UDC 547.92.02

64. Yukichi Kishida: On the Absolute Configuration of Natural 24-Alkylsterols.*1

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Recently, it was shown[1] that the 24-ethyl group in the stigmasterol series should have α-configuration in the extended Plattner's convention.[2] This conclusion was based on the direct chemical evidence; i.e. (+)-2-ethyl-3-methylbutanal, the ozonolysis product of 3,5-cyclo-6-methoxy-22-stigmastene, was interconverted to a reference compound, (−)-(S)-2,3-dimethylpentane.[3~8],*3

This paper deals with another chemical proof for the α-configuration for 24-ethyl group in the stigmasterol series.

The absolute configuration of monoterpene series has been determined by the excellent work of Freudenberg[4~6] and others.[7,8] (+)-Limonene (I),[9~11] with the absolute configuration as shown by this formula, was catalytically reduced in an autoclave under high-pressure hydrogen by a known method to (+)-*p*-menth-1-ene (II).[9,11~13] (II) was converted to a mixture of *trans*-glycol, (+)-*trans*-*p*-menthane-1,2-diols[9,10](III), according to the method recently reported by Newhall.[9] The identity was made by converting it to (+)-tetrahydrocarvone (IV) whose semicarbazone melted at 190~191°. Oxidation of (III) with periodic acid in 25% pyridine yielded a levorotatory keto-aldehyde, 3-isopropyl-6-oxoheptanal[10,12,13] (V), $[\alpha]_D^{25}$ −5.93° (77.8%), which on further oxidation with permanganate in neutral medium gave the corresponding keto-acid, (+)-3-isopropyl-6-oxoheptanoic acid (VI),[11,13,14] $[\alpha]_D^{25}$ +2.14° (59.2%). Application of Lemieux reagent[15] for direct oxidation of (III) also gave the keto-acid (VI) in 68.5% yield. (VI) was identified with an authentic sample*4 as its semicarbazone, m.p. 159~160°, by infrared and mixed melting point. Oxidation of the keto-aldehyde (V) either with silver oxide in dilute alkaline medium or with chromium trioxide in dil. acetic acid yielded a neutral product (VII), $b.p_{12}$

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*1 This constitutes Part XIX of a series entitled "Steroid Studies" by K. Tsuda. Part XVIII. E. Oki: This Bulletin, 8, 229 (1960).

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*3 The specific notation of absolute configuration, which was proposed by Cahn, Ingold, and Prelog, was used in this paper (cf: R. S. Cahn, C. K. Ingold, V. Prelog: Experientia, **12**, 81(1956)).

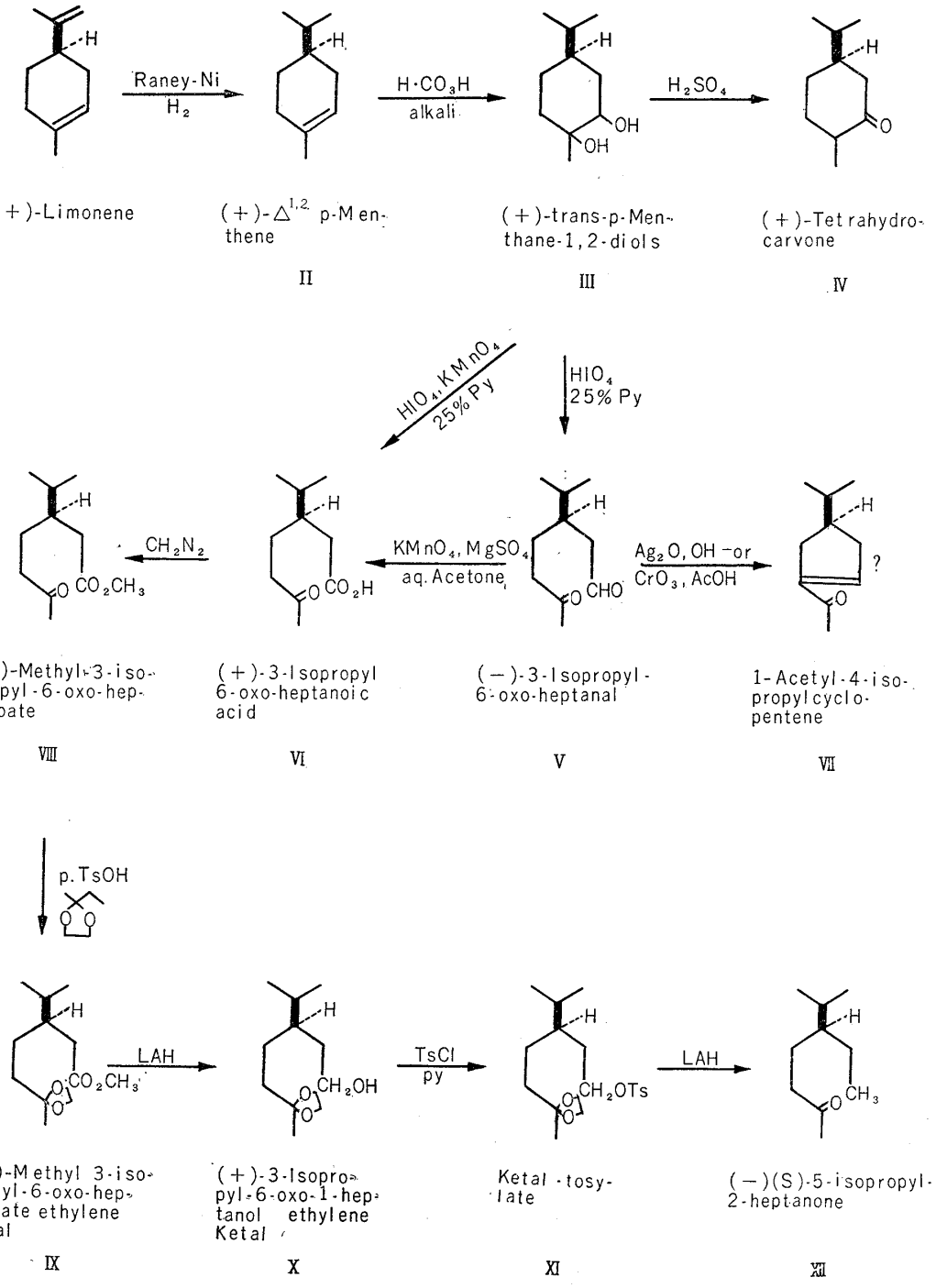
*4 The sample was kindly supplied by Mr. Y. Hanada, Camphor Research Department, The Central Research Institute, Japan Monopoly Corporation, Tokyo, for which a grateful acknowledgement is expressed.

