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

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Structural analogs of 1233A, a microbial metabolite inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) synthase, were designed and synthesized. The 2-oxetanone moiety was left intact. All analogs prepared were tested for inhibition of HMG-CoA synthase activity and sterol synthesis in mouse liver and for effect on serum triglyceride levels. Of these analogs, *trans*-4-[2-[3-(7-carboxy-2-naphthyl)phenyl]ethyl]-3-hydroxymethyl-2-oxetanone (4a) showed the highest inhibitory activity *in vitro*, and also had *in vivo* inhibitory activity without causing any increase in triglyceride level.

Keywords HMG-CoA synthase; inhibitor; cholesterol biosynthesis; 1233A analog; triglyceride level; structure–activity relationship

Subsequent to the discovery[1] of the microbial metabolite 1233A as an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) synthase, we started a series of studies directed toward the development of structural analogs of 1233A. We have already obtained analogs showing potent inhibitory activity.[2] Among them, compound **2** showed *in vivo* activity comparable to that of 1233A (**1**), but greatly increased the serum triglyceride level, unlike 1233A (**1**). In addition, compound **3** showed moderate activity *in vivo* with a slight triglyceride increment. We consequently started to investigate analogs of **3** to obtain a highly active analog without the triglyceride level increment.

The 1233A analogs reported[2] were designed to mimic the folded structure of 1233A by the introduction of an aromatic ring, as illustrated in Fig. 1. However, it is probable that such folded structures (*e.g.*, conformer I) are not thermodynamically stable and that these structures (*e.g.*, **2** and **3**) are more compact than that of 1233A. This characteristic might be related to the increase of the triglyceride concentration and to the low activity *in vivo* shown by these 1233A analogs.[2] On the basis of this hypothesis, we attempted to mimic the extended structure of 1233A (conformer III shown in Fig. 2).

There are two methylenes between the 2-oxetanone and the aromatic rings in **2** and **3**. If an aromatic ring is regarded as a substitute for the $\alpha\beta,\gamma\delta$-unsaturated system of 1233A, these structures of **2** and **3** are inconsistent with the fact that there are six sp^3 carbons (not including the methyl group) between the 2-oxetanone ring and the unsaturated moiety in 1233A. The number of methylenes in the reported[2] analogs was decided experimentally as the optimum. Hence, the aromatic ring A (*e.g.*, in analog **3**) should be regarded not as an isoster of the $\alpha\beta,\gamma\delta$-unsaturated system of 1233A, but rather as an isoster of the carbon block from position 6 to position 9 of 1233A. Therefore, in this study, the first ring A was mostly fixed as ring A_1 of conformer III. When the structure of **3** is compared with that of conformer III (Fig. 2), the second aromatic ring B of **3** should be more distant from the ring A. Hence, elongation of the structure of **3**, *i.e.*, the introduction of methylenes and hetero atoms between aromatic rings A and B, was planned. Also, imaginary rings A_1, B_1, C_1 and D_1 were inserted into the extended structure of 1233A and some combinations of these were investigated, as shown in Fig. 2. This report describes the structure–activity relationships of mimics of 1233A with aromatic rings.

Chemistry 2-Oxetanones were prepared from the corresponding key alkanols (**23a—c**) by the procedure shown in Chart 1. All analogs are racemic and their physical data are listed in Table I.

The procedures shown in Chart 1 are similar to those reported[2,3] except for the method used for obtaining the *anti*-3-hydroxycarboxylic ester **25**. Aldol reaction of propanal **24** gave **25** as a mixture of *anti*- and *syn*-isomers. Previously,[2,3] this mixture was treated with triphenylmethyl chloride and separated into its isomers by column chromatography, but the two isomers could not be

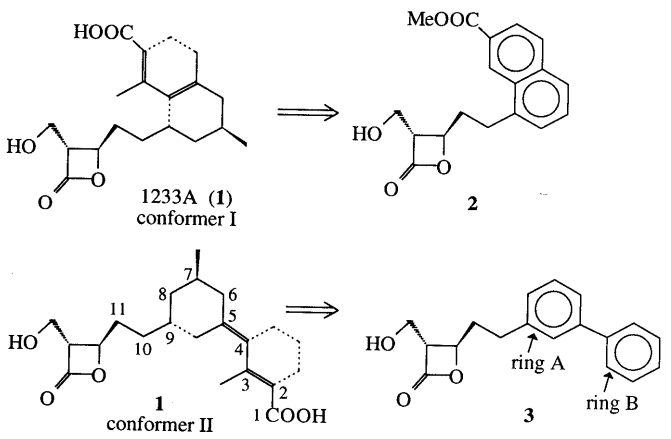


Fig. 1. Drug Design Based on the Folded Structure of 1233A (**1**)

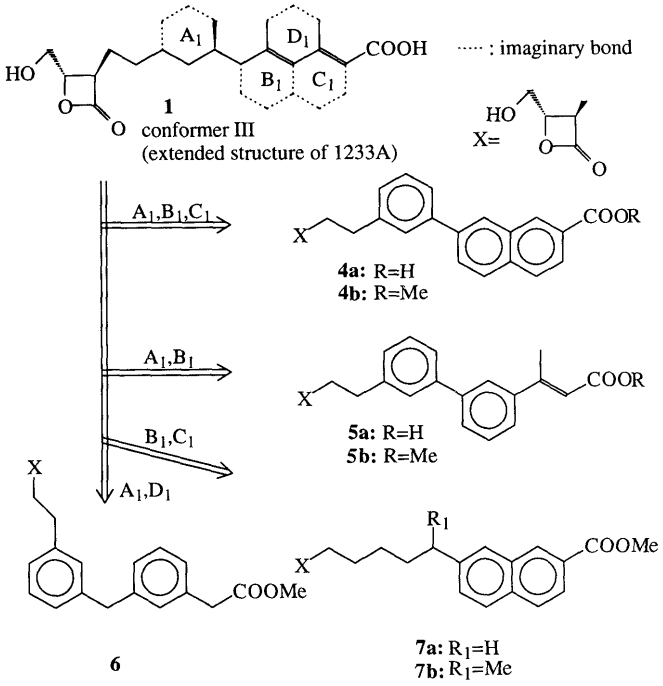


Fig. 2. Drug Design by the Combination of Imaginary Rings

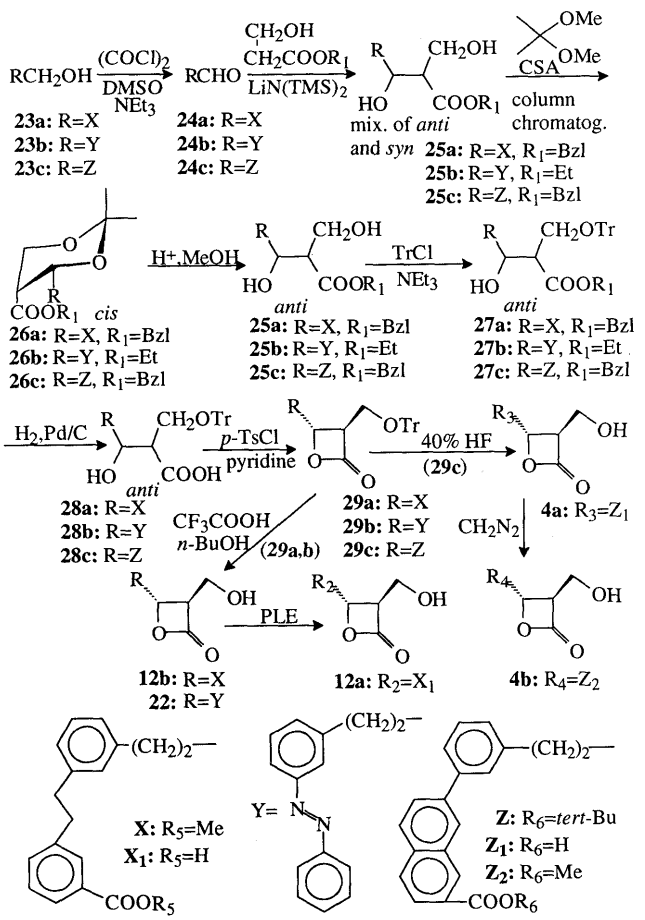


Chart 1. Typical Procedure for Synthesis of 2-Oxetanones

separated completely by one pass. We therefore had to repeat the chromatography to obtain the required amount. In this study, we investigated another procedure. Compound **25**, the product of aldol condensation, was treated with 2,2-dimethoxypropane to give a mixture of *trans*- and *cis*-dioxanes, **26** in the ratio of *ca.* 1 : 1, which were easily separated by one pass of column chromatography. The hydrolysis of the *cis*-isomer of the dioxane **26** gave *anti*-**25**, which was treated as reported[2] previously to give a *trans*-2-oxetanone **12b** and **22**. Analog **12a** with a carboxyl group was prepared by the hydrolysis of **12b** with porcine liver esterase (PLE) as reported.[2] However, the hydrolysis of **4b** by PLE was not successful. Thus, the propanol **23c** with a *tert*-butoxycarbonyl group was prepared and treated as described above to give the 3-triphenylmethoxymethyl-2-oxetanone **29c**, and deprotection with 40% hydrogen fluoride gave **4a**. Compound **4a** was treated with diazomethane to give the corresponding methyl ester **4b**.

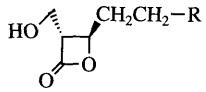
The key alkanols were synthesized as shown in Charts 2—7 and their physical data are listed in Table II.

As shown in Chart 2, the Grignard reaction of the benzaldehyde **32** with 2-(3-bromophenyl)-4,4-dimethyloxazoline followed by deprotection and hydrogenolysis gave the propanol **35**. The propanols **37a**—**c** were prepared similarly. The Wittig reaction of **32** with substituted benzylphosphonium bromide followed by hydrogenation and deprotection gave the propanols **40** and **23a**. As shown in Chart 3, the aldol reaction of **32** with methyl 3-acetylbenzoate followed by the reduction gave the propanol **42**. The propanol **44** was prepared in a manner similar to the procedure shown in Chart 2. The benzaldehyde **32** was converted by Wittig reaction, reduction and Swern oxidation to the pentanal **46**, which was treated as described for the preparation of **23a** to give **48**. As Chart 4 shows, the alkylation of methyl 3-hydroxybenzoate with the benzylbromide **49** (prepared from **31**) gave the propanol **50**. The organo zinc compound prepared from **49** was coupled with methyl 3-bromophenylacetate to give the propanol **51**. Chart 5 shows the procedure for propanols **23b** and **58** with a hetero atom linkage, and as shown in Chart 6, the aryl coupling of **59** followed by the Wittig–Horner reaction gave the propanol **61**. As shown in Chart 7, benzyl alcohol **63** prepared by the aryl coupling of **62** was treated as reported[2] to give the propanol **64**, hydrolysis and esterification of which gave the propanol **23c** with a *tert*-butoxycarbonyl group. The naphthaldehyde **65** was converted by Wittig reaction and reduction to the hexanol **66**. The heptanol **69** was prepared *via* Wittig reaction of **68**, which was prepared from **65** by Grignard reaction and oxidation.

