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Author	佐藤, 良博(Sato, Yoshihiro) 園田, よし子(Sonoda, Yoshiko)
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Synthesis of Lanosterol Analogs with Modified Side Chains*

YOSHIHIRO SATO and YOSHIKO SONODA

佐藤良博, 園田よし子

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*-3 β -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-3 β -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-3 β -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 permanganate 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-3 β -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

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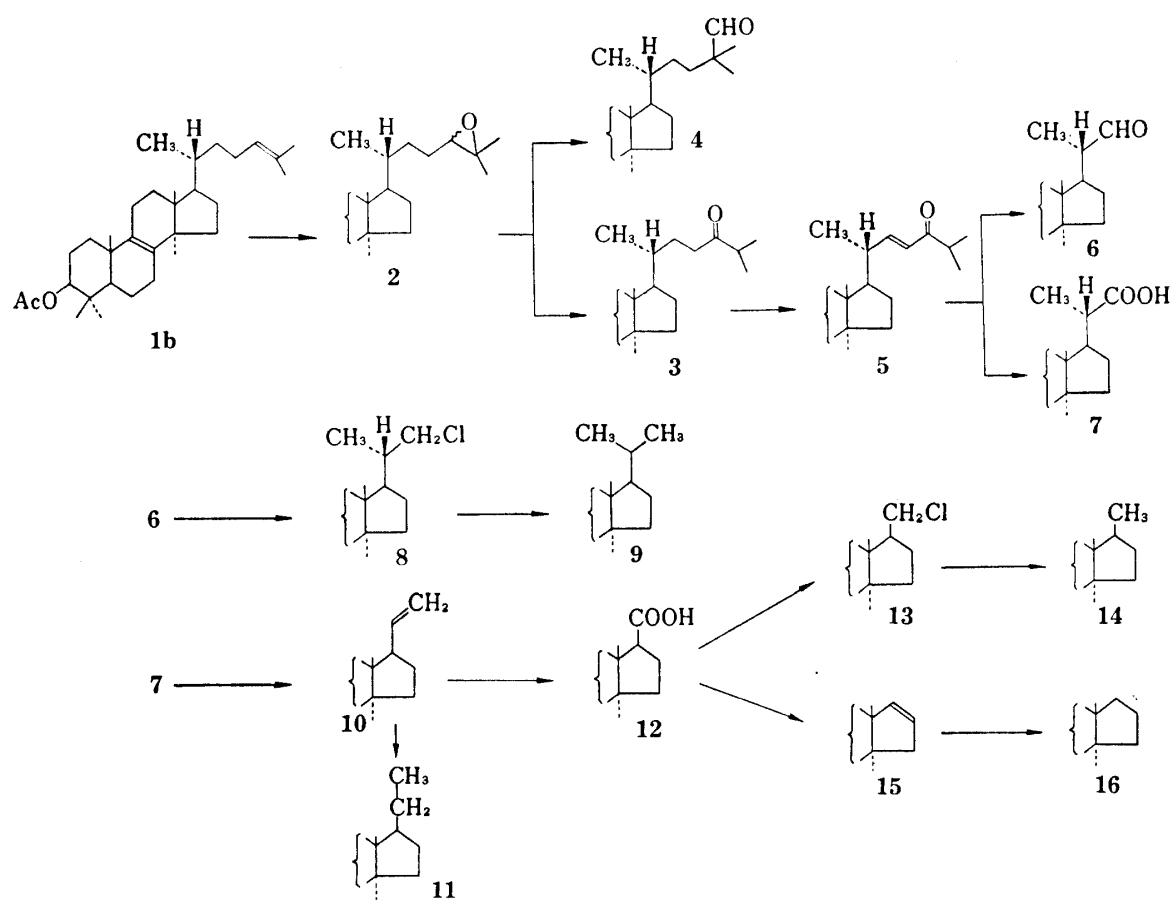