1) K. Tsuda, Y. Kishida, R. Hayatsu: Abstracts of the 3rd Symposium on Natural Organic Compounds, Tokyo, October 17~18, 1959; Chem. & Ind. (London), **1959**, 1411; succeeding paper is to be published in J. Am. Chem. Soc., **82**, (1960).
2) Pl. A. Plattner: Helv. Chim. Acta, **34**, 1693(1951). Plattner convention originally defined the asymmetry at C-20, but it was later extended to other positions in the steroid side-chain as cited by Fieser (L.F. Fieser, M. Fieser: "Steroids," 350(1959), Reinhold Publ. Corp., New York.).
3) P. A. Levene, R. E. Marker: J. Biol. Chem., **111**, 299(1935).
4) K. Freudenberg, W. Lwowski: Ann., **587**, 213(1954).
5) K. Freudenberg, W. Lwowski, W. Hohmann: *Ibid.*, **594**, 76(1955).
6) K. Freudenberg, W. Hohmann: *Ibid.*, **584**, 54(1953).
7) P. A. Levene, R. E. Marker: J. Biol. Chem., **91**, 77, 405(1931).
8) A. Fredga, J. K. Miettinen: Acta Chem. Scand., **1**, 371(1947).
9) W. F. Newhall: J. Org. Chem., **23**, 1274(1958).
10) H. Meerwein: J. prakt. Chem., [II], **113**, 9(1926).
11) H. A. Smith, J. F. Fuzek, H. A. Meriwether: J. Am. Chem. Soc., **71**, 3769(1949).
12) S. Kataoka, Y. Hanada: Bull. Agr. Chem. Soc. Japan, **20**, suppl. 223, 236(1956).
13) J. Braun, G. Werner: Ber., **62**, 1050(1929).
14) R. U. Lemieux, E. Rudolf: Can. J. Chem., **33**, 1701, 1710, 1714(1955).
15) O. Wallach: Ann., **392**, 69(1912); cf. A. Angeli, E. Rimini: Gazz. chim. ital., **26**, 40, 318(1890).

91~92.5°, whose infrared and ultraviolet spectra indicated the presence of a conjugated keto-ene system.

Although the precise assignment for the structure has not been attempted, it seems to be an isomer of isocamphor[15] or pinolone,[16,17] 1-acetyl-4-isopropylcyclopentene, from the course of reaction.

(VI) was converted to the corresponding keto-ester, methyl (+)-3-isopropyl-6-oxohep-



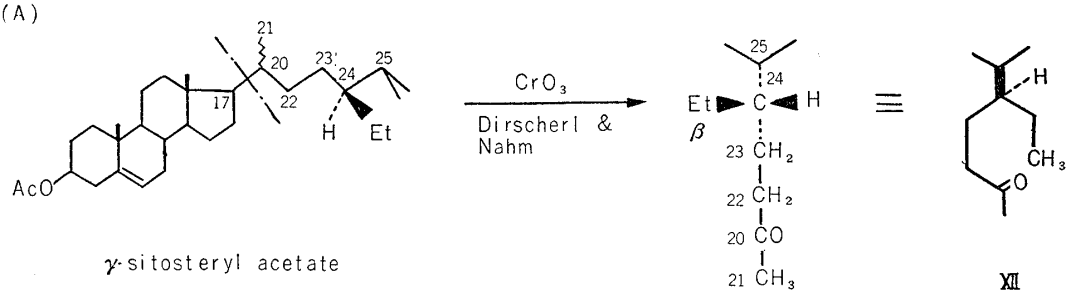
*5 To avoid side reaction of diazomethane to a carbonyl compound, Schlotterbecker reaction, this reaction was conducted with one molar equivalent of diazomethane in a shorter time at 0° to 5°.

16) O. Wallach: Ann., **384**, 193(1911).