Inhibition of HMG-CoA Synthase and Cholesterol Biosynthesis in the Mouse Liver The 2-oxetanones, which were synthesized as 1233A analogs, were evaluated for inhibitory activity against HMG-CoA synthase in a cell-free system and against cholesterol biosynthesis in mouse liver, and tests were also performed to ascertain whether the 2-oxetanones increased triglyceride levels. The procedures for these evaluations were reported previously.[2,4] The results are summarized in Table III.

The 2-oxetanones **8**, **10** and **15** with methylenes between the two aromatic rings of **3** showed increased inhibitory activity *in vitro* with increase in the number of methylenes, though **17** with four methylenes was less active than **15**

TABLE I. 4-Sustituted-3-hydroxymethyl-2-oxetanones



Compd.	R	mp (°C)	Formula	Elementary analysis Calcd (Found)			MS M^+	High MS Calcd (Found)	^{1}H-NMR ($CDCl_3$) δ[a]
				C	H	N			
8	3-$C_6H_5CH_2C_6H_4$–	Oil	$C_{19}H_{20}O_3$				296	296.1412 (296.1408)	1.90 (1H, br s), 2.05—2.30 (2H, m), 2.60—2.87 (2H, m), 3.24—3.40 (1H, m), 3.56—4.07 (2H, m), 4.00 (2H, s), 4.59 (1H, dt, J=4.0, 6.8 Hz), 7.00—7.50 (9H, m)
9	3-(3-MeOOC$C_6H_5CH_2$)C_6H_4–	Oil	$C_{21}H_{22}O_5$				354	354.1467 (354.1448)	1.86—2.37 (3H, m), 2.11—2.93 (2H, m), 3.30—3.55 (1H, m), 3.35—4.16 (2H, m), 3.86 (3H, s), 4.00 (2H, s), 4.53 (1H, dt, J=3.2, 7.2 Hz), 6.90—7.95 (8H, m)
10	3-[$C_6H_5(CH_2)_2$]C_6H_4–	74.5—75.5	$C_{20}H_{22}O_3$	77.39 (77.45	7.14 7.18)		310	310.1569 (310.1603)	1.74 (1H, br s), 1.85—2.45 (2H, m), 2.52—2.86 (2H, m), 2.90 (4H, s), 3.23—3.45 (1H, m), 3.55—4.18 (2H, m), 4.64 (1H, dt, J=4.2, 6.8 Hz), 7.13—8.30 (9H, m)
11	3-[2-MeOOC$C_6H_5(CH_2)_2$]C_6H_4–	Oil	$C_{22}H_{24}O_5$				368	368.1624 (368.1634)	1.88—2.30 (2H, m), 2.39 (1H, br t), 2.51—3.00 (4H, m), 3.10—3.42 (3H, m), 3.55—4.18 (2H, m), 3.88 (3H, s), 4.57 (1H, dt, J=4.2, 7.2 Hz), 6.90—7.55 (7H, m), 7.80—7.96 (1H, m)
12b	3-[3-MeOOC$C_6H_5(CH_2)_2$]C_6H_4–	71—73	$C_{22}H_{24}O_5$	71.72 (71.59	6.57 6.69)		368		1.85—2.35 (2H, m), 2.40—3.08 (3H, m), 2.93 (4H, s), 3.26—3.45 (1H, m), 3.58—4.18 (2H, m), 3.89 (3H, s), 4.57 (1H, dt, J=4.0, 7.2 Hz), 6.88—8.00 (8H, m)
12a	3-[3-HOOC$C_6H_5(CH_2)_2$]C_6H_4–	113—115	$C_{21}H_{22}O_5$				354		1.92—2.30 (2H, m), 2.53—3.22 (2H, m), 2.93 (4H, s), 3.27—3.50 (1H, m), 3.66—4.10 (2H, m), 4.56 (1H, dt, J=3.6, 7.2 Hz), 5.73 (2H, br s), 6.90—8.13 (8H, m) (in DMSO-d_6)
13	3-[4-MeOOC$C_6H_5(CH_2)_2$]C_6H_4–	97.5—98.5	$C_{22}H_{24}O_5$	71.72 (71.85	6.57 6.69)		368		1.82—2.20 (3H, m), 2.60—2.87 (2H, m), 2.93 (4H, s), 3.24—3.46 (1H, m), 3.90 (3H, s), 3.70—4.08 (2H, m), 4.52 (1H, dt, J=3.6, 7.2 Hz), 6.85—7.32 (6H, m), 7.92 (2H, d, J=7.6 Hz)
14	3-[3,4-(MeOOC)$_2C_6H_5(CH_2)_2$]C_6H_4–	Oil	$C_{24}H_{26}O_7$				426	426.1679 (426.1692)	1.90—2.19 (2H, m), 2.28 (1H, br s), 2.58—2.87 (2H, m), 2.92 (4H, s), 3.27—3.46 (1H, m), 3.90 (6H, s), 3.72—4.05 (2H, m), 4.52 (1H, dt, J=4.0, 7.2 Hz), 6.81—7.72 (7H, m)
15	3-[$C_6H_5(CH_2)_3$]C_6H_4–	Oil	$C_{21}H_{24}O_3$				324	324.1725 (324.1757)	1.58—2.38 (4H, m), 2.46—2.98 (7H, m), 3.27—3.41 (1H, m), 3.57— 4.18 (2H, m), 4.58 (1H, dt, J=4.3, 6.8 Hz), 6.90—7.53 (9H, m)
16	3-[3-MeOOC$C_6H_5(CH_2)_3$]C_6H_4–	Oil	$C_{23}H_{26}O_5$				382	382.1780 (382.1784)	1.72 (1H, br s), 1.82—2.32 (4H, m), 2.48—2.90 (6H, m), 3.28—3.47 (1H, m), 3.66—4.12 (2H, m), 3.91 (3H, s), 4.59 (1H, dt, J=4.3, 7.2 Hz), 6.92—7.47 (6H, m), 7.74—7.95 (2H, m)
17	2-[$C_6H_5(CH_2)_4$]C_6H_4—	66—68	$C_{22}H_{26}O_3$	78.08 (77.71	7.74 7.84)		338		1.40—2.34 (7H, m), 2.42—2.89 (6H, m), 3.27—3.41 (1H, m), 3.55— 4.10 (2H, m), 4.57 (1H, dt, J=4.0, 6.6 Hz), 6.90—7.53 (9H, m)

TABLE I. (continued)

Compd.	R	mp (°C)	Formula	Elementary analysis Calcd (Found)			MS M^+	High MS Calcd (Found)	^{1}H-NMR ($CDCl_3$) δ[a]
				C	H	N			
18	3-[3-MeOOCC$_6$H$_5$(CH$_2$)$_4$]C$_6$H$_4$–	Oil	$C_{24}H_{28}O_5$				396	396.1937 (396.1977)	1.45—1.86 (4H, m), 1.90—2.40 (3H, m), 2.42—2.86 (6H, m), 3.25—3.47 (1H, m), 3.57—4.10 (2H, m), 3.90 (3H, s), 4.59 (1H, dt, J=4.2, 7.2 Hz), 6.90—7.46 (6H, m), 7.74—7.98 (2H, m)
19	3-[3-MeOOCC$_6$H$_5$(CH$_2$)$_6$]C$_6$H$_4$–	Oil	$C_{26}H_{32}O_5$				424	424.2250 (424.2224)	1.02—1.88 (9H, m), 1.87—2.33 (2H, m), 2.33—2.95 (6H, m), 3.28—3.42 (1H, m), 3.58—4.02 (2H, m), 3.84 (3H, s), 4.57 (1H, dt, J=4.0, 6.8 Hz), 6.82—7.95 (8H, m)
4b	3-(7-MeOOC-2-C$_{10}$H$_6$)C$_6$H$_4$–	106.5—108	$C_{24}H_{22}O_5$	73.83 (73.91	5.68 5.65)		390		1.69 (1H, br s), 1.98—2.40 (2H, m), 2.70—3.02 (2H, m), 3.30—3.52 (1H, m), 3.60—4.20 (2H, m), 3.98 (3H, s), 4.68 (1H, dt, J=4.1, 7.0 Hz), 7.13—8.22 (9H, m), 8.67 (1H, s)
4a	3-(7-HOOC-2-C$_{10}$H$_6$)C$_6$H$_4$–	178.5—180.5	$C_{23}H_{20}O_5$	73.39 (73.11	5.36 5.35)		376		2.06—2.40 (2H, m), 2.72—3.05 (2H, m), 3.37—3.50 (1H, m), 3.70—4.00 (2H, m), 4.68 (1H, dt, J=4.1, 6.8 Hz), 5.16 (2H, br s), 7.19—8.26 (9H, m), 8.65 (1H, s) (in DMSO-d_6)
5b	3-[3-[MeOOCCH=C(CH$_3$)]C$_6$H$_4$]C$_6$H$_4$– (*trans*)	Oil	$C_{23}H_{24}O_5$				380	380.1624 (380.1653)	1.67 (1H, br s), 1.90—2.38 (2H, m), 2.62 (3H, d, J=1.0 Hz), 2.73—2.98 (2H, m), 3.32 (1H, m), 3.77 (3H, s), 3.65—4.17 (2H, m), 4.65 (1H, dt, J=3.6, 7.2 Hz), 6.21 (1H, d, J=1.0 Hz), 7.13—7.68 (8H, m)
5a	3-[3-[HOOCCH=C(CH$_3$)]C$_6$H$_4$]C$_6$H$_4$– (*trans*)	109—111	$C_{22}H_{22}O_5$	72.12 (72.09	6.05 6.36)		366		1.97—2.48 (2H, m), 2.63 (3H, d, J=1.0 Hz), 2.72—3.02 (2H, m), 3.34—3.53 (1H, m), 3.70—4.13 (2H, m), 4.65 (1H, dt, J=3.6, 7.2 Hz), 5.30—6.20 (2H, br s), 6.23 (1H, d, J=1.0 Hz), 7.08—7.75 (8H, m)
6	3-(3-MeOOCCH$_2$C$_6$H$_4$)CH$_2$C$_6$H$_4$–	Oil	$C_{22}H_{24}O_5$				368	368.1624 (368.1612)	1.84—2.50 (3H, m), 2.53—2.94 (2H, m), 3.17—3.38 (1H, m), 3.59 (2H, s), 3.68 (3H, s), 3.93 (2H, s), 3.40—4.10 (2H, m), 4.51 (1H, dt, J=4.2, 6.8 Hz), 6.93—7.48 (8H, m)
7a	3-(7-MeOOC-2-C$_{10}$H$_6$)(CH$_2$)$_3$–	73.5—74.5	$C_{21}H_{24}O_5$				356	356.1624 (356.1638)	1.30—1.98 (9H, m), 2.80 (2H, t, J=7.2 Hz), 3.30—3.47 (1H, m), 3.70—4.15 (2H, m), 3.98 (3H, s), 4.58 (1H, dt, J=3.6, 7.2 Hz), 7.35—8.08 (5H, m), 8.53 (1H, s)
7b	7-MeOOC-2-C$_{10}$H$_6$CH(CH$_3$)(CH$_2$)$_2$–	Oil	$C_{22}H_{26}O_5$				370	370.1780 (370.1772)	1.33 (2H, d, J=7.2 Hz), 1.50—2.12 (10H, m), 2.73—3.01 (1H, m), 3.24—3.46 (1H, m), 3.66—4.18 (2H, m), 3.98 (3H, s), 4.55 (1H, dt, J=4.1, 7.2 Hz), 7.35—8.10 (5H, m), 8.57 (1H, s)
20	3-(3-MeOOCC$_6$H$_4$OCH$_2$)C$_2$H$_4$–	Oil	$C_{21}H_{22}O_6$				370	370.1416 (370.1456)	2.02—2.40 (3H, m), 2.68—2.74 (2H, m), 3.26—3.45 (1H, m), 3.60—4.10 (2H, m), 3.90 (3H, s), 4.58 (1H, dt, J=3.6, 7.2 Hz), 5.10 (2H, s), 7.04—7.71 (8H, m)
21	3-(3-MeOOCC$_6$H$_4$CONH)C$_6$H$_4$–	127—130	$C_{21}H_{21}NO_6$	65.78 (65.41	5.52 5.52	3.65 3.75)	383		2.04—2.40 (2H, m), 2.60 (1H, br s), 2.71—2.94 (2H, m), 3.30—3.47 (1H, m), 3.72—4.10 (2H, m), 3.97 (3H, s), 4.61 (1H, dt, J=4.2, 7.2 Hz), 6.96—8.55 (9H, m)
22	3-C$_6$H$_5$–N=N–C$_6$H$_4$–	70—72	$C_{18}H_{18}N_2O_3$				310	310.1317 (310.1307)	1.96 (1H, br s), 2.05—2.40 (2H, m), 2.78—3.05 (2H, m), 3.33—3.56 (1H, m), 3.68—4.20 (2H, m), 4.66 (1H, dt, J=4.2, 7.2 Hz), 7.36—8.16 (9H, m)

