[Chem. Pharm. Bull. 28(5)1509—1525(1980)]

Mevalonolactone Derivatives as Inhibitors of 3-Hydroxy-3-methylglutaryl Coenzyme A Reductase

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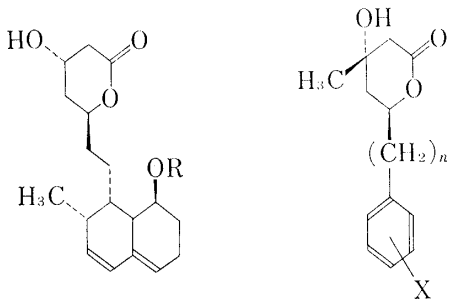
(Received November 1, 1979)

Mevalonolactone derivatives were prepared *via* stereo- and regioselective bromolactonization of γ,δ-unsaturated acids and their structure-activity relationship in connection with their inhibitory activity *in vitro* against 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, a rate-limiting enzyme in cholesterol biosynthesis, was investigated.

Keywords——mevalonolactone derivatives; stereo- and regioselective bromolactonization; participation of hydroxy group; tri-*n*-butyltin hydride reduction; HMG CoA reductase; structure-activity relationship

It has been shown by clinical and nutritional studies that a high cholesterol level in the blood may be one of the major causes of atherosclerosis and coronary heart disease. Therapeutic research has therefore been largely focussed on lowering the cholesterol level in serum lipoprotein.

Recently, with the aid of an enzyme inhibitory assay related to cholesterol biosynthesis, two compounds, ML-236A and B,[2] have been isolated from cultures of *Penicillium citrinum* in our laboratories. The latter has also been independently isolated from *P. brevicompatum* by Brown *et al.*[3] and designated as compactin. ML-236B was shown to be a potent competitive inhibitor of rat liver microsomal 3-hydroxy-3-methyl glutaryl coenzyme A (HMG CoA) reductase (EC 1.1.1.34), the rate-limiting enzyme in cholesterol biosynthesis, and a similar effect has been found with extracts of human fibroblast.[4] This metabolite has a partial structure similar to that of mevalonolactone, which is a significant intermediate in cholesterol biosynthesis. Moreover, it was found in this study that the introduction of a methyl group at the carbon atom bearing the hydroxy group in synthetic δ-lactones enhanced the inhibitory potency. Therefore, we attempted to prepare various mevalonolactone analogs (**1a**—**z**) in order to investigate the structure–activity relationship.



1a—**z**

ML-236A: R=H
ML-236B: R=COCH(CH$_3$) CH$_2$CH$_3$ (compactin)

Chart 1

1) Location: *a, c) 1-2-58 Hiromachi Shinagawa-ku, Tokyo 140 Japan*; *b*) Present address: *College of Medical Technology, Kumamoto University.*
2) A. Endo, M. Kuroda, and K. Tanzawa, *FEBS Letters*, **72**, 323 (1976); *idem*, *J. Antibiotics*, **29**, 1346 (1976).
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Results and Discussion

a) Synthesis

A great many syntheses of mevalonic acid and its derivatives have been reported, involving the Reformatsky reaction,[5] the Grignard reaction,[6,7] and the reaction of carbanions of acetic acid,[8] its esters[9,10] and its homologs[11] with β-functionalized ketones such as 4-acetoxy-2-butanone. However, such methods are not suitable for the synthesis of mevalonolactone analogs having two or more asymmetric centers since they afford stereoisomeric mixtures. The inefficiency of the methods mentioned above led us to seek a new approach for the synthesis of mevalonolactone derivatives. Our strategy involves stereo- and regioselective halolactonization of acyclic γ,δ-unsaturated acids (**4a**—**z**) in anticipation of a neighboring group effect of the hydroxy group at C-3.

