Synthesis and Biological Activity of New 3-Hydroxy-3-methylglutaryl Coenzyme A (HMG-CoA) Synthase Inhibitors: 2-Oxetanones with a Side Chain Mimicking the Folded Structure of 1233A

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To mimic the folded side chain conformation of 1233A (1), which is a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) synthase inhibitor, 1233A analogs with aromatic rings in the side chain were synthesized. The 2-oxetanone moiety was kept intact. Among 1233A and its synthetic analogs, *trans*-3-hydroxymethyl-4-[2-(7-methoxycarbonyl-1-naphthyl)ethyl]-2-oxetanone (23) showed the highest HMG-CoA synthase inhibitory activity *in vitro*. The structure–activity relationship at the side chain is discussed.

Keywords 3-hydroxy-3-methylglutaryl coenzyme A synthase; 1233A analog; inhibitor; cholesterol biosynthesis; 2-oxetanone; structure–activity relationship

An elevated concentration of plasma cholesterol is generally accepted to play a causal role in the development of atherosclerotic coronary heart diseases.[1] The statins, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, have proved to be a safe and powerful means to reduce the plasma cholesterol level in hypercholesterolemic patients.

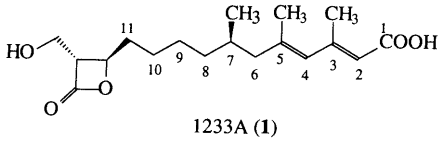
The antibiotic 1233A (**1**), isolated independently from *Scopulariopsis* sp.[2] and *Fusarium* sp.,[3] was reported to be a potent and specific inhibitor of HMG-CoA synthase. It has also demonstrated that 1233A can inhibit ^{14}C-acetate incorporation into sterols in cultured cells,[2,3] rat plasma,[3] and mouse liver.[4] Since HMG-CoA synthase constitutes an early enzyme in the cholesterol synthetic pathway[5] and is regulated profoundly in response to cellular cholesterol,[5,6] it represents an important control point for cholesterogenesis. In contrast to HMG-CoA reductase inhibitors, however, HMG-CoA synthase inhibitors,[7,8] *e.g.*, 1233A (**1**),[2,3] have not been well examined. Hence, the potential of HMG-CoA synthase inhibitors as a new type of hypocholesterolemic drug prompted us to examine synthetic 1233A analogs.

Our previous results[2] implied that the 2-oxetanone moiety of 1233A with the hydroxymethyl group responsible for the inhibitory activity should be kept intact in this study. We also reported[9] that 2-oxetanones with a simple alkanoic acid as a side chain were less active than 1233A. The lower activity could be attributed to some extent to the lack of the conjugated system, *i.e.*, $\alpha\beta$, $\gamma\delta$-unsaturated carboxylic acid system in the side chain. The hypothetical folded structure, *e.g.*, conformer A or conformer B, deduced from a comparison of the activities of methylene homologues (**14**, **15** and **17**—**20**) with that of 1233A, was supposed to play an important role in the interaction of 1233A with the target enzyme. Thus, we envisioned that appropriate aromatic rings should be introduced into the side chain of synthetic analogs to mimic the folded side chain of 1233A (**1**). The naphthalene ring would be a suitable replacement for the folded structure having the $\alpha\beta$, $\gamma\delta$-unsaturated system. A number of analogs designed on the basis of this idea were tested for their inhibitory activities against HMG-CoA synthase and cholesterol biosynthesis in mouse liver and showed higher activities than those reported previously.[9] We report biological results and new findings on the structure–activity relationships regarding the side chain of 2-oxetanone derivatives.

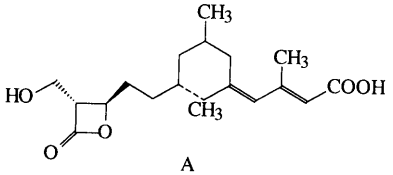
Chemistry

The 2-oxetanones listed in Table I were prepared from the corresponding alkanals. These key alkanals were prepared by routes A—G (in Charts 1—5) and their physical data are summarized in Table II.

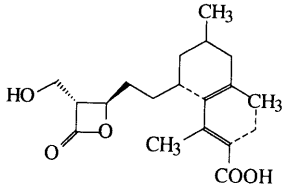
In route A, Wittig condensation[10] of **33** with catalytic hydrogenation gave saturated acetals **35**, but their acid



1233A (**1**)