a) Measured in 90 Hz unless otherwise noted.

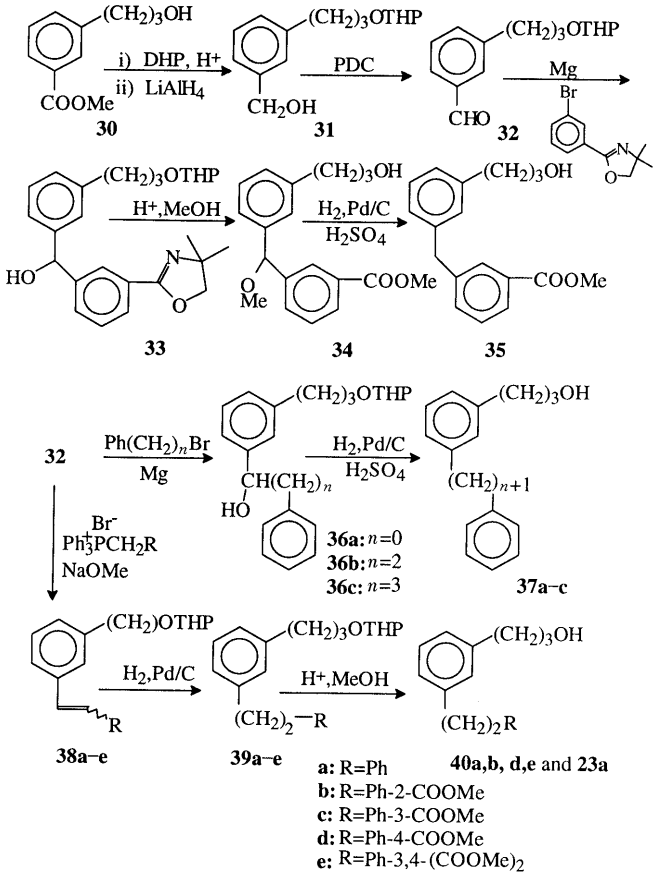


Chart 2. Synthesis of Propanols **35**, **37**, **40** and **23a**

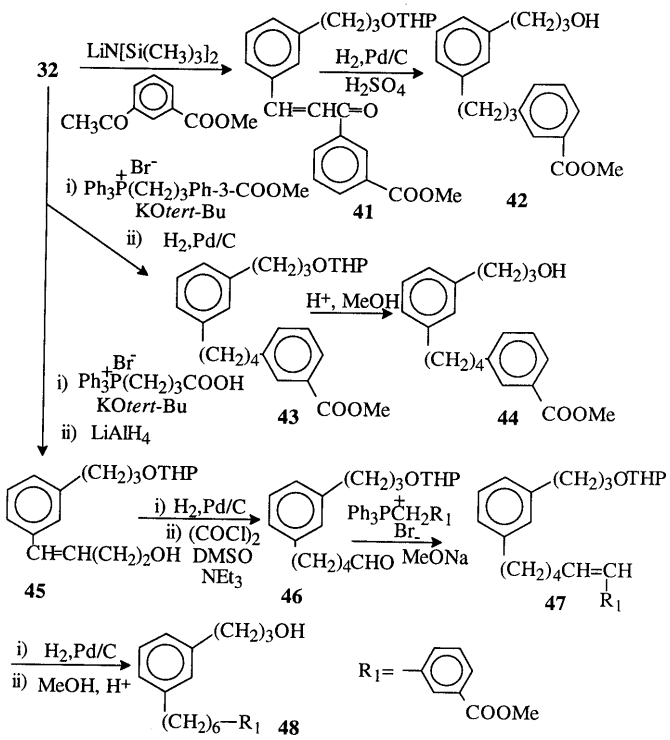


Chart 3. Synthesis of Propanols **42**, **44** and **48**

with three methylenes. Among 2-oxetanones with a methoxycarbonyl group, although the analog **9** with one methylene showed low activity, the analogs (**12b**, **16** and **18**) with two to four methylenes showed high activities, which were similar to each other. The introduction of six methylenes (**19**) caused decrease of activity, probably because of the great difference in size from 1233A. Although many compounds were active *in vivo*, it is unclear why others (*e.g.*, **11** and **18**) did not show significant inhibitory activity *in vivo*.

In the 2-oxetanones with two methylenes between the aromatic rings, a methoxycarbonyl group was introduced into ring B. In these analogs, the *meta*-substituted compound (**12b**) had higher activity *in vitro* and *in vivo* than the *ortho*- and *para*-substituted ones (**11** and **13**). Since only **12b** could be regarded as a mimic fixed by rings

