. Torigoe, J. Fishman: Tetrahedron Letters, **1963**, 1251.
18) A. Tahara: J. Org. Chem., **21**, 442 (1956).
19) L. F. Fieser: J. Am. Chem. Soc., **75**, 4386 (1953).

Cu_2Cl_2 (500 mg.) was added to a solution of 3β-hydroxycholest-4-en-6-one (V, 3.0 g.) in Et_2O (180 ml.). To the resulting suspension, a Grignard reagent prepared from Mg (1.55 g.), CH_3I (4.35 ml.) and Et_2O (75 ml.) was added dropwise with vigorous stirring at room temperature. After stirring was continued for an hour, excess Grignard reagent was decomposed by addition of ice. Organic layer was washed with 10% NH_4Cl, 5% Na_2CO_3 and H_2O, and dried (Na_2SO_4). The solvent was removed by evaporation, and the residue was recrystallized from Me_2CO-Et_2O to give 3β-hydroxy-4β-methyl-5α-cholestan-6-one (VI, 1.1 g.), m.p 150~165°. Twice recrystallization from Me_2CO afforded an analytical sample as colorless needles, m.p. 175.5~177.5°. $[\alpha]_D^{28}$ +29° (c=1.20), IR $\nu_{max}^{CS_2}$ cm^{-1} : 3660 (-OH), 1716 (C=O). ORD (c=0.14, EtOH) : $[\alpha]_{318}$ −103° (trough), $[\alpha]_{274}$ +441° (peak). *Anal.* Calcd. for $C_{28}H_{48}O_2$: C, 80.71; H, 11.61. Found : C, 80.75; H, 11.71.

b) By $Cu(OAc)_2$ Catalized Reaction——To a Grignard reagent prepared from Mg (6.4 g.), CH_3I (17 ml.) and Et_2O (200 ml.), a solution of 3β-hydroxycholest-4-en-6-one (V, 8.8 g.) and $Cu(OAc)_2$ (0.88 g.) in tetrahydrofuran (210 ml.) was added dropwise with vigorous stirring at 0~−5°. After stirring was continued at the same temperature for 3 hr., the resulting suspension was allowed to stand overnight at room temperature. The excess Grignard reagent was decomposed by addition of ice, and the organic layer was washed with 10% NH_4Cl, 5% Na_2CO_3, and H_2O. After drying (Na_2SO_4), the solvent was evaporated and the residue was recrystallized from Me_2CO to give 3β-hydroxy-4β-methyl-5α-cholestan-6-one (VI, 4.3 g.), m.p. 161~169°. Recrystallization from the same solvent afforded a pure sample, m.p. 175~177° (3.4 g.), which was identical with the compound obtained above in all respects.

3β-Acetoxy-4β-methyl-5α-cholestan-6-one (VII)——A solution of 3β-hydroxy-4β-methyl-5α-cholestan-6-one (VI, 200 mg.) in pyridine (3.0 ml.) and Ac_2O (3.0 ml.) was allowed to stand overnight at room temperature, and poured into H_2O. The product was extracted with Et_2O, and Et_2O layer was washed with 10% HCl, 5% Na_2CO_3 and H_2O, and dried (Na_2SO_4). After evaporation of the solvent, the residue was recrystallized from Me_2CO-MeOH to give the acetate (VII, 160 mg.), m.p. 142~144°. Recrystallization from the same solvent afforded an analytical sample as colorless needles, m.p. 145~146.5°. $[\alpha]_D^{28}$ −2° (c=1.12), IR $\nu_{max}^{CS_2}$ cm^{-1} : 1742 (-OAc), 1720 (C=O). ORD (c=0.15, EtOH) : $[\alpha]_{316}$ −224° (trough), $[\alpha]_{270}$ +368° (peak). *Anal.* Calcd. for $C_{30}H_{50}O_3$: C, 78.55; H, 10.99. Found : C, 78.34; H, 10.84.

3β-Hydroxy-4β-methyl-5β-cholestan-6-one (VIII)——A solution of 3β-hydroxy-4β-methyl-5α-cholestan-6-one (VI, 100 mg.) and KOH (100 mg.) in MeOH (10 ml.) was refluxed for 2 hr., and poured into 10% HCl. The product was extracted with Et_2O, and Et_2O layer was washed with 5% Na_2CO_3 and H_2O, and dried (Na_2SO_4). The solvent was evaporated to dryness, and the residue was recrystallized from MeOH-Me_2CO to give 3β-hydroxy-4β-methyl-5β-cholestan-6-one (VIII, 60 mg.), m.p. 169~170.5°. Further recrystallization from the same solvent afforded an analytical sample as colorless needles, m.p. 170~171.5°. $[\alpha]_D^{23}$ −16° (c=0.57), IR $\nu_{max}^{CS_2}$ cm^{-1} : 3625 (-OH), 1704 (C=O). ORD (c=0.16, EtOH) : $[\alpha]_{310}$ −825° (trough), $[\alpha]_{272}$ +1065° (peak). *Anal.* Calcd. for $C_{28}H_{48}O_2$: 80.71; H, 11.61. Found : C, 80.53; H, 11.80.