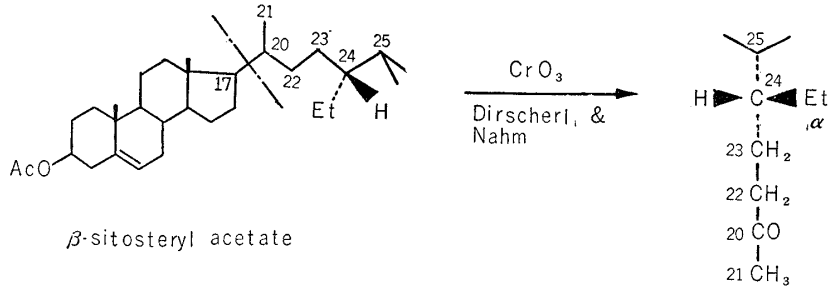
17) H. Schmidt: Ber., **80**, 533(1947).

tanoate (VIII), $[\alpha]_D^{25}$ +2.04°, with one mole of diazomethane*5 in nearly quantitative yield. Ketalation of (VIII) in boiling 2-ethyl-2-methyl-1,3-dioxolane[18] in the presence of *p*-toluenesulfonic acid gave a dextrorotatory ketal ester, methyl 3-isopropyl-6-oxoheptanoate ethyleneketal (IX), $[\alpha]_D^{25}$ +4.56°, in a good yield. The latter was reduced with lithium aluminum hydride to a ketal-alcohol, (+)-3-isopropyl-6-oxo-1-heptanol ethyleneketal (X), $[\alpha]_D^{25}$ +5.71°, in 76.5% yield. Careful treatment of (X) with *p*-toluenesulfonyl chloride in pyridine at room temperature afforded its tosylate (XI), λ_{max}^{EtOH} 224 mμ (ε 11,100), which on further purification gave a sample with λ_{max}^{EtOH} 224 mμ (ε 13,450)*6 in 62.9% yield. The

(A)



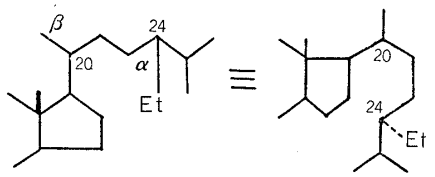
γ-sitosteryl acetate



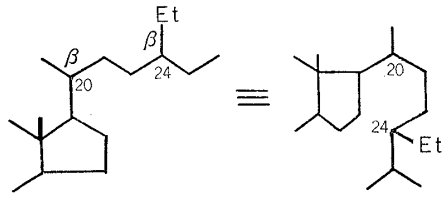
β-sitosteryl acetate

(B)

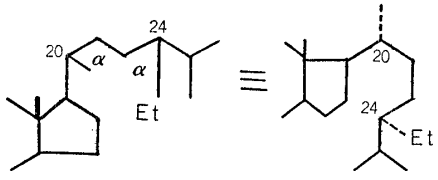
20β(normal)−24α(stigmastanol)



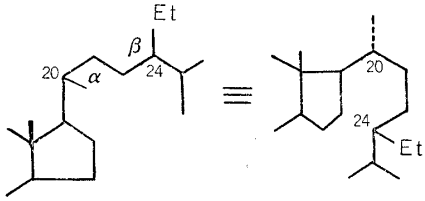
20β(normal)−24β(clionasterol)



20α(iso)−24α(unknown)



20α(iso)−24β(palysterol ?)



*6 The ε values of other pure tosylates at their main λ_{max} (224 mμ) are 12,000~13,000 (for example, 3,5-cyclo-6-methoxy-22-tosyloxybisnorcholane has $\varepsilon_{244.5\ m\mu}$ 12,6000). This sample seems to be pure, although the crystallization of it has not been successful.

18) H. J. Dauben, Jr., B. Loeken, H. J. Ringold : J. Am. Chem. Soc., 76, 1359(1954).

purified tosylate was finally reduced with lithium aluminum hydride and successive treatment with hydrochloric acid gave a levorotatory ketone, (−)-5-isopropyl-2-heptanone (XII), b.p_{70} 125°, $[\alpha]_D^{25}$ −2.92°, which on distillation were highly vesicatory. Its semicarbazone and 2,4-dinitrophenylhydrazone melted at 148.5° and 76.5°, respectively, almost agreeing with the reported values.[19,21] The infrared spectra of the levorotatory ketone showed the carbonyl bands*7 at 1723 and 1166 cm^{-1}, and the isopropyl bands[22] at 1390 and 1370 cm^{-1}.

Thus, the unequivocal interconversion certifies the absolute configuration of (XII), (−)-(S)-5-isopropyl-2-heptanone, as is formulated in (A), corresponding to the β-configuration in the steroidal side chain at C-24 when the latter is expressed in the Plattner's convention.[2] In 1943, Dirscherl and Nahm[19] obtained a dextrorotatory isomer of (XII), (+)-5-isopropyl-2-heptanone (XII′), directly from β-sitosteryl acetate (22,23-dihydrostigmasteryl acetate) by chromium trioxide oxidation, while they also obtained a levorotatory isomer of the ketone from γ-sitosteryl acetate (an epimer of β-sitosterol at C-24). Therefore, the 24-ethyl group of the stigmasterol series must have α-configuration in the Plattner's convention.[2] This series of interconversion is thus a further proof of the earlier conclusion[1] which contradicts the deduction of Bergmann and others.[23~26]

Accordingly, the older representation of C_{29} natural sterols must be entirely reversed in regard to configurations at C-24 as is formulated in (B).*8

Experimental*9

All boiling points and melting points are uncorrected. Optical rotations of liquid substances were measured in a semimicro-tube (5 cm.) at 25°, without a solvent unless otherwise stated. The values thus obtained are directly comparable for Marker's rule and are highly reliable especially in regard to the direction of optical rotation. All solvents used were purified to avoid ambiguity of the results, for instance, "pure dry ether" means the ether that was freshly redistilled over $LiAlH_4$ after usual processing for purification and drying over sodium. Evaporation of a solvent and distillation of liquid product were performed in nitrogen atmosphere.