Chart 1

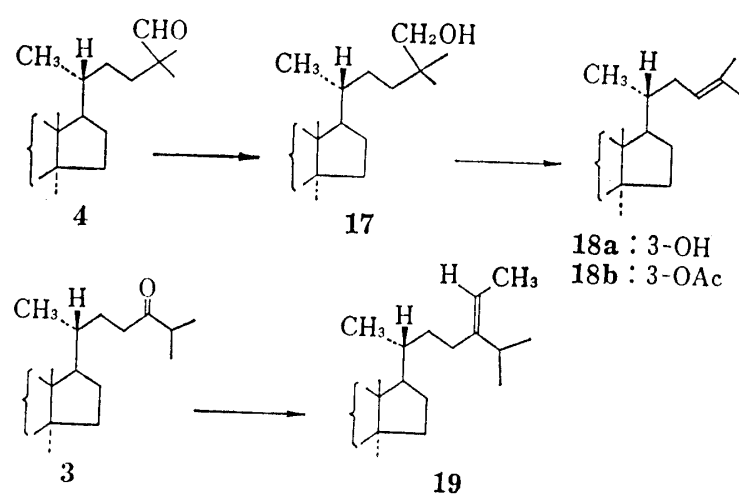


Chart 2

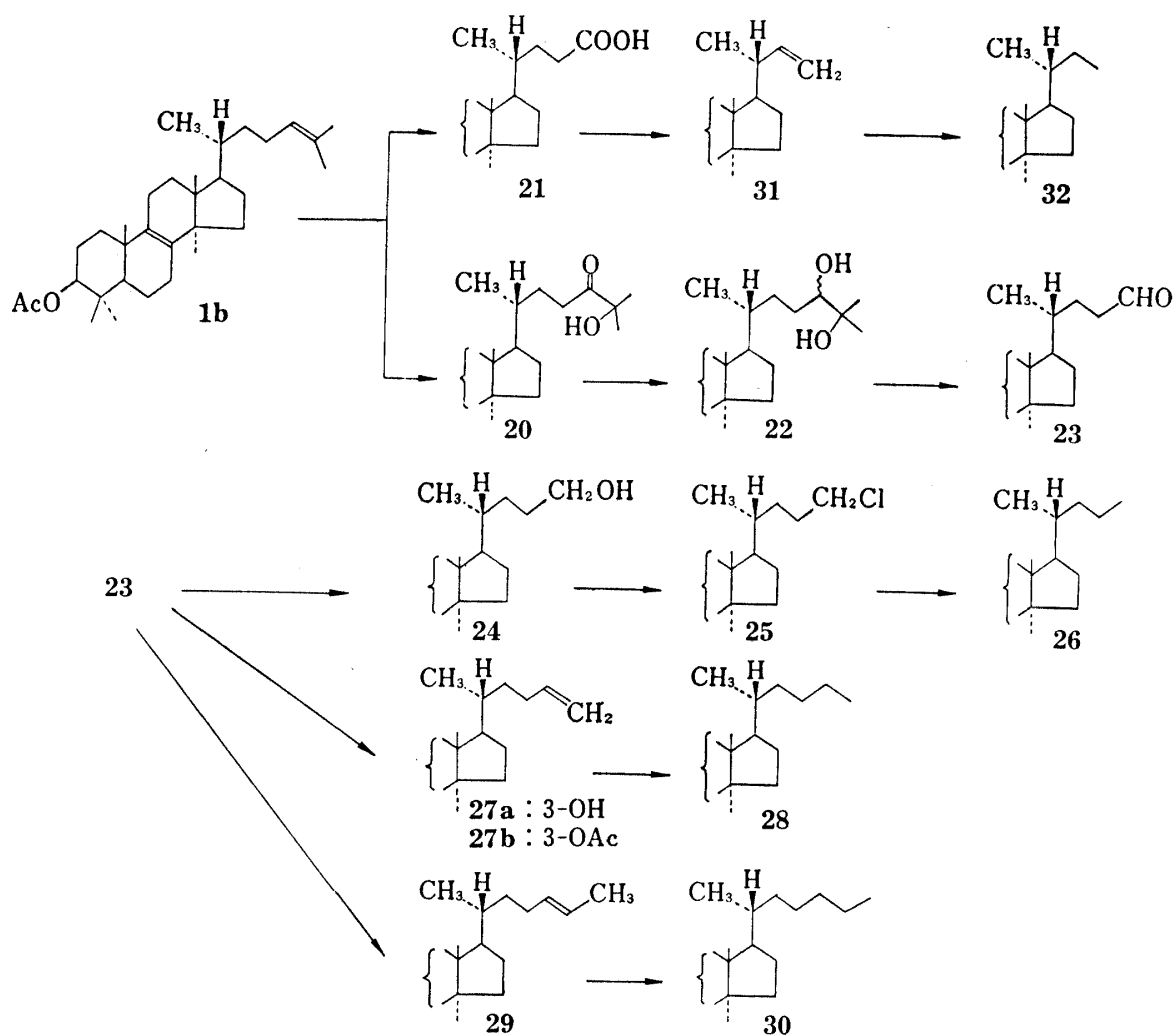


Chart 3

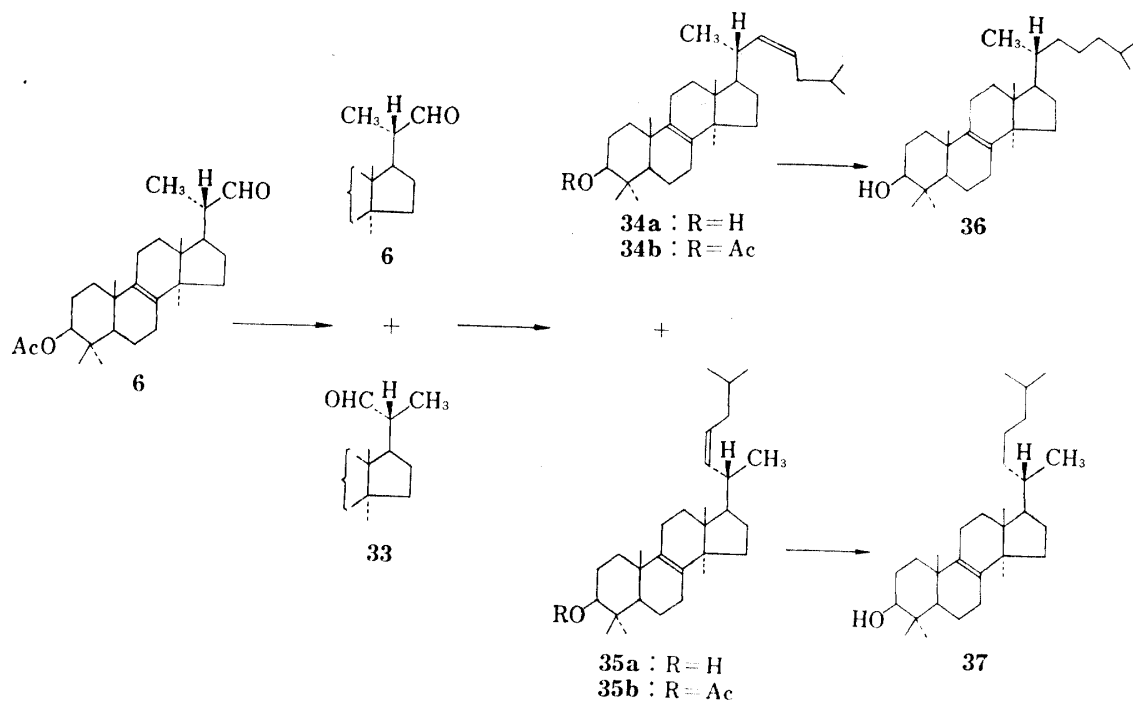
olefinic protons at 5.50—5.80 ppm. Catalytic hydrogenation of **15** with 5% palladium on charcoal, followed by alkaline hydrolysis, afforded **20,21,22,23,24,25,26,27**-octanorlanost-8-en-3β-ol (**16**). In order to prepare the 23-nor analog (**18b**), the alcohol (**17**) obtained by treatment of the 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 24,25-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-3 β -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-3 β -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-3 β -ol and its acetate. Catalytic hydrogenation of the 24,25-unsaturated compounds (**27a** and **29**) afforded 26,27-dinorlanost-8-en-3 β -ol (**28**) and 27-norlanost-8-en-3 β -ol (**30**), respectively. In order to synthesize the tetranor analog, the carboxylic acid (**21**) was treated with lead tetraacetate in the presence of Cu²⁺-pyridine to give 3 β -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-3 β -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 approximately 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°, [α]_D²⁰ +33°. Hydrogenation of **34a** in a similar manner afforded 24-dihydrolanosterol (**36**), mp 146–146.5°, [α]_D²⁰ +63°. The PMR spectra of **36** and **37** were very similar in CDCl₃ 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.