SYNTHESIS AND BIOLOGICAL ACTIVITIES OF NEW HMG-COA SYNTHASE INHIBITORS: 2-OXETANONES WITH A SIDE CHAIN CONTAINING BIPHENYL, TERPHENYL OR PHENYLPYRIDINE

Hirokazu Hashizume,* Hajime Ito, Naoaki Kanaya,+ Hajime Nagashima,+ Hiroyuki Usui,+ Reiko Oshima,+ Munefumi Kanao,+ Hiroshi Tomoda,++ Toshiaki Sunazuka,++ Tohru Nagamitsu,++ Hidetoshi Kumagai,++ and Satoshi Ōmura++

Fuji Chemical Industries, Ltd., 530 Chokeiji, Takaoka, Toyama 933, Japan

+Daiichi Pharmaceutical Co., Ltd., 16-13, Kitakasai 1-Chome, Edogawa-ku, Tokyo 134, Japan

++Research Center for Biological Function, The Kitasato Institute, 9-1, Shirokane 5-Chome, Minato-ku, Tokyo 108, Japan

Abstract - A series of 1233A analogs containing biphenylyl, terphenylyl or phenylpyridyl groups in their side chain were synthesized and tested for the inhibitory activities against 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) synthase and inhibition for the cholesterol biosynthesis in the mouse liver. The compounds with an oxetane, cyclobutanone or γ-butyrolactone ring as isosters of a 2-oxetanone ring were entirely inactive. Among sythetic analogs, *anti*-4-[3-[2-(5-isopropyl-2-pyridyl)-ethyl]-phenyl]ethyl]-3-hydroxymethyl-2-oxetanone (**10b**) was most active *in vitro*. The structure-activity relationships on the transformations of 2-oxetanone and its side chain were obtained.

We reported[1] 2-oxetanones with a side chain mimicking the folded structure of 1233A (**1**) as potent 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) synthase inhibitors. Among the compounds, compound (**2**) showed higher inhibitory activity than that of 1233A (**1**). However, it increased the triglyceride level in serum. On the way of our investigation, we found that compound (**3**) showed high activity *in vivo* with small triglyceride level increment. Standing on the above results, we started the investigation on the analogs of **3**.

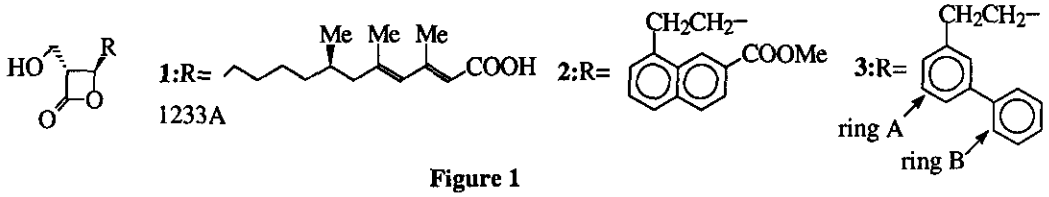


Figure 1

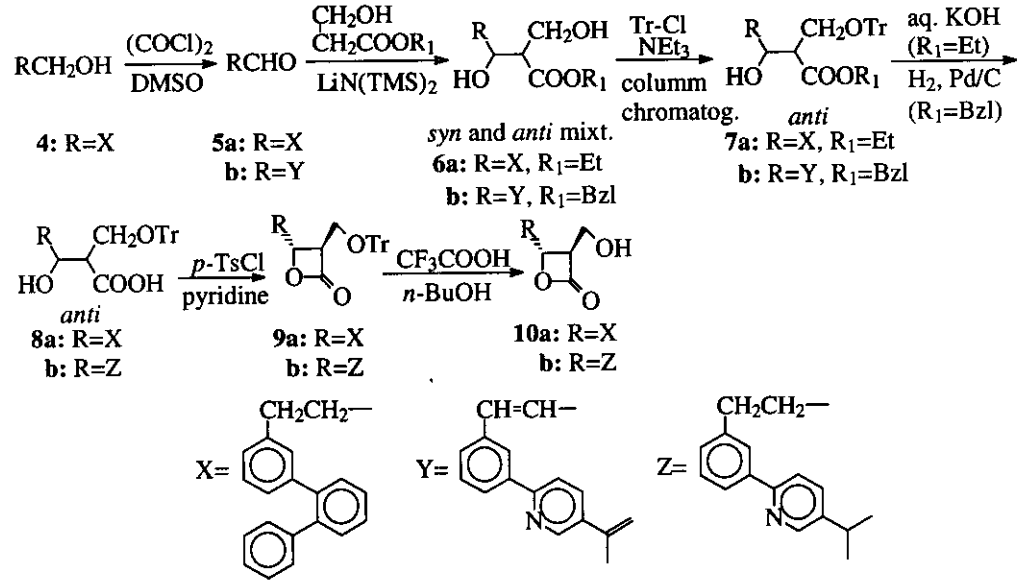
A benzene ring was introduced to the ring A or B of **3**, since activity enhancement *in vitro* was observed for a number of analogs with a higher lipophilic and bulky side chain.[1] On the other hand, these analogs tended to increase triglyceride level.[1] Thus, in some analogs, B-ring of **3** was replaced by a pyridine ring to suppress the triglyceride increment.

The low *in vivo* activities of reported 1233A analogs[1] could be attributed to the instability of 2-oxetanone ring to hydrolytic enzymes such as an esterase and lipase in blood. In some analogs, the 2-oxetanone ring was replaced with cyclobutanone, oxetane or γ-butyrolactone to avoid the anticipated unfavorable hydrolysis. In this report, we describe the structure-activity relationships on 1233A analogs concerning with the side chain and isosteric transformation of the 2-oxetanone ring.

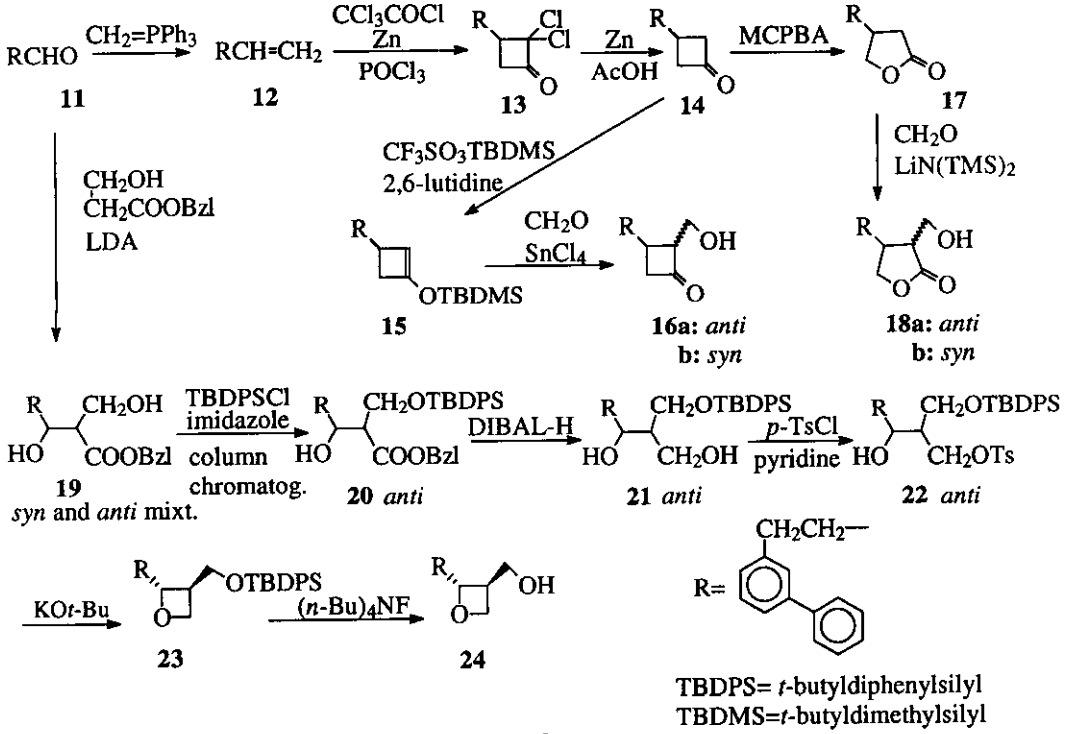
CHEMISTRY

The compounds tested in this study were racemic and prepared by the typical procedure[1] outlined in Schemes 1 and 2 from the corresponding substituted phenyl propanols, propenals or propanal (*e.g.* **4**, **5b** or **11**), which were prepared as shown in Schemes 3-7. All 2-oxetanones were *anti*-form and their physical data were shown in Table I. In the preparation of **10b** shown in Scheme 1, the hydrogenation of two double bonds and hydrogenolysis of benzyl ester were accomplished by one step (**7b** → **8b**).