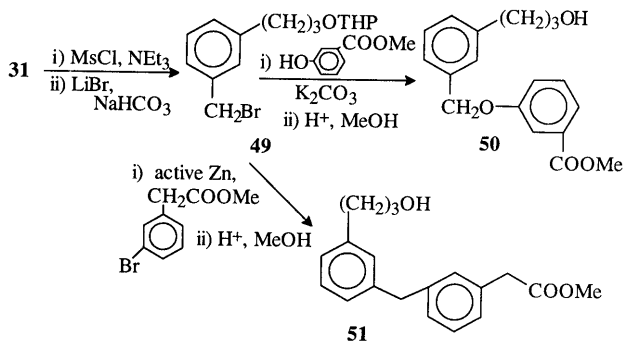


Chart 4. Synthesis of Propanols **50** and **51**

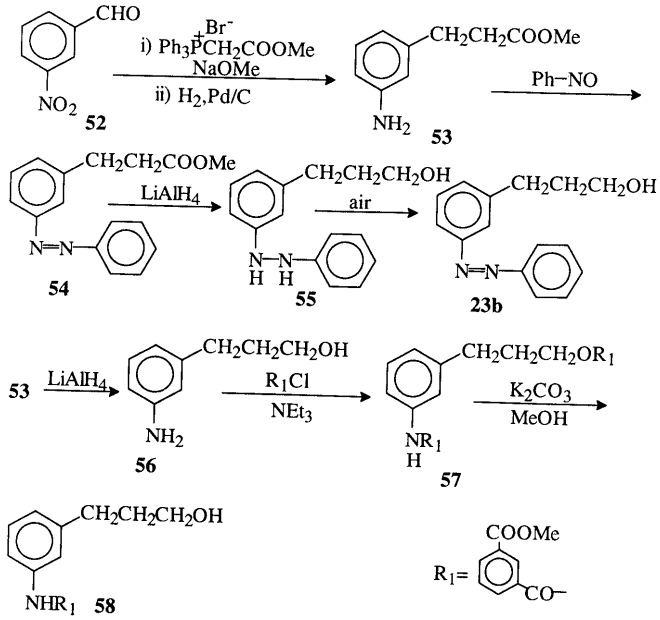


Chart 5. Synthesis of Propanols **23b** and **58**

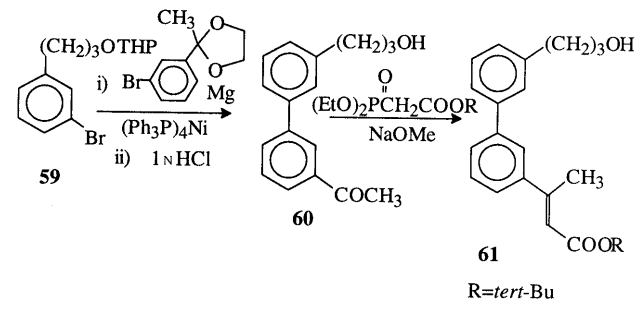


Chart 6. Synthesis of Propanol **61**

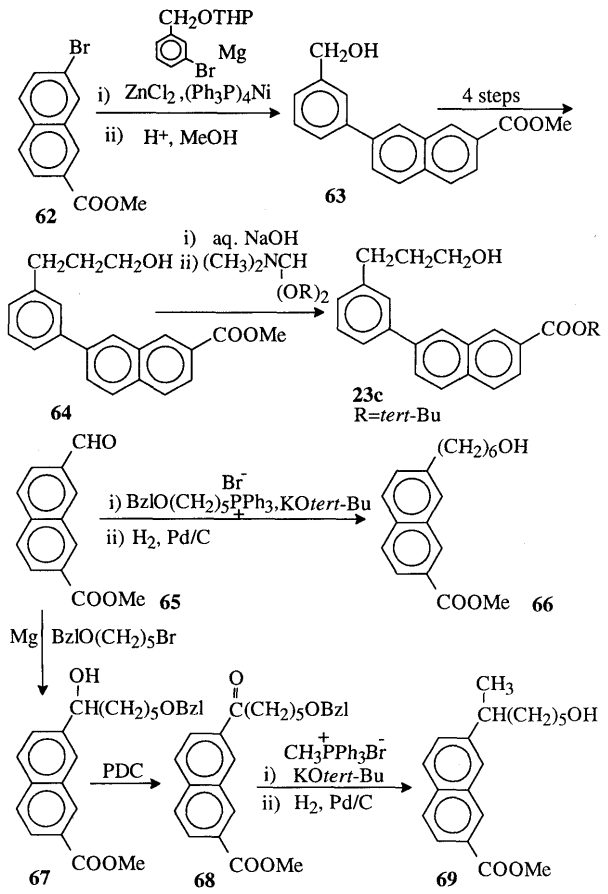


Chart 7. Synthesis of Propanols **23c**, **66** and **69**

A_1 and C_1 (Fig. 2), this result was as expected. Introduction of two methoxycarbonyl groups decreased the activity (**14**). The 2-oxetanones with hetero atom linkage showed either lower activity *in vitro* than the corresponding carbon analogs (**20** and **21** *vs.* **12b**), or equal activity (**22** *vs.* **10**). As for *in vivo* activity, only **68** was significantly active.

The 2-oxetanones **4a**, **b** and **5a**, **b**, designed as shown in Fig. 2, were as active as 1233A *in vitro*, but only **4a** was significantly active *in vivo*. The reason for this is unknown. When the activities of the biphenyl analogs **4b** and **5b** are compared with that of **3**, the extension of a conjugated system can be expected to result in high activity. The 2-oxetanone **4a** with a phenylnaphthyl group showed the highest activity *in vitro* in this study. It is interesting that **6** had high activity *in vivo*, although its activity *in vitro* was low. The 2-oxetanone **7a** containing five methylenes between the aromatic ring and the 2-oxetanone ring, and the similar analog **7b**, with a methyl group on the methylene chain, showed low activity *in vitro*. This indicates that the aromatic ring A_1 is necessary for synthetic 1233A analogs to show high inhibitory activity.

It is notable that 2-oxetanones with a carboxyl group showed similar activity to that of the corresponding methyl esters (**12a** *vs.* **12b**, **4a** *vs.* **4b** and **5a** *vs.* **5b**). This relationship is similar to that in the case of 1233A and its corresponding methyl esters,[4a] indicating that these analogs mimic the structure of 1233A.

Increase in Serum Triglyceride Level 2-Oxetanones with a methoxycarbonyl group did not significantly increase the triglyceride level in serum (**11**, **12b**, **13**, **16**, **18**, **6**, **20** and **21**), while those without that group did increase it (**8**, **10**, **15**, **17** and **22**). In particular, 2-oxetanones with a carboxyl group had almost no effect on the triglyceride level (**12a**, **4a** and **5a**), indicating that a carboxyl group in the side chain prevents the increase of this level. 2-Oxetanones with the side chain designed by the combination of imaginary rings shown in Fig. 2 also had little effect on this level (**4a**, **b**, **5a**, **b**, **6** and **7b**).

Conclusion

By means of the strategy described above, we obtained highly active 1233A analogs (*e.g.*, **4a**) which did not cause any triglyceride increment. While previous compounds with a carboxyl group were much less active than the corresponding methyl esters,[2] our compounds were more active than, or as active as the corresponding methyl esters (*e.g.*, **12a** *vs.* **12b** and **4a** *vs.* **4b**). This finding is consistent with the previously reported relationship[4a] between the activities of 1233A and its methyl ester and indicates that these analogs can be regarded as a substitute for 1233A. An aromatic ring separated from the 2-oxetanone ring by two methylenes was essential for high inhibitory activity. Among the compounds, **4a** showed comparable inhibitory activity *in vivo* to 1233A (**1**), and did not affect serum triglyceride level.

Experimental

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

3-[3-(2-Tetrahydropyranyloxy)propyl]benzyl Alcohol (31) Compound **30** was treated with 2,3-dihydropyran and *p*-TsOH to give the tetrahydropyran (THP)-protected propanol (100%). A solution of this compound (10.1 g, 36.3 mmol) in Et_2O was added dropwise to a suspension of $LiAlH_4$ (1.38 g, 3.64 mmol) in Et_2O (70 ml) at ambient temperature. The mixture was refluxed for 1 h. After cooling, unreacted $LiAlH_4$ was decomposed with MeOH. The resultant mixture was poured into water. The organic layer was separated, dried and concentrated to give **31** (7.14 g, 78.5%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.37—2.30 (9H, m), 2.60—2.88 (2H, m), 3.20—4.10 (4H, m), 4.54—4.82 (3H, m), 7.10—7.40 (4H, m).

3-[3-(2-Tetrahydropyranyloxy)propyl]benzaldehyde (32) Pyridinium dichromate (PDC) (82.0 g, 218 mmol) was added to a solution of **31** (27.2 g, 109 mmol) in CH_2Cl_2 (27 ml). The mixture was stirred overnight at ambient temperature and filtered. The filtrate was concentrated. The residue was chromatographed on a silica gel column with *n*-hexane–AcOEt (3 : 1) to give **32** (19.8 g, 73.4%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.37—2.16 (8H, m), 2.83 (2H, t, J=6.8 Hz), 3.28—4.04 (4H, m), 4.59 (1H, br s), 7.41—7.60 (2H, m), 7.60—7.87 (2H, m), 10.0 (1H, s). IR (neat): 1700 cm^{-1}.

α-[3-(4,4-Dimethyloxazolin-2-yl)phenyl]-3-[3-(2-tetrahydropyranyloxy)propyl]benzyl Alcohol (33) The amidation of 3-bromobenzoyl chloride with 2,2-dimethyl-2-aminoethanol, followed by treatment with $SOCl_2$ gave 3-(3-bromophenyl)-4,4-dimethyl-2-oxazoline (oil). A solution of this compound (4.61 g, 18.1 mmol) in tetrahydrofuran (THF) (46 ml) was added dropwise to Mg turnings (0.44 g, 18.1 mmol). The

