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Sub Title	
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Publisher	共立薬科大学
Publication year	1981
Jtitle	共立薬科大学研究年報 (The annual report of the Kyoritsu College of Pharmacy). No.26 (1981.) ,p.87- 91
JaLC DOI	
Abstract	
Notes	抄録
Genre	Technical Report
URL	https://koara.lib.keio.ac.jp/xoonips/modules/xoonips/detail.php?koara_id=AN00062898-00000026-0087

Synthesis of Lanosterol Analogs with Modified Side Chains*

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In the course of our investigations in the field of cholesterol biosynthesis, we became interested in preparing lanosterol analogs with modified side chains. We recently reported a synthesis of the deuterated and undeuterated 21- and 22-methyl derivatives of pentanor analogs of dihydrolanosterol and chloesterol, and the relationship between their T_1 values and structures. We now wish to report a synthesis of twelve analogs of lanosterol with different sizes of side chain and 20-iso-24-dihydrolanosterol in order to investigate the effects of lanosterol analogs on cholesterol biosynthesis from lanosterol.

In this investigation, we used commercial lanosteryl acetate (**1b**) as the starting material. First, treatment of **1b** with peracid afforded the 24,25-epoxide (**2**), as described by Boar *et al.*, and **2** was further transformed into the 24-oxo compound (**3**) together with the aldehyde (**4**) by boron trifluoride-etherate treatment. Dehydrogenation of the former compound (**3**) with selenium dioxide afforded the unsaturated ketone (**5**) whose structure was determined to be 22-*trans*-3β-acetoxy-lanosta-8,22-dien-24-one on the basis of its PMR spectrum and also its IR spectrum (α,β-unsaturated ketone band at 1690 cm^{-1}). Oxidation of **5** with potassium permanganate under neutral conditions afforded an aldehyde (**6**) and a carboxylic acid (**7**) in 70% and 13% yields, respectively. Subsequent reduction of **6** with sodium borohydride afforded the corresponding 22-alcohol, which was further transformed to 23,24,25,26,27-pentanorlanost-8-en-3β-ol (**9**) *via* the 22-chloro compound (**8**) as described previously. On treatment with lead tetraacetate in the presence of Cu^{2+}-pyridine, the carboxylic acid (**7**) gave an olefin compound (**10**) in 48% yield, and this was converted to 22,23,24,25,26,27-hexanorlanost-8-en-3β-ol (**11**) by catalytic hydrogenation with 5% palladium on charcoal followed by alkaline hydrolysis. On the other hand, treatment of **10** with sodium periodate and potassium permangnate in the presence of potassium carbonate gave a carboxylic acid (**12**) which, on treatment with ethyl chloroformate and triethylamine in tetrahydrofuran and then reduction of the product with sodium borohydride, was converted to a 20-alcohol. Subsequent treatment of the alcohol, without further purification, with phosphoryl chloride in pyridine gave a chloro compound (**13**), which was converted to 21,22,23,24,25,26,27-heptanorlanost-8-en-3β-ol (**14**) by reductive dehalogenation with lithium aluminum hydride.

The compound with no alkyl side chain was prepared from the carboxylic acid (**12**). On treatment with lead tetraacetate as described above (**7**—**10**), **12** gave a decarboxylated compound (**15**), whose PMR spectrum exhibited a multiplet assigned to C-16 and C-17