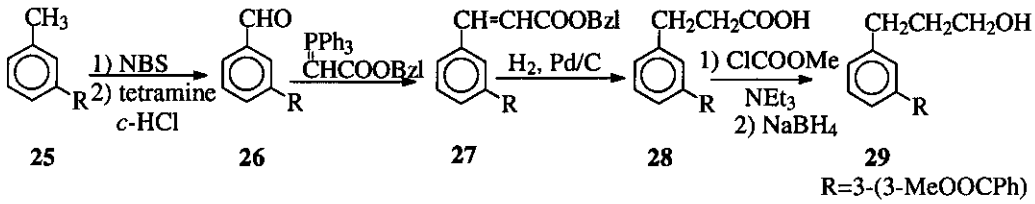
Scheme 2 shows the preparations of cyclobutanones, γ-butyrolactones and oxetanes. Cyclobutanone (**14**) was prepared *via* the [2+2] cycloaddition of olefin (**12**) with dichlorodiketene prepared[2] *in situ* and the dehalogenation. The aldol condensation[3] of **14** with formaldehyde was performed *via* the Lewis acid-catalyzed reaction of silyl enol ether (**15**) to obtain *anti*-cyclobutanone (**16a**) and *syn*-one (**16b**) in the ratio of 2:1. The Baeyer-Villiger oxidation of **14** followed by aldol condensation provided *anti*-γ-butyrolactone (**18a**)



