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Effects of Lanosterol Analogs on Cholesterol Biosynthesis from Lanosterol*

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The biosynthesis of cholesterol from lanosterol involves the removal of the three methyl groups, reduction of the Δ^{24}-double bond, and the migration of double bonds. However, very few studies have been carried out on the inhibition of cholesterol biosynthesis from lanosterol.

Recently, we reported the synthesis of various analogs of lanosterol (**1**—**13**) as shown in Fig. 1. This paper describes studies on the effects of these analogs on cholesterol biosynthesis from [24-^{3}H]-lanosterol in rat hepatic subcellular preparations (S-10) by the methods of Gibbons *et al.* [24-^{3}H]-Lanosterol was synthesized from 3β-acetoxylanost-8-en-24-one (**14**) as described in Chart 1.

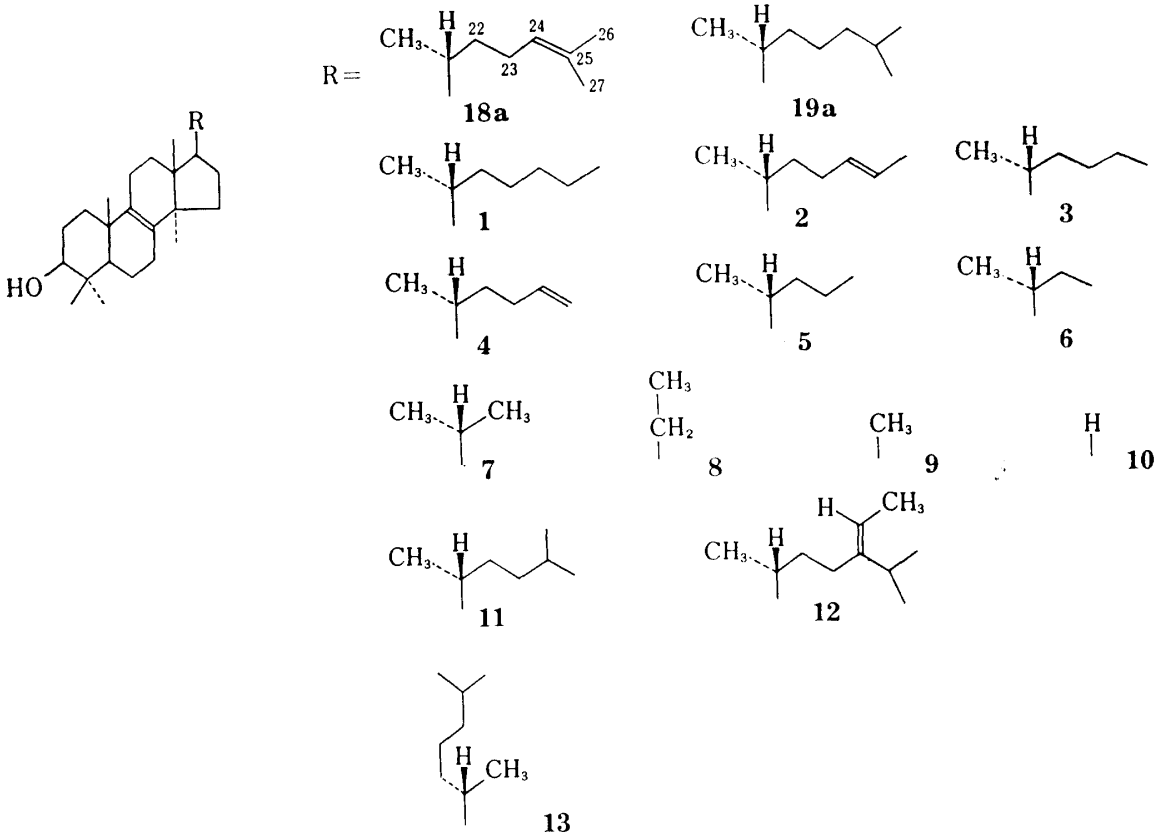

Fig. 1

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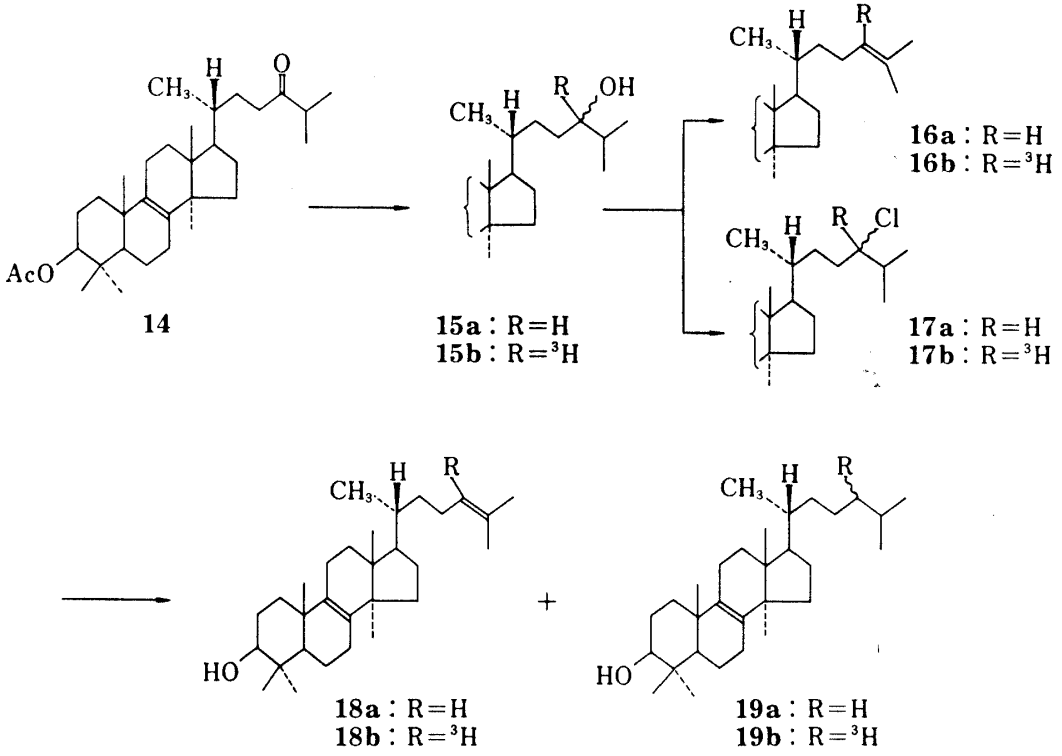