TABLE II. Substituted Alkanols

$R-(CH_2)_3-OH$

Compd.	R	mp (°C)	Formula	MS M^+	High MS Calcd (Found)	^{1}H-NMR ($CDCl_3$) δ
37a	3-$C_6H_5CH_2C_6H_4$–	Oil	$C_{16}H_{18}O$	226	226.1358 (226.1369)	1.42 (1H, br s), 1.60—2.05 (2H, m), 2.54—2.80 (2H, m), 3.69 (2H, t, J=6.4 Hz), 4.00 (2H, s), 7.05—7.96 (9H, m)
35	3-(3-MeOOCC$_6H_5CH_2$)C_6H_4–	Oil	$C_{18}H_{20}O_3$	284		1.67 (1H, br s), 1.52—2.07 (2H, m), 2.50—2.80 (2H, m), 3.64 (2H, t, J=6.5 Hz), 3.87 (3H, s), 3.99 (2H, s), 6.85—8.02 (8H, m)
40a	3-[$C_6H_5(CH_2)_2$]C_6H_4–	Oil	$C_{17}H_{20}O$	240	240.1514 (240.1510)	1.57 (1H, br s), 1.60—2.02 (2H, m), 2.50—2.80 (2H, m), 2.89 (4H, s), 3.61 (2H, t, J=6.5 Hz), 6.90—7.45 (9H, m)
40b	3-[2-MeOOCC$_6H_5(CH_2)_2$]C_6H_4–	Oil	$C_{19}H_{22}O_3$	298 (FD)		1.60 (1H, br s), 1.70—2.03 (2H, m), 2.50—2.98 (4H, m), 3.10—3.37 (2H, m), 3.64 (2H, t, J=6.5 Hz), 3.90 (3H, s), 6.94—7.51 (7H, m), 7.80—7.96 (1H, m)
23a	3-[3-MeOOCC$_6H_5(CH_2)_2$]C_6H_4–	Oil	$C_{19}H_{22}O_3$	298 (FD)		1.52 (1H, s), 1.66—2.00 (2H, m), 2.58—2.80 (2H, m), 2.96 (4H, s), 3.67 (2H, t, J=6.8 Hz), 3.95 (3H, s), 7.00—7.50 (6H, m), 7.86—8.03 (2H, m)
40d	3-[4-MeOOCC$_6H_5(CH_2)_2$]C_6H_4–	Oil	$C_{19}H_{22}O_3$	298 (FD)		1.52 (1H, s), 1.66—2.00 (2H, m), 2.53—2.80 (2H, m), 2.91 (4H, s), 3.61 (2H, t, J=6.8 Hz), 3.90 (3H, s), 6.87—7.30 (6H, m), 7.93 (2H, d, J=7.6 Hz)
40e	3-[3,4-$(MeOOC)_2C_6H_5(CH_2)_2$]C_6H_4–	Oil	$C_{21}H_{24}O_5$	356	356.1624 (356.1656)	1.63—1.98 (2H, m), 2.20 (1H, br s), 2.50—2.74 (2H, m), 2.93 (4H, s), 3.60 (2H, t, J=6.8 Hz), 3.92 (6H, s), 6.80—7.72 (7H, m)
37b	3-[$C_6H_5(CH_2)_3$]C_6H_4–	Oil	$C_{18}H_{22}O$	254	254.1671 (254.1671)	1.38 (1H, br s), 1.66—2.18 (4H, m), 2.48—2.83 (6H, m), 3.66 (2H, t, J=6.5 Hz), 6.90—7.48 (9H, m)
42	3-[3-MeOOCC$_6H_5(CH_2)_3$]C_6H_4–	Oil	$C_{20}H_{24}O_3$	312 (FD)		1.68 (1H, br s), 1.73—2.17 (4H, m), 2.47—2.85 (6H, m), 3.67 (2H, t, J=6.5 Hz), 3.90 (3H, s), 6.90—7.45 (6H, m), 7.75—7.96 (2H, m)
37c	3-[$C_6H_5(CH_2)_4$]C_6H_4–	Oil	$C_{19}H_{24}O$	268	268.1827 (268.1830)	1.30—2.05 (7H, m), 2.28—2.96 (6H, m), 3.64 (2H, t, J=6.5 Hz), 6.88—7.45 (9H, m)
44	3-[3-MeOOCC$_6H_5(CH_2)_4$]C_6H_4–	Oil	$C_{21}H_{26}O_3$	327 (M^++1) (FAB)		1.30—2.06 (7H, m), 2.45—2.80 (6H, m), 3.65 (2H, t, J=6.8 Hz), 3.89 (3H, s), 6.90—7.40 (6H, m), 7.71—7.91 (2H, m)
48	3-[3-MeOOCC$_6H_5(CH_2)_6$]C_6H_4–	Oil	$C_{23}H_{30}O_3$	354	354.2195 (354.2187)	1.14—2.08 (11H, m), 2.43—2.83 (6H, m), 3.67 (2H, t, J=6.5 Hz), 3.90 (3H, s), 6.86—7.94 (8H, m)
50	3-(3-MeOOCC$_6H_4OCH_2$)C_6H_4–	Oil	$C_{18}H_{20}O_4$	300	300.1362 (300.1368)	1.55 (1H, br s), 1.70—2.12 (2H, m), 2.63—2.90 (2H, m), 3.69 (2H, t, J=7.2 Hz), 3.92 (3H, s), 5.12 (2H, s), 7.10—7.84 (8H, m)
51	3-(3-MeOOCC$H_2C_6H_4$)$CH_2C_6H_4$–	Oil	$C_{19}H_{22}O_3$	298	298.1569 (298.1553)	1.50 (1H, br s), 1.62—1.99 (2H, m), 2.47—2.75 (2H, m), 2.83—3.94 (5H, m), 3.60 (3H, s), 6.83—7.38 (9H, m)
23b	3-C_6H_5–N=N–C_6H_4–	Oil	$C_{15}H_{16}N_2O$	240	240.1263 (240.1252)	1.65 (1H, br s), 1.77—2.16 (2H, m), 2.71—3.00 (2H, m), 3.73 (2H, t, J=6.8 Hz), 7.37—8.16 (9H, m)
58	3-(3-MeOOCC$_6H_4$CONH)C_6H_4–	90.5—92.5	$C_{18}H_{19}NO_4$ [a]	313	313.1314 (313.1339)	1.50 (1H, br s), 1.70—2.07 (2H, m), 2.61—2.85 (2H, m), 3.67 (2H, t, J=6.8 Hz), 3.95 (3H, s), 6.90—8.50 (9H, m)
61	3-[3-[*tert*-C_4H_9OOCCH=C(CH_3)]C_6H_4]C_6H_4– (*trans*)	Oil	$C_{23}H_{28}O_3$	352	352.2039 (352.2039)	1.54 (9H, s), 1.74—2.14 (3H, m), 2.57 (3H, d, J=1.8 Hz), 2.65—2.92 (2H, m), 3.71 (2H, t, J=6.8 Hz), 6.12 (1H, q, J=1.8 Hz), 7.05—7.73 (8H, m)
23c	3-(7-*tert*-C_4H_9OOC-2-$C_{10}H_6$)C_6H_4–	Oil	$C_{24}H_{26}O_3$	362		1.37 (1H, br s), 1.64 (9H, s), 1.79—2.17 (2H, m), 2.70—2.93 (2H, m), 3.76 (2H, t, J=7.2 Hz), 7.30—8.20 (9H, m), 8.68 (1H, s)
66	7-MeOOC-2-$C_{10}H_6(CH_2)_3$–	68.5—69	$C_{18}H_{22}O_3$ [b]	286		1.10—1.90 (9H, m), 2.80 (2H, t, J=7.2 Hz), 3.64 (2H, t, J=5.8 Hz), 4.00 (3H, s), 7.44 (1H, dd, J=8.3, 2.2 Hz), 7.67—7.90 (3H, m), 8.00 (1H, dd, J=8.3, 2.2 Hz), 8.54 (1H, s)
69	7-MeOOC-2-$C_{10}H_6CH(CH_3)(CH_2)_2$–	Oil	$C_{19}H_{24}O_3$	300	300.1725 (300.1742)	0.80—1.90 (9H, m), 1.34 (3H, d, J=7.2 Hz), 2.88 (1H, q, J=7.2 Hz), 3.59 (2H, t, J=5.6 Hz), 3.98 (3H, s), 7.45 (1H, dd, J=7.9, 1.8 Hz), 7.65—7.92 (3H, m), 8.01 (1H, dd, J=7.9, 1.8 Hz), 8.57 (1H, s)

a) Elementary analysis Calcd: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.82; H, 6.21; N, 4.70. *b*) Elementary analysis Calcd: C, 75.49; H, 7.74. Found: C, 75.30; H, 7.73.

TABLE III. *In Vitro* and *in Vivo* Assays (Mice, $n=6$)

Compd.	*In vitro* test	*In vivo* test		
	Inhibition of HMG-CoA synthase IC_{50} (μM)	Dose mg/kg (*p.o.*)	Inhibition of sterol synthesis (%) in liver	Increase of serum triglyceride level (× factor)[a]
3	0.85	500	76.1 (++)[b]	1.29
8	0.45	500	59.7 (+)	1.49[c]
9	1.60		n.d.	n.d.
10	0.51	400	41.9 (−)	1.89[d]
11	0.89	200	0.60 (−)	1.08
12b	0.33	500	83.4 (++)	1.14
12a	0.27	500	49.5 (+)	0.98
13	0.93	200	46.1 (+)	1.18
14	1.75		n.d.	n.d.
15	0.22	500	86.8 (++)	2.49[d]
16	0.43	200	19.6 (+)	0.99
17	0.35	500	70.8 (++)	1.74[d]
18	0.33	200	28.0 (−)	1.10
19	1.65		n.d.	n.d.
4b	0.34	200	15.7 (−)	1.18
4a	0.13	200	51.7 (+)	1.00
5b	0.20	200	19.5 (−)	0.97
5a	0.30	200	43.4 (−)	0.94
6	1.30	200	63.6 (+)	1.08
7a	1.58		n.d.	n.d.
7b	2.00	200	36.1 (+)	1.01
20	0.72	200	50.0 (+)	1.02
21	2.90	200	33.6 (−)	0.94
22	0.56	300	21.7 (−)	1.78[d]
1 (1233A)	0.20	500	83.0 (++)	1.03

a) The triglyceride level of the control groups was assigned a value of 1.00. *b*) +, significant inhibition (<70%); ++, significant inhibition (>70%); −, not significant. *c*) $p<0.05$ *vs.* control. *d*) $p<0.01$ *vs.* control. n.d.: Not determined.

mixture was refluxed for 20 min. To the cooled mixture, a solution of **32** (3.0 g, 12.1 mmol) in THF (15 ml) was added dropwise. The reaction mixture was refluxed for 20 min. The resultant mixture was poured into saturated aqueous NH_4Cl and extracted with Et_2O. The extract was dried and concentrated. The residue was chromatographed on a silica gel column with *n*-hexane–AcOEt (2 : 1) to afford **33** (4.80 g, 93.8%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (6H, s), 1.20—2.12 (9H, m), 2.52—2.80 (2H, m), 3.16—4.00 (4H, m), 4.07 (2H, s), 4.43—4.65 (1H, m), 5.82 (1H, s), 6.95—8.16 (8H, m).

Methyl 3-[3-(3-Hydroxypropyl)-α-methoxybenzyl]benzoate (34) A solution of **33** (4.80 g, 11.3 mmol) and concentrated H_2SO_4 (10 ml) in MeOH (200 ml) was refluxed for 2 d. The cooled mixture was poured into 10% Na_2CO_3 and extracted with $CHCl_3$. The extract was dried and concentrated. The residue was chromatographed on a silica gel column with *n*-hexane–AcOEt (1 : 1) to give **34** (2.98 g, 83.7%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.59 (1H, s), 1.67—2.05 (2H, m), 2.55—2.83 (2H, m), 3.38 (3H, s), 3.64 (2H, t, J=6.5 Hz), 3.90 (3H, s), 5.26 (1H, s), 7.00—8.14 (8H, m). IR (neat): 1720, 1290 cm^{-1}.

Methyl 3-[3-(3-Hydroxypropyl)benzyl]benzoate (35) Concentrated H_2SO_4 (0.8 ml) and 5% Pd–C (1.5 g, 50% wet) were added to a solution of **34** (2.98 g, 9.48 mmol) in MeOH (60 ml). The mixture was stirred for 2.5 h under an H_2 atmosphere and filtered. The filtrate was concentrated and the residue was redissolved in CH_2Cl_2. The resultant solution was washed with water, dried and concentrated to give **35** (2.29 g, 85.6%) as an oil. IR (neat): 1720, 1290 cm^{-1}.

3-[3-(3-Phenylpropyl)phenyl]propanol (37b) Compound **32** was treated with 2-phenylethyl bromide[5] and magnesium in the similar manner to the preparation of **33** and **35** to give **37b** (77.4%) as an oil.

Compounds **37a** (81.6%) and **37c** (86.0%) were prepared in a similar manner to the preparation of **37b**.

Methyl 3-[2-[3-[3-(2-Tetrahydropyranyloxy)propyl]phenyl]ethenyl]benzoate (38c) Sodium metal (2.35 g, 102 mmol) was dissolved in MeOH (200 ml), 3-methoxycarbonylbenzylphosphonium bromide (38.6 g, 78.6 mmol, mp 238—240 °C), prepared from methyl 3-bromomethylbenzoate and triphenylphosphine, was added to the solution. The mixture was stirred for 10 min, then a solution of **32** (15.0 g, 60.4 mmol) in MeOH (100 ml) was added dropwise at room temperature. After stirring for 1 h, the reaction mixture was concentrated and the residue was dissolved in $CHCl_3$. The solution was washed with water, dried and concentrated. The residue was chromatographed on a silica gel column with *n*-hexane–AcOEt (5 : 1) to give the mixture of *trans*- and *cis*-**38c** (21.8 g, 94.9%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.37—2.14 (8H, m), 2.35—2.90 (2H, m), 3.18—4.04 (4H, m), 3.87 and 3.93 (total 3H, each s), 4.46—4.65 (1H, m), 6.56—8.25 (10H, m).