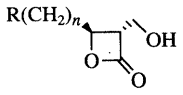
A



B

Fig. 1. 1233A and Its Folded Conformers

TABLE I. Physical Data for Substituted 2-Oxetanones



Compd.	R	n	mp (°C)	Formula	Analysis Calcd C, H, N (Found C, H, N)	MS M+	HR-MS Calcd (Found)	^{1}H-NMR ($CDCl_3$) δ
2	C_6H_5	2	Oil	$C_{12}H_{14}O_3$		206 (FD)		2.00—2.30 (2H, m), 2.67—2.87 (3H, m), 3.27—3.41 (1H, m), 3.62—4.05 (2H, m), 4.58 (1H, dt, J=2.4, 4.8 Hz), 7.25 (5H, s)
3	3-Me-C_6H_4	2	41.0—42.0 (*n*-Hexane)	$C_{13}H_{16}O_3$	70.89, 7.32 (70.62, 7.41)	220 (EI)		1.65 (1H, s), 1.90—2.28 (2H, m), 2.33 (3H, s), 2.62—2.87 (2H, m), 3.26—3.48 (1H, m), 3.60—4.15 (2H, m), 4.58 (1H, dt, J=3.6, 7.2 Hz), 6.90—7.25 (4H, m)
4	3-Cl-C_6H_4	2	Oil	$C_{12}H_{13}ClO_3$		240 (EI) 242	240.0553 (240.0554)	2.00—2.33 (2H, m), 2.43 (1H, br t), 2.60—2.95 (2H, m), 3.30—3.50 (1H, m), 3.67—4.20 (2H, m), 4.61 (1H, dt, J=3.6, 7.2 Hz), 7.00—7.55 (4H, m)
5	3-HO-C_6H_4	2	85—88 ($CHCl_3$)	$C_{12}H_{14}O_4$			222.0892 (222.0897)	1.70 (1H, s), 1.98—2.33 (2H, m), 2.57—2.91 (2H, m), 3.22—3.43 (1H, m), 3.60—4.18 (2H, m), 4.58 (1H, dt, J=4.1, 7.0 Hz), 5.41 (1H, s), 6.49—7.40 (4H, m)
6	2-MeOOC-C_6H_4	2	Oil	$C_{14}H_{16}O_5$		264 (FD)		2.00—2.30 (2H, m), 2.67—2.87 (3H, m), 3.27—3.41 (1H, m), 3.70—4.20 (2H, m), 3.90 (3H, s), 4.65 (1H, dt, J=3.6, 7.2 Hz), 7.20—8.00 (4H, m)
7	2-HOOC-C_6H_4	2	Oil	$C_{13}H_{14}O_5$		250 (FD)		2.05—2.35 (2H, m), 3.05—3.73 (2H, m), 3.90—4.05 (2H, m), 4.58—4.80 (3H, m), 7.34—7.68 (3H, m), 8.04—8.15 (1H, m)
8	3-MeOOC-C_6H_4	2	59.5—60.5 (IPE–AcOEt)	$C_{14}H_{16}O_5$	63.37, 6.15 (63.62, 6.10)	264 (EI)		2.05—2.45 (3H, m), 2.74—2.96 (2H, m), 3.35—3.50 (1H, m), 3.70—4.20 (2H, m), 3.93 (3H, s), 4.62 (1H, dt, J=3.6, 7.2 Hz), 7.35—7.55 (2H, m), 7.85—8.00 (2H, m)
9	3-HOOC-C_6H_4	2	Waxy solid	$C_{13}H_{14}O_5$			250.0841 (250.0853)	1.93—2.32 (2H, m), 2.66—3.00 (2H, m), 3.30—3.47 (1H, m), 3.61—4.03 (2H, m), 4.46—4.80 (3H, m), 7.30—7.55 (2H, m), 7.80—8.00 (2H, m)
10	4-MeOOC-C_6H_4	2	98.5—99.5 (IPE–$CHCl_3$)	$C_{14}H_{16}O_5 \cdot 1/4H_2O$	62.81, 6.11 (62.56, 6.19)	264 (EI)		2.05—2.35 (3H, m), 2.74—2.94 (2H, m), 3.35—3.55 (1H, m), 3.70—4.15 (2H, m), 3.90 (3H, s), 4.60 (1H, dt, J=3.6, 7.2 Hz), 7.34 (2H, d, J=7.9 Hz), 8.02 (2H, d, J=7.9 Hz)
11	3-EtOOC-C_6H_4	2	Oil	$C_{15}H_{18}O_5$			278.1154 (278.1140)	1.40 (3H, t, J=7.2 Hz), 2.05—2.35 (3H, s), 2.74—3.00 (2H, m), 3.34—3.50 (1H, m), 3.70—4.20 (2H, m), 4.40 (2H, q, J=7.2 Hz), 4.62 (1H, dt, J=3.6, 7.2 Hz), 7.35—7.55 (2H, m), 7.85—8.05 (2H, m)
12	3-*n*-PrOOC-C_6H_4	2	Oil	$C_{16}H_{20}O_5$			292.1311 (292.1305)	1.03 (3H, t, J=7.8 Hz), 1.57—2.04 (2H, m), 2.00—2.48 (2H, m), 2.57—3.23 (3H, m), 3.30—3.55 (1H, m), 3.63—4.17 (2H, m), 4.27 (2H, t, J=6.6 Hz), 4.67 (1H, dt, J=4.0, 6.8 Hz), 7.20—8.00 (4H, m)
13	3-*n*-HexylOOC-C_6H_4	2	Oil	$C_{19}H_{26}O_5$			334.1780 (334.1795)	0.75—2.00 (11H, m), 2.00—2.35 (3H, m), 2.74—3.05 (2H, m), 3.34—3.55 (1H, m), 3.70—4.23 (2H, m), 4.35 (2H, t, J=6.8 Hz), 4.63 (1H, dt, J=4.0, 6.8 Hz), 7.36—7.56 (2H, m), 7.85—8.10 (2H, m)
14	1-$C_{10}H_7$	1	93.0—94.0 (*n*-Hexane–AcOEt)	$C_{15}H_{14}O_3$	74.36, 5.83 (74.11, 5.69)	242 (EI)		1.90 (1H, br t), 3.30—4.20 (5H, m), 5.02 (1H, dt, J=3.6, 7.2 Hz), 7.35—8.10 (7H, m)
15	1-$C_{10}H_7$	2	Oil	$C_{16}H_{16}O_3$			256.1100 (256.1096)	1.95—2.42 (2H, m), 2.70—3.40 (4H, m), 3.40—4.08 (2H, m), 4.66 (1H, dt, J=3.9, 6.8 Hz), 7.20—8.10 (7H, m)
16	2-$C_{10}H_7$	2	89.0—90.0 (IPE)	$C_{16}H_{16}O_3$	74.98, 6.29 (74.71, 6.35)	256 (EI)		1.76—2.50 (3H, m), 2.64—3.08 (2H, m), 3.33—3.45 (1H, m), 3.45—4.05 (2H, m), 4.60 (1H, dt, J=4.8, 6.5 Hz), 7.10—7.95 (7H, m)
17	1-$C_{10}H_7$	3	Oil	$C_{17}H_{18}O_3$			270.1256 (270.1244)	1.60—2.35 (5H, m), 3.05—3.25 (2H, m), 3.26—3.42 (1H, m), 3.65—4.15 (2H, m), 4.50—4.70 (1H, m), 7.25—8.10 (7H, m)
18	1-$C_{10}H_7$	4	Oil	$C_{18}H_{20}O_3$			284.1412 (284.1432)	1.30—2.10 (6H, m), 2.39 (1H, br t), 3.10 (2H, t, J=7.2 Hz), 3.25—3.45 (1H, m), 3.65—4.15 (2H, m), 4.57 (1H, dt, J=3.9, 7.2 Hz), 7.25—8.10 (7H, m)
19	1-$C_{10}H_7$	5	Oil	$C_{19}H_{22}O_3$			298.1569 (298.1552)	1.20—2.00 (8H, m), 2.06 (1H, br t), 3.08 (2H, t, J=7.2 Hz), 3.25—3.45 (1H, m), 3.65—4.15 (2H, m), 4.57 (1H, dt, J=3.6, 7.2 Hz), 7.20—8.15 (7H, m)

TABLE I. (continued)

Compd.	R	n	mp (°C)	Formula	Analysis: Calcd C, H, N (Found C, H, N)	MS M^+	HR-MS Calcd (Found)	^{1}H-NMR ($CDCl_3$) δ
20	1-$C_{10}H_7$	6	52.5—54.5 (*n*-Hexane–IPE)	$C_{20}H_{24}O_3$	76.89, 7.74 (76.80, 7.70)		312.1725 (312.1700)	1.20—2.00 (10H, m), 2.11 (1H, br t), 3.08 (2H, t, J=7.2 Hz), 3.25—3.45 (1H, m), 3.65—4.15 (2H, m), 4.57 (1H, dt, J=3.6, 6.9 Hz), 7.20—8.15 (7H, m)
21	3-MeOOC-1-$C_{10}H_6$	2	Oil	$C_{18}H_{18}O_5$			314.1154 (314.1140)	2.10—2.50 (2H, m), 2.50—2.92 (1H, br s), 3.05—3.50 (3H, m), 3.60—4.16 (2H, m), 3.86 (3H, s), 4.65 (1H, dt, J=3.9, 6.8 Hz), 7.42—8.20 (5H, m), 8.45 (1H, s)
22	4-MeOOC-1-$C_{10}H_6$	2	Oil	$C_{18}H_{18}O_5$		314 (FD)		2.10—2.48 (3H, m), 2.95—3.50 (3H, m), 3.66—4.22 (2H, m), 3.98 (3H, s), 4.65 (1H, dt, J=3.9, 6.8 Hz), 7.20—8.12 (5H, m), 8.81—9.02 (1H, m)
23	7-MeOOC-1-$C_{10}H_6$	2	91.0—92.0 (*n*-Hexane–AcOEt)	$C_{18}H_{18}O_5$	68.78, 5.77 (68.67, 5.83)	314 (EI)		2.17—2.41 (2H, m), 2.92 (1H, br s), 3.16—3.30 (2H, m), 3.34—3.48 (1H, m), 3.81—4.20 (2H, m), 3.96 (3H, s), 4.69 (1H, dt, J=3.6, 6.8 Hz), 7.31—8.00 (5H, m), 8.74 (1H, s)
24	7-HOOC-1-$C_{10}H_6$	2	110—113 (*n*-Hexane–AcOEt)	$C_{17}H_{16}O_5 \cdot 1/3H_2O$	70.58, 5.48 (70.29, 5.23)	300 (EI)		2.12—2.42 (2H, m), 3.17—4.15 (5H, m), 4.67 (1H, dt, J=3.6, 7.2 Hz), 7.40—8.10 (7H, m), 8.80 (1H, s)
25	7-Me-1-$C_{10}H_6$	2	Oil	$C_{17}H_{18}O_3$			270.1256 (270.1242)	1.80—2.44 (3H, m), 2.53 (3H, s), 2.43—2.86 (2H, m), 3.43—4.22 (3H, m), 4.47—4.78 (1H, m), 6.95—8.05 (6H, m)
26	3-C_6H_5–C_6H_4	2	87.0—88.0 (*n*-Hexane–AcOEt)	$C_{18}H_{18}O_3$	76.57, 6.43 (76.63, 6.43)	282 (EI)		2.03—2.31 (2H, s), 2.35—2.60 (1H, m), 2.72—2.93 (2H, m), 3.28—3.42 (1H, m), 3.55—4.23 (2H, m), 4.63 (1H, dt, J=2.6, 6.0 Hz), 7.10—7.63 (9H, m)
27	$(C_6H_5)_2CH$	1	115—116 (*n*-Hexane–AcOEt)	$C_{18}H_{18}O_3$	76.57, 6.43 (76.63, 6.34)	282 (EI)		2.03—2.31 (2H, m), 2.35—2.60 (1H, m), 2.72—2.93 (2H, m), 4.63 (1H, dt, J=2.6, 6.0 Hz), 7.10—7.63 (9H, m)
28	$(C_6H_5)_2CH$	2	Oil	$C_{18}H_{18}O_3$	76.57, 6.43 (76.64, 6.29)	282 (EI)		2.05 (1H, br t), 2.49—2.69 (2H, m), 3.21—3.92 (3H, m), 4.03—4.20 (1H, m), 4.45 (1H, dt, J=4.0, 6.8 Hz), 7.05—7.45 (10H, m)
29	9-Anthracenyl	2	115—117 (IPE)	$C_{20}H_{18}O_3$			306.1256 (306.1261)	2.12—2.50 (2H, m), 2.95 (1H, br s), 3.14—3.48 (2H, m), 3.60—4.10 (3H, m), 4.68 (1H, dt, J=4.1, 7.2 Hz), 7.40—7.70 (5H, m), 7.80—8.50 (4H, m)
30	4-Quinolinyl	2	Oil	$C_{15}H_{15}NO_3$			257.1052 (257.1050)	2.26—2.54 (3H, m), 3.15—3.40 (2H, m), 3.46 (1H, q, J=5.5 Hz), 3.85—4.10 (2H, m), 4.69 (1H, m), 7.60 (1H, m), 7.73 (2H, m), 8.03 (1H, m), 8.13 (1H, d, J=8.2 Hz), 8.77 (1H, s) (in 500 MHz)