* 本報告は Chen. Pharm. Bull., **29**, 356 (1981) に発表。

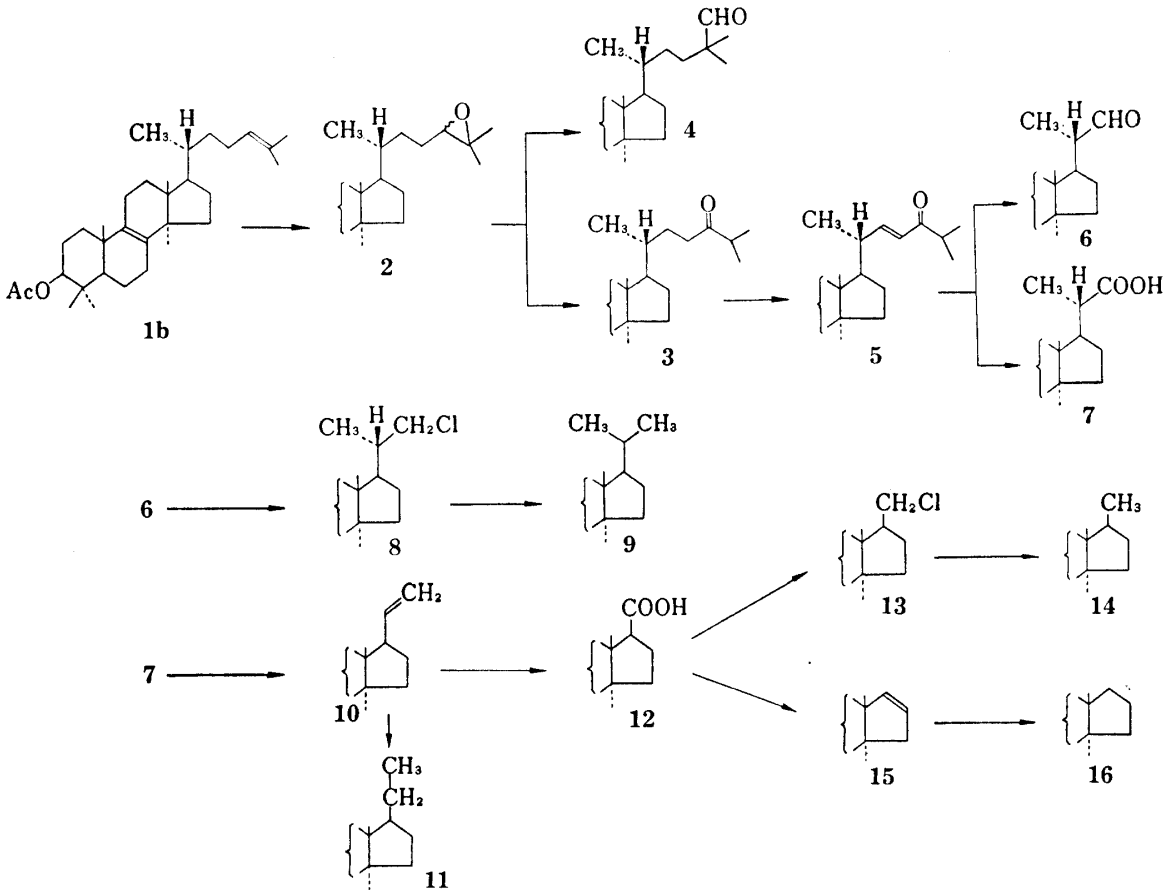


Chart 1

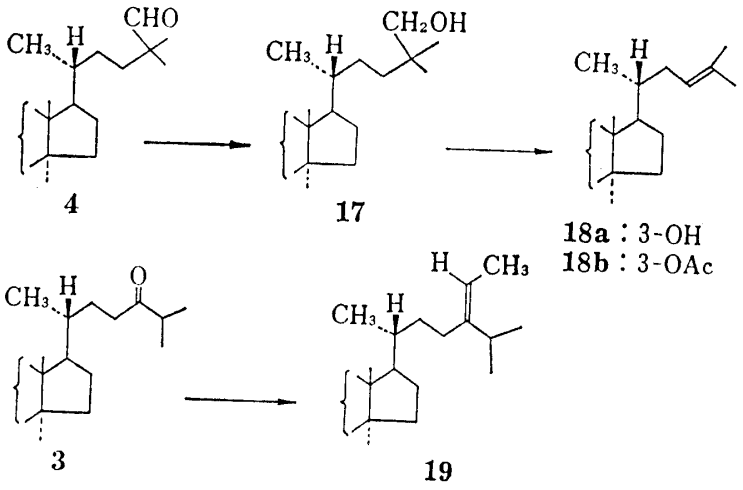


Chart 2

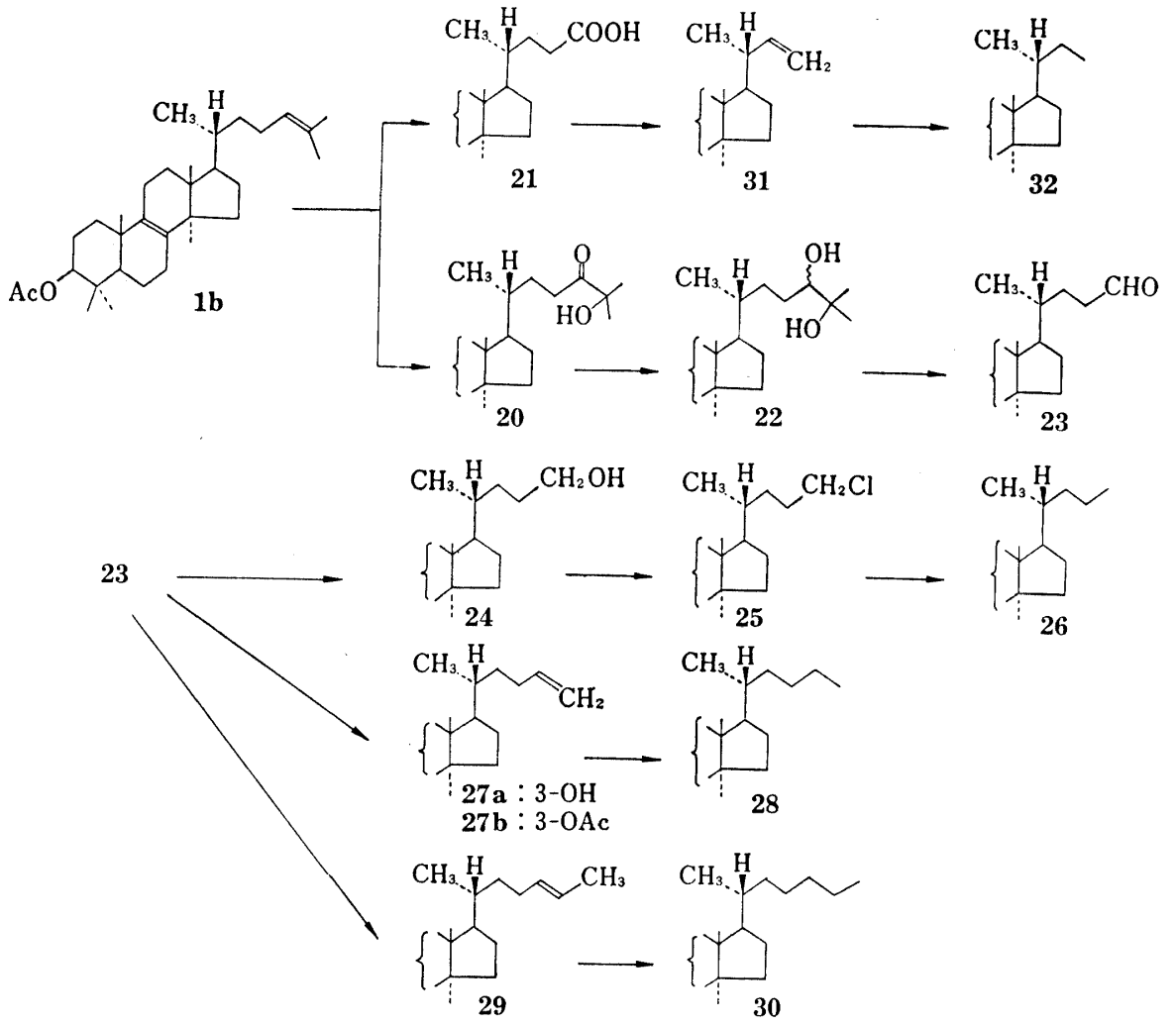


Chart 3

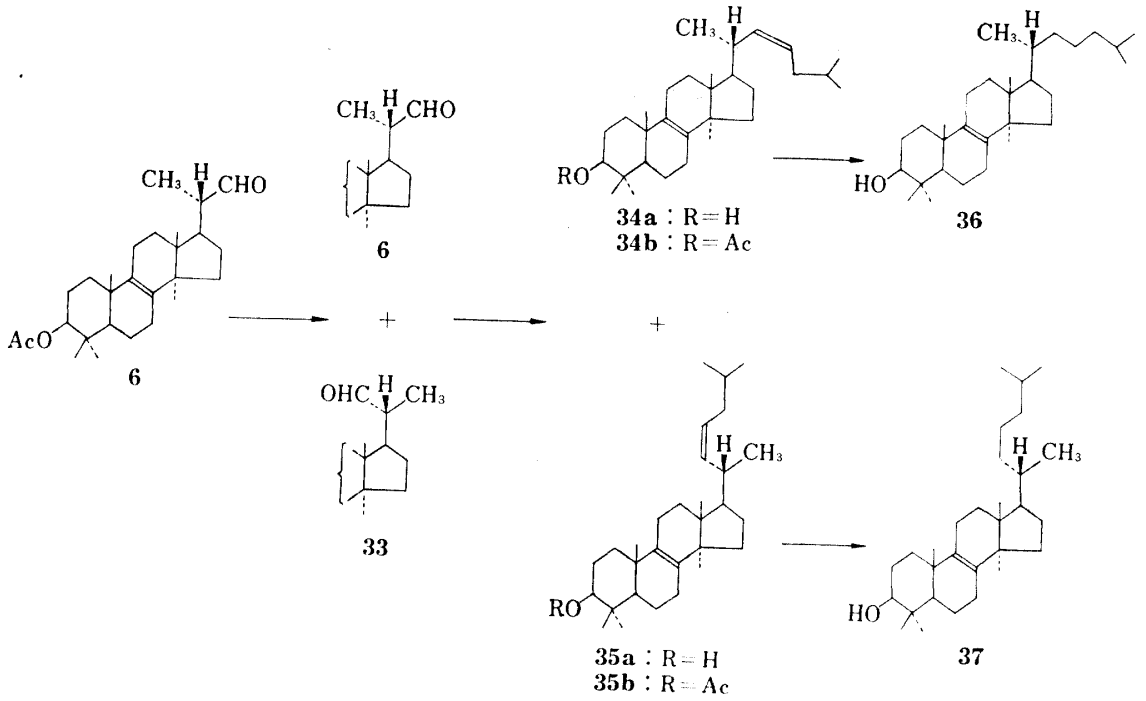
olefinic protons at 5.50—5.80 ppm. Catalytic hydrogenation of **15** with 5% palladium on charcoal, followed by alkaline hydrolysis, afforded 20,21,22,23,24,25,26,27-octanorlanost-8-en-3β-ol (**16**). In order to prepare the 23-nor analog (**18b**), the alcohol (**17**) obtained by treatment of the aldehyde (**4**) with sodium borohydride was reacted with lead tetraacetate in benzene. Alkaline hydrolysis of the product (**18b**) afforded 23-norlanost-8-en-3β-ol (**18a**). Further, the 24-ethylidene compound (**19**) was prepared by the Wittig reaction of the 24-oxo-compound (**3**) with ethyl triphenylphosphonium bromide in 82% yield.

As a starting material for the synthesis of nor-, dinor-, and trinor-analogs of lanosterol, the 24-aldehyde (**23**) was prepared as follows. Oxidation of lanosteryl acetate (**1b**) by the procedure of Habermehl *et al.* afforded the 24-carboxylic acid (**21**) and the ketol compound (**20**). Reduction of the ketol (**20**) with sodium borohydride gave the 24ξ, 25-diol (**22**). Subsequent oxidative cleavage of the diol (**22**) with periodate in dioxane afforded 3β-acetoxy-25,26,27-trinorlanost-8-en-24-al (**23**) in 76% yield. Reduction of **23** with