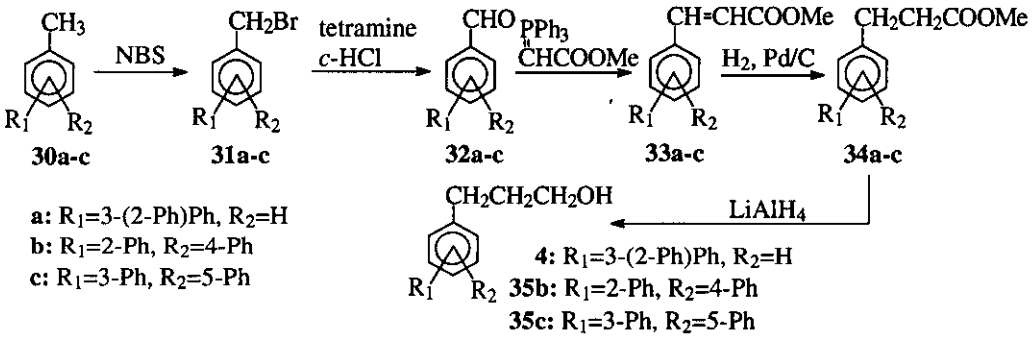
Scheme 1



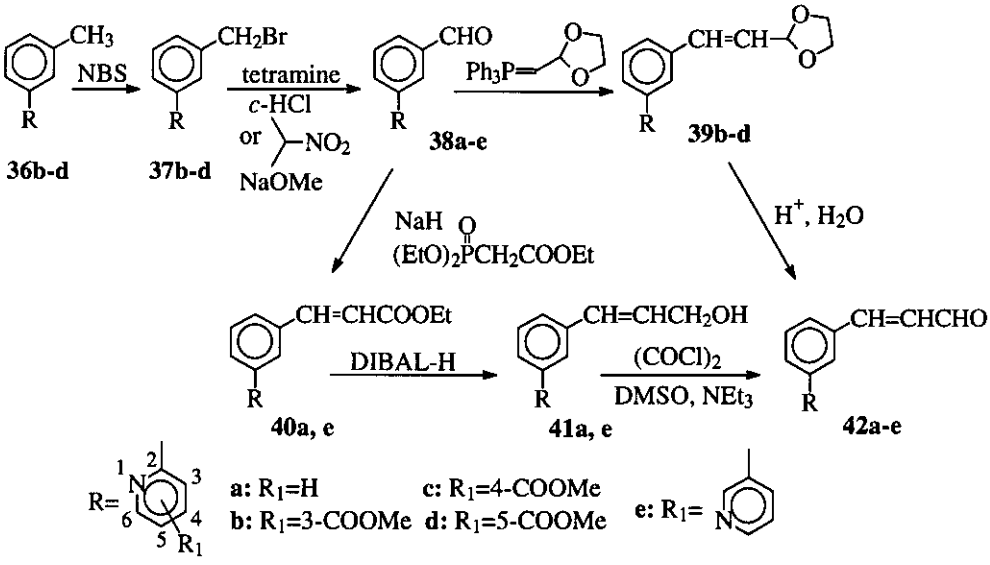
Scheme 2



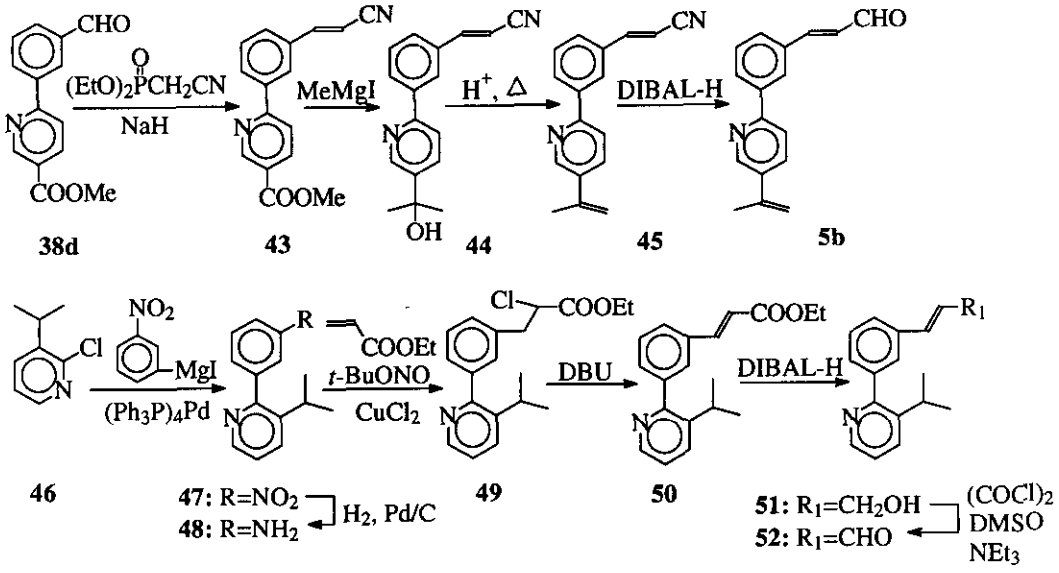
Scheme 3



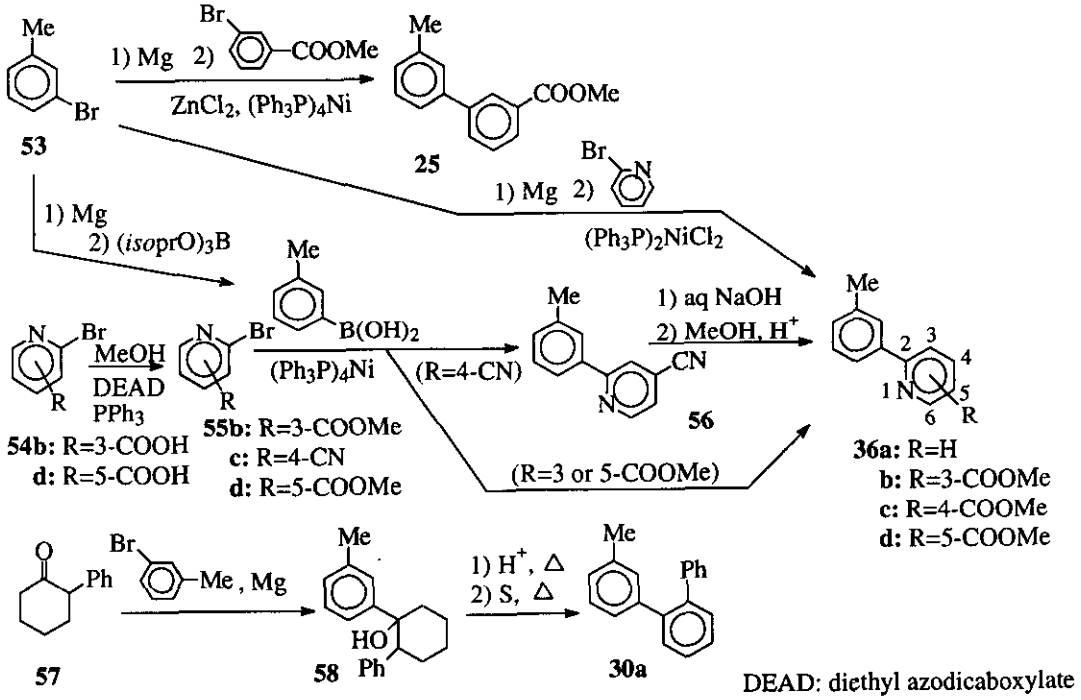
Scheme 4



Scheme 5

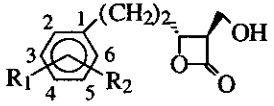


Scheme 6



Scheme 7

Table I. Physical Data for 4-Substituted-3-Hydroxymethyl-2-Oxetanones



Compd.	R_1	R_2	mp °C	formula	Elementary Analysis cacld. C, H, N (found C, H, N)	Ms (M^+)	High ms calcd (found)	^{1}H-Nmr ($CDCl_3$) δ [a]
59	3-(3-MeOOC-phenyl)	H	syrup	$C_{20}H_{20}O_5$		340	340.1311 (340.1283)	2.02-2.46 (2H, m), 2.73-3.02 (2H, m), 3.34-3.54 (1H, m), 3.70-4.22 (2H, m), 3.95 (3H, s), 4.65 (1H, dt, *J*=4.0, 6.8 Hz), 6.05 (1H, br s), 7.10-8.37 (8H, m)
60	3-(3-HOOC-phenyl)	H	141-143	$C_{19}H_{18}O_5$	69.93, 5.56 (69.91, 5.83)			1.97-2.43 (2H, m), 2.53-3.10 (2H, m), 3.33-3.53 (1H, m), 3.66-4.13 (2H, m), 4.67 (1H, dt, *J*=4.0, 6.8 Hz), 6.05 (2H, br s), 7.10-8.37 (8H, m)
61	2-Phenyl	4-Phenyl	syrup	$C_{24}H_{22}O_3$		358	358.1569 (358.1594)	1.55-2.25 (2H, m), 2.40-2.95 (3H, m), 3.00-3.14 (1H, m), 3.35-4.00 (2H, m), 4.42 (1H, dt, *J*=4.0, 6.8 Hz), 7.20-7.70(13H, m)
62	3-Phenyl	5-Phenyl	118.8-120.5	$C_{24}H_{22}O_3$	80.42, 6.19 (80.34, 6.04)	358		1.70 (1H, br t), 2.15-2.43 (2H, m), 2.80-3.03 (2H, m), 3.30-3.55 (1H, m), 3.70-4.20 (2H, m), 4.70 (1H, dt, *J*=4.0, 6.8 Hz), 7.40-7.80 (13H, m)
10a	3-(2-Biphenylyl)	H	75-77	$C_{24}H_{22}O_3$	80.42, 6.19 (80.26, 6.12)	358	358.1569 (358.1597)	1.50-2.20 (2H, m), 1.95-2.25 (1H, m), 2.30-2.75 (2H, m), 3.05-3.35 (1H, m), 3.50-4.15 (2H, m), 4.41 (1H, dt, *J*=4.2, 6.6 Hz), 6.70-7.65 (13H, m)
63	3-(2-Pyridyl)	H	syrup	$C_{17}H_{17}NO_3$		283	283.1208 (283.1226)	2.12-2.22 (1H, m), 2.28-2.38 (1H, m), 2.82-2.95 (2H, m), 3,35(1H, q, *J*=4.4 Hz), 3.74 (1H, dd, *J*=4.4, 12.2 Hz) 3.96 (1H, dd, *J*=4.9, 12.2 Hz), 4.60-4.62 (1H, m), 7.26-7.32 (2H, m) 7.43 (1H, t, *J*=7.6 Hz), 7.72-7.77 (2H, m),7.82 (1H, dt, *J*=2.0, 8.5 Hz), 7.85 (1H, s), 8.68 (1H, dd, *J*=1.0, 4.9 Hz)[b]
64	3-(3-Pyridyl)	H	syrup	$C_{17}H_{17}NO_3$		283		2.15-2.30 (2H, m), 2.78-2.95 (2H, m), 3.39-3.43 (1H, m), 3.76 (1H, dd, *J*=3.9, 11.7 Hz), 3.92 (1H, dd, *J*=4.9, 11.7 Hz), 4.64-4.70 (1H, m), 7.26-7.29 (1H, m), 7.40-7.46 (4H, m), 7.92 (1H, dt, *J*=2.0, 7.8 Hz), 8.59 (1H, dd, *J*=1.5, 4.9 Hz), 8.83 (1H, d, *J*=1.5 Hz)[b]

continuation of Table I.

Compd.	R_1	R_2	mp °C	formula	Elementary Analysis cacld. C, H, N (found C, H, N)	Ms (M^+)	High ms calcd (found)	^{1}H-Nmr ($CDCl_3$) δ [a]
65	3-(3-Isopropyl-2-pyridyl)	H	syrup	$C_{20}H_{23}NO_3$	73.82, 7.12, 4.30 (73.85, 7.24, 4.33)	325		1.19 (6H, d, *J*=6.8 Hz), 2.05-2.17 (2H, m), 2.29-2.38 (1H, m), 2.77-2.94 (2H, m), 3.10-3.19 (2H, m), 3.41 (1H, dd, *J*=3.9, 11.7 Hz), 3.76 (1H, dd, *J*=4.4, 11.7 Hz), 4.54-4.60 (1H, m), 7.25-7.32 (4H, m), 7.38 (1H, t, J=7.3 Hz), 7.76 (1H, dd, *J*=1.4, 7.8 Hz), 8.44 (1H, dd, *J*=1.4, 4.4 Hz)[b]
10b	3-(5-Isopropyl-2-pyridyl)	H	92-94	$C_{20}H_{23}NO_3$	73.82, 7.12, 4.30 (73.96, 6.93, 4.53)	325		1.31 (6H, d, *J*=6.8 Hz), 2.08-2.20 (2H, m), 2.27-2.37 (1H, m), 2.81-2.93 (2H, m), 2.95-3.05 (1H, m), 3.31-3.36 (1H, m), 3.78 (1H dd, *J*=3.9, 12.2 Hz), 3.95 (1H, dd, *J*=4.9, 12.2 Hz), 4.59-4.65 (1H, m), 7.25 (1H, d, *J*=5.4 Hz), 7.41 (1H, t, *J*=7.5 Hz), 7.66-7.7 (3H, m), 7.81 (1H, s), 8.53 (1H, s)[b]
66	3-(3-MeOOC-2-Pyridyl)	H	syrup	$C_{19}H_{19}NO_5$		341	341.1263 (341.1261)	2.08-2.18 (1H, m), 2.30-2.40 (1H, m), 2.78-2.87 (1H, m), 2.87-2.96(1H, m), 3.24 (1H, q, *J*=4.4 Hz), 3.61 (1H, dd, *J*=4.4, 11.7 Hz), 3.74 (3H, s), 3.86 (1H, dd, *J*=4.4, 11.7 Hz), 4.54-4.60 (1H, m), 7.27-7.41 (5H, m), 8.15 (1H, dd, *J*=4.4,11.7 Hz), 8.75 (1H, dd, *J*=1.5, 4.9 Hz)[b]
67	3-(4-MeOOC-2-Pyridyl)	H	119-120	$C_{19}H_{19}NO_5$	66.85, 5.61, 4.10 (66.76, 5.57, 4.29)	341		2.11-2.22 (1H, m), 2.25-2.35 (1H, m), 2.80-2.95 (2H, m), 3.24 (1H, br s), 3.37-3.42 (1H, m), 3.80 (1H, dd, *J*=3.9, 11.2 Hz), 3.99 (3H, s), 3.96 (1H, dd, *J*=4.4, 11.7 Hz), 4.59-4.66 (1H, m), 7.30 (1H, d, *J*=7.3 Hz), 7.43 (1H, t, *J*=7.8 Hz), 7.79 (1H, d, *J*=7.8 Hz), 7.83 (1H, d, *J*=7.3 Hz), 7.88 (1H, s), 8.28 (1H, s), 8.80 (1H, d, *J*=5.4 Hz)[b]
68	3-(5-MeOOC-2-Pyridyl)	H	133-135	$C_{19}H_{19}NO_5$	66.85, 5.61, 4.10 (66.72, 5.56, 3.92)	341		2.12-2.22 (2H, m), 2.27-2.38 (1H, m), 2.82-2.98 (2H, m), 3.37-3.42 (1H, m), 3.84 (1H, dd, *J*=3.9, 11.7 Hz), 3.98 (3H, s), 4.00 (1H, dd, *J*=4.9, 11.7 Hz), 4.62 (1H, dt, *J*=4.4, 6.8 Hz), 7.33 (1H, d, *J*=7.8 Hz), 7.45 (1H, t, *J*=7.8 Hz), 7.80-7.86 (2H, m), 7.93 (1H, s), 8.37 (1H, dd, *J*=2.4, 8.3 Hz), 9.26 (1H, d, *J*=1.5 Hz)[b]

[a] measured in 90 MHz unless noted otherwise
[b] measured in 400 MHz on a JEOL-JNM-EX400.

Table II. Physical Data for Substituted Phenylpropanols R_1,R_2-Phenyl-$CH_2CH_2CH_2OH$

Compd.	R_1	R_2	mp °C	Formula	Ms (M^+)	^{1}H-Nmr (90 MHz, $CDCl_3$) δ
29	3-(3-MeOOC-Phenyl)	H	syrup	$C_{17}H_{18}O_3$	270	1.42 (1H, br s), 1.73-2.16 (2H, m), 2.60-2.97 (2H, m), 3.74 (2H, t, *J*=6.8 Hz), 3.96 (3H, s), 7.10-8.30 (8H, m)
4	3-(2-Biphenylyl)	H	syrup	$C_{21}H_{20}O$	288	1.15-1.40 (1H, br s), 1.45-1.85 (2H, m), 2.40-2.65 (2H, m), 3.30-3.55 (2H, m), 6.80-7.65 (13H, m),
35b	2-Phenyl	4-Phenyl	syrup	$C_{21}H_{20}O$	288	1.30 (1H, s), 1.55-1.90 (2H, m), 2.61-2.85 (2H, m), 3.48 (2H, t, *J*=6.8 Hz), 7.20-7.70 (13H, m)
35c	3-Phenyl	5-Phenyl	94-95	$C_{21}H_{20}O$	288	1.35 (1H, br s), 1.75-2.20 (2H, m), 2.65-3.00 (2H, m), 3.65-4.03 (2H, m), 7.30-7.95 (13H, m)