hydrolysis did not give propanals **37**. Hence, the propanals were prepared by the acid hydrolysis of **34** with catalytic hydrogenation. Since the yields were low due to simultaneous partial reduction of the aldehyde group, other routes, *i.e.*, routes B and C in Chart 2, were investigated. Although these routes have more steps than route A, they gave better overall yields. Route B was adopted for the preparation of propanals **37h—j, m** without a methoxycarbonyl group. Route C was adopted for the preparation of propanals **37k, l** with a methoxycarbonyl group *via* hydrogenolysis of benzyl ester to differentiate between two ester groups in **38k, l**. Swern oxidation of **42** gave propanals **37**.

In route D, the hydrogenolysis of 2-chloropropanals[11] **44** gave propanals **45**. In route E, propanols **46a, b**, alkyl analogs of the propanol **42l**, were prepared by transesterification of **42l** and oxidized to give propanals **47**. Route F afforded **51** from **33a**. In route G, the Grignard reaction of 7-methyl-1-tetralone[12] (**52**) gave **53**, followed by conversion to a naphthalene ring with deprotection and oxidation to give the propanal **56**.

By using the typical procedure[9] shown in Chart 5, 2-oxetanones were prepared. Aldol condensation of key alkanals **37** with benzyl or ethyl 3-hydroxypropanoate[9] gave a mixture of *syn*- and *anti*-**57** in the ratio of *ca.* 1 : 1. The mixture of **57a** was separated by silica gel chromatography. However, the mixture was usually separated after triphenylmethylation, as in the case of **58b**. The *anti*-isomers[13] **58a, b** were hydrolyzed or hydrogenolyzed according to the propanoate ester used to give **59a, b**, and then lactonization with deprotection afforded the *trans*-2-oxetanones **23** and **26**, respectively. Analogs **7**, **9** and **24** which contain free carboxylic acid in the side chain, were prepared from the corresponding methyl esters **6**, **8** and **23**. These esters were selectively hydrolyzed by porcine liver esterase (PLE) to give the free carboxylic acids **7**, **9** and **24**. The usual aqueous alkali treatment was not successful because of the ring opening of the 2-oxetanone. The 2-oxetanones prepared in this study were of *trans* form, and were optically inactive.

Biological Results and Discussion

The compounds listed in Table I were evaluated for HMG-CoA synthase inhibitory activity by the reported[2] procedure, and the results are summarized in Table III.

The distance between the 2-oxetanone ring and the

TABLE II. Physical Data for Alkanals

$R-(CH_2)_n-CHO$

Compd.	R	n	mp (°C)	Method No.[a]	Formula	^{1}H-NMR ($CDCl_3$) δ
37h	3-Me-C_6H_4	2	Oil	B	$C_{10}H_{12}O$	2.72—3.11 (4H, m), 2.33 (3H, m), 6.92—7.35 (4H, m), 9.80 (1H, t, J=1.2 Hz)
37i	3-Cl-C_6H_4	2	Oil	B	C_9H_9ClO	2.55—2.70 (4H, m), 6.95—7.50 (4H, m), 7.00—7.55 (4H, m), 9.83 (1H, t, J=1.2 Hz)
37j	3-BzlO-C_6H_4	2	Oil	B	$C_{16}H_{16}O_2$	2.61—3.07 (4H, m), 5.05 (2H, s), 6.70—7.53 (9H, m), 9.81 (1H, t, J=1.2 Hz)
37k	2-MeOOC-C_6H_4	2	Oil	C	$C_{11}H_{12}O_3$	2.70—2.97 (2H, m), 3.13—3.40 (2H, m), 3.90 (3H, s), 7.16—7.56 (3H, m), 7.85—8.00 (1H, m), 9.84 (1H, t, J=1.2 Hz)
37l	3-MeOOC-C_6H_4	2	Oil	C	$C_{11}H_{12}O_3$	2.75—3.15 (4H, m), 3.93 (3H, s), 7.30—7.50 (2H, m), 7.82—8.60 (2H, m), 9.82 (1H, t, J=1.2 Hz)
45a	4-MeOOC-C_6H_4	2	Oil	D	$C_{11}H_{12}O_3$	2.71—2.90 (2H, m), 2.92—3.12 (2H, m), 3.90 (3H, s), 7.27 (2H, d, J=7.9 Hz), 7.95 (2H, d, J=7.9 Hz), 9.81 (1H, t, J=1.2 Hz)
45b	3-EtOOC-C_6H_4	2	Oil	D	$C_{12}H_{14}O_3$	1.42 (3H, t, J=7.2 Hz), 2.71—2.91 (2H, m), 2.92—3.12 (2H, m), 4.38 (2H, q, J=7.2 Hz), 7.24—7.45 (2H, m), 7.80—7.95 (2H, m) 9.80 (1H, t, J=1.2 Hz)
47a	3-*n*-PrOOC-C_6H_4	2	Oil	E	$C_{13}H_{16}O_3$	1.03 (3H, t, J=7.3 Hz), 1.55—2.05 (2H, m), 2.65—3.20 (4H, m), 4.27 (2H, t, J=6.5 Hz), 7.20—8.10 (4H, m), 9.82 (1H, t, J=1.2 Hz)
47b	3-*n*-HexylOOC-C_6H_4	2	Oil	E	$C_{16}H_{22}O_3$	0.75—1.95 (11H, m), 2.59—3.13 (4H, m), 4.32 (2H, t, J=6.8 Hz), 7.30—7.50 (2H, m), 7.76—8.00 (2H, m), 9.81 (1H, t, J=1.2 Hz)
37m	Ph-3-Ph	2	Oil	B	$C_{15}H_{14}O$	2.66—3.13 (4H, m), 7.08—7.63 (9H, m), 9.80 (1H, t, J=1.2 Hz)
37a	1-$C_{10}H_7$[b]	2	Oil	A	$C_{13}H_{12}O$	2.62—3.63 (4H, m), 7.20—8.00 (7H, m), 9.87 (1H, t, J=1.2 Hz)
37e	2-$C_{10}H_7$	2	61—63.0	A	$C_{13}H_{12}O$	2.60—3.26 (4H, m), 7.20—7.90 (7H, m), 9.80 (1H, s)
51a	1-$C_{10}H_7$	4	Oil	F	$C_{15}H_{16}O$	1.55—1.85 (4H, m), 2.30—2.55 (2H, m), 2.95—3.20 (2H, m), 7.20—8.10 (7H, m), 9.77 (1H, t, J=1.2 Hz)
51b	1-$C_{10}H_7$	5	Oil	F	$C_{16}H_{18}O$	1.20—2.05 (6H, m), 2.29—2.57 (2H, m), 3.05 (2H, t, J=6.1 Hz), 7.21—8.10 (7H, m), 9.74 (1H, t, J=1.2 Hz)
51c	1-$C_{10}H_7$	6	Oil	F	$C_{17}H_{20}O$	1.20—2.00 (8H, m), 2.31—2.56 (2H, m), 3.05 (2H, t, J=6.1 Hz), 7.21—8.10 (7H, m), 9.74 (1H, t, J=1.2 Hz)
56	3-Me-1-$C_{10}H_6$	2	Oil	G	$C_{14}H_{14}O$	2.56 (3H, s), 2.70—3.00 (2H, m), 3.18—3.50 (2H, m), 7.00—7.86 (6H, m), 9.86 (1H, t, J=1.2 Hz)
37b	3-MeOOC-1-$C_{10}H_6$	2	Oil	A	$C_{15}H_{14}O_3$	2.60—3.68 (4H, m), 3.96 (3H, s), 7.30—8.20 (5H, m), 8.46 (1H, s), 9.87 (1H, t, J=1.2 Hz)
37c	4-MeOOC-1-$C_{10}H_6$	2	Oil	A	$C_{15}H_{14}O_3$	2.58—3.65 (4H, m), 3.85 (3H, s), 7.20—8.20 (5H, m), 8.80—9.00 (1H, m), 9.77 (1H, t, J=1.2 Hz)
37d	7-MeOOC-1-$C_{10}H_6$	2	52—53	A	$C_{15}H_{14}O$	2.76—3.05 (2H, m), 3.32—3.60 (2H, m), 3.95 (3H, s), 7.26—8.10 (5H, m), 8.73 (1H, t, J=0.2 Hz) 9.86 (1H, t, J=1.2 Hz)
37f	9-Anthracenyl	2	84—87.0 (*n*-Hexane)	A	$C_{17}H_{14}O$	2.74—2.98 (2H, m), 3.18—3.45 (2H, m), 7.42—8.10 (7H, m), 8.93—9.25 (2H, m), 10.05 (1H, t, J=1.2 Hz)
37g	4-Quinolinyl	2	Oil	A	$C_{12}H_{11}NO$	2.96 (2H, t, J=6.7 Hz), 3.44 (2H, t, J=6.7 Hz), 7.28—8.28 (6H, m), 9.96 (1H, t, J=1.2 Hz)