Chart 1

When [24-^{3}H]-lanosterol (18 μM) was incubated with S-10 which had been preincubated with 23,24,25,26,27-pentanordihydrolanosterol (**7**) at a concentration of 20 μM, cholesterol biosynthesis was 82% inhibited. This pentanor compound completely halted cholesterol biosynthesis at a concentration of 40 μM.

Therefore, other lanosterol analogs and related compounds were tested at a concentration of 40 μM without preincubation. Among the tested compounds, 27-nordihydrolanosterol (**1**) was the most potent inhibitor (81% inhibition) of cholesterol biosynthesis (Table I). On the other hand, 24-*trans*-27-norlanosterol (**2**) showed 78% inhibition. The 26,27-dinor analogs (**3** and **4**) and tri-, tetra- and pentanor analogs (**5**, **6** and **7**) of dihydrolanosterol also showed strongly inhibitory effects (47—67%). The hexa- and heptanor analogs (**8** and **9**) were considerably less inhibitory, and the octanor analog (**10**) showed no activity. Therefore, the inhibitory activities of the analogs **1** to **10** increased with increase in the length of the side chain. In addition, 23-norlanosterol (**11**) and the [24(28)Z]-24-ethylidene compound (**12**) showed strongly inhibitory effects. However, cyclolaudenol whose ring imposes conformational changes as compared with lanosterol, showed no activity. These results indicated that the action of the analogs appears to be related to the conformation of the side chain and the skeleton. The addition of lanosterol (**18a**), which is the substrate itself, decreased the cholesterol formation to 16.8%. This can be explained as being due to the dilution of [24-^{3}H]-lanosterol (18 μM) by unlabeled lanosterol (40 μM). A similar

Table I. Cholesterol Biosynthesis during Incubation of S-10 Fraction of Rat Liver Homogenate with [24-^{3}H]-Lanosterol in the Presence of Lanosterol Analogs, Related Compounds, Cholesterol and 25-Hydroxycholesterol

Compound	Lanosterol Fr. (%)	Cholesterol Fr. (%)	Inhibition (%)
None (control)	24.7	22.4	—
Lanosterol (L) (**18a**)	46.9	16.8	25
24-Dihydrolanosterol (DHL) (**19a**)	40.2	18.4	18
Cholesterol	47.6	17.4	22
27-Nor-DHL (**1**)	81.8	4.3	81
24-*trans*-27-Nor-L (**2**)	76.1	5.0	78
26,27-Dinor-DHL (**3**)	71.2	7.4	67
26,27-Dinor-L (**4**)	66.0	10.5	53
25,26,27-Trinor-DHL (**5**)	68.0	8.9	60
24,25,26,27-Tetranor-DHL (**6**)	65.3	11.0	51
23,24,25,26,27-Pentanor-DHL (**7**)	63.0	11.8	47
22,23,24,25,26,27-Hexanor-DHL (**8**)	37.4	19.9	11
21,22,23,24,25,26,27-Heptanor-DHL (**9**)	33.5	20.6	8
20,21,22,23,24,25,26,27-Octanor-DHL (**10**)	22.8	22.2	1
23-Nor-L (**11**)	60.4	10.8	52
[24(28)Z]-24-Ethylidene-DHL (**12**)	58.9	8.8	61
20-Iso-DHL (**13**)	33.5	19.5	13
25-Hydroxycholesterol	52.1	12.2	46
25-Hydroxy-DHL	71.8	7.6	66
Cyclolaudenol (**20**)	24.5	22.6	0

effect occurs in the case of dihydrolanosterol (**19a**). However, the addition of cholesterol showed an inexplicable 22% inhibition in this experiment. Further, the 20-iso-24-dihydrolanosterol (**13**) showed 13% inhibition. This result indicates that the 20-iso compound (**13**), which has a different orientation in the side chain as compared with the 20-normal compound (**19a**), exhibited no apparent inhibitory activity. The addition of 25-hydroxycholesterol, which is known to be a potent inhibitor of hydroxymethylglutlaryl-CoA reductase activity in L cell culture, caused 46% inhibition in this experiment. 25-Hydroxy-24-dihydrolanosterol showed a higher inhibitory effect than 25-hydroxycholesterol.

Table I shows that, on the other hand, recovery yields of the starting material increase in parallel to the rates of inhibition. The above results show that these lanosterol analogs, with both a side chain longer than that of the hexanor analog (**8**) and the C-20 normal configuration, were potent inhibitors of cholesterol biosynthesis, and suggest that these compounds may inhibit 14α-demethylation of lanosterol.