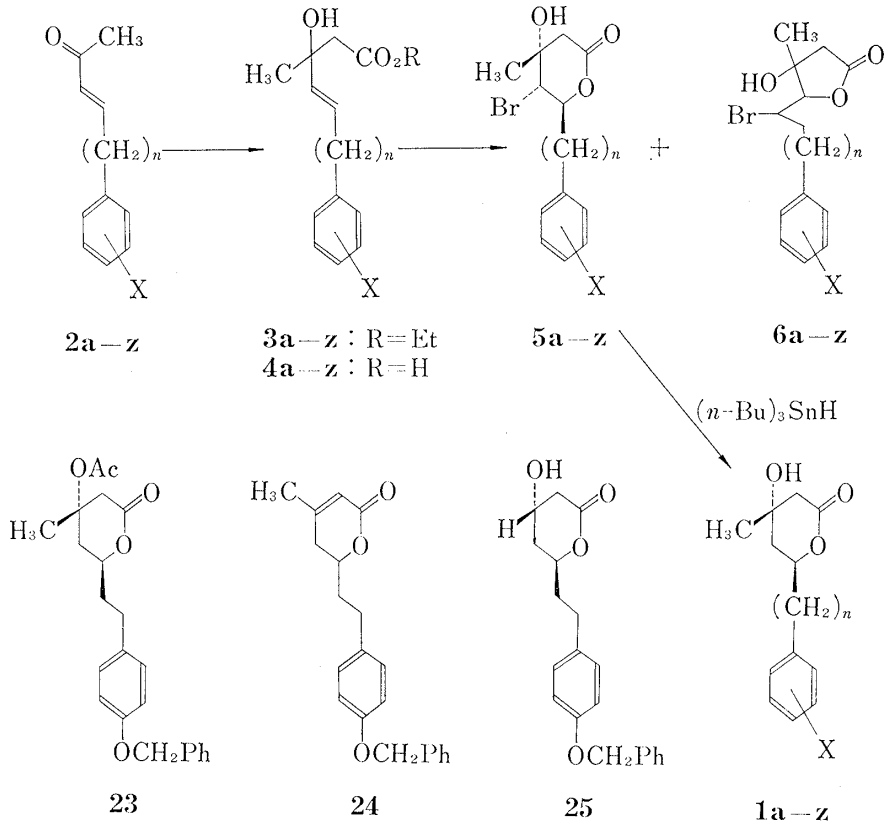

Chart 2

Various acids (**4a**—**z**) were prepared as follows. Witting reaction of the aldehydes gave good yields of the corresponding α,β-unsaturated ketones (**2a**—**z**), which successfully underwent Reformatsky reaction to furnish the acid esters (**3a**—**z**). These esters were readily hydrolyzed to the acids (**4a**—**z**) in a basic medium.

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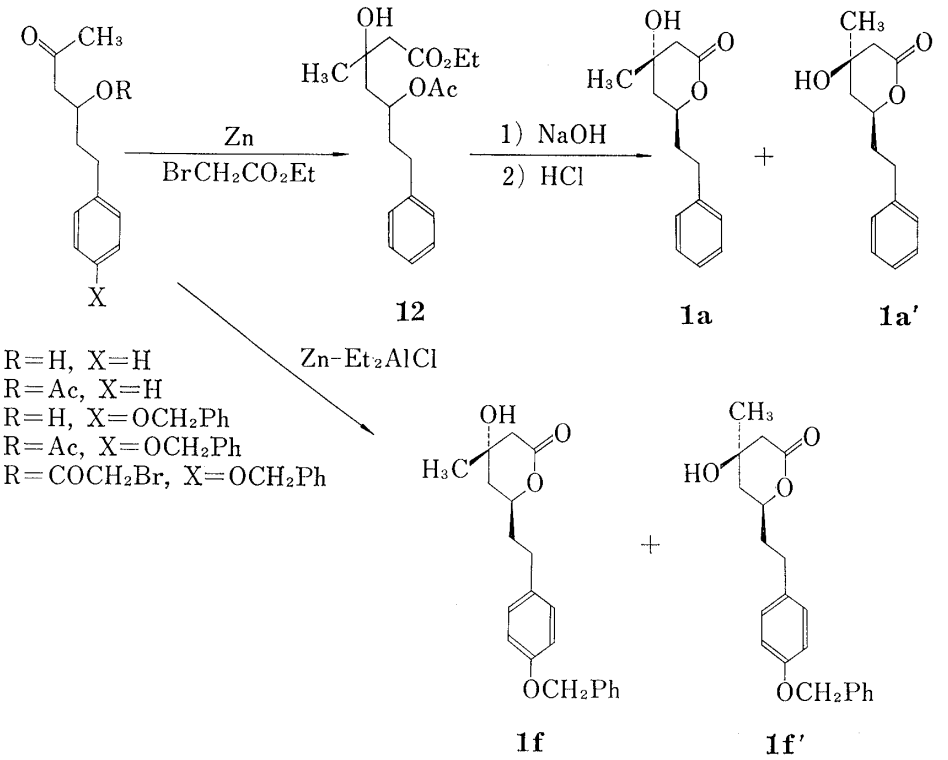
On treatment with bromine in a nonpolar solvent such as CCl_4, the acid **4a** (X=H, n=2) was converted into a bromolactone (**5a**; X=H, n=2), ν_{max}^{Nuiol}: 1710 cm^{-1}, albeit in low yield, while in a polar solvent such as MeOH or DMF at 0° in the presence of sodium bicarbonate, **4a** gave a mixture of **5a**, its stereoisomer, and a regioisomer (**6a**; X=H, n=2), ν_{max}^{liquid}: 1765, 1750 cm^{-1}. At lower temperature (−70°), the bromolactonization occurred stereo- and regioselectively to give **5a** in 70% yield, together with a small amount of **6a**, whereas in the case of **4g** (X=*p*-OCH_2Ph, n=0), the stereoselectivity decreased and a stereoisomeric mixture (**5g**/**5g′**=1.8) was obtained.