a) The capital letter indicates the route by which the alkanal was prepared. *b*) Known compound (ref. 15).

aromatic moiety was varied by changing the methylene number in a series of compounds, *i.e.*, **14**, **15** and **17**—**20**. The order of their activities was **15** > **18** ≒ **19** ≒ **20** ≫ **17** > **14**. Inhibitory activities of these analogs against HMG-CoA synthase varied remarkably with the distance between the 2-oxetanone ring and the aromatic moiety. The analog **15** with two methylenes showed the highest activity. The result is apparently inconsistent with the high activity of 1233A, which has six sp^3 carbons between the oxetanone ring and the conjugated system. To explain our results in relation to the side chain of 1233A, the hypothetical folded conformer A or B (Fig. 1) was considered to bind at the active site of the enzyme. The conformer A or B corresponds to the synthetic analogs containing benzene or naphthalene rings in the side chain, respectively. In the synthetic analogs, the aromatic rings would fix the side chain in the folded form, as shown in Fig. 1.

When the aromatic ring was a benzene, a *meta*-substituted compound had higher activity than *ortho*- and *para*-substituted ones (**6**, **8** and **10**). Among the substituents, alkoxycarbonyl groups provided relatively high activities (**2**—**10**) and their activities increased with increase in the number of carbons in the ester part (**8** and **11**—**13**). The hexyl ester analog **13** was half as active as 1233A. Alkyl ester analogs were more active than the corresponding carboxylic acids (**6** *vs.* **7** and **8** *vs.* **9**).

When the aromatic ring was a naphthalene, the α-substituted compound showed higher activity than the β-substituted one (**15** *vs.* **16**). Several analogs with a methoxycarbonyl group were as active as the unsubstituted analog (**15** *vs.* **21** and **22**). However, analog **23** with a methoxycarbonyl group at position 7 in the naphthalene ring showed the highest activity *in vitro* and its activity was 2-fold that of 1233A. In contrast, its free acid form **24** showed low activity. The methoxycarbonyl group could be changed to a methyl group without a marked change in activity (**23** *vs.* **25**) and this indicated that a lipophilic group in position 7 contributes to the high

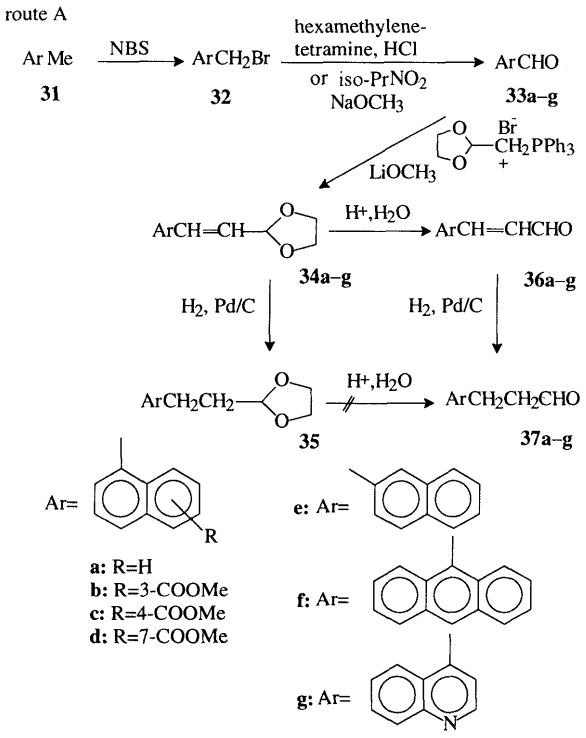


Chart 1. Synthesis of Propanals

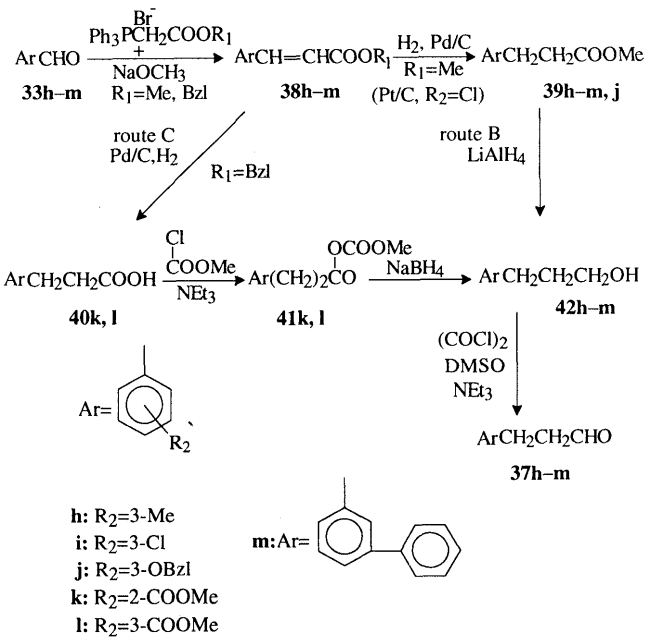


Chart 2. Synthesis of Propanals

activity of these analogs.

Among the benzene, naphthalene, biphenyl and anthracene analogs, the order of activity was **29**>**26**>**15**≫**2**. This order is parallel to the order of lipophilicity and to that of bulkiness of their rings. Similarly, diphenylmethane analogs were slightly more active than the corresponding benzene analog (**2** *vs.* **27** and **28**), and the quinoline analog was less active than the naphthalene analog (**15** *vs.* **30**).