Table III. Physical Data for Sustituted Phenylpropenals 3-R-Phenyl-CH=CHCHO

Compd.	R	mp °C	formula	Elementary Analysis cacld. C, H, N (found C, H, N)	Ms (M^+)	^{1}H-Nmr (90 MHz, $CDCl_3$) δ
42a	2-Pyridyl	syrup	$C_{14}H_{11}NO$		209	6.80 (1H, dd, *J*=7.4, 16.2 Hz), 7.26-7.31 (1H, m), 7.42-7.90 (5H, m), 8.04 (1H, dt, *J*=1.8, 6.6 Hz), 8.23 (1H, s), 8.67-8.73 (1H, m), 9.73 (1H, d, *J*=7.4 Hz)
42b	3-MeOOC-2-Pyridyl	syrup	$C_{16}H_{13}NO_3$		267	3.73 (3H, s), 6.76 (1H, dd, *J*=7.4, 15.8 Hz), 7.32-7.69 (5H, m), 7.79 (1H, s), 8.18 (1H, dd, *J*=1.8, 7.9 Hz), 8.80 (1H, dd, *J*=1.8, 4.8 Hz), 9,73 (1H, d, *J*=7.4 Hz)
42c	4-MeOOC-2-Pyridyl	95-97	$C_{16}H_{13}NO_3$	71.90, 4.90, 5.24 (71.62, 4.51, 5.10)	267	3.99 (3H, s), 6.83 (1H, dd, *J*=7.4, 15.8 Hz), 7.50-7.68 (3H, m), 7.84 (1H, dd, *J*=0.9, 8.3 Hz), 8.11 (1H, dd, *J*=2.0, 7.0 Hz), 8.31 (2H, br s), 8.86(1H, d, *J*=5.3 Hz), 9.75 (1H, d, *J*=7.4 Hz)
42d	5-MeOOC-2-Pyridyl	151-153	$C_{16}H_{13}NO$ .1/4H_2O	70.71, 5.01, 5.15 (70.81, 5.00, 5.06)	267	3.99 (3H, s), 6.82 (1H, dd, *J*=7.4, 15.8 Hz), 7.50-7.74 (3H, m), 7.85 (1H, dd, *J*=0.9, 8.3 Hz), 8.11 (1H, ddd, *J*=1.8, 2.2, 7.0 Hz), 8.29-8.45 (2H, m), 9.30-9.32 (1H, m), 9.75 (1H, d, *J*=7.4 Hz)
42e	3-Pyridyl	syrup	$C_{14}H_{11}NO$		209	6.79 (1H, dd, *J*=7.4, 16.2 Hz), 7.35-7.75 (5H, m), 7.76 (1H, s), 7.91 (1H, dt, *J*=1.8, 7.9 Hz), 8.66 (1H, dd, *J*=1.8, 4.8 Hz), 8.87 (1H, d, *J*=1.8 Hz), 9.76 (1H, d, *J*=7.4 Hz)
5b	5-Isopropenyl-2-pyridyl	73-75	$C_{17}H_{15}NO$	81.90, 6.06, 5.62 (82.05, 6.09, 5.80)	249	2.21 (3H, s), 5.22 (1H, t, *J*=1.3 Hz), 5.50 (1H, s), 6.81 (1H, dd, *J*=7.4 Hz, 16.2 Hz), 7.40-8.10 (6H, m), 8.24 (1H, s), 8.8-8.90 (1H, m), 9.74 (1H, d, *J*=7.9 Hz)
52	3-Isopropyl-2-pyridyl	syrup	$C_{17}H_{17}NO$		251	1.21 (6H, d, *J*=7.2 Hz), 3.12 (1H, septet, *J*=7.0 Hz), 6.75 (1H, dd, *J*=7.4, 15.8 Hz), 7.22-7.80 (7H, m), 8.52 (1H, dd, *J*=1.8, 4.8 Hz), 9.75 (1H, d, *J*=7.4 Hz)

Table IV. Physical Data for Substituted Toluenes 3-R-C_6H_6Me

Compd	R	mp ℃	Formula	Ms (M^+)	^{1}H-Nmr (90 MHz, $CDCl_3$) δ
25	3-MeOOC-Phenyl	syrup	$C_{15}H_{14}O_2$	226	2.43 (3H, s), 3.94 (3H, s), 7.10-8.35 (8H, m)
36a	2-Pyridyl	syrup	$C_{12}H_{11}N$	169	2.43 (3H, s), 7.10-7.50 (3H, m), 7.60-7.90 (4H, m), 8.68 (1H, ddd, *J*=4.6, 1.5, 1.3 Hz)
36b	3-MeOOC-2-Pyridyl	syrup	$C_{14}H_{13}NO_2$	227	2.40 (3H, s), 3.69 (3H, s), 7.23-7.41 (5H, m), 8.07 (1H, dd, *J*=2.0, 7.8 Hz), 8.76 (1H, dd, *J*=2.0, 4.8 Hz)
36c	4-MeOOC-2-Pyridyl	syrup	$C_{14}H_{13}NO_2$	227	2.44 (3H, s), 3.97(3H, s), 7.25-7.46(2H, m), 7.70-7.88 (3H, m), 8.28 (1H, s), 8.81 (1H, d, *J*=5.0 Hz)
36d	5-MeOOC-2-Pyridyl	91-93	$C_{14}H_{13}NO_2$	227	2.44 (3H, s), 3.97 (3H, s), 7.20-7.50 (2H, m), 7.70-8.00 (3H, m), 8.34 (1H, dd, *J*=1.8, 8.8 Hz), 9.27 (1H, dd, *J*=0.9, 2.4 Hz)
30a	2-Biphenylyl	syrup	$C_{19}H_{16}$	244	2.24 (3H, s), 6.80-7.65 (13H, m)

Table V *In vitro* and *In vivo* Assays (mice, n=6)

	In vitro test	*In vivo* test		
Compd.	Inhibition of HMG-CoA synthase $IC_{50}(\mu M)$	Dose mg/kg p.o.	Inhibition of sterol synthesis in liver %	Increase of serum triglyceride level ×fold[a]
3	0.85	500	76.1 (++)[b]	1.27
59	0.73	200	41.7 (-)	1.01
60	2.30	200	22.5 (-)	1.04
61	0.19	450	-127.0 (-)	9.78*[c]
62	2.50		n.d.[d]	n.d.
10a	0.23	350	35.7 (-)	1.55**
63	0.64	500	33.0 (-)	1.36*
64	15.60	450	9.7 (-)	1.03
65	3.04	150	67.8 (+)	1.16
10b	0.16	500	63.6 (+)	1.25*
66	25.1		n.d.	n.d.
67	0.70	200	39.0 (-)	0.92
68	0.92	450	-77.0(-)	1.07
14	>190		n.d.	n.d.
16a	>180		n.d.	n.d.
16b	>170		n.d.	n.d.
17	>190		n.d.	n.d.
18a	>190		n.d.	n.d.
18b	>170		n.d.	n.d.
24	>170		n.d.	n.d.
1	0.20	500	83.0 (-)	1.03

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

and *syn*-one (**18b**) in the ratio of 3:1. Compound (**20**) prepared similarly to the manner described in Scheme 1 was reduced and cyclized to give *anti*-oxetane (**24**). The stereochemical assignment of **16**, **18** and **24** was secured by ^{1}H-nmr study of NOE.

Schemes 3 and 4 show the procedures for the preparation of propanols. Propenals were prepared in the manner shown in Scheme 5. These were modified procedures from that reported[1]. The preparation of two propenals (**5b** and **52**) were outlined in Scheme 6. The propanols and propenals were listed in Tables II and III, respectively.

Preparation of some toluene derivatives, from which corresponding propanols and propenals were derived, is shown in Scheme 7. Toluene derivatives (**25** and **36a-d**) were prepared by transition metal mediated cross-coupling reactions. Methylterphenyl (**30a**) was prepared by the Grignard reaction of **57** followed by dehydration and aromatization. Physical data of these toluenes were listed in Table IV.

INHIBITION AGAINST HMG-COA SYNTHASE AND CHOLESTEROL BIOSYNTHESIS IN MOUSE LIVER.

The 2-oxetanones listed in Table I were tested for the inhibitory activities against HMG-CoA synthase in cell free system, inhibition of the cholesterol biosynthesis in mouse liver[1] and serum triglyceride increments. The results are summarized in Table V.

As seen on 2-oxetanone (**59**), introduction of a methoxycarbonyl group on B-ring of **3** did not modulate inhibitory activity, and that of a carboxy group caused loss of the activity (**60**). The relationship that methyl ester (**59**) was more active than its free acid (**60**), was consistent with that between **2** and its free acid.[1] Whereas, the relationship was inconsistent with that 1233A (**1**) and its methyl ester were equally active.[4]

In 2-oxetanones with a terphenylyl group (**61**, **62** or **10a**), depending on the structure of terphenylyl group, their inhibitory activities *in vitro* varied significantly. Thus, **61** and **10a** showed comparable activities to 1233A (**1**), however, **62** showed lower activity. The results indicate that a shape of lipophilic group in the side chain was correlated to the activity of 2-oxetanones analog. Unexpectedly, all of these compounds showed only low activities compared to 1233A (**1**) *in vivo*.

Pyridine analogs (**10b** and **63-68**) showed wide range of activities by orientation and substituent of pyridine ring. Thus, **10b** with an isopropyl group at the position 5 showed the highest inhibition *in vitro*, which was comparable to that of 1233A. Some analogs (**63**, **67** and **68**) were similarly active to the corresponding benzene analogs (**3** and **59**), and others (**64-66**) were less active. Among the positions on the pyridine ring, the

positions 4 and 5 were preferred to be substituted (**10b**, **67** and **68**). As for *in vivo* activities, only analogs (**65** and **10b**) were active.

In spite of their structural similarities to 2-oxetanone ring, derivatives of cyclobutanones (**13**, **14** and **16a-b**), γ-butyrolactones (**17** and **18a-b**) and 2-oxetane (**24**) were entirely inactive regardless of their stereochemistries. Our group,[5] Greenspan *et al.*[6] and Mayer *et al.*[7] proposed that the mechanism of inhibition with 1233A against HMG-CoA synthase was irreversible. Above results would support the inhibitory mechanism, *i.e.*, acylation of the enzyme by the ring-opening of 2-oxetanone.

In spite of our expectation, pyridine analogs of **3** (*e.g.* **63** and **64**) did not differ from **3** in terms of serum triglyceride level increment. Analog **10b** which showed the highest inhibitory activity also increased the triglyceride level. Among 2-oxetanones with a terphenyl, only **61** with a benzene ring at position 6 on A-ring of **3** showed the extreme increment of triglyceride level. We reported[1] that the distance between the 2-oxetanone and aromatic rings in the side chain has a great concern to the triglyceride increment. A benzene ring at *ortho* position on the A-ring is closer to the 2-oxetanone ring than that at other positions. Hence, the result also supports our hypothesis. In contrast with the effect of lipophilic group, It is notable that the analogs with a polar substituent in the side chain did not increase the serum triglyceride level (**3** *vs.* **59** and **60**, **10b** *vs.* **68**).