Methyl 3-[2-[3-[3-(2-Tetrahydropyranyloxy)propyl]phenyl]ethyl]benzoate (39c) A solution of **38c** (13.3 g, 35.0 mmol) in MeOH (130 ml) was mixed with 5% Pd–C (50% wet, 4.3 g), and the whole was stirred for 3 h under an H_2 atmosphere at room temperature, then filtered. The filtrate was concentrated to give **39c** (9.84 g, 73.6%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.37—2.10 (8H, m), 2.54—2.78 (2H, m), 2.94 (4H, s), 3.32—3.86 (4H, m), 3.92 (3H, s), 4.58 (1H, br s), 6.93—7.40 (6H, m), 7.80—8.00 (2H, m).

Methyl 3-[2-[3-(3-Hydroxypropyl)phenyl]ethyl]benzoate (23a) A mixture of **39c** (4.85 g, 12.7 mmol) in MeOH (48 ml) and *p*-TsOH·H_2O (0.48 g, 2.5 mmol) was stirred at 40 °C for 1 h and then poured into water. The resultant mixture was extracted with $CHCl_3$. The extract was washed with water, dried and concentrated. The residue was chromatographed on a silica gel column with *n*-hexane–AcOEt (3 : 1) to give **23a** (3.46 g, 91.0%) as an oil. IR (neat): 1720, 1285 cm^{-1}.

Compounds **40a, b** (89.7 and 85.5%) and **40d, e** (91.3 and 95.1%) were prepared similarly.

Methyl 3-[3-[3-(3-Hydroxypropyl)phenyl]propyl]benzoate (42) A solution of lithium bistrimethylsilylamide in THF (1 mol/l, 35.9 ml) was added dropwise to a solution of methyl 3-acetylbenzoate (5.81 g, 32.6 mmol) over 15 min at −60 °C, and the mixture was stirred for 15 min. A solution of **32** (6.75 g, 27.2 mmol) in THF (20 ml) was added dropwise at −60 °C. After stirring for 1 h at this temperature, the reaction mixture was poured into saturated aqueous NH_4Cl and extracted with Et_2O. The extract was dried and concentrated. The residue was chromatographed on a silica gel column with *n*-hexane–AcOEt (3 : 1) to give **41** (6.82 g, 58.8%) as an oil. This product was treated in the manner described for the preparation of **35** to give **42** (1.07 g, 21.3% based on **41**) as an oil. IR (neat): 1720, 1290 cm^{-1}.

Methyl 3-[4-[3-(3-Hydroxypropyl)phenyl]butyl]benzoate (44) *N*-Bromosuccinimide (NBS) (6.11 g, 34.4 mmol) and triphenylphosphine (9.02 g, 34.4 mmol) were added to a solution of **30**[2] (6.07 g, 31.6 mmol) in benzene (36 ml) at 0—10 °C. The mixture was stirred for 1 d at ambient temperature and concentrated. The residue was chromatographed on a silica gel column with *n*-hexane–AcOEt (3 : 1) to give methyl 3-(3-bromopropyl)benzoate (5.20 g, 64.0%) as an oil. This product was refluxed for 48 h with triphenylphosphine (5.83 g, 22.2 mmol) in CH_3CN (52 ml) and cooled. The precipitate was collected by filtration and dried to give 3-(3-methoxycarbonylphenyl)propyltriphenylphosphonium bromide (8.21 g, 78.2%) as crystals (mp, 131—131.5 °C). This compound (8.12 g, 15.6 mmol) and **32** (2.99 g, 12.0 mmol) were treated with KO*tert*-Bu (1.89 g, 16.8 mmol) in dimethyl sulfoxide (DMSO) (21 ml) as described for the transformation from **38c** to **23a** to give **44** (1.55 g, 39.5%) as an oil. IR (neat): 1720, 1285 cm^{-1}.

5-[3-[3-(2-Tetrahydropyranyloxy)propyl]phenyl]pentanal (46) KO-*tert*-Bu (3.53 g, 31.5 mmol) was added to a solution of 3-carboxypropylphosphonium bromide[6] (6.74 g, 15.7 mmol) in DMSO (40 ml) at ambient temperature. The mixture was stirred for 15 min, then a solution of **32** (3.00 g, 12.1 mmol) in DMSO (12 ml) was added. The whole was stirred for 3 h and poured into water. The resultant mixture was extracted with Et_2O. The aqueous layer was acidified with concentrated HCl and extracted with Et_2O. The extract was dried and concentrated. The residue (3.34 g) was reduced with $LiAlH_4$ (0.598 g, 15.8 mmol) as described for the preparation of **31** to give **45** (2.27 g, 61.7%). This compound was reduced catalytically and oxidized by Swern's method in a similar manner to that used for the preparation of **24c** to give **46** (55.9%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.22—2.15 (12H, m), 2.28—3.06 (6H, m), 3.23—4.05 (4H, m), 4.42—4.74 (1H, m), 6.86—7.37 (4H, m), 9.74 (1H, t, J=1.2 Hz).

Methyl 3-[6-[3-(3-Hydroxypropyl)phenyl]hexyl]benzoate (48) Compound **46** was treated as described for the preparation of **23a** to give **48** (68.2%) as an oil.

3-[3-(2-Tetrahydropyranyloxy)propyl]benzyl Bromide (49) Methanesulfonyl chloride (4.78 g, 41.7 mmol) was added dropwise to a solution

of **31** (8.70 g, 34.8 mmol) and NEt_3 (4.40 g, 43.5 mmol) in CH_2Cl_2 (90 ml) at 0—5 °C. The mixture was stirred for 30 min, then washed with saturated aqueous NH_4Cl, dried and concentrated. A solution of the residue (11.7 g) in THF (35 ml) was added dropwise to a suspension of LiBr (4.53 g, 52.2 mmol) and $NaHCO_3$ (5.84 g, 69.5 mmol) in THF (90 ml). The resultant mixture was stirred overnight at room temperature and filtered. The filtrate was washed with saturated aqueous NaCl, dried and concentrated. The residue was chromatographed on a silica gel column with *n*-hexane–AcOEt (5 : 1) to give **49** (9.87 g, 90.7%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.30—2.15 (8H, m), 2.56—2.90 (2H, m), 3.26—4.10 (4H, m), 4.50 (2H, s), 4.60 (1H, br s), 6.95—7.56 (4H, m).

Methyl 3-[3-(3-Hydroxypropyl)benzyloxy]benzoate (50) Methyl 3-hydroxybenzoate (2.19 g, 14.4 mmol), K_2CO_3 (1.99 g, 14.4 mmol) and KI (0.40 g, 2.4 mmol) were added to a solution of **49** (3.75 g, 12.0 mmol) in DMF (19 ml). The mixture was stirred for 3 h, poured into water and extracted with benzene. The extract was washed with water, dried and concentrated to give an oily product (4.85 g). This oil was treated with *p*-TsOH·H_2O (0.46 g, 2.4 mmol) in MeOH (48 ml) in a similar manner to that used for the preparation of **23a** to give **50** (3.08 g, 85.7%) as an oil. IR (neat): 1720, 1290 cm^{-1}.

Methyl 3-[3-(3-Hydroxypropyl)benzyl]phenylacetate (51) A piece of lithium lump (0.41 g, 59 mmol) was dissolved in a solution of naphthalene (8.43 g, 65.8 mmol) in THF (30 ml) by stirring overnight at room temperature under an N_2 atmosphere. To this mixture, a solution of anhydrous $ZnCl_2$ (6.08 g, 44.6 mmol) in THF (20 ml) was added dropwise, followed by stirring for 1 h. A solution of **49** (3.11 g, 9.93 mmol) in THF (11 ml) was added dropwise at ambient temperature. The resultant mixture was stirred for 3 h and refluxed for 1 h. After addition of a solution of $Ni(PPh_3)_4$[7] prepared from $Ni(PPh_3)_2Cl_2$ (0.243 g, 0.371 mmol), PPh_3 (0.195 g, 0.743 mmol) and DIBAL-H (1 mol/l in THF, 0.74 ml) in THF (8.5 ml), a solution of methyl 3-bromophenylacetate (1.49 g, 6.50 mmol) in THF (15 ml) was added. The reaction mixture was stirred overnight at room temperature, poured into saturated aqueous NH_4Cl and extracted with Et_2O. The extract was washed with water, dried and concentrated. The residue was chromatographed on a silica gel column with *n*-hexane–AcOEt (10 : 1) to give an oily product. This product was treated with *p*-TsOH·H_2O in MeOH as described for the preparation of **23a** to give **51** (0.77 g, 39.6% based on methyl 3-bromophenylacetate) as an oil. IR (neat): 1730, 1250 cm^{-1}.

Methyl 3-(3-Aminophenyl)propanoate (53) 3-Nitrobenzaldehyde (**52**) was treated with methoxycarbonylmethylphosphonium bromide and NaOMe as described for the preparation of **38c**, followed by catalytic reduction to give **53** (27.7%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 2.49—2.76 (2H, m), 2.76—3.06 (2H, m), 3.48 (2H, s), 3.78 (3H, s), 6.50—7.45 (4H, m).

Methyl 3-(3-Phenylazophenyl)propanoate (54) Nitrosobenzene (1.16 g, 10.8 mmol) was added to a solution of **53** (1.93 g, 10.8 mmol) in AcOH (9.7 ml). The mixture was stirred for 1 h at room temperature, poured into water and extracted with $CHCl_3$. The extract was washed with saturated aqueous $NaHCO_3$, dried, and concentrated. The residue was chromatographed on a silica gel column with *n*-hexane–AcOEt (3 : 1) to give **54** (2.26 g, 78.2%) as a red oil. ^{1}H-NMR ($CDCl_3$) δ: 2.59—2.87 (2H, m), 2.93—3.22 (2H, m), 3.70 (3H, s), 7.37—8.10 (9H, m).

3-(3-Phenylazophenyl)propanol (23b) A solution of **54** (2.20 g, 8.20 mmol) in THF (10 ml) was added dropwise to a suspension of $LiAlH_4$ (0.311 g, 8.20 mmol) in THF (10 ml). The mixture was refluxed for 1 h. The resultant mixture was poured into water, acidified with concentrated HCl, and extracted with Et_2O. The extract was concentrated. A solution of the residue in toluene (70 ml) was bubbled for 2 h with air in the presence of NaOH pellets and concentrated. The residue was chromatographed on a silica gel column with *n*-hexane–AcOEt (2 : 1) to give **23b** (1.69 g, 85.8%) as a red oil.