(+)-Limonene(I)[9~11]—Commercial (+)-limonene*10 was repeatedly distilled through packed column over NaOH in N_2. Pale yellow liquid, b.p. 175~176°, $[\alpha]_D^{25}$ + 117°; $[\alpha]_D^{25}$ + 117.8° (c=1.8611, $CHCl_3$), n_D^{20} 1.4710, d_4^{25} 0.840. IR $\nu_{max}^{liq.}$ cm^{-1} : 1680, 1650, 886, 798 ($\Delta^{1,2}$ and $\Delta^{8,9}$).

1,2-*p*-Menthene[11,12]**(II)**—A mixture of 136.2 g. of (+)-limonene(I) and 13 g. of Raney Ni was shaken in a 500-cc. autoclave under high-pressure of H_2. During 4 hr. 1 mole of H_2 was absorped and distillation of the product, after removal of the catalyst, gave 130 g. of *p*-menth-1-ene, b.p. 174.8~176.1°, $[\alpha]_D^{25}$ +77.8° to +86.4°, d_4^{25} 0.81514, n_D^{26} 1.4530~1.4544. IR $\nu_{max}^{liq.}$ cm^{-1} : 1680, 798 ($\Delta^{1,2}$), and 1390, 1370 (isopropyl).

***trans*-*p*-Menthane-1,2-diol (III)**[9]—A solution of 200 cc. of 98~100% HCOOH and 75.2 g. of 35% H_2O_2 was added dropwise under stirring to 120 cc. of *p*-menth-1-ene (II) over 1 hr. at 35°. Stirring was further continued for 2 hr. at the same temperature. The excess peroxide was decomposed with

*7 The locations of these bands agree with those of Nos. 304 (2-heptanone) and 5312 (methyl isopropyl ketone) listed in The Sadtler Standard Spectra (1958).

*8 In (B), two kinds of representations, one of which has newly been proposed by Fieser and Fieser (see Footnote 2), are used.

*9 The author is indebted to Mr. T. Onoe, Miss C. Furukawa, and Miss H. Otsuka for microanalysis. Thanks are also due to Messrs. O. Amakasu and H. Higuchi for the measurement of infrared spectra.

*10 The product of Matheson Coleman & Bell Division, The Matheson Co., Inc., U.S.A., was used and the quality of the product was guaranteed.

19) W. Dirscherl, H. Nahm : Ann., **555**, 57(1443).
20) *Idem* : Ber., **76B**, 635(1943).
21) *Idem* : Ann., **558**, 231(1947).
22) K. Suga, S. Watanabe : Nippon Kagaku Zasshi, **80**, 286(1959).
23) W. Bergmann, E. M. Low : J. Org. Chem., **12**, 67(1947).
24) W. M. Stokes, W. Bergmann : *Ibid.*, **16**, 1817(1951); *ibid.*, **17**, 1194(1952).
25) W. Klyne, W. M. Stokes : J. Chem., Soc., **1954**, 1987.
26) L. F. Fieser, M. Fieser : "Steroids," 350(1959), Reinhold Publ. Corp., New York.

5 g. of Na_2SO_3 and most of HCOOH was distilled off under diminished pressure below 50°. The residue to which 100 cc. of 95% EtOH was added, was made alkaline (pH 11~12) by addition of EtOH-KOH and stirred for 3 hr. to hydrolyse the monoformate. The reaction mixture was rendered acid (pH 6) with conc. HCl and EtOH was evaporated at 50° *in vacuo*. The residue was extracted with ether and the solvent was evaporated. Fractional distillation gave *trans*-glycols as a fraction of highly viscous liquid, $b.p_3$ 112~116°, which on redistillation gave a fraction of $b.p_2$ 100~105°, $[\alpha]_D^{25}$ +23.4°(c=9.00, acetone). This partly solidified and the hydrous crystals obtained from the mixture of *trans*-glycols gave a sample of anhydrous crystals of m.p. 89° after recrystallization from CCl_4 as reported before.[10]

For the next reaction the mixture of *trans*-glycols was directly used. The proof of the mixture was made by converting them to tetrahydrocarvone.

(+)-Tetrahydrocarvone (IV)[9,10]—A mixture of 5 g. of *trans*-glycols (III) and 50 cc. of 10% H_2SO_4 was refluxed for 2 hr. and the mixture was steam-distilled to give 3.1 g. of pale yellow liquid which was directly converted to its semicarbazone (2.3 g. of semicarbazide·HCl, 2.76 g. of crystalline AcONa, and EtOH containing 6.9 cc. of water). Three recrystallizations from EtOH gave white needles of m.p. 190~191°, $[\alpha]_D^{26}$ +11.06°(c=1.917, $CHCl_3$). *Anal.* Calcd. for $C_{11}H_{21}ON_3$: C, 62.52; H, 10.02; N, 19.89. Found: C, 62.63; H, 9.76; N, 19.71.