EXPERIMENTAL

Melting points were measured on a Yanagimoto hot stage apparatus and were uncorrected. In work up, extracted solutions were dried over anhydrous $MgSO_4$, and concentrated under reduced pressure (rotary evaporator). ^1H Nmr spectra were measured on a JEOL FX-90 unless noted otherwise and are reported in parts per million relative to tetramethylsilane as the internal standard. Ir spectra were measured on a Hitachi 270-30 infrared spectrophotometer. Mass spectra were measured on a JEOL-HX110, JEOL JMS-AX505W, or JEOL JMS-D300 spectrometer. Physical data of 2-oxetanones were listed in Table I. Physical data of substituted propanols, propenals and toluenes were listed in Tables II, III and IV, respectively. All starting materials were commercially available unless indicated otherwise.

Methyl 3-(3-Methylphenyl)benzoate (25). A solution of 3-bromotoluene (**53**) (34.2 g, 200 mmol) in THF (170 ml) was added dropwise to Mg turnings (5.84 g, 240 mmol). The mixture was refluxed for 1 h and the resultant mixture was added to a solution of $ZnCl_2$ (30.0 g, 240 mmol) in THF (350 ml) under N_2 atmosphere

at -10℃. After stirring for 3 h, a solution of $(Ph_3P)_4Ni$[8] in THF prepared from $(Ph_3P)_2NiCl_2$ (3.14 g, 4.80 mmol), PPh_3 (2.64 g, 10.1 mmol) and DIBAL-H (1 mol/l in THF, 9.60 ml) were added and then methyl 3-bromobenzoate (25.1 g, 116.3 mmol) was added. The mixture was stirred overnight and poured into water (1 l). The resultant mixture was acidified with *c*-HCl and extracted with Et_2O. The extract was washed with saturated aqueous $NaHCO_3$, dried and concentrated. The residue was chromatographed on silica gel column and the elution with hexane-AcOEt (20:1) gave **25** (25.7 g, 97.8%) as an oil.

3-(2-Pyridyl)toluene (36a). The compound was prepared by the method of Pridgen *et al.*[9] A solution of Grignard reagent prepared from 3-bromotoluene (**53**) (17.4 g, 0.10 mmol) and Mg (2.31 g, 95.0 mmol) in Et_2O (90 ml), was added dropwise for 40 min to a solution of 2-bromopyridine (11.1 g, 70 mmol) and $(Ph_3P)_2NiCl_2$ (0.48 g, 0.74 mmol) in Et_2O (50 ml) under N_2 atmosphere in ice bath. The mixture was stirred for 25.5 h and poured into 2*N*-HCl (200 ml). The separated aqueous layer was made basic with aqueous NaOH and extracted with Et_2O. The extract was dried and concentrated. The residue was chromatographed on silica gel column and the elution with hexane-AcOEt (20:1) gave **36a** (9.57 g, 81.0 %) as an oil.

Methyl 6-Bromonicotinate (55d). A solution of PPh_3 (2.62 g, 10 mmol) in Et_2O (10 ml) was added dropwise to a solution of diethyl azodicarboxylate (1.74 g, 10 mmol), 6-bromonicotinic acid[10] (**54d**) (2.00 g, 9.90 mmol) and MeOH (0.48 g, 15 mmol) in Et_2O (10 ml) at room temperature. After stirring for 70 min, the mixture was filtered. The filtrate was concentrated. The residue was chromatographed on silica gel column and the elution with hexane-AcOEt (50:1) gave **55d** (1.70 g, 79.0%) as a pale yellow crystal. mp 106-108℃. ^1H Nmr ($CDCl_3$) δ: 3.96 (3H, s), 7.59 (1H, d, *J*=8.3 Hz), 8.13 (1H, dd, *J*=2.4, 8.3 Hz), 8.96 (1H, d, *J*=2.4 Hz). EI-ms (m/z): 215, 217 (M^+), 184, 186.

Methyl 6-(3-Methylphenyl)nicotinate (36d). Compound (**36d**) was prepared by the method of Thompson *et al.*[11] To a solution of **55d** (2.55 g, 11.8 mmol) and $(Ph_3P)_4Pd$ (0.40 g, 0.35 mmol) in toluene (25 ml), a solution of 3-tolylboronic acid (1.92 g, 14.1 mmol) prepared from 3-tolylmagnesium bromide and triisopropyl borate[10] in MeOH (7.5 ml) and 2*M* aqueous Na_2CO_3 (50 ml) were added. After stirring for 2.5 h under Ar atmosphere at 80℃, the mixture was poured into a mixture of $CHCl_3$ (100 ml), 2*M*-aqueous Na_2CO_3 (50 ml) and c-NH_4Cl (5 ml). The separated organic layer was washed with water, dried and concentrated. The residue was chromatographed on silica gel column and the elution with hexane-AcOEt (25:1) gave **36d** (2.12 g, 79.0%) as a colorless crystal. mp 91-93℃.

Compounds (**56** and **36b**) were prepared in a similar manner to the preparation of **36d**.

Methyl 2-(3-Tolyl)isonicotinate (36c). Compound (**56**) (8.35 g, 43 mmol) was hydrolyzed with NaOH (7.5 g, 188 mmol) in 70% EtOH (200 ml) and acidified to give the corresponding acid (8.42 g, 92%). This product was added to a mixture of *c*-H_2SO_4 (5.7 g) and MeOH (110 ml). The mixture was refluxed for 22 h. After concentration, the resultant mixture was made basic with $NaHCO_3$ and extracted with AcOEt. The extract was dried and concentrated to give **36c** (8.5 g, 88% based on **56**) as an oil.

3-Methyl-[1,1':2',1'']-terphenyl (30a). A solution of the Grignard reagent obtained from 3-bromotoluene (**53**) (16.3 g, 95.2 mmol) and Mg (2.11 g, 86.6 mmol) in Et_2O (82 ml) was added dropwise to a solution of 2-phenylcyclohexanone (**57**) (10.0 g, 57.5 mmol) in Et_2O (50 ml). The mixture was refluxed for 1 h and poured into saturated aqueous NH_4Cl. The resultant mixture was extracted with Et_2O. The extract was dried, and concentrated. The residue was recrystallized from hexane to give **58** (12.5 g, 81.3%) as a syrup. To a solution of the product in toluene (63 ml), *p*-TsOH·H_2O (0.89 g, 4.69 mmol) was added. The mixture was refluxed for 2 h with Dean-Stark apparatus. The reaction mixture was washed with saturated aqueous $NaHCO_3$, dried and concentrated to give a syrup (11.2 g). This syrup with S (1.44 g, 45.0 mmol) was stirred for 30 min at 210-220℃. The mixture was chromatographed on silica gel column and the elution with hexane-AcOEt (20:1) gave **30a** (5.60 g, 48.9% based on **58**) as a syrup.

Methyl 3-[3-(3-Hydroxypropyl)phenyl]benzoate (29). Compound (**25**) was treated as reported[1] to give **29** as a syrup.

3-([1,1':2',1'']-3-Terphenylyl)propanol (4). Compound (**30a**) was treated as reported[1] to give **4** as a syrup. Compunds (**35b,c**) were also prepared from **30b,c**[12] similarly

3-[3-(3-Pyridyl)phenyl]propenal (42e). A solution of Grignard reagent prepared from 2-(3-bromophenyl)-1,3-dioxolane (25.0 g, 109 mmol) and Mg (2.53 g, 104 mmol) was added to a solution of 3-bromopyridine (12.0 g, 75.9 mmol) and $(Ph_3P)_2NiCl_2$ (0.52 g, 0.79 mmol) in Et_2O (100 ml). The mixture was stirred for 3 days, then poured into 1*N*-HCl (300 ml). The resultant mixture was stirred for 10 min. The separated aqueous layer was made basic with 2*M* aqueous K_2CO_3 and extracted with Et_2O. The extract was dried and concentrated. The residue was chromatographed on silica gel column and the elution with $CHCl_3$-acetone (50:1) gave **38e** (2.88 g, 21.0%) as a pale yellow syrup. ^1H Nmr ($CDCl_3$) δ: 7.30-8.00 (5H, m), 8.10 (1H, s), 8.65 (1H, dd, *J*=1.3, 4.8 Hz), 8.90 (1H, d, *J*=2.2 Hz), 10.11 (1H, s). EI-ms (m/z): 183 (M^+). To a suspension of NaH (0.68 g, 60% net, 17 mmol) in THF (15 ml), a solution of diethyl ethoxycarbonylmethylphosphonate (3.81 g, 17 mmol) in THF (5 ml) was added and then **38e** in THF (15 ml)

was added. The mixture was stirred for 30 min at room temperature. After concentration, the mixture was poured into water and extracted with $CHCl_3$. The extract was dried and concentrated. The residue was chromatographed on silica gel column and the elution with $CHCl_3$-MeOH (100:1) gave **40e** (3.60 g, 90%) as a pale yellow crystal. A solution of **40e** (3.38 g, 13.3 mmol) in THF (30 ml) was cooled to -70℃. DIBAL-H (1 mol/l, in hexane, 30 ml) was added dropwise over 20 min. The mixture was stirred at -20℃ for 1 h. After $Na_2SO_4 \cdot 10H_2O$ (20 g) was added, the mixture was filtered. The filtrate was concentrated. The residue was chromatographed on silica gel column and the elution with $CHCl_3$-MeOH (50:1) gave **41e** (2.19 g, 78%) as a syrup. This product was oxidized by Swern method to give **42e** (94% based on **41e**) as a syrup.