The resulting bromolactones were usually crystalline and easily separable from the reaction mixture, and were used for subsequent reduction without further purification. Since these bromolactones are sensitive to acids, it is advisable to scavenge the resulting hydrogen bromide during preparative synthesis. The bromolactones were also unstable to bases, as exemplified by the result that triethylamine converted **5a** into the triethylammonium salt of the acid (**4a**).

On treatment with a threefold excess of n-Bu_3SnH,[12–15] **5a** afforded a desired mevalonolactone analog (**1a**; X=H, n=2), in 83% yield, either at ambient temperature overnight or under



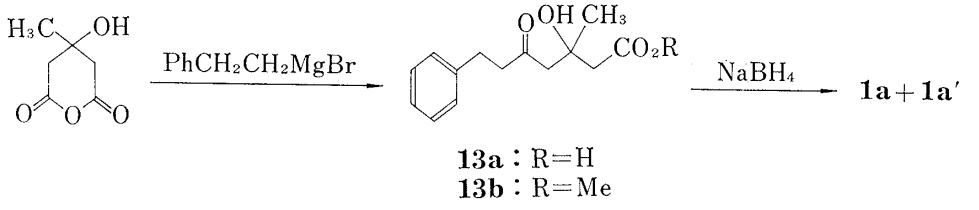


Chart 3

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reflux for several hours. Other reagents such as Zn–AcOH, Zn–EtOH, and $NaBH_4$–DMSO, or a catalytic hydrogenolysis procedure were unsatisfactory for the reduction. In this fashion, other bromolactones furnished good yields of mevalonolactones, which have the same relative stereostructure of the δ-lactone moiety as ML-236B. The stereochemistry will be discussed in the next section.

Consequently, the bromolactonization of γ,δ-unsaturated acids was found to be a convenient tool for stereo- and regioselective synthesis of mevalonolactones.

On the other hand, other isomers were prepared as follows. A β-acetoxyketone (**8**; X=H) obtainable by aldol condensation[16,17] was treated with ethyl bromoacetate under Reformatsky reaction conditions to yield a diastereomeric mixture (**12**) in 51% yield; this mixture cyclized on standing in an aqueous acid for several days at room temperature, to give a mixture of **1a** and its stereoisomer (**1a'**) (**1a'**/**1a**=*ca.* 2). In the case of **10** (X=*p*-OCH_2Ph), elimination of acetic acid occurred in preference to Reformatsky reaction to give **3f**. The intramolecular Reformatsky reaction[18] of the β-bromoacetoxyketone **11** (X=*p*-OCH_2Ph) was effected with Et_2AlCl[19] to afford **1f** and **1f'** (**1f'**/**1f**=*ca.* 2). The mevalonolactone derivative (**1a**) was also accessible from 3-hydroxy-3-methylglutaric acid[20]; its anhydride[21] reacted with a fourfold excess of phenethylmagnesium bromide to provide a ketoacid (**13a**)[22,23] in 45% yield. Sodium borohydride reduction of **13b** at −70° gave **1a** and **1a'** (**1a**/**1a'**=*ca.* 1) in 79% yield. However, no further elaboration of the above procedure was attempted.

b) Stereochemistry

In the proton magnetic resonance (PMR) spectrum of the bromolactone (**5a**), the vicinal coupling constant ($J_{4,5}$=10.0 Hz) between C_4-H (δ 4.00, d) and C_5-H (δ 4.73, ddd) shows these hydrogens to be *trans*-oriented axially in the half-chair conformation. The *trans* relationship is certainly predictable from mechanistic considerations, while the spectral data tell us nothing further with regard to the orientation of the hydroxy substituent.