(−)-3-Isopropyl-6-oxoheptanal[10,12,13] **(Keto-aldehyde) (V)**—A solution of 19.4 g. of $HIO_4 \cdot 2H_2O$ in 60 cc. of water was added dropwise to a stirred solution of 12 g. of the glycols in 120 cc. of pyridine and 300 cc. of water during 1 hr. at 1~2°. Stirring was continued for 6 hr. so as to bring the final temperature to 26° and pH of the reaction mixture at the final stage was 6. The mixture was extracted 3 times with $CHCl_3$, the extract was made acid, washed with saturated NaCl solution, and dried over Na_2SO_4. After evaporation of the solvent, the extract was distilled in N_2 to give keto-aldehyde as a pale yellow liquid, $b.p_{3.5}$ 97~99°. Redistillation gave 9.44 g. (77.8%) of pure sample, $b.p_4$ 97~99°, $[\alpha]_D^{25}$−5.93°, d_4^{25} 0.93955, $n_D^{26.5}$ 1.4477. IR $\nu_{max}^{liq.}$ cm^{-1}: 2720, 1715~1730, 1164 (H>C=O, >C=O) and 1390, 1370 (isopropyl). *Anal.* Calcd. for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.74; H, 10.68.

(+)-3-Isopropyl-6-oxoheptanoic Acid[10,12,13] **(Keto-acid) (VI)**—i) From Keto-aldehyde (V): To a stirred suspension of 41.92 g. of the keto-aldehyde (V) and 13.7 g. of anhyd. Mg_2SO_4 in 300 cc. of pure acetone (freshly distilled over $KMnO_4$ before use) and 500 cc. of water, 35.6 g. of powdered $KMnO_4$ was added in small portions during 45 min. at 2~3°. After addition of $KMnO_4$, the mixture was further stirred for 2 hr. to room temperature (20°). The reaction mixture (pH 7.0) was made alkaline with KOH and steam-distilled to remove the unreacted keto-aldehyde and the solvent. MnO_2 was filtered off and it was washed with hot H_2O until the washing became colorless. The filtrate and the washings were combined, then made acid with conc. HCl, and extracted 3 times with ether. The extract was washed 3 times with H_2O and distilled in N_2 to give 32.32 g. (70%) of a yellow liquid of $b.p_4$ 140~148°. Redistillation in N_2 atmosphere gave 27.15 g. (59.2% from the keto-aldehyde) of pure keto-acid (VI) as a pale yellow liquid, $b.p_4$ 147~149°, $[\alpha]_D^{25}$ +2.14°, d_4^{25} 1.0168, n_D^{27} 1.4530. IR $\nu_{max}^{liq.}$ cm^{-1}: 3000~3300, 1710, 1277, 1163 (>C=O, $-CO_2H$) and 1390, 1370 (isopropyl). *Anal.* Calcd. for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.60; H, 9.93.

Semicarbazone: To a solution of 325 mg. of semicarbazide hydrochloride and 390 mg. of $AcONa \cdot 3H_2O$ in ca. 10 cc. of 80% EtOH 0.5 g. of keto-acid was added and the mixture was warmed for 30 min. After standing overnight, white needles of the semicarbazone precipitated. This was recrystallized 3 times from MeOH, m.p. 159~160°. There was observed no depression of the melting point when it was mixed with an authentic sample kindly supplied by Mr. Hanada.*4 *Anal.* Calcd. for $C_{11}H_{21}O_3N_3$: C, 54.30; H, 8.70; N, 17.27. Found: C, 54.45; H, 8.65; N, 16.98.

ii) From *trans*-Glycols (III): To a cooled solution of 41.13 g. of glycols in 400 cc. of pyridine and 267 cc. of water was added dropwise a mixed solution of 90.7 g. of $HIO_4 \cdot 2H_2O$ in 267 cc. of H_2O and 12.8 g. of $KMnO_4$ powder in 267 cc. of H_2O. During the addition the temperature was kept below 5° with efficient stirring and cooling. The mixture was further stirred for 5 hr. up to room temperature, made alkaline with NaOH, and extracted with ether or steam-distilled. The cooled alkaline mixture was made acid and extracted 3 times with ether (filtration of the MnO_2 prior to the extraction was desirable to carry out the work smoothly).

The extract was washed 3 times with saturated NaCl solution, dried over Na_2SO_4, and evaporated to dryness. The residue was distilled twice to give 30.5 g. (68.5%) of the keto-acid as a pale yellow liquid, $b.p_4$ 149°.

Semicarbazone: m.p. 159~160°. *Anal.* Calcd. for $C_{11}H_{21}O_3N_3$: C, 54.30; H, 8.70; N, 17.27. Found: C, 54.57; H, 8.92; N, 17.34. This was identified with the semicarbazone prepared from the keto-aldehyde (V) by mixed m.p. and infrared spectra.