Table IV shows the inhibitory activities of **13**, **23**, **26**—

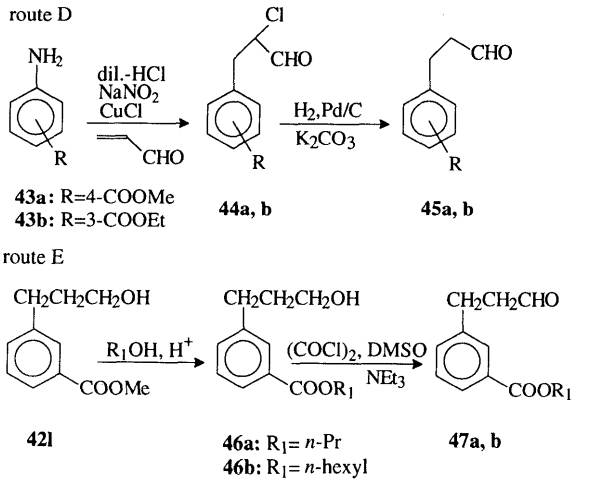


Chart 3. Synthesis of Propanals

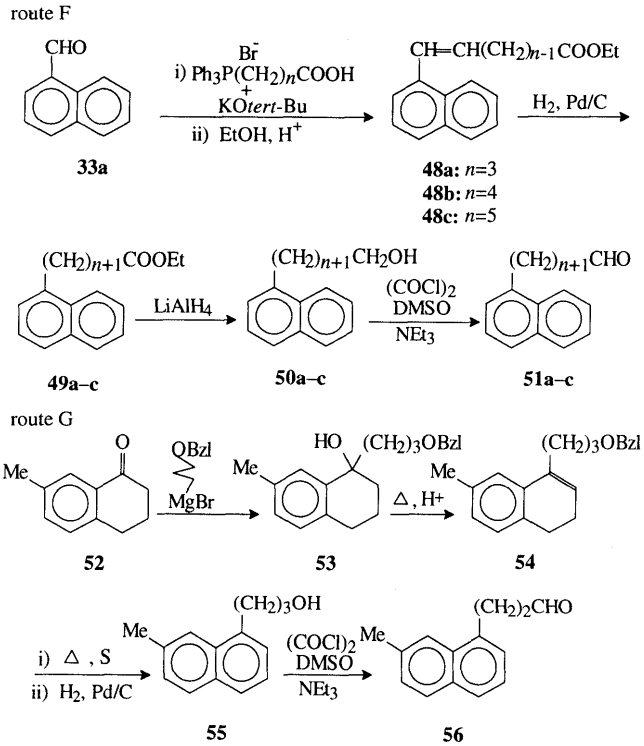


Chart 4. Synthesis of Alkanals

28 and 1233A (**1**) against cholesterol biosynthesis in mouse liver and small intestine. Compounds **23**, **26** and 1233A inhibited cholesterol biosynthesis in the liver and small intestine, whereas compounds **13**, **27** and **28** did not. Compound **23** and **27**, unlike 1233A, markedly increased the serum triglyceride level. This indicated that the triglyceride level increment does not parallel HMG-CoA synthase inhibition. Analog **26** showed high inhibitory activity without significant triglyceride increment. Although the mechanism of the triglyceride level increment is not clear at present, the level was apparently related to the distance between the 2-oxetanone ring and the aromatic one and the bulkiness of the aromatic ring. Further studies on the relation between structure and triglyceride level increment are in progress.

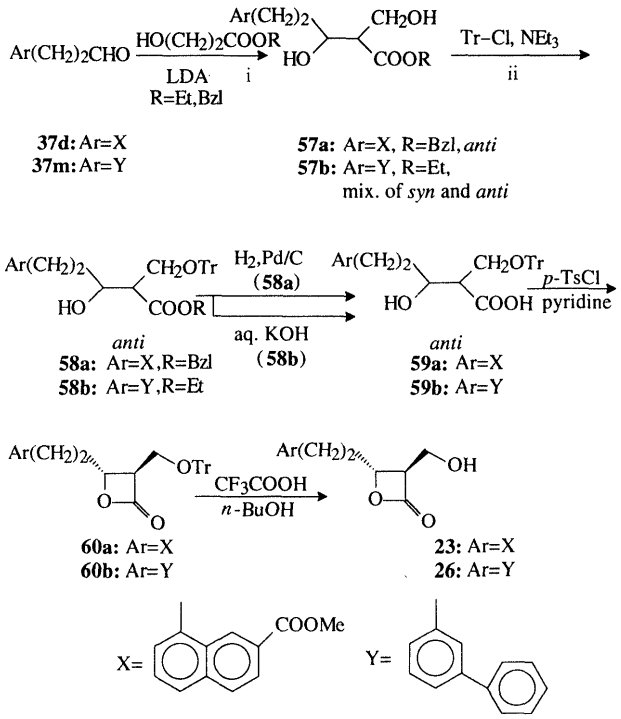


Chart 5. Typical Procedure for the Synthesis of 2-Oxetanones

Compound **57a** (i) and **58b** (ii) were separated by column chromatography.

TABLE III. Inhibitory Activities of 1233A towards HMG-CoA Synthase

Compd.	IC_{50} (μM)	Compd.	IC_{50} (μM)	Compd.	IC_{50} (μM)
2	22.5	**12**	1.2	**22**	1.9
3	20	**13**	0.5	**23**	0.1
4	13.5	**14**	33.3	**24**	2.2
5	6.4	**15**	1.0	**25**	0.3
6	11.3	**16**	5.8	**26**	0.8
7	200	**17**	14.7	**27**	23.5
8	3.3	**18**	3.9	**28**	12.3
9	149	**19**	4.0	**29**	0.5
10	15	**20**	3.5	**30**	16.3
11	1.4	**21**	1.7	**1**	0.2

TABLE IV. Results of *in Vivo* Assay (Mice, $n=6$)

Compd.	Dose (mg/kg *p.o.*)	Inhibition of sterol synthesis (%)		Increase in serum triglyceride level ($\times$ fold)[a]
		Liver	Small intestine	
13	500	−17.0 ns	−2.4 ns	1.29 ns
23	500	80.6[b]	62.7[b]	11.9[b]
26	500	76.1[b]	16.2 ns	1.27 ns
27	500	6.0 ns	−53.1 ns	11.4[b]
28	500	6.0 ns	−3.2 ns	1.59[c]
1233A (**1**)	500	83.0[b]	68.5[b]	0.91 ns
Pravastatin	10	91.0[b]	41.3 ns	1.03 ns

a) The triglyceride level of the control groups was assigned a value of 1.00. *b*) $p<0.01$; *c*) $p<0.05$; ns, not significant *vs.* control.

Conclusion

The 1233A analogs with a side chain designed according to our strategy of mimicking the folded structure of 1233A by the introduction of aromatic rings, especially a naphthalene ring, showed high inhibitory activities. The folded structure appears to play an important role in the interaction of 1233A with the target enzyme.

Experimental

Melting points were measured on a Yanagimoto hot stage apparatus and are uncorrected. Solutions were dried over $MgSO_4$, and concentrated under reduced pressure (rotary evaporator). ^{1}H-NMR spectra were measured on a JEOL FX-90 instrument unless otherwise noted and chemical shift values are given in parts per million relative to tetramethylsilane as an internal standard. IR spectra were measured on a Hitachi 270-30 infrared spectrophotometer. Mass spectra were measured on a JEOL JMS-HX110, JEOL JMS-AX505W or JEOL JMS-D300 spectrophotometer. The results of elementary analyses of carbon, hydrogen and nitrogen were within $\pm 0.4\%$ of the theoretical values. Physical data of 2-oxetanones and alkanals are listed in Tables I and II, respectively. All starting materials were commercial products unless otherwise indicated.

Of the alkanals, 3-phenylpropanal was obtained commercially, and 1-naphthylacetaldehyde,[14] 4-(1-naphthyl)butanal,[15] 3,3-diphenylpropanal[16] and 4,4-diphenylbutanal[17] were prepared according to the cited methods.

Methyl 8-Methyl-2-naphthoate (31d) K_2CO_3 (55.1 g, 399 mmol) and CH_3I (355.7 g, 2.50 mol) were added to a solution of 8-methyl-2-naphthoic acid[18] (46.4 g, 249 mmol) in acetone (1160 ml). The mixture was refluxed for 2 h, then isopropylether (IPE) (1200 ml) and water (1000 ml) were added. The organic layer was separated, dried and concentrated to give **31d** (49.4 g, 99.0%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 2.69 (3H, s), 3.94 (3H, s), 7.23—8.11 (5H, m), 8.5 (1H, t, $J=0.9$ Hz).

Methyl 8-Bromomethyl-2-naphthoate (32d) Compound **31d** (49.4 g, 247 mmol) and *N*-bromosuccinimide (NBS) (43.4 g, 247 mmol) were dissolved in benzene (150 ml), and benzoyl peroxide (4.77 g, 19.7 mmol) was added. The mixture was refluxed for 2 h, cooled and filtered. The filtrate was concentrated. The residue was subjected to silica gel column with *n*-hexane–AcOEt (20 : 1) to give **32d** (64.2 g, 93.2%), mp 107—108.0 °C (IPE). ^{1}H-NMR ($CDCl_3$) δ: 4.00 (3H, s), 4.98 (2H, s), 7.39—8.17 (5H, m), 8.89 (1H, t, $J=0.6$ Hz). EI-MS *m/z*: 277 (M^+), 279 (M^+).