Methyl 3-[3-[3-(3-Hydroxypropyl)phenyl]aminocarbonyl]benzoate (58) Methyl 3-chlorocarbonylbenzoate (3.97 g, 20 mmol) and NEt_3 (4.27 ml, 30.0 mmol) were added to a solution of 3-(3-aminophenyl)propanol (**56**) (3.02 g, 20.0 mmol) in CH_2Cl_2 (30 ml) prepared by the reduction of **53** with $LiAlH_4$. The mixture was stirred for 1 h, washed with water, dried, and concentrated. The residue was chromatographed on a silica gel column with *n*-hexane–AcOEt (1 : 1) to give **57** (4.39 g, 46.2%) as an oil. Anhydrous K_2CO_3 powder (1.91 g, 13.8 mmol) was added to a solution of **57** in MeOH (30 ml). The mixture was stirred for 30 min at room temperature, poured into water and extracted with $CHCl_3$. The extract was washed with water, dried and concentrated. The residue was chromatographed on a silica gel column with *n*-hexane–AcOEt (1 : 1) to give **58** (2.79 g, 96.4% based on **57**) as a solid, mp 90.5—92.0 °C. IR (KBr): 1730, 1650 cm^{-1}.

3-[3-(3-Acetylphenyl)phenyl]propanol (60) A solution of Grignard reagent prepared from 2-(3-bromophenyl)-2-methyl-1,3-dioxolane (25.0 g, 102.7 mmol) and magnesium (3.0 g, 123.2 mmol) in THF (125 ml) was added dropwise to a solution of anhydrous $ZnCl_2$ (15.4 g, 113 mmol) in THF (108 ml) at −10 °C. The mixture was stirred for 1 h at this temperature. A solution of $(Ph_3P)_4Ni$[7] (2.05 mmol) prepared as described for the preparation of **51** was added. A solution of **59** (15.4 g, 51.5 mmol) in THF (30 ml) was then added dropwise at room temperature. After stirring for 1 h, the reaction mixture was treated as described for the preparation of **51** to give **60** (6.08 g, 46.5 %) as an oil. ^{1}H-NMR ($CDCl_3$) δ 1.71 (1H, br s), 1.80—2.12 (2H, m), 2.65 (3H, s), 2.67—2.96 (2H, m), 3.70 (2H, t, J=6.8 Hz) 7.20—8.00 (7H, m), 8.17 (1H, t, J=1 Hz). IR (neat): 1685, 1250 cm^{-1}. EI-MS *m/z*: 254 (M^+). HR-MS Calcd for $C_{17}H_{18}O_2$: 254.1307. Found: 254.1337.

***tert*-Butyl *trans*-3-[3-[3-(3-Hydroxypropyl)phenyl]phenyl]-2-butenoate (61)** Compound **60** was treated with diethyl *tert*-butoxycarbonylmethylphosphonate in a similar manner to that described for the preparation of **38c** to give a mixture of **61** with its *cis*-isomer. The mixture was separated by a column chromatography (SiO_2, *n*-hexane–AcOEt 3 : 1) to give **61** (56.8%) as an oil. IR (neat): 1705, 1635, 1140 cm^{-1}. The stereochemistry was decided by comparison of the chemical shift (6.11 ppm) of the α-proton in the NMR spectrum with that of commercial *trans*-3-phenyl-2-butenate (Aldrich Co.). The chemical shift of this proton in the *cis*-isomer of **61** was 5.86 ppm.

Methyl 7-[3-(3-Hydroxypropyl)phenyl]-2-naphthoate (64) Methyl 7-bromo-2-naphthoate[8] (**62**) was treated with THP-protected 3-bromobenzyl alcohol as described for the preparation of **60** to give **63** (62.1%) as an oil. This product was oxidized with PDC as described for the preparation of **32**, and treated in the reported manner[2] for the preparation of 3-substituted propanols to give **64** (35.3% based on **63**) as crystals, mp 92—93 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (1H, br s), 1.80—2.18 (2H, m), 2.30—2.46 (2H, m), 3.77 (2H, t, J=6.8 Hz), 4.00 (3H, s), 7.20—8.20 (9H, m), 8.68 (1H, s). IR (neat): 1710, 1340, 1280, 1100 cm^{-1}. EI-MS *m/z*: 320 (M^+). *Anal.* Calcd for $C_{21}H_{20}O_3$: C, 78.72; H, 6.30. Found: C, 78.32; H, 6.39.

***tert*-Butyl 7-[3-(3-Hydroxypropyl)phenyl]-2-naphthoate (23c)** Compound **64** was hydrolyzed with 2 N NaOH to give the corresponding carboxylic acid (92%). A solution of this acid (5.08 g, 16.6 mmol) and *N*,*N*-dimethylformamide (DMF)–di-*tert*-butylacetal (11.9 ml, 49.8 mmol) in benzene–THF (1 : 1, 100 ml) was refluxed for 1 h. The mixture was washed with 5% aqueous Na_2CO_3, dried and concentrated. The residue was chromatographed on a silica gel column with *n*-hexane–AcOEt (3 : 1) to give **23c** (2.25 g, 37.4%) as an oil.

Methyl 7-(6-Hydroxyhexyl)-2-naphthoate (66) Methyl 7-formyl-2-naphthoate (**65**) (mp 128—130 °C) was prepared from 7-methylnaphthoic acid[8] by esterification, bromination with NBS and oxidation[2] with hexamethylenetetramine. The treatment of 5-benzyloxypentyl bromide[9] with triphenylphosphine gave the corresponding phosphonium compound (mp 109.5—110.5 °C), with which **65** was treated in the presence of KO*tert*-Bu as described for the preparation of **44** to give **66** as crystals, mp 68.5—69 °C. IR (neat): 1710 cm^{-1}.

Methyl 7-(6-Benzyloxy-1-hydroxyhexyl)-2-naphthoate (67) A solution of Grignard reagent prepared from 5-benzyloxypentyl bromide[9] (6.15 g, 23.9 mmol) and Mg turnings (0.61 g, 25 mmol) in THF (36 ml), was added dropwise to a solution of **65** (8.19 g, 38.2 mmol) in THF (36 ml) containing hexamethylphosphoramide (HMPA) (10 ml) at 60 °C. The mixture was stirred for 1.5 h, poured into saturated aqueous NH_4Cl (150 ml) and extracted with Et_2O. The extract was dried and concentrated. The residue was chromatographed on a silica gel column with *n*-hexane–AcOEt (2 : 1) to give **67** (3.29 g, 35.1% based on 5-benzyloxypentyl bromide) as crystals, mp 83—85.0 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.20—2.06 (9H, m), 3.45 (2H, t, J=5.8 Hz), 3.99 (3H, s), 4.49 (2H, s), 4.88 (1H, t, J=6.1 Hz), 7.32 (5H, s), 7.50 (1H, dd, J=7.6, 2.2 Hz), 7.79—7.96 (3H, m), 8.08 (1H, dd, J=7.6, 2.2 Hz), 8.60 (1H, s). IR (KBr): 1720, 1290 cm^{-1}.

Methyl 7-(6-Benzyloxyhexanoyl)-2-naphthoate (68) PDC (8.40 g, 22.3 mmol) was added to a solution of **67** (4.38 g, 11.2 mmol) in CH_2Cl_2 (44 ml). The mixture was stirred overnight and filtered. The filtrate was washed with water, dried and concentrated. The residue was chromatographed on a silica gel column with *n*-hexane–AcOEt (3 : 1) to give **68** (3.82 g, 87.8%) as crystals, mp 87—88°C. ^{1}H-NMR ($CDCl_3$) δ: 1.36—2.00 (6H, m), 3.11 (2H, t, J=7.2 Hz), 3.52 (2H, t, J=5.8 Hz), 4.01 (3H, s), 4.52 (2H, s), 7.20—7.46 (5H, m), 7.83—8.26 (4H, m), 8.55

(1H, s), 8.72 (1H, s). IR (KBr): 1715, 1690, 1630, 1440, 1280 cm^{-1}. FAB-MS *m/z*: 391 ($M^+ + 1$). *Anal.* Calcd for $C_{25}H_{26}O_4$: C, 76.90; H, 6.71. Found: C, 76.79; H, 6.51.

Methyl 7-(6-Hydroxy-2-heptyl)-2-naphthoate (69) A solution of methyltriphenylphosphonium bromide (6.99 g, 19.6 mmol) in THF (38 ml) was treated with KO*tert*-Bu (2.20 g, 19.6 mmol), and the mixture was stirred for 10 min at ambient temperature. After the addition of a solution of **68** (3.82 g, 9.78 mmol) in THF (20 ml), the mixture was stirred for 40 min, poured into water, acidified with 2 N HCl and extracted with AcOEt. The extract was dried and concentrated. The residue was chromatographed on a silica gel column with *n*-hexane–AcOEt (5 : 1) to give an oily product (2.29 g, 60.2%). This product was reduced catalytically to give **69** (1.67 g, 56.8%) as an oil. IR (neat): 1710 cm^{-1}.

***tert*-Butyl 7-[3-(2-Formylethyl)phenyl]-2-naphthoate (24c)** A solution of DMSO (2.90 ml, 43.2 mmol) in CH_2Cl_2 (10 ml) was added dropwise to a solution of $(COCl)_2$ (1.85 ml, 21.6 mmol) in CH_2Cl_2 (26 ml) at −40 °C. The mixture was stirred for 10 min, then a solution of **23c** (2.61 g, 7.20 mmol) in CH_2Cl_2 (6 ml) was added dropwise. Stirring was continued for 25 min, and Et_3N (13 ml) was then added dropwise. The mixture was stirred for 5 min, washed with water, dried and concentrated. The residue was chromatographed on a silica gel column with *n*-hexane–AcOEt (4 : 1) to give **24c** (2.35 g, 90.6%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.67 (9H, s), 2.73—3.20 (4H, m), 7.14—8.16 (9H, m), 8.58 (1H, s), 9.87 (1H, t, J=1.2 Hz). IR (KBr): 1725, 1710, 1340, 1290, 1105 cm^{-1}.