1-Acetyl-4-isopropylcyclopentene (?) (VII)—i) Ag_2O was freshly prepared from 18.9 g. of $AgNO_3$ and 4.9 g. of NaOH in water. After washing the oxide with water, it was mixed with 4 g. of NaOH

in 100 cc. of water with stirring. To this suspension was added a solution of 9.4 g. of the keto-aldehyde in 30 cc. of EtOH and black Ag_2 deposited within 10 min. The solution was extracted 3 times with benzene and the extract, after usual processing, gave 4.05 g. of neutral liquid of $b.p_{12}$ 91～92.5°. UV λ_{max}^{EtOH} : 238 mμ (ε 9,680). IR $\nu_{max}^{liq.}$ cm^{-1} : 1671. 1621, 1239. Semicarbazone : m.p. 214～215°. The identity of this semicarbazone with that obtained by the procedure described in (ii) was made by mixed m.p. and infrared spectra. *Anal.* Calcd. for $C_{11}H_{19}ON_3$: C, 63.12; H, 9.15; N, 20.08. Found : C, 63.09; H, 9.16; N, 20.05. The alkaline aqueous layer was again acidified and extracted with benzene as usual. This extract did not give a sufficient amount of acid substance.

ii) To a stirred solution of 7.2 g. of the keto-aldehyde in 100 cc. of 50% AcOH a solution of 3.06 g. of CrO_3 in 20 cc. of 50% AcOH was added under cooling. Stirring was continued for additional 2 hr. at room temperature. The mixture was diluted with a large volume of H_2O and extracted with Et_2O. The extract was washed with dil. KOH, the alkaline solution was acidified, and again extracted with ether. Acid substance weighed 3.67 g. and the neutral part weighed 3.98 g. The latter after two distillations gave 1.57 g. of a colorless liquid, $b.p_{14}$ 96～100°. This neutral liquid solidified on standing in a refrigerator for a long time. UV λ_{max}^{EtOH} 238 mμ (ε 9,250). IR $\nu_{max}^{liq.}$ cm^{-1} : 1671, 1621, 1239.
Semicarbazone : m.p. 214～215°. *Anal.* Calcd. for $C_{11}H_{19}ON_3$ C, 63.12; H, 9.15; N, 20.08. Found : C, 63.12; H, 9.21; N, 20.11.

Methyl (+)-3-Isopropyl-6-oxoheptanoate (Keto-ester) (VIII)—A solution of 51.7 g. of *p*-tolylsulfonylmethylnitrosoamide in 450 cc. of Et_2O was added dropwise to a stirred solution containing 14.4 g. of KOH, 84.2 cc. of carbitol, and 24-cc. portion of Et_2O and H_2O over 45 min. at 65°. In two traps, cooled in dry ice-acetone, was collected the generated CH_2N_2 as an ethereal solution. This solution was added to a solution of 32 g. of the keto-acid (VI), $[\alpha]_D$ +2.14°, in ca. 50 cc. of ether at 0° to 5°, and then left to stand for 1 hr. at 5°. After decomposition of the excess CH_2N_2 with a small amount of AcOH and successive elimination of AcOH by washing with 2% Na_2CO_3 and H_2O, the ether was distilled off, and the residue was distilled to give 32.82 g. (95.5%) of the ester, $b.p_{12}$ 127～135°. Redistillation of it afforded 29.91 g. (84.7%) of pure colorless liquid of $b.p_{13}$ 129～131°, $[\alpha]_D^{25}$ +2.04°, d_4^{25} 0.97262, n_D^{25} 1.4422, IR $\nu_{max}^{liq.}$ cm^{-1} : 1740, 1725, 1390, 1371. The infrared spectrum was entirely identical with that of the keto-ester prepared via glycol → keto-acid → keto-ester. *Anal.* Calcd. for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found : C, 65.87; H, 10.04.
Semicarbazone : m.p. 110.5～111.5°. *Anal.* Calcd. for $C_{12}H_{23}O_3N_3$: C, 56.01; H, 9.01; N, 16.33. Found: C, 56.15; H, 8.95; N, 16.58.

Methyl (+)-3-Isopropyl-6-oxoheptanoate Ethyleneketal (Ketal-ester) (IX)—A solution of 29.33 g. of the keto-ester (VIII), $[\alpha]_D$ +2.04°, and 900 cc. of 2-ethyl-2-methyl-1,3-dioxolane containing 606 mg. of *p*-toluenesulfonic acid monohydrate was refluxed for 3 hr. Then 410 cc. of an azeotropic mixture of 1,3-dioxolane and butanone was distilled off slowly through Vigrougx column during 9 hr. When cool, the mixture was washed with dil. $NaHCO_3$ and saturated NaCl solution 3 times. Aqueous layer was reëxtracted with ether and the extract was washed as usual. The combined organic parts were distilled, after the solvents had been removed through Vigrougx column, to give 34.68 g. (84.5%) of colorless liquid of the ketal-ester, $b.p_{11}$ 141～144°, $[\alpha]_D^{25}$ +4.56°, d_4^{25} 1.0103, $n_D^{25.5}$ 1.4474. IR $\nu_{max}^{liq.}$ cm^{-1} : 1743 (ester), 1390, 1370 (isopropyl), 1060, 1047, 947, 858 (ketal). *Anal.* Calcd. for $C_{13}H_{24}O_4$: C, 63.90; H, 9,90. Found : C, 63.85; H, 9.72.