sodium borohydride gave a primary alcohol (**24**), which was transformed to the chloro compound (**25**) in 60% yield by treatment with phosphoryl chloride in pyridine. Reductive dehalogenation of **25** with lithium aluminum hydride gave 25,26,27-trinorlanost-8-en-3β-ol (**26**) in 90% yield. To obtain nor- and dinor-analogs, on the other hand, Wittig reactions of the aldehyde (**23**) were performed. On treatment with methyl triphenylphosphonium bromide in the presence of *n*-butyl lithium, **23** gave 26,27-dinorlanosta-8,24-dien-3β-ol (**27a**) and its acetate (**27b**) in 24% and 48% yields, respectively. The structure of **27a** The reaction of **23** with ethyl triphenylphosphonium bromide in a similar manner afforded 27-norlanosta-8,24-dien-3β-ol and its acetate. Catalytic hydrogenation of the 24,25-unsaturated compounds (**27a** and **29**) afforded 26,27-dinorlanost-8-en-3β-ol (**28**) and 27-norlanost-8-en-3β-ol (**30**), respectively. In order to synthesize the tetranor analog, the carboxylic acid (**21**) was treated with lead tetraacetate in the presence of Cu^{2+}-pyridine to give 3β-acetoxy-24,25,26,27-tetranorlanosta-8,22-diene (**31**). Catalytic hydrogenation of **31** in the presence of 5% palladium on charcoal and subsequent alkaline hydrolysis afforded 24,25,26,27-tetranorlanost-8-en-3β-ol (**32**).

In addition to the synthesis of lanosterol analogs with a modified side chain, the synthesis of 20-iso-24-dihydrolanosterol was also required for biological experiments. Our synthetic route to 20-iso-24-dihydrolanosterol (**37**) is shown in Chart 4. As a starting material for this experiment, the 20-aldehyde (**6**) was used. Treatment of **6** with sulfuric acid in methanol gave an 20-iso-and normal-aldehyde mixture, as determined by PMR spectroscopy.

The Wittig reaction of an aldehyde mixture (**6** and **33**) with isoamyl triphenylphosphonium iodide afforded the 22-dehydro-24-dihydrolanosterol isomer (**34a** and **35a**) and their acetates (**34b** and **35b**), in 46% and 18% yields, respectively. The stereoisomer, **34a** and **35a**, were separated by column chromatography on silica gel, furnishing **35a** as the less polar product; the ratio of the stereoisomers was apporximately 1 : 1. The Δ^{22} compound (**34a**) was identical with 22-dehydro-24-dihydrolanosterol prepared by the Wittig reaction of the 20-normal aldehyde (**6**). Consequently, **35a** is the 20-iso-Δ^{22}-compound. Inspection of the PMR spectra of **34a** and **35a** revealed that the 18-methyl signals were substantially different (0.74 and 0.62 ppm, respectively). In the mass spectra of **34a** and **35a**, some appreciable differences were observed in their fragmentation patterns; they gave base peaks at *m/e* 111 and 69, respectively. The IR spectra (KBr) of **34a** and **35a** exhibited absorption bands at 735 and 730 cm^{-1}, respectively, which suggest the *cis* configuration of their Δ^{22} double bonds. Catalytic reduction of the iso-compound (**35a**) afforded the corresponding dihydro compound, whose structure was elucidated as 20-iso-24-dihydrolanosterol (**37**), mp 171.5—172°, $[\alpha]_D^{19}$ +33°. Hydrogenation of **34a** in a similar manner afforded 24-dihydrolanosterol (**36**), mp 146—146.5°, $[\alpha]_D^{19}$ +63°. The PMR spectra of **36** and **37** were very similar in $CDCl_3$ but some chemical-shift differences were observed in 14- and 18-methyls in hexadeuterobenzene (1.03 and 0.84 ppm for 24-dihydrolanosterol



Cart 4

and 1.01 and 0.82 ppm for 20-iso-24-dihydrolanosterol, respectively). The 21-methyl groups in the above compounds were not observed because of overlapping with other signals. In GLC on 1.5% OV-17, the relative retention time of the iso-compound (**37**) relative to that of the normal compound (**36**) was 0.88. Corey–Pauling–Koltun (CPK) model examination of **36** and **37** thus obtained clearly indicated that their side chains have different orientations.