Compounds (**42a**) was prepared in a similar manner to the preparation of **42e**.

Methyl 6-(3-Formylphenyl)nicotinate (38d). Compound (**36d**) was treated as reported[1] to give **38d** as a pale yellow crystal. mp 114-117℃. ^{1}H Nmr ($CDCl_3$) δ: 3.39 (3H, s), 7.58-8.04 (3H, m), 8.30-8.56(3H, m), 9.28-9.31 (1H, m), 10.12 (1H, s). EI-ms (m/z): 241 (M^+). Anal. Calcd for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60; N, 5.81. Found: C, 69.42; H, 4.45; N, 6.04.

Methyl 6-[3-(2-Formylethenyl)phenyl]nicotinate (42d). Compound (**38d**) was treated with 2-(1,3-dioxolanyl)methyltriphenylphosphonium bromide[13] and LiOMe followed by hydrolysis as reported previously[1] to give **42d** as a crystal. mp 151-153℃.

Propenals (**42b,c**) were prepared in a similar manner to the preparation of **42d**.

Methyl 6-[3-(2-Cyanoethenyl)phenyl]nicotinate (43). A solution of diethyl cyanomethylphosphonate (5.49 g, 31 mmol) in THF (10 ml) was added dropwise to a suspension of NaH (1.24 g, 60% net, 31 mmol) in THF (50 ml) in ice bath. The mixture was stirred for 10 min. A solution of **38d** (7.37 g, 30.5 mmol) in THF (80 ml) was added dropwise. The mixture was stirred for 30 min, concentrated and poured into water. The precipitate was filtered to give a mixture of *syn* and *anti*-**43** (6.90 g, 86 %) as a pale yellow crystal. mp 143-155℃. ^{1}H Nmr ($CDCl_3$) δ: 3.99 (3H, s), 5.56 (1/9H, d, J=14 Hz), 6.02 (8/9H, d, J=16.6 Hz), 7.51 (1H, d, J=16.4 Hz), 7.55 (2H, d, J=5.3 Hz), 7.82 (1H, dd, J=0.9, 8.3 Hz), 8.04-8.14 (1H, m), 8.21 (1H, s), 8.39 (1H, dd, J=2.2, 8.3 Hz), 9.29 (1H, d, J=1.5 Hz), ir (KBr) cm^{-1}: 2216, 1726, 1622, 1602. EI-ms (m/z): 264(M^+), 263. Anal. Calcd for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.57; N, 10.60. Found: C, 72.58; H, 4.87; N, 10.32.

3-[2-[5-(2-Hydroxyisopropyl)pyridyl]]cinnamonitrile (44). A solution of methylmagnesium bromide in Et_2O (3 mol/l, 22 ml) was added dropwise over 20 min to a solution of **43** (6.90 g, 26.1 mmol) in THF (60 ml) at -10 ~ -20℃. After stirring for 40 min, the mixture was poured into saturated aqueous NH_4Cl (500 ml)

and extracted with AcOEt. The extract was dried and concentrated. The residue was chromatographed on silica gel column and the elution with $CHCl_3$-MeOH (100:1) gave **44** (4.97 g, 72.0%) as a pale yellow crystal. mp 131-133℃. ^{1}H Nmr ($CDCl_3$) δ: 1.63 (6H, s), 5.52 (1/8H, d, J=14 Hz), 5.98 (7/8H, d, J=16.8 Hz), 7.37-8.10 (7H, m), 8.80 (1H, d, J=2.0 Hz), ir (KBr) cm^{-1}: 2216. EI-ms (m/z): 264(M^+), 249.

***anti*-3-[2-(5-Isopropenylpyridyl)]cinnamaldehyde (5b).** To a solution of **44** (4.96 g, 18.8 mmol) in toluene (80 ml), *p*-TsOH·H_2O (0.16 g, 0.84 mmol) and *p*-hydroquinone (0.08 g) were added. The mixture was refluxed for a day with Dean-Stark apparatus. The cooled reaction mixture was washed with saturated aqueous $NaHCO_3$, dried and concentrated. The residue was chromatographed on silica gel column and the elution with hexane-AcOEt (4:1) gave **45** (2.39 g, 52%) as a crystal. This product was treated in a similar manner to the preparation of **41e** to give **5b** (1.39 g, 47%) as a crystal. mp 73-75℃.

2-Chloro-3-isopropylpyridine (46). Methyl 2-chloronicotinate was treated by a similar manner to the preparations of **44** and **45** followed by the catalytic reduction with Pt/C to give **46** as a syrup. ^{1}H Nmr ($CDCl_3$) δ: 1.26 (6H, d, J=7.0 Hz), 3.35 (1H, septet, J=7.0 Hz), 7.20 (1H, dd, J=4.8, 7.7 Hz), 7.62 (1H, dd, J=2.0, 7.7 Hz), 8.22 (1H, dd, J=2.0, 4.6 Hz).

3-[2-(3-Isopropylpridyl)]aniline (48). 3-(2-Propyl)-2-(3-nitrophenyl)pyridine was prepared from **46** and 3-bromonitorbenzene in the presence of $(Ph_3P)_4Pd$ as a catalyst in a similar manner to the preparation of **25**. To a solution of this compound (8.50 g, 35.1 mmol), 10% Pd/C (50% wet, 0.7 g) was added. The mixture was stirred for 17 h under H_2 atmosphere at room temperature and filtered. The filtrate was concentrated. The residue was recrystallized from hexane-AcOEt to give **48** (6.32 g, 85%) as a colorless crystal. mp 101-102℃. ^{1}H Nmr ($CDCl_3$) δ: 1.17 (6H, d, J=6.8 Hz), 3.20 (1H, septet, J=7.0 Hz), 3.59 (2H, br s), 6.67-6.83 (3H, m), 7.15-7.30 (2H, m), 7.69 (1H, dd, J=1.5, 8.1 Hz), 8.47 (1H, dd, J=1.5, 4.6 Hz). EI ms (m/z): 212 (M^+), 211. Anal. Calcd for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60; N, 13.19. Found: C, 79.19; H, 7.66; N, 12.89.

Ethyl 2-Chloro-3-[3-[2-(3-isopropylpyridyl)]phenyl]propanoate (49). Compound (**49**) was prepared by the method of Doyle *et al.*[14] A solution of **48** (6.32 g, 29.8 mmol) was added dropwise over 40 min to a mixture of cupric chloride (4.84 g, 36.0 mmol), *t*-butyl nitrite (4.61 g, 45.0 mmol) and ethyl acrylate (60 ml, 563 mmol) in MeCN (60 ml) at room temperature. After stirring for 17 h, the mixture was poured into 10% HCl (600 ml) and extracted with Et_2O. $NaHCO_3$ was added to the separated aqueous layer and the resultant mixture was extracted with CH_2Cl_2. The extract was washed with water, dried and concentrated. The residue was chromatographed on silica gel column and the elution with hexane-AcOEt (10:1) gave **49** (5.46 g, 55%)

as a pale yellow syrup. ^{1}H Nmr ($CDCl_3$) δ: 1.18 (6H, d, *J*=7.0 Hz), 1.22 (3H, t, *J*=7.2 Hz), 2.95-3.32 (2H, m), 3.46 (1H, dd, *J*=6.8, 14.0 Hz), 4.19 (2H, q, *J*=7 Hz), 4.47 (1H, t, *J*=7 Hz), 7.23-7.41 (5H, m), 7.71 (1H, dd, *J*=1.8, 7.9 Hz), 7.99 (1H, dd, *J*=1.8, 4.6 Hz)

Ethyl 3-[2-(3-Isopropylpridyl)]cinnamoate (50). To a solution of **49** (5.96 g, 18.0 mmol) in dioxane (80 ml), DBU (4.11 g, 27.5 mmol) was added. The mixture was stirred for 3.5 h at 120℃ and the resultant mixture was filtered. The filtrate was concentrated. The residue was chromatographed on silica gel column and the elution with CH_2Cl_2-EtOH (100:1) gave **50** (5.34 g, 100%) as a syrup. ^{1}H Nmr ($CDCl_3$) δ: 1.19 (6H, d, *J*=6.8 Hz), 1.32 (3H, t, *J*=7.2 Hz), 2.90-3.30 (1H, m), 4.26 (2H, q, *J*=7.2 Hz), 6.47 (1H, d, *J*=16.0 Hz), 7.28 (1H, dd, *J*=4.8, 7.2 Hz), 7.42-7.65 (4H, m), 7.73 (1H, dd, *J*=1.8, 7.9 Hz), 7.74 (1H, d, *J*=16.0 Hz), 8.51 (1H, dd, *J*=1.8, 4.8 Hz). FAB ms (m/z): 294 (M^++1), 198, 161.

3-[2-(3-Isopropylpyridyl)]cinnamaldehyde (52). Compound (**50**) was treated with DIBAL-H followed by the Swern oxidation to give **52** as a syrup.

3-([1,1':2',1'']-3-Terphenylyl)propanal (5a). Compound (**4**) was treated by Swern oxidation to give **5a** (Y=39.6%) as a syrup. ^{1}H Nmr ($CDCl_3$) δ: 2.35-2.60 (2H, m), 2.65-2.90 (2H,m), 6.80-7.60 (13H, m), 9.62 (1H, s). EI ms (m/z): 286 (M^+).

Compounds (**29** and **35b-c**) were treated similarly to give the corresponding propanals.