Methyl 8-Formyl-2-naphthoate (33d) Sodium metal (5.29 g, 230 mmol) was dissolved in MeOH (300 ml) and compound **32d** (64.2 g, 230 mmol) and 2-nitropropane (21.2 g, 242 mmol) were added. The mixture was stirred for 3 h at room temperature followed by stirring for 4 h at 40 °C. Then, it was concentrated and dissolved in $CHCl_3$. The resultant solution was washed with 10% aqueous NaOH and saturated aqueous NaCl, dried and concentrated. The residue was subjected to silica gel column with *n*-hexane–AcOEt (20 : 1) to give **33d** (41.3 g, 83.8%), mp 103—104.0 °C (*n*-hexane–AcOEt). ^{1}H-NMR ($CDCl_3$) δ: 4.01 (3H, s), 7.63—8.15 (5H, m), 9.91 (1H, t, $J=0.6$ Hz), 10.43 (1H, s). IR (KBr): 1720, 1700 cm^{-1}.

Methyl 8-(2-Formylethenyl)-2-naphthoate (36d) Compound **36d** was synthesized by a similar procedure to the method of Cresp *et al.*[10] as follows. Compound **33d** (42.6 g, 199 mmol) and 1,3-dioxolan-2-ylmethyltriphenylphosphonium bromide (128.1 g, 298 mmol) were dissolved in *N*,*N*-dimethyl formamide (DMF) (800 ml), then a solution of $LiOCH_3$ (11.4 g, 300 mmol) in MeOH (800 ml) was added dropwise over 4 h at 70—80 °C. The mixture was cooled, concentrated, poured into water (1000 ml) and extracted with AcOEt. The extract was dried and concentrated. The residue was dissolved in tetrahydrofuran (THF) (500 ml) containing 10% aqueous HCl (500 ml) and stirred for 1 h at room temperature. The mixture was then poured into water (1000 ml) and extracted with CH_2Cl_2. The extract was washed with water, dried and concentrated. The residue was recrystallized from MeOH (220 ml) to give **36d** (20.21 g, 42.1%), mp 150—152.0 °C. ^{1}H-NMR ($CDCl_3$) δ: 4.01 (3H, s), 6.82 (1H, dd, $J=7.9$, 7.9 Hz), 7.51—8.44 (6H, m), 8.88 (1H, t, $J=0.7$ Hz), 9.94 (1H, d, $J=7.9$ Hz). IR (KBr): 1725, 1675 cm^{-1}. EI-MS *m/z*: 240 (M^+).

Methyl 8-(2-Formylethyl)-2-naphthoate (37d) A solution of compound **36d** (20.78 g, 47.9 mmol) in THF (400 ml) was stirred for 2 h with 5% Pd/C (8.0 g, 50% wet) in an H_2 atmosphere at room temperature and then filtered. The filtrate was concentrated and the obtained residue was subjected to silica gel column chromatography with *n*-hexane–AcOEt (20 : 1) to give **37d** (12.34 g, 59.0%), mp 52—53.0 °C (*n*-hexane–AcOEt).

Compounds **37a**—**g** were prepared in a manner similar to that de-

scribed for the preparation of **37d**.

Methyl 3-(3-Biphenylyl)propenoate (38m) $NaOCH_3$ (2.80 g, 51.9 mmol) was added to a solution of 3-biphenylaldehyde (**33m**) (6.51 g, 34.6 mmol) and methoxycarbonylmethyltriphenylphosphonium bromide (18.7 g, 45.0 mmol) in CH_2Cl_2 (100 ml). The mixture was stirred overnight at room temperature, washed with water, dried and concentrated. The residue was subjected to silica gel column chromatography with *n*-hexane–AcOEt (3 : 1) to give **38m** (8.00 g, 97.1%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 3.84 (3H, s), 6.48 (1H, d, J=16.2 Hz), 7.33—7.80 (9H, m), 7.75 (1H, d, J=7.2 Hz).

Methyl 3-(3-Biphenylyl)propanoate (39m) A solution of **38m** (7.83 g, 32.9 mmol) in MeOH (160 ml) was stirred for 1 h with 5% Pd/C (3.9 g, 50% wet) in an H_2 atmosphere at room temperature and then filtered. The filtrate was concentrated to give **39m** (5.62 g, 69.6%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 2.67—2.76 (2H, m), 2.94—3.13 (2H, m), 3.66 (3H, s), 7.10—7.65 (9H, m).

3-(3-Biphenylyl)propanol (42m) A solution of **39m** (5.43 g, 22.6 mmol) in Et_2O (27 ml) was added dropwise to a suspension of $LiAlH_4$ (0.86 g, 22.6 mmol) in Et_2O (54 ml). The mixture was refluxed for 1 h and then cooled in an ice bath. MeOH was added dropwise until no further reaction occurred. This mixture was added to dilute HCl and the whole was extracted with Et_2O. The extract was dried and concentrated to give **42m** (4.80 g, 100%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.73—2.06 (3H, m), 2.65—2.82 (2H, m), 3.64 (2H, t, J=6.8 Hz), 7.06—7.64 (9H, m).

3-(3-Biphenylyl)propanal (37m) (Swern Oxidation) A solution of dimethyl sulfoxide (DMSO) (2.2 ml) in CH_2Cl_2 (6 ml) was added dropwise to a solution of $(COCl)_2$ (1.36 ml, 15.5 mmol) in CH_2Cl_2 (34 ml) at −40 °C. The mixture was stirred for 10 min, then a solution of **42m** (3.00 g, 14.1 mmol) in CH_2Cl_2 (12 ml) was added dropwise. Stirring was continued for 25 min, and Et_3N (9.8 ml) was then added dropwise. The mixture was stirred for 5 min, washed with water, dried and concentrated. The residue was subjected to silica gel column chromatography with *n*-hexane–AcOEt (4 : 1) to give **37m** (2.267 g, 89.5%) as an oil.

Compounds **37h—j** were prepared in a manner to that described for the preparation of **37m**.

Benzyl 3-(3-Methoxycarbonylphenyl)propenoate (38l) Methyl 3-formylbenzoate (**33l**) (18.0 g, 110 mmol) and benzyloxycarbonylmethyltriphenylphosphonium bromide (69.92 g, 142 mmol) were treated in a similar manner to that described for the preparation of **38m** to give a mixture of *trans*- and *cis*-**38l** (21.4 g, 65.6%). *trans* Form: mp 109.5—110.5 °C (AcOEt). ^{1}H-NMR ($CDCl_3$) δ: 3.93 (3H, m), 5.29 (2H, s), 6.58 (1H, d, J=15.5 Hz), 7.20—8.00 (10H, m).

3-(3-Methoxycarbonylphenyl)propanoic Acid (40l) Compound **38l** was treated in a similar manner to that described for the preparation of **39m** to give **40l** (7.14 g, 94.4%), mp 80.5—81.5 °C ($CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 2.56—2.89 (2H, m), 2.90—3.10 (2H, m), 3.93 (3H, s), 7.32—7.55 (2H, m), 7.80—8.10 (2H, m), 8.62 (1H, br s).

Methyl 3-(3-Hydroxypropyl)benzoate (42l) Compound **42l** was synthesized according to the method described by Ishizumi *et al.*[19] as follows. Methyl chloroformate (3.05 ml) was added dropwise to a solution of **40l** (7.14 g, 34.3 mmol) and NEt_3 (2.1 ml) in THF (50 ml) at −15 °C. The mixture was stirred for 30 min and filtered. The filtrate was added dropwise to a solution of $NaBH_4$ (3.05 g, 92.6 mmol) in water (50 ml) at 5—10 °C followed by stirring for 2 h at room temperature. After acidification with 5% HCl, the mixture was extracted with AcOEt. The extract was washed with 5% aqueous Na_2CO_3, dried and concentrated to give **42l** (4.85 g, 72.8%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.63 (1H, br s), 1.72—2.10 (2H, m), 2.63—2.90 (2H, m), 3.69 (2H, t, J=5.4 Hz), 3.92 (3H, s), 7.28—7.52 (2H, m), 7.70—8.00 (2H, m).

Compound **42k** was prepared by this method. Compounds **42k, l** were treated in a similar manner to that described for the preparation of **37m** to give the corresponding propanals **37k, l**.