(+)-3-Isopropyl-6-oxo-1-heptanol Ethyleneketal (Ketal-alcohol) (X)—To a suspension of 1.22 g. of $LiAlH_4$ in 200 cc. of pure dry ether a solution of 10 g. of the ketal-ester (IX), $[\alpha]_D$ +4.52°, in 50 cc. of pure dry ether was added dropwise, under cooling with ice and vigorous stirring. Stirring was continued for 2 hr. at room temperature, the excess hydride was decomposed with saturated solution of NH_4Cl and then with H_2O under cooling. The separated aqueous layer was reëxtracted 3 times with pure Et_2O, the combined whole ethereal solution was washed 5 times with saturated NaCl solution, and dried over Na_2SO_4. Et_2O was evaporated through a short column and the residual liquid was distilled *in vacuo* to give 6.76 g. (76.5%) of the ketal-alcohol as colorless and slightly viscous liquid, $b.p_{1.8}$ 122.5～124°, $[\alpha]_D^{25}$ +5.71°, d_4^{25} 0.9865, n_D^{24} 1.4601, IR $\nu_{max}^{liq.}$ cm^{-1} : 3370, 1090, 1055, 947, 858 (OH, ketal). *Anal.* Calcd. for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18. Found : C, 66.60; H, 11.19.

3-Isopropyl-6-oxo-1-heptanol Ethyleneketal *p*-Toluenesulfonate (Ketal-tosylate) (XI)—To a stirred solution of 13.0 g. of the ketal-alcohol (X), $[\alpha]_D$ +5.71°, in 40 cc. of pure dry pyridine, a solution of 12.60 g. of *p*-toluenesulfonyl chloride (m.p. 69°) in 85 cc. of pure dry pyridine was added under cooling. The mixture was stirred for 2 hr. and then kept overnight at room temperature. Water was added, stirred for 3 hr. at 15°, and the mixture was extracted 3 times with benzene. The extract was washed successively twice with water, 3 times with dil. $NaHCO_3$, and 3 times with H_2O. The solvent including pyridine was evaporated below 40° under diminished pressure. The residual slightly colored oil of crude ketal-alcohol tosylate, λ_{max}^{EtOH} 224 mμ (ε 11,100), weighed 16.03 g. (72.1%). The values at the main maximum of several runs of the same experiment were within a range of 9,120～11,100 and the yields were within 61～72.1%. To this crude ketal-tosylate, petr. ether (b.p. 40～60°) was added,

the mixture was digested at 40°, and rapidly cooled in a dry ice-acetone bath. The solidified ketal-tosylate was obtained by either centrifugal separation or careful decantation. Repeated purification to remove a trace of pyridine gave 13.99 g. (62.9%) of pure sample of ketal-tosylate. UV λ_{max}^{EtOH} : 224 mμ (ε 13,450). IR $\nu_{max}^{liq.}$ cm^{-1} : 1369, 1190, 1175 (tosyl), 1065, 1045, 948, 860 (ketal).

The sample deposited colorless crystals partly on longer standing in a refrigerator, but neither their recrystallization nor crystallization of the whole liquid was successful.

(−)-5-Isopropyl-2-heptanone (XII)—i) To a stirred suspension of 2.5 g. of $LiAlH_4$ in 250 cc. of pure dry ether a solution of 4.85 g. of the ketal-tosylate (XI), UV λ_{max}^{EtOH} 224 mμ (ε 9,120), in 300 cc. of pure dry ether was added under cooling. The mixture was stirred for 16 hr. and then kept overnight at room temperature. The excess hydride was decomposed with water, made acid with dil. HCl and the aqueous layer was reëxtracted 3 times with ether. The combined ether solution was washed with water, 7% KOH, and H_2O until neutral, and dried over Na_2SO_4. The ether was distilled off through a short column below 45° and the residual oil was distilled under reduced pressure to give 1.2 g. (59.4%) of a faint yellow crude ketone, $b.p_{67}$ 116～130°. Since this crude sample contained a small amount of impurities consisting of secondary alcoholic material and ketal compound from infrared, it was further purified as described below.

To a solution of 1.2 g. of the crude ketone in 30 cc. of 80% AcOH, 1.4 g. of CrO_3 was added. The mixture was kept 2 hr. at room temperature (15°), treated with EtOH to decompose the excess oxidant, diluted with water, and extracted 3 times with Et_2O. The extract was washed as usual and dried over Na_2SO_4. After the solvent was evaporated, the residue was transferred into a four-stage Kügel-flask and distilled repeatedly to give 372.2 mg. of pure ketone as faint yellow liquid, $b.p_{70}$ 135° (bath temp.). $[\alpha]_D^{26}$ −5.57 (α_D^{26} −0.207°; c=3.715, Et_2O). The infrared spectrum of this sample did not exhibit any absorption bands due to impurities and was entirely identical with that of the pure ketone (described below).