The acidic cyclization of **4a** or its *tert*-butylester gave a β,γ-unsaturated lactone (**14**); ν_{max}^{liquid}: 1740 cm^{-1}, λ_{max}: end absorption, which is distinguishable from an α,β-unsaturated lactone. The ultraviolet (UV) spectrum of 3-methyl-2-hexen-5-olide[11] shows an absorption at 216.8 nm (ε 11000). On treatment with NBA in aqueous acetone, **14** was converted into a bromolactone (**5a'**); ν_{max}^{Nujol}: 3520, 1730 cm^{-1}, in 51% yield.

Comparing the PMR spectra of **5a** and **5a'**, the chemical shift of C_4-H (δ 4.00, d, $J_{4,5}$=10.0 Hz) in the former appears in the same region as that in the latter (δ 4.02, t, $J_{4,5}=J_{4,2e}$=2.0 Hz), and this is also the case for the chemical shifts of the protons at C-5 in **5a** and **5a'**. Moreover, comparison of the infrared (IR) spectra and molecular formulae indicates these compounds to be stereoisomeric. The significant difference in the PMR spectra lies in the splitting pattern. The small J-value in **5a'** shows that the bromine atom is located axially and that the alkyl side chain is situated equatorially, namely, both substituents are postulated as *cis*-oriented with respect to each other in the half-chair conformation. The W-shaped long-range[24] coupling of 2.0 Hz observed between C_{4e}-H and C_{2e}-H is in accord with this assignment. In addition, since it has been proved[25] that a cyclic olefin undergoes heterolytic fission to

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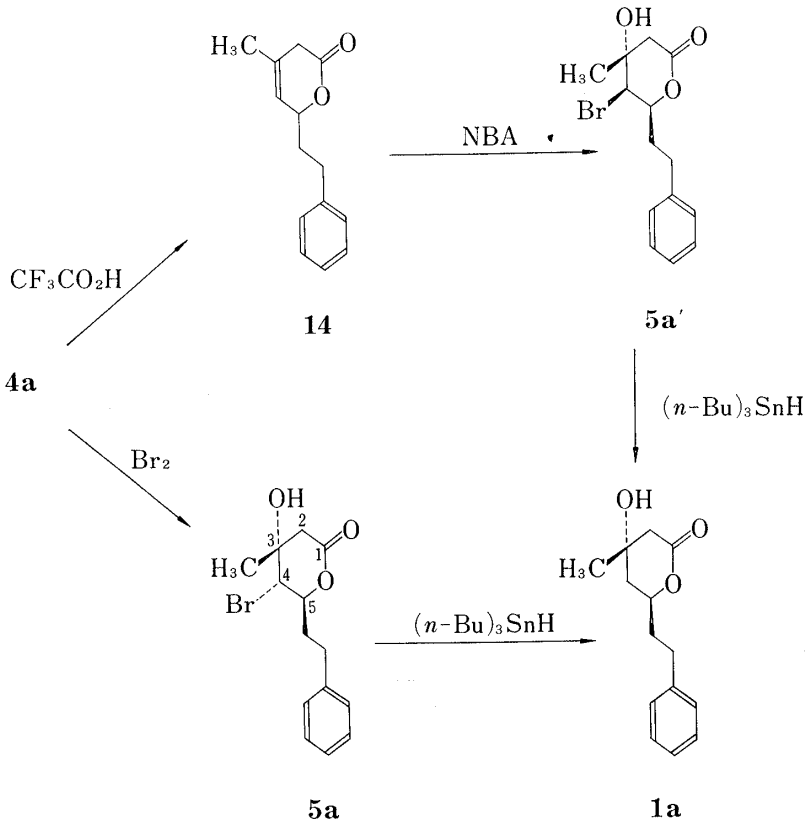

Chart 4

give a *trans* bromohydrin, the hydroxy substituent must be *trans*-oriented to the alkyl side chain.

Tri-*n*-butyltin hydride successfully converted the bromolactone (**5a'**) into a mevalonolactone derivative identical with **1a** obtained from **5a** by means of the same reagent. Thus, the stereostructure of the mevalonolactone derivative obtained *via* the bromolactonization is depicted as **1a**; this is also supported by comparison of the chemical shift of C_5-H (δ 4.73) in the PMR spectrum of **1a** with those in ML-236B (δ 4.62)[3] and (3*S*, 5*S*)-3-hydroxyhexan