Methyl 4-(2-Formylethyl)benzoate (45a) Methyl 4-(2-chloro-2-formylethyl)benzoate (**44a**) (1.09 g, 48.1 mmol), prepared from **43a** by the method of Kanao *et al.*,[11] was dissolved in MeOH (11 ml), then K_2CO_3 (0.66 g) and 5% Pd/C (0.4 g, 50% wet) were added. The mixture was stirred under an H_2 atmosphere, filtered and concentrated. The residue was subjected to silica gel column chromatography with *n*-hexane–AcOEt (2 : 1) to give **45a** (0.57 g, 61.6%) as an oil.

Compound **45b** was prepared in a manner similar to that described for the preparation of **45a**.

***n*-Hexyl 3-(3-Hydroxypropyl)benzoate (46b)** Compound **42l** (1.22 g, 6.28 mmol) was dissolved in *n*-hexanol (12 ml) and *p*-TsOH (0.12 g, 0.62 mmol) was then added. The mixture was stirred for 2 h at 130—140 °C, dissolved in benzene (20 ml), washed with saturated aqueous $NaHCO_3$, dried and concentrated. The residue was subjected to silica gel column chromatography with $CHCl_3$ to give **46b** (1.26 g, 75.9%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.80—2.20 (14H, m), 2.66—2.95 (2H, m), 3.57—3.90 (2H, m), 4.35 (2H, t, J=7 Hz), 7.35—7.55 (2H, m), 7.87—8.10 (2H, m).

Compounds **46a** was prepared by this method and compounds **46a, b** were treated in a similar manner to that described for the preparation of **37m** to give the corresponding propanals **47a, b**.

Ethyl 6-(1-Naphthyl)-5-hexenoate (48b) A solution of 4-carboxybutyltriphenylphosphonium bromide[20] (19.95 g, 44 mmol) in DMSO (42 ml) was treated with KO*tert*-Bu (9.88 g, 88.0 mmol) at ambient temperature. The mixture was stirred for 20 min. A solution of 1-naphthaldehyde (**33a**) (6.25 g, 40.0 mmol) in DMSO (20 ml) was added. The mixture was stirred for 2 h, poured into water (200 ml) and extracted with $CHCl_3$. The aqueous layer was acidified with concentrated HCl and extracted with $CHCl_3$. The extract was washed with water, dried and concentrated to give an oil (13.3 g), which was dissolved in EtOH (250 ml). Acetyl chloride (15 ml) was added dropwise and the mixture was refluxed for 2 h then concentrated. The residue was dissolved in $CHCl_3$, and this solution was washed with saturated aqueous $NaHCO_3$, dried and concentrated. The residue was subjected to silica gel column chromatography with $CHCl_3$ to give **48b** (8.71 g, 81.1%, a mixture of *trans* and *cis* forms) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.00—1.40 (3H, m), 1.50—2.55 (6H, m), 3.91—4.30 (2H, m), 5.74—6.40 (1H, m), 6.31—8.22 (8H, m).

Ethyl 6-(1-Naphthyl)hexanoate (49b) Compound **48b** was treated in a similar manner to that described for the preparation of **39m** to give **49b** as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, J=6.8 Hz), 1.35—2.00 (6H, m), 2.30 (2H, t, J=6.8 Hz), 3.06 (2H, t, J=7.2 Hz), 4.15 (2H, q, J=6.8 Hz), 7.25—8.20 (7H, m).

6-(1-Naphthyl)hexanol (50b) Compound **49b** was treated in a similar manner to that described for the preparation of **42m** to give **50b** as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.20—2.00 (9H, m), 3.06 (2H, t, J=7.2 Hz), 3.61 (2H, t, J=5.4 Hz), 7.20—8.15 (7H, m).

Compounds **50a, c** were also prepared by this method, and compounds **50a—c** were treated in a similar manner to that described for the preparation of **37m** to give the corresponding alkanals **51a—c**.

3-(7-Methyl-1-naphthyl)propanol (55) A solution of 3-benzyloxypropyl bromide[21] (5.58 g, 24.4 mmol) and 7-methyl-1-tetralone[12] (**52**) (2.88 g, 18.0 mmol) in Et_2O (14 ml) was added to Mg ribbon (0.70 g, 28.8 mmol). The mixture was refluxed for 1 h, cooled, poured into saturated aqueous NH_4Cl (41 ml) and extracted with Et_2O. The extract was washed with water, dried and concentrated. The residue was subjected to silica gel column chromatography with *n*-hexane–AcOEt (5 : 1) to give **53** (4.07 g, 72.7%) as an oil. To a solution of this compound in toluene (25 ml), *p*-TsOH (25 mg, 0.133 mmol) was added. This mixture was refluxed for 2 h with a Dean Stark apparatus to remove water, and then washed with saturated aqueous $NaHCO_3$, dried and concentrated. The residue was subjected to silica gel column chromatography with *n*-hexane–AcOEt (20 : 1) to give **54** (3.58 g, 93.1%) as an oil. A mixture of **54** and sulfur (0.41 g, 12.8 mmol) was stirred for 30 min at 220 °C, and subjected to silica gel column chromatography with *n*-hexane–AcOEt (10 : 1) to give 3-(7-methyl-1-naphthyl)propyl benzyl ether (2.60 g, 73.4%) as an oil. To a solution of this product in MeOH (26 ml), 5% Pd/C (0.52 g, 50% wet) was then added. The mixture was stirred for 5 h under an H_2 atmosphere at room temperature and filtered. The filtrate was concentrated to leave the residue, which was subjected to silica gel column chromatography with *n*-hexane–AcOEt (2 : 1) to give **55** (1.63 g, 91.0%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.58 (1H, br s), 1.76—2.16 (2H, m), 2.48 (3H, s), 2.95—3.22 (2H, m), 3.55—3.82 (2H, m), 7.10—7.90 (6H, m).

Compound **55** was treated in a similar manner to that described for the preparation of **37m** to give the propanal **56**.

Benzyl 3-Hydroxy-2-hydroxymethyl-5-(7-methoxycarbonyl-1-naphthyl)-pentanoate (57a) A solution of diisopropylamine (15.8 g, 156 mmol) in dry THF (88.3 ml) was cooled to −40 °C and a solution of *n*-BuLi in hexane (1.6 mol/l) (86.1 ml, 138 mmol) was added dropwise over 25 min followed by stirring for 5 min under an N_2 atmosphere. The reaction mixture was warmed to 0 °C and then cooled to −78 °C. A solution of benzyl 3-hydroxypropanoate[9] (10.6 g, 58.8 mmol) in dry THF (32 ml) was added dropwise over 20 min followed by stirring for 10 min. The mixture was warmed to −20 °C, stirred for a further 10 min and cooled

to −78 °C again, followed by stirring for 10 min. A solution of methyl 8-(2-formylethyl)-2-naphthoate (**37d**) (15.8 g, 64.7 mmol) in dry THF (65 ml) was added dropwise to the above mixture over 30 min and the whole was stirred for 50 min. The reaction was quenched with saturated aqueous NH_4Cl (450 ml) and the mixture was stirred. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were dried and concentrated to give an orange oil. This oil was subjected to silica gel column chromatography with *n*-hexane–AcOEt (2:1) to give *anti*-**57a** (3.11 g) and *syn*-**57a** (2.85 g), each as an oil. The combined yield was 24.0%. *anti*-**57a**: ^{1}H-NMR ($CDCl_3$) δ: 1.88—2.18 (2H, m), 2.63—2.83 (1H, m), 2.97—3.59 (4H, m), 3.77—4.16 (3H, m), 3.96 (3H, s), 5.17 (2H, s), 7.30—8.12 (10H, m) 8.80 (1H, s). *syn*-**57a**: ^{1}H-NMR ($CDCl_3$): 1.84—2.13 (2H, m), 2.52—2.74 (1H, m), 2.78—3.44 (4H, m), 3.96 (3H, s), 3.90—4.17 (2H, m), 4.16—4.40 (1H, m), 5.18 (2H, s), 7.23—8.10 (10H, m), 8.80 (1H, s).

Benzyl *anti*-3-Hydroxy-5-(7-methoxycarbonyl-1-naphthyl)-2-triphenylmethoxymethylpentanoate (58a) A solution of *anti*-**57a** (2.84 g, 6.72 mmol) in CH_2Cl_2 (28.4 ml) was cooled in an ice-water bath. 4-Dimethylaminopyridine (0.163 g, 1.33 mmol), triphenylmethyl chloride (2.81 g, 10.1 mmol) and triethylamine (1.08 g, 10.8 mmol) were then added. The reaction mixture was stirred overnight at room temperature, diluted with CH_2Cl_2 (150 ml), washed with saturated aqueous $NaHCO_3$, dried and concentrated. The residue was subjected to silica gel column chromatography with *n*-hexane–AcOEt (4:1) to give **58a** (4.08 g, 89.9%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.62—1.86 (2H, m), 2.68—3.35 (4H, m), 3.47 (2H, d, J=5.9 Hz), 3.92 (3H, s), 3.85—4.10 (1H, m), 5.18 (2H, s), 7.00—8.10 (25H, m), 8.81 (1H, s).