3β-Acetoxy-4β-methyl-5β-cholestan-6-one (IX). a) By Isomerization of 3β-Acetoxy-4β-methyl-5α-cholestan-6-one (VII)——A solution of VII (200 mg.) in AcOH (20 ml.) containing 2 drops of H_2SO_4 was warmed on steam bath for 2 hr., and poured into H_2O. The product was extracted with Et_2O, and Et_2O layer was washed with H_2O, 5% Na_2CO_3 and H_2O, and dried (Na_2SO_4). The solvent was evaporated to dryness, and the residue was recrystallized from MeOH-Me_2CO to give 3β-acetoxy-4β-methyl-5β-cholestan-6-one (IX, 110 mg.), m.p. 118~121°. Further recrystallization from MeOH gave an analytical sample as colorless plates, m.p. 120~121.5°. $[\alpha]_D^{27}$ 0° (c=1.02), IR $\nu_{max}^{CS_2}$ cm^{-1} : 1738 (-OAc), 1705 (C=O). ORD (c=0.17, EtOH) : $[\alpha]_{309}$ −771° (trough), $[\alpha]_{238}$ +711 (peak). *Anal.* Calcd. for $C_{30}H_{50}O_3$: C, 78.55; H, 10.99. Found : C, 78.60; H, 10.91.

b) By Acetylation of 3β-Hydroxy-4β-methyl-5β-cholestan-6-one (VIII)——A solution of VIII (1.3 g.) in pyridine (10 ml.) and Ac_2O (10 ml.) was allowed to stand overnight at room temperature, and poured into H_2O. The product was extracted with Et_2O, and Et_2O layer was washed with 10% HCl, 5% Na_2CO_3 and H_2O, and dried (Na_2SO_4). The solvent was evaporated to dryness, and the residue was recrystallized from MeOH-Me_2CO to give colorless plates (IX, 1.1 g.), m.p. 104~120°. Further recrystallization from the same solvent afforded a pure sample, m.p. 118~121°, which was identical with the compound obtained above in all respects.

4β-Methyl-5α-cholestan-3β-ol (X). a) From 3β-Hydroxy-4β-methyl-5β-cholestan-6-one (VIII)——A solution of VIII (200 mg.) and KOH (400 mg.) in diethyleneglycol (8 ml.) and 80% $NH_2NH_2 \cdot H_2O$ (1.2 ml.) was heated at 140~160° for 30 min., and 190~210° for 2 hr., and poured into H_2O. The product was extracted with Et_2O, and Et_2O layer was washed well with H_2O, and dried (Na_2SO_4). After evaporation of the solvent, the residue was chromatographed on alumina (4.0 g.). 4β-Methyl-5α-cholestan-3β-ol (X, 98 mg.), m.p. 160.5~161.5° was eluted by hexane-benzene (1:1). $[\alpha]_D^{18}$ +14° (c=0.94), IR : $\nu_{max}^{CS_2}$ 3630 cm^{-1} (-OH), no carbonyl band. *Anal.* Calcd. for $C_{28}H_{50}O \cdot \frac{1}{2}H_2O$: C, 81.68; H, 12.49. Found : C, 81.95; H, 12.38.

b) From 3β-Hydroxy-4β-methyl-5α-cholestan-6-one (VI)——VI (200 mg.) was reduced as the same manner described above. X (83 mg.), m.p. 158~161° was obtained, the infrared spectrum of which was the same as that for the compound obtained above.

4β-Methyl-5α-cholestan-3-one (XI)——8*N* CrO_3 solution (0.1 ml.)[20] was added to a solution of 4β-methyl-5α-cholestan-3β-ol (X, 80 mg.) in alcohol free Me_2CO (20 ml.) at 5～10°. After the resulting suspension was stirred for 5 min. at the same temperature, H_2O was added and the product was extracted with Et_2O. Et_2O layer was washed with 5% Na_2CO_3 and H_2O, and dried (Na_2SO_4). The solvent was removed by evaporation, and the residue was recrystallized from Et_2O-MeOH to give 4β-methyl-5α-cholestan-3-one (XI, 52 mg.), m.p. 125～126.5°, $[\alpha]_D^{24}$ +34° (c=0.94) as colorless needles. (reported[4] m.p. 126～127°, $[\alpha]_D$ +36°).