***Ethyl anti*-3-Hydroxy-5-([1,1':2',1'']-3-terphenylyl)-2-trityloxymethylpentanoate (7a).** Compound (**5a**) was condensed with benzyl 3-hydroxypropanoate[15] treated with triphenylmethyl chloride and separated by column chromatography as reported[1] to give **7a** as a syrup. ^{1}H Nmr ($CDCl_3$) δ: 1.27 (3H, t, *J*=7.2 Hz), 1.40-1.94 (2H, m), 2.30-3.18 (4H, m), 3.60-4.27(3H, m), 4.20 (2H, q, *J*=7.2 Hz), 6.85-7.64 (28H, m).

***anti*-4-[2-([1,1':2',1'']-3-Terphenylyl)ethyl]-3-trityloxymethyl-2-oxetanone (9a).** Compound (**7a**) was hydrolyzed with aqueous KOH and lactonized with *p*-TsCl as reported[1] to give **9a** (Y=70.1%) as a crystal. mp 164-166℃. ^{1}H Nmr ($CDCl_3$) δ: 1.50-2.20 (2H, m), 2.35-2.70 (2H, m), 3.00-3.25 (2H, m), 3.35-3.65 (1H, m), 4.36 (1H, dt, *J*=3.7, 7.0 Hz), 6.70-7.65 (28H, m). FD ms (m/z): 600 (M^+). Anal. Calcd for $C_{43}H_{36}O_3$: C, 85.97; H, 6.04. Found: C, 85.83; H, 6.03.

***anti*-3-Hydroxymethyl-4-[2-([1,1':2',1'']-3-terphenylyl)ethyl]-2-oxetanone (10a).** Compound (**9a**) was treated with CF_3COOH as reported previously[1] to give **10a** as a crystal. mp 75-77℃.

Compounds (**61** and **62**) were prepared in a similar manner to the preparation of **10a.**

***anti*-3-Hydroxy-5-[3-[2-(5-isopropylpyridyl)]phenyl]-2-trityloxymethylpentanoic Acid (8b).** Benzyl *anti*-5-[3-[5-(2-propenyl)-2-pyridyl]phenyl]-3-hydroxy-2-trityloxymethyl-4-pentenoate (**7b**) (0.75 g, 1.12 mmol) was prepared from **5b** in a similar manner to that reported.[1] To a solution of this compound in EtOH (15 ml), 5% Pd/C (50% wet, 0.15 g) was added. The mixture was stirred for 24 h under H_2 atmosphere at room temperature and the resultant mixture was filtered. The filtrate was concentrated to give **8b** (0.51 g, 78%) as a syrup. ^{1}H Nmr ($CDCl_3$) δ: 1.23 (3H, s), 1.31 (3H, s), 1.50-1.80 (2H, m), 2.60-3.10 (3H, m), 3.47 (2H, d, J=5.7 Hz), 3.70-4.00 (1H, m), 6.52 (2H, br s), 7.14-7.70 (22H, m), 8.63 (1H, s).

***anti*-3-Hydroxymethyl-4-[2-[3-[2-(5-isopropylpyridyl)]phenyl]ethyl]-2-oxetanone (10b).** Compound (**8b**) was treated as reported[1] to give **10b** as a crystal. mp 92-94℃.

Compounds (**59** and **63-68**) were prepared in a similar manner to the preparation of **10b.**

***anti*-4-[2-[3-(3-Carboxyphenyl)phenyl]ethyl]-3-hydroxymethyl-2-oxetanone (60).** Compound (**59**) was treated with porcine liver esterase (PLE) as reported[1] to give **60** as a solid. mp 141-143℃.

4-(3-Biphenylyl)-1-butene (12). KO*t*-Bu (1.55 g, 13.8 mmol) was added to a solution of methyltriphenylphosphonium bromide (5.68 g, 15.9 mmol) in Et_2O (21.2 ml). The mixture was refluxed for 15 min. A solution of **11** (2.18 g, 10.4 mmol) in Et_2O (10.6 ml) was added. The mixture was refluxed for 15 min, poured into water and extracted with AcOEt. The extract was dried and concentrated. The residue was chromatographed on silica gel column and the elution with hexane-AcOEt (50:1) gave **12** (2.15 g, 99%) as a syrup. ^{1}H Nmr ($CDCl_3$) δ: 2.37-2.45 (2H, m), 2.50-2.78 (2H, m), 4.95 (1H, d, J=17 Hz), 5.15 (1H, d, J=11 Hz), 5.68-6.05 (1H, m), 7.34-7.61 (9H, m). EI ms (m/z): 208 (M^+). High ms: Calcd for $C_{16}H_{16}$: 208.1251 Found: 208.1246.

3-[2-(3-Biphenylyl)ethyl]-2,2-dichlorocyclobutanone (13). Compound (**13**) was prepared by the method of Dprès *et al.*[2] Active Zn (4.47 g, 68.3 mmol) was added to a solution of **12** (2.37 g, 11.4 mmol) in Et_2O (30 ml), $POCl_3$ (4.24 ml, 45.6 mmol) and CCl_3COCl (76.7 ml, 45.6 mmol) in Et_2O (30 ml) was added dropwise for 3 h with sonication.[2] The mixture was refluxed for 16 h and filtered. The filtrate was washed with water and saturated aqueous $NaHCO_3$, dried and concentrated. The residue was chromatographed on silica gel column and the elution with hexane-AcOEt (50:1) gave **13** (2.31 g, 66.0%) as a syrup. ^{1}H Nmr ($CDCl_3$) δ: 1.80-1.92 (2H, m), 2.05-2.22 (3H, m), 2.25-2.41 (2H, m), 7.21-7.85 (9H, m), ir ($CHCl_3$) cm^{-1}: 1810. EI ms (M/z): 318, 320, 322 (M^+). High ms Calcd for $C_{18}H_{16}OCl_2$: 318.0577, 320.0547, 322.0518. Found: 318.0559, 320.0554, 322.0503.

3-[2-(3-Biphenylyl)ethyl]cyclobutanone (14). Zn (0.138 g, 2.17 mmol) was added to a solution of **13** (1.38 g, 0.43 mmol) in CH_3COOH (4.3 ml). The mixture was stirred for 2 h at 70℃ under Ar atmosphere, poured into the mixture of saturated aqueous $NaHCO_3$ and *c*-NH_4OH and extracted with AcOEt. The extract was dried and concentrated. The residue was chromatographed on silica gel column and the elution with hexane-AcOEt (20:1) gave **14** (0.107 g, 66.0%) as a syrup. ^1H Nmr ($CDCl_3$) δ: 1.80-1.95 (2H, m), 2.00-2.25 (3H, m), 2.25-2.43 (4H, m), 7.30-7.61 (9H, m), ir (KBr) cm^{-1}: 1770. EI ms (m/z): 250 (M^+). High ms Calcd for $C_{18}H_{18}O$: 250.1357. Found: 250.1371.

***anti* and *syn*-3-[2-(3-Biphenylyl)ethyl]-2-hydroxymethylcyclobutanone (16a-b).** To a solution of **14** (0.100 g, 0.40 mmol) in CH_2Cl_2 (2.0 ml), 2,6-lutidine (93 μl, 0.80 mmol) and *t*-butyldimethylsilyl *trifluoromethanesulfonate* (138 μl, 0.60 mmol) were added dropwise in an ice-bath. The mixture was stirred for 15 h, poured into water and extracted with CH_2Cl_2. The extract was dried and concentrated. The residue was chromatographed on silica gel column and the elution with hexane-AcOEt (100:1) gave **15** (0.099 g, 68.0%) as a syrup. A solution of this syrup in CH_2Cl_2 (1.5 ml) was added dropwise to a mixture of $SnCl_4$ (0.47 μl, 0.4 mmol) in CH_2Cl_2 (3 ml) and HCHO (prepared by heating of paraformaldehyde 0.37 g) in Et_2O (1 ml) for 20 min under Ar atmosphere at -78℃. The mixture was stirred for 1 h and poured into saturated aqueous $NaHCO_3$. After standing for 1 h, the organic layer was separated, dried and concentrated. The residue was separated by ptlc (silica gel, hexane-AcOEt (1:1)) to give **16a** (10.7 mg) and **16b** (8.2 mg) as a syrup, respectively. Combined yield based on recovered cyclobutanone was 54%. **16a**: ^1H Nmr ($CDCl_3$) δ: 1.90-2.10 (2H, m), 2.20-2.43 (1H, m), 2.55-2.82 (4H, m), 2.93-3.20 (1H, m), 3.70-3.90 (2H, m), 7.30-7.61 (9H, m), ir (KBr) cm^{-1}: 1770, 2850-2950, 3200-3600. EI ms (m/z): 280 (M^+). High ms calcd for $C_{19}H_{20}O_2$: 280.1463. Found 280.1460. **16b**: ^1H Nmr ($CDCl_3$) δ: 1.90-2.13 (2H, m), 2.22-2.46 (1H, m), 2.50-2.85 (4H, m), 3.04-3.28 (1H, m), 3.71-3.92 (2H, m), 7.30-7.60 (9H, m), ir (KBr) cm^{-1}: 1760 2850-2950, 3200-3600. EI ms (m/z): 280 (M^+). High ms calcd for $C_{19}H_{20}O_2$: 280.1463. Found 280.1458. NOE between C-2 and c-3 protons (cyclobutanone numbering) was observed in **16b** and not observed in **16a**.