***anti*-3-Hydroxy-5-(7-methoxycarbonyl-1-naphthyl)-2-triphenylmethoxymethylpentanoic Acid (59a)** A solution of **58a** (1.37 g, 2.06 mmol) in EtOH (26 ml) was stirred for 2 h with 5% Pd/C (0.6 g, 50% wet) under an H_2 atmosphere and then filtered. The filtrate was concentrated to give **59a** (1.17 g, 98.8%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.71—1.96 (2H, m), 2.67—2.85 (1H, m), 3.12—3.31 (2H, m), 3.51 (2H, d, J=5.9 Hz), 3.91 (3H, s), 3.80—4.14 (1H, m), 4.73 (2H, br s), 6.90—8.10 (20H, m), 8.80 (1H, s).

***trans*-4-[2-(7-Methoxycarbonyl-1-naphthyl)ethyl]-3-triphenylmethoxymethyl-2-oxetanone (60a)** Compound **59a** (1.00 g, 1.74 mmol) was dissolved in pyridine (18.8 ml) and cooled in an ice bath and then *p*-TsCl (1.30 g, 6.82 mmol) was added. The mixture was stirred for 10 min followed by standing overnight at 5 °C. After addition of MeOH (10 ml), the mixture was diluted with CH_2Cl_2 (150 ml), washed with water, dried and concentrated. The residue was subjected to silica gel column chromatography with $CHCl_3$ to give **60a** (0.90 g, 94.2%) as an amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 2.13—2.45 (2H, m), 3.13—3.37 (2H, m), 3.28 (2H, d, J=3.3 Hz), 3.46—3.68 (1H, m), 3.95 (3H, s), 4.59 (1H, dt, J=4.1, 6.6 Hz), 7.00–8.14 (20H, m), 8.74 (1H, s).

***trans*-3-Hydroxymethyl-4-[2-(7-methoxycarbonyl-1-naphthyl)ethyl]-2-oxetanone (23)** Compound **60a** (0.90 g, 1.61 mmol) was dissolved in *n*-BuOH (20 ml). The solution was cooled in an ice-water bath and CF_3COOH (8.8 g, 86.3 mmol) was added dropwise. The mixture was stirred for 2 h at room temperature, poured into saturated aqueous $NaHCO_3$ (100 ml) and extracted with AcOEt (300 ml). The extract was dried and concentrated. The residue was subjected to silica gel column chromatography with $CHCl_3$ to give **23** (0.403 g, 79.5%) as white crystals. mp 91—92.0 °C (*n*-hexane–AcOEt). IR (KBr): 1820, 1700 cm^{-1}. Nuclear Overhauser effect (NOE) between 3-C$\underline{H}_2$OH and 4-$\underline{H}$ on the 2-oxetanone ring was observed, whereas it was not observed in the *cis*-form of **23** prepared alternatively from *syn*-**57a**.

Compounds **5**, **6**, **8**, **10**—**13**, **21** and **22** were prepared in a manner similar to that described for the preparation of **23**.

Ethyl *anti*-3-Hydroxy-5-(3-biphenylyl)-2-triphenylmethoxymethylpentanoate (58b) Treatment of 3-(3-biphenylyl)propanal (**37m**) with ethyl 3-hydroxypropanoate[9] in a manner similar to that described for the preparation of **57a** gave a mixture of *anti*- and *syn*-**57b**. The mixture was treated in a manner similar to that described for the preparation of **58a** and separated by column chromatography to give **58b** as an oil and the *syn* product. The combined yield was 60.6%. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=6.8 Hz), 1.50—1.78 (3H, m), 2.50—3.07 (2H, m), 3.45 (2H, d, J=5.8 Hz), 3.80—4.20 (1H, m), 4.22 (2H, q, J=6.8 Hz), 7.00—7.60 (24H, m).

***trans*-4-[2-(3-Biphenylyl)ethyl]-3-triphenylmethoxymethyl-2-oxetanone (60b)** A 1 N KOH solution (5.6 ml) was added dropwise to a solution of **58b** (1.59 g, 2.78 mmol) in EtOH (6 ml) in an ice-bath. The mixture was stirred overnight at room temperature. After the removal of EtOH, the mixture was acidified with 2 N HCl and extracted with Et_2O. The extract was dried and concentrated. The residue was treated in a similar manner to that described for the preparation of **60a** to give **60b** (0.762 g, 52.1%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.86—2.46 (2H, m), 2.50—3.00 (2H, m), 3.10—3.84 (3H, m), 4.55 (1H, dt, J=4.2, 7.0 Hz), 7.00—7.60 (24H, m). EI-MS *m/z*: 524 (M^+). *Anal.* Calcd. for $C_{37}H_{32}O_3$: C, 84.70; H, 6.15. Found: C, 84.42; H, 6.40.

***trans*-3-Hydroxymethyl-4-[2-(3-biphenylyl)ethyl]-2-oxetanone (26)** Compound **60b** was treated in a similar manner to that described for the preparation of **23** to give **26** (80.5%) as an oil.

Compounds **2**—**4**, **14**—**20** and **27**—**30** were prepared in a manner similar to that described for the preparation of **26**.

***trans*-3-Hydroxymethyl-4-[2-(7-carboxy-1-naphthyl)ethyl]-2-oxetanone (24).** A solution of **23** (34 mg, 0.171 mmol) in 10% aqueous MeOH (68 ml) was treated with porcine liver esterase (6300 units). The mixture was stirred at room temperature with dropwise addition of 0.02 N NaOH to maintain the pH between 6.5 and 7.0 until the pH no longer changed. The reaction mixture was concentrated and extracted with $CHCl_3$ and then the extract was concentrated. The residue was chromatographed on silica gel with $CHCl_3$ to give **24** (13 mg, 40.0%), mp 110—113 °C (*n*-hexane–AcOEt).

Compounds **7** and **9** were prepared in a manner similar to that described for the preparation of **24**.

***In Vitro* Assay** Compounds were evaluated for inhibitory activity towards HMG-CoA synthase by the method described previously.[2]

***In Vivo* Assay** Compounds were evaluated for inhibitory activity on cholesterol biosynthesis in standard chow-fed male ddY mice at 5 weeks of age. In this assay, incorporation of ^{14}C-acetate radioactivity into digitonin-precipitable sterols was measured according to the method described by Endo *et al.*[22] with slight modifications. Briefly, the compounds were administered orally to the animals as a suspension in 0.5% methylcellulose at the indicated doses (Table IV). Control animals received 0.5% methylcellulose alone. ^{14}C-Acetate was injected intraperitoneally (800 μCi/kg body wt.) 2 h after *p.o.* administration of the test compounds. After a labeling period of 40 min, blood was collected under diethylether anesthesia, then the animals were killed and the liver and small intestines were immediately removed. Samples of liver and small intestine were used to determine the rate of cholesterol synthesis in these organs, and blood samples were used to determine serum triglyceride concentration.

For the cholesterol synthesis assay, samples of liver and small intestine (about 1 g each) were homogenized in 5 ml of 15% KOH–ethanol, saponified at 75 °C for 2 h, and extracted with petroleum ether. The extracts were evaporated to dryness, and the residue was redissolved in 1 ml of 0.1% cholesterol–acetone solution, and precipitated by mixing the solution with 2 ml of 0.5% digitonin–50% ethanol solution. After standing overnight, the precipitated digitonide was collected on glass filters, which were then washed with acetone, air-dried and placed in scintillation vials. The digitonide trapped on the glass filters was dissolved in 0.5 ml of Hyamine 10-X (Packard) for 10 min at room temperature and counted in a liquid scintillation counter. The values of percent inhibition shown in Table IV were calculated from the rate of cholesterol synthesis expressed as radioactivity (dpm) per g of wet weight of tissue.

The serum triglyceride level was determined enzymatically using a commercial assay kit (Triglyceride E-Test, Wako).

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