Benzyl *cis*-4-[3-(7-*tert*-Butoxycarbonyl-2-naphthyl)phenyl]-2,2-dimethyl-1,3-dioxane-5-carboxylate (*cis*-26c) Compound **24c** (2.35 g, 6.52 mmol) was condensed with benzyl 3-hydroxypropanoate[3] in the reported[2,3] manner to give a mixture of *anti*- and *syn*-**25c** (1.91 g, 54.2%) as an oil. 2,2-Dimethoxyethane (2.17 ml, 17.7 mmol) and (±)-10-camphorsulfonic acid (0.082 g, 0.353 mmol) were added to a solution of this product in CH_2Cl_2 (19 ml) under cooling in ice bath. The mixture was stirred for 3 h at room temperature, washed with saturated aqueous $NaHCO_3$, dried and concentrated. The residue was chromatographed on a silica gel column with *n*-hexane–AcOEt (5 : 1) to give the *trans*-isomer of **26c** (0.860 g, 41.9%) and the *cis*-isomer of **26c** (0.891 g, 43.4 %), each as an oil, in that order. *trans*-**26c**: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.43, 1.45 (each 3H, each s), 1.66 (9H, s), 1.77—1.91 (2H, m), 2.66—2.72 (2H, m), 2.87—2.92 (1H, m), 3.97 (1H, dd, J=5.9, 12.0 Hz), 4.02 (1H, t, J=12.0 Hz), 4.05—4.09 (1H, m), 5.07, 5.11 (each 1H, d, J=12.2 Hz), 7.13 (1H, d, J=7.3 Hz), 7.21—7.28 (5H, m), 7.39 (1H, d, J=7.8 Hz), 7.47 (1H, s), 7.53 (1H, d, J=7.8 Hz), 7.82 (1H, dd, J=1.5, 8.1 Hz), 7.91 (1H, d, J=8.8 Hz), 7.93 (1H, d, J=8.8 Hz), 8.02 (1H, dd, J=2.0, 8.8 Hz), 8.12 (1H, s), 8.59 (1H, s). *cis*-**26c**: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.43, 1.48 (each 3H, each s), 1.66 (9H, s), 1.86—1.94 (1H, m), 2.04—2.16 (1H, m), 2.49 (1H, q, J=3.9 Hz), 2.68—2.76 (1H, m), 2.85—2.92 (1H, m), 4.04 (2H, dd, J=4.4, 11.8 Hz), 4.17 (1H, dd, J=2.4, 11.8 Hz), 5.18 (2H, s), 7.16 (1H, d, J=7.3 Hz), 7.21—7.41 (6H, m), 7.50 (1H, s), 7.55 (1H, d, J=7.8 Hz), 7.81 (1H, dd, J=2.0, 8.8 Hz), 7.88 (1H, d, J=8.8 Hz), 7.93 (1H, d, J=8.8 Hz), 8.02 (1H, dd, J=1.5, 8.8 Hz), 8.11 (1H, s), 8.59 (1H, s). Nuclear Overhauser effect (NOE) was observed as shown in Fig. 3.

Benzyl *anti*-5-[3-(7-*tert*-Butoxycarbonyl-2-naphthyl)phenyl]-3-hydroxy-2-hydroxymethylpentanoate (*anti*-25c) A solution of *cis*-**26c** (0.891 g, 1.53 mmol) in MeOH (9 ml) was treated with *p*-TsOH·H_2O (0.058 g, 0.305 mmol). The mixture was stirred for 2 h at room temperature, poured into saturated aqueous $NaHCO_3$ (20 ml) and extracted with $CHCl_3$. The extract was dried and concentrated to give *anti*-**25c** (0.827 g, 99.7%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.66 (9H, s), 1.78—2.12 (2H, m), 2.61—3.15 (5H, m), 3.80—4.20 (3H, m), 5.19 (2H, s), 7.09—8.18 (14H, m), 8.60 (1H, s).

Benzyl *anti*-5-[3-(7-*tert*-Butoxycarbonyl-2-naphthyl)phenyl]-3-hydroxy-2-triphenylmethoxymethylpentanoate (27c) Triphenylmethyl chloride (0.64 g, 2.30 mmol), 4-dimethylaminopyridine (DMAP) (10 mg, 0.78 mmol) and NEt_3 (0.34 ml, 2.45 mmol) were added to a solution of *anti*-**25c** (0.827 g, 1.53 mmol) in CH_2Cl_2. The mixture was stirred overnight, washed with water, dried and concentrated. The residue was chromatographed on silica gel column with *n*-hexane–AcOEt (3 : 1) to give **27c** (1.05 g, 87.6%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.67 (9H, s), 1.40—1.84 (2H, m), 2.60—2.98 (4H, m), 3.49 (2H, d, J=5.8 Hz), 3.86—4.12 (1H, m), 5.22 (2H, s), 7.00—8.16 (29H, m), 8.60 (1H, s).

***trans*-4-[2-[3-(7-*tert*-Butoxycarbonyl-2-naphthyl)phenyl]ethyl]-3-triphenylmethoxymethyl-2-oxetanone (29c)** A mixture of a solution of **27c** (1.05 g, 1.34 mmol) in EtOH (20 ml) and 5% Pd–C (0.6 g, 50% wet)

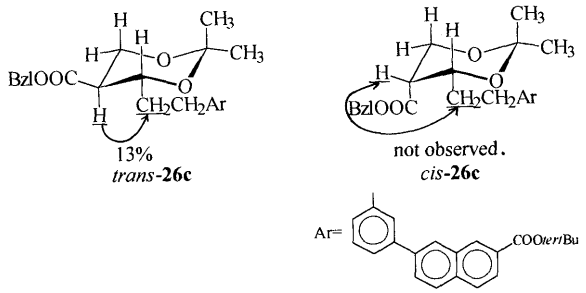


Fig. 3

was stirred for 5 h under an H_2 atmosphere at room temperature. The resultant mixture was filtered and the filtrate was concentrated. The residue (0.878 g) was taken up in pyridine (17.6 ml), and *p*-TsCl (0.967 g, 5.08 mmol) was added at 5 °C, followed by stirring for 10 min and standing overnight in refrigerator. After addition of MeOH (10 ml), the mixture was diluted with CH_2Cl_2 (100 ml), washed with water, dried and concentrated. The residue was chromatographed on a silica gel column with *n*-hexane–AcOEt (3 : 1) to give **29c** (0.568 g, 62.8%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.67 (9H, s), 2.04—2.40 (2H, m), 2.70—3.00 (2H, m), 3.14—3.65 (3H, m), 4.51 (1H, dt, J=3.8, 7.2 Hz), 7.00—8.15 (24H, m), 8.16 (1H, s). FAB-MS *m/z*: 674 (M^+). IR (neat): 1820, 1710 cm^{-1}.

***trans*-4-[2-[3-(7-Carboxy-2-naphthyl)phenyl]ethyl]-3-hydroxymethyl-2-oxetanone (4a)** A solution of **29c** (0.550 g, 0.815 mmol) in THF (5.5 ml) was treated with 40%-HF (5.5 ml) under cooling in an ice bath. The mixture was stirred for 1 h at room temperature and diluted with $CHCl_3$. The solution was washed twice with water, dried and concentrated. The residue was recrystallized from benzene to give **4a** (0.157 g, 51.2%) as crystals, mp 178.5—180.5 °C. IR (KBr): 1815, 1695 cm^{-1}.

Compound **5a** was prepared from **61** in eight steps in the similar manners as described for the preparation of **4a**.

***trans*-3-Hydroxymethyl-4-[2-[3-(7-methoxycarbonyl-2-naphthyl)phenyl]ethyl]-2-oxetanone (4b)** Diazomethane solution was added to a solution of **4a** (0.051 g, 0.135 mmol) in Et_2O (5 ml) until the yellow color persisted. The mixture was stirred for 1 h and concentrated. The residue was chromatographed on a silica gel column with $CHCl_3$ gave **4b** (0.048 g, 91.2%) as crystals, mp 106.5—108 °C. IR (KBr): 1805, 1725 cm^{-1}.

Compound **5b** (85.1%) was prepared in a similar manner to that described for the preparation of **4b**.

***trans*-3-Hydroxymethyl-4-[2-[3-[2-(3-methoxycarbonylphenyl)ethyl]-phenyl]ethyl]-2-oxetanone (12b)** Compound **23a** was treated as described for the transformation of **23c** to **29c**, to give **29a** (19.1%) as an oil. To a suspension of **29a** (1.20 g, 1.97 mmol) in *n*-BuOH (24 ml), CF_3COOH (12.0 ml) was added dropwise at 5—10 °C. The mixture was stirred for 2 h at room temperature, diluted with AcOEt (200 ml), washed with saturated aqueous $NaHCO_3$, dried and concentrated. The residue was chromatographed on a silica gel column with $CHCl_3$–MeOH (100 : 1) to give **12b** (0.67 g, 92.5%) as crystals, mp 71—73 °C. IR (KBr): 1820, 1730, 1290 cm^{-1}.

Compounds **6**—**21** were prepared from the corresponding propanols as described for the preparation of **12b**.

***trans*-4-[2-[3-[2-(3-Carboxyphenyl)ethyl]phenyl]ethyl]-3-hydroxymethyl-2-oxetanone (12a)** A solution of **12b** (0.339 g, 0.92 mmol) in MeOH (5 ml) was added to a solution of PLE (6300 units) in water (680 ml). The mixture was stirred at room temperature with the dropwise addition of 0.02 N NaOH to maintain the pH at 6.5—7.0 until the pH no longer changed (about 4 h). After acidification with 2 N HCl, the mixture was extracted with Et_2O. The extract was dried and concentrated. The residue was chromatographed on a silica gel column with $CHCl_3$–MeOH (200 : 1) to give **12a** (0.176 g, 54.0%) as crystals, mp 113—115 °C. IR (KBr): 1815, 1690 cm^{-1}.

***trans*-4-[2-(3-Phenylazophenyl)ethyl]-3-triphenylmethoxymethyl-2-oxetanone (29b)** Compound **23b** was treated as described for the transformation of **23c** to *anti*-**27c** to give *anti*-**27b** (15.1%). This compound was hydrolyzed with aqueous KOH and lactonized in a similar manner to that described for the preparation of **29c** to give **29b** (49.8%) as red crystals, mp 141—143 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.00—2.37 (2H, m), 2.63—3.00 (2H, m), 3.10—3.86 (3H, m), 4.58 (1H, dt, J=3.6, 7.2 Hz), 6.80—8.10 (24H, m), FD-MS *m/z*: 552 (M^+). IR (KBr): 1820 cm^{-1}.

***trans*-3-Hydroxymethyl-4-[2-(3-phenylazophenyl)ethyl]-2-oxetanone**

(22) Compound **29b** was deprotected with CF_3COOH in a similar manner to that described for the preparation of **12b** to give **22** (49.8%) as red crystals, mp 70—72.0 °C. IR (KBr): 1805 cm^{-1}.

Inhibition of HMG-CoA Synthase[4] (*in Vitro* Assay) and of the Biosynthesis of Cholesterol in Mouse Liver[2] (*in Vivo* Assay) Analogs synthesized were tested by the reported procedures.[2,4]

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