3-[2-(3-Biphenylyl)ethyl]butyrolactone (17). To a solution of **14** (0.107 g, 0.43 mmol) in CH_2Cl_2 (4.3 ml), 3-chloroperbenzoic acid (0.111 g, 0.65 mmol) was added. The mixture was stirred for 40 min and poured into 10% Na_2CO_3. After stirring for 10 min, the resultant mixture was extracted with CH_2Cl_2. The extract was dried and concentrated. The residue was chromatographed on silica gel column and the elution with hexane-AcOEt (10:1) gave **17** (0.104 g, 91 %) as a syrup. ^1H Nmr ($CDCl_3$) δ: 1.85-2.02 (2H, m), 2.15-2.41 (1H, m),

2.54-2.83 (4H, m), 3.81-4.00 (1H, m), 4.34-4.50 (1H, m), 7.30-7.61 (9H, m), ir (KBr) cm^{-1}: 1760, 2890-3050, 3200-3600. EI ms (m/z): 266 (M^+). High ms: Calcd for $C_{18}H_{18}O_2$: 266.1307. Found: 266.1306.

***anti* and *syn*-3-[2-(3-Biphenylyl)ethyl]-2-hydroxymethylbutyrolactone (18a-b).** Compound (**17**) was treated by a similar manner to the preparation of **6a** except the use of HCHO and separated with ptlc (silica gel, hexane-AcOEt (1:1)) to give *anti*-**18a** and *syn*-**18b** (combined yield: 24%) as a syrup, respectively. **18a**: ^1H Nmr ($CDCl_3$) δ: 1.81-2.04 (2H, m), 2.40-2.52 (1H, m), 2.61-2.84 (3H, m), 3.61-4.00 (3H, m), 4.31-4.56 (1H, m), 7.48-7.72 (9H, m), ir (KBr) cm^{-1}: 1750, 2800-3000, 3200-3550. EI ms (m/z): 296 (M^+). High ms calcd for $C_{19}H_{20}O_3$: 296.1412. Found: 296.1401. **18b**: ^1H Nmr ($CDCl_3$) δ: 1.81-2.02 (2H, m), 2.42-2.55 (1H, m), 2.60-2.80 (3H, m), 3.61-4.04 (3H, m), 4.30-4.51 (1H, m), 7.40-7.72 (9H, m), ir (KBr) cm^{-1}: 1750, 2800-3000, 3200-3550. EI ms (m/z): 296 (M^+). High ms calcd for $C_{19}H_{20}O_3$: 296.1412. Found: 296.1410. NOE between C-2 and C-3 protons (butyrolactone numbering) was observed in **18b** and not observed in **18a**.

Benzyl *anti*-5-[2-(3-Biphenylyl)ethyl]-2-(*t*-butyldiphenylsilyloxymethyl)-3-hydroxypentanoate (20). Compound (**11**) was treated by the manner reported previously[1] to give **19**, which was treated with TBDPS-Cl and imidazole in a similar manner to the preparation of **7a** to give **20** as a syrup. ^1H Nmr ($CDCl_3$) δ: 1.01 (9H, s), 1.51-1.96 (2H, m), 2.45 (1H, br s), 2.61-2.93 (3H, m), 3.90-4.25 (3H, m), 5.10 (2H, s), 6.93-7.80 (24H, m).

***anti*-5-[2-(3-Biphenylyl)ethyl]-2-(*t*-butyldiphenylsilyloxymethyl)pentan-1,3-diol. (21).** A solution of DIBAL-H (1 mol/l, in hexane, 4.46 ml) was added dropwise to a solution of **20** (0.301 g, 0.48 mmol) in Et_2O (9.5 ml) at -78℃. The mixture was stirred for 5.8 h under Ar atmosphere, warmed gradually to room temperature and stirred for 2.3 h before quenching with 10% H_2SO_4. The resultant mixture was extracted with Et_2O. The extract was dried and concentrated. The residue was chromatographed on silica gel column and the elution with hexane-AcOEt (3:1) gave **21** (0.225 g, 89%) as a syrup. ^1H Nmr ($CDCl_3$) δ: 1.10 (9H, s), 1.64-2.11 (3H, m), 2.53 (2H, br s), 2.61-2.90 (2H, m), 3.82-4.13 (5H, m), 7.10-7.80 (19H, m).

***anti*-5-[2-(3-Biphenylyl)ethyl]-2-(*t*-butyldiphenylsilyloxymethyl)-1-*p*-toluenesulfonyloxypenatan-3-ol (22).** To a solution of **21** (87 mg, 0.17 mmol) in CH_2Cl_2 (1.7 ml), pyridine (3.2 μl, 0.39 mmol) and *p*-TsCl (38 mg, 0.20 mmol) were added . The mixture was stirred for 7 h at 0℃, poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The extract was dried and concentrated. The residue was separated by ptlc (silica gel, hexane-AcOEt (1:1)) to give **22** (60 mg, 53%) as a syrup. ^1H Nmr ($CDCl_3$) δ: 1.01 (9H, s), 1.51-1.96 (3H, m), 2.43 (3H, s), 2.53-2.90 (3H, m), 3.63-4.16 (3H, m), 4.22-4.54 (2H, m), 7.00-8.06 (23H, m).

***anti*-2-[2-(3-Biphenylyl)ethyl]-3-(*t*-butyldiphenylsilyloxymethyl)oxetane (23).** To a solution of **22** (60 mg, 0.088 mmol) in THF (1.6 ml), KO*t*-Bu (20 mg, 0.18 mmol) was added at 0℃. After stirring for 20 min, water was added. The mixture was extracted with AcOEt. The extract was dried and concentrated. The residue was separated by ptlc (silica gel, hexane-AcOEt (2:1)) to give **23** (35 mg, 79%) as a syrup. ^{1}H Nmr ($CDCl_3$) δ: 1.04 (9H, s), 1.92-2.31 (2H, m), 2.62-2.94 (3H, m), 3.80 (2H, dd, *J*=4.0, 7.2 Hz), 4.40 (1H, t, *J*=6.5 Hz), 6.92-7.80 (19H, m).

***anti*-2-[2-(3-Biphenylyl)ethyl]-3-hydroxymethyloxetane (24).** Compound (**23**) (34 mg, 0.07 mmol) was added to a solution 1*M*-tetrabutylammolonium fluoride in THF (350 μl, 0.35 mmol). The mixture was stirred for 50 min at room temperature. After dilution with water, the mixture was extracted AcOEt. The extract was dried and concentrated. The residue was separated by ptlc (silica gel, hexane-AcOEt (1:3)) to give **24** (16 mg, 89%) as a syrup. ^{1}H Nmr ($CDCl_3$) δ: 1.70 (1H, br s), 2.00-2.29 (2H, m), 2.65-2.88 (3H, m), 3.83 (2H, d, *J*=7 Hz), 4.42 (1H, t, *J*=7 Hz), 4.57-4.68 (2H, m), 7.15-7.65 (9H, m). ^{13}C Nmr ($CDCl_3$, 75 MHz): 141.94, 141.37, 128.82, 128.69, 127.31, 127.27, 127.21, 127.14, 124.81, 84.47, 70.31, 63.80, 42.49, 38.70, 30.54, ir (KBr) cm^{-1}: 960, 2800-3100, 3200-3550. NOE between C-2 and C-3 protons (oxetane numbering) was not observed.

Inhibition against HMG-CoA Synthase (*in vitro* Assay).

Inhibitory activities against HMG-CoA synthase were assayed as reported previously.[4]

Inhibition against Cholesterol Biosynthesis in Mouse Liver (*in vivo* Assay).

Compounds were evaluated for their abilities to inhibit the cholesterol synthesis in standard chow-fed male ddY mouse by the manner reported.[1]

REFERENCES

1. H. Hashizume, H. Ito, K. Yamada, H. Nagashima, M. Kanao, H. Tomoda, T.Sunazuka, H. Kumagai, and S. Ōmura, *Chem. Pharm. Bull.*, 1994, **42,** 512.
2. J.-P. Dpres and A. E. Green, *J. Org. Chem.*, 1980, **45**, 2036.
3. B. Ermst, *Angew. Chem. Int. Ed. Engl.*, 1988, **27**, 797.
4. H. Tomoda, H. Kumagai, H. Tanaka, and S. Ōmura, *Biochim. Biophys. Acta*, 1987, **922**, 351.
5. H. Tomoda, H. Kumagai, H. Tanaka, and S. Ōmura, *J. Antibiotics,* 1992, **46**, 1139.
6. M. D. Greenspan, H. G. Bull, J. B. Yudkovitz, D. P. Hanf, and A. W. Albert, *Biochem. J.*, 1993, **289**, 889.
7. R. J. Mayer, P. Louis-Flamberg, J. D. Elliott, M. Fisher, and J. Leber, *Biochem. Biophys. Res. Commun.*, 1990, **169**, 610.

8. E. Negishi, A. O. King, and N. Okukado, *J. Org. Chem.*, 1977, **42**, 1821.

9. L. N. Pridgen, *J. Heterocycl. Chem.*, 1975, **12**, 443.

10. J. E. Thorpe, Ger. Patent 2,718,976 [*Chem. Abstr.*, 1978, **88**, 50866z].

11. W. J. Thompson, J. Gaudino, K. Burdeska, H. Fuhrer, G. Kabas, and A. E. Siegrist, *J. Org. Chem.*, 1984, **49**, 5237.

12. H. E. Zimmolerman, D. F. Juers, J. M. McCall, and B. Schroder, *J. Am. Chem. Soc.*, 1971, **93**, 3662.

13. T. M. Cresp, M. V. Sargent, and P. Vogel, *J. Chem. Soc., Perkin Trans.* I, **1974**, 37.

14. M. P. Doyle, B. Siegfried, R. C. Elliott, and J. F. Dellaria Jr., *J. Org. Chem.*, 1977, **42**, 2431.

15. T. Sunazuka, K. Tsuzuki, H. Kumagai, H. Tomoda, H. Tanaka, H. Nagashima, H. Hashizume, and S. Ōmura, *J. Antibiotics*, 1992, **45**, 1139.

Received, 18th February, 1994