Semicarbazone : Prepared from EtOH solution of this sample, 292 mg. of semicarbazide·HCl, and 359 mg. of $AcONa \cdot 3H_2O$. The sample of m.p. 142～144° was recrystallized repeatedly from 50% EtOH and then 4 times from benzene-petr. ether (b.p. 40～60°) to give a sample of m.p. 148°. The latter sample was identical in m.p. and infrared spectrum with the corresponding sample obtained by the method of (ii). *Anal.* Calcd. for $C_{11}H_{23}ON_3$: C, 61.93; H, 10.87; N, 19.70. Found : C, 61.99; H, 10.87; N, 19.47.

ii) To a stirred suspension of 7.22 g. of $LiAlH_4$ in 750 cc. of pure dry ether was added dropwise a solution of 13.99 g. of the pure ketal-tosylate ($\varepsilon_{224m\mu}^{EtOH}$ 13,450) under cooling with ice. The mixture was stirred for additional 16.5 hr. at 20° and then left to stand for 28 hr. at 10～15°. The excess hydride was decomposed with H_2O and the acidified mixture was further stirred for additional 3 hr. The aqueous layer was reëxtracted 3 times with ether and the whole ethereal solution was worked up as described in (i) to afford 4.16 g. (71.9%) of pale yellow-colored, crude ketone, $b.p_{69}$ 125° (bath temp., 150～170°). Since this ketone had highly frothy and vesicatory nature on distillation *in vacuo*, it was further purified by repeated fractional distillation in a 50-cc. flask with packed column. Three redistillations gave 1.02 g. of a forerun of $b.p_{70}$ 122～125° and 2.89 g. of pure ketone, $b.p_{70}$ 125°, $[\alpha]_D^{25}$ −2.92°; $[\alpha]_D^{27}$ −4.40°(α_D^{27} −0.274°, c=6.785, Et_2O). n_D^{25} 1.4308, d_4^{25} 0.8308. IR $\nu_{max}^{liq.}$ cm^{-1} : 1723, 1166 (>C=O), 1390, 1370 (isopropyl), 955. *Anal.* Calcd. for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found : C, 76.77; H, 12.89.

Semicarbazone : Prepared as described in (i). The colorless needles which precipitated directly from the reaction mixture melted at 148.5° and three recrystallizations from MeOH did not raise the m.p. Seven more recrystallizations from benzene-petr. ether (b.p. 40～60°) also did not raise the m.p. $[\alpha]_D^{25}$ −0.64°; α_D^{25} −0.019°(10-cm. tube, c=2.965, $CHCl_3$). *Anal.* Calcd. for $C_{11}H_{23}ON_3$: C, 61.93; H, 10.87; N, 19.70. Found : C, 61.91; H, 10.73; N, 19.61.

2,4-Dinitrophenylhydrazone : Prepared as usual and the first crop of the sample, yellow microneedles, melted at 75～76°. It was recrystallized 3 times from MeOH to give a sample of m.p. 76.5°, $[\alpha]_D^{28.5}$ +4.3°; $\alpha_D^{28.5}$ +0.028°(c=0.65, MeOH). *Anal.* Calcd. for $C_{16}H_{24}O_4N_4$: C, 57.13; H, 7.19; N, 16.66. Found : C, 57.19; H, 7.16; N. 16.48.

The reported constants (for the ketone obtained from β-sitosterol)[19-21] : $b.p_{16}$ 80～92°, $[\alpha]_D^{26}$ +2.54°; $[\alpha]_D^{26}$ +3.11°(c=3.5, Et_2O); $[\alpha]_D^{16}$ +3.96°(another run); semicarbazone, m.p. 141～142°, $[\alpha]_D^{20}$ +4.5°(c=2.86, $CHCl_3$); 2,4-dinitrophenylhydrazone, m.p. 86～87°.

For the ketone obtained from γ-sitosterol : $b.p_{12}$ 40～62°, $[\alpha]_D^{21}$ −2.4°(c=10.0, Et_2O); semicarbazone, m.p. 140～142°; m.p. 142～143°, $[\alpha]_D^{25.5}$ −1.8°(c=2.5, $CHCl_3$).

For the racemic ketone prepared by synthesis : $b.p_{14}$ 84～86°; semicarbazone, m.p. 141～143°; 2,4-dinitrophenylhydrazone, m.p. 75～76° or m.p. 77～78°.

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Summary

(+)-Limonene (I) was converted to (+)-*trans*-*p*-menthane-1,2-diol (III) via dihydrolimonene (II) by known methods. (III) was converted to (+)-3-isopropyl-6-oxoheptanoic acid (VI), either by direct oxidation of (III) with Lemieux reagent or by two-step oxidation via keto-aldehyde, 3-isopropyl-6-oxoheptanal (V). (VI) was, in turn, converted to its (+)-ester (VIII), (+)-ketal-alcohol (X), ketal-alcohol tosylate (XI) and finally to a levorotatory ketone, 5-isopropyl-2-heptanone (XII). Since the (−)-ketone (XII) has the same absolute configuration around its asymmetric carbon as (+)-limonene (I), (XII) must be (−)-(S)-5-isopropyl-2-heptanone, corresponding to the 24β-ethyl in the steroid side-chain. The antipode of (XII), (+)-(R)-ketone (XII′), has already been obtained directly from β-sitosterol by Dirscherl and Nahm. Hence the ethyl group of the stigmasterol series must have α-configuration in the extended Plattner's convention proposed by Fieser and Fieser. This result confirmed the recent conclusion which contradicted the deduction of Bergmann and others. The author proposes the revision of the older representation of C_{29}-natural sterols in regard to the C-24 configurations.

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