4α-Methyl-5α-cholestan-3-one (XII)——A solution of 4β-methyl-5α-cholestan-3-one (XI, 50 mg.) in EtOH (5 ml.) and 10% H_2SO_4 (0.1 ml.) was refluxed for 2 hr., and poured into H_2O. The product was extracted with Et_2O, and Et_2O layer was washed with 5% Na_2CO_3 and H_2O, and dried (Na_2SO_4). The solvent was evaporated to dryness, and the residue was recrystallized form Et_2O-MeOH to give 4α-methyl-5α-cholestan-3-one (XII), m.p. 114～116°. Further recrystallization from the same solvent gave a pure sample as colorless needles. m.p. 121～123.5°, $[\alpha]_D^{24}$ +24° (c=1.03). (reported[4] m.p. 121～123°, $[\alpha]_D$ +26°).

4β-Methyl-5α-cholestane-3,6-dione (XXIII)——8*N* CrO_3 solution (0.25 ml.) was added to a solution of 3β-hydroxy-4β-methyl-5α-cholestan-6-one (VI, 200 mg.) in alcohol free Me_2CO (15 ml.) at 5～10°, and stirring was continued for 3 min. at the same temperature. The resulting suspension was poured into H_2O, and the precipitates were collected by filtration, washed with H_2O, and dried. Recrystallization from MeOH-Me_2CO gave 4β-methyl-5α-cholestane-3,6-dione (XXIII, 120 mg.), m.p. 182～186°. Recrystallization from the same solvent afforded an analytical sample as colorless leaflets. m.p. 181～183°, $[\alpha]_D^{28}$ −2° (c=1.20), IR : $\nu_{max}^{CS_2}$ 1720 cm^{-1} (C=O). *Anal.* Calcd. for $C_{28}H_{46}O_2$: C, 81.10; H, 11.18. Found : C, 81.06; H, 11.29.

4β-Methyl-5β-cholestane-3,6-dione (XXIV)——8*N* CrO_3 solution (0.2 ml.) was added to a solution of 3β-hydroxy-4β-methyl-5β-cholestan-6-one (VIII, 100 mg.) in alcohol free Me_2CO (10 ml.) at 5～10°, and stirring was continued for 10 min. at the same temperature. The resulting suspension was poured into H_2O, and the product was extracted with Et_2O. Et_2O layer was washed with 5% Na_2CO_3 and H_2O, and dried (Na_2SO_4). The solvent was evaporated, and the residue was recrystallized from MeOH-Me_2CO to give 4β-methyl-5β-cholestane-3,6-dione (XXIV, 80 mg.), m.p. 191～192°. Further recrystallization from the same solvent afforded an analytical sample as colorless needles. m.p. 191～192°, $[\alpha]_D^{23}$ −91° (c=0.54). IR : $\nu_{max}^{CS_2}$ 1710 cm^{-1} (C=O). *Anal.* Calcd. for $C_{28}H_{46}O_2$: C, 81.10; H, 11.18. Found : C, 81.25; H, 11.30.

4α-Methyl-5α-cholestane-3,6-dione (XXV). a) From 4β-Methyl-5α-cholestane-3,6-dione (XXIII)——A solution of XXIII (100 mg.) in AcOH (10 ml.) containing 3 drops of H_2SO_4 was heated on steam bath for 1 hr., and poured into H_2O. The product was extracted with Et_2O, and Et_2O layer was washed with 5% Na_2CO_3 and H_2O, and dried (Na_2SO_4). After evaporation of the solvent, the residue was recrystallized from MeOH-Me_2CO to give 4α-methyl-5α-cholestane-3,6-dione (XXV, 60 mg.), m.p. 120～124°. Further recrystallization from the same solvent afforded an analytical sample as colorless needles. m.p. 121.5～124°, $[\alpha]_D^{23}$ −21° (c=0.46), IR : $\nu_{max}^{CS_2}$ 1710 cm^{-1} (C=O). *Anal.* Calcd. for $C_{28}H_{46}O_2$: C, 81.10; H, 11.18. Found : C, 81.28; H, 11.23.

b) From 4β-Methyl-5β-cholestane-3,6-dione (XXIV)——XXIV (34 mg.) was treated as the same manner described above, and the same compound, m.p. 121～124° was obtained as colorless needles.

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Summary

The Grignard reaction of 3β-hydroxycholest-4-en-6-one (V) was undertaken in the presence of cuprous chloride or cupric acetate. 1,4-Addition product was isolated, and its structure was proved to be 3β-hydroxy-4β-methyl-5α-cholestan-6-one (VI). Some transformations related to this compound were made. From observations of the Grignard reaction and other reactions of α,β-unsaturated steroidal ketones reported in literature, it may be concluded that the configuration of alkyl group newly introduced by 1,4-addition should be axially oriented.

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20) A solution of CrO_3 (26.72 g.) in H_2SO_4 (23 ml.) diluted with H_2O to a volume of 100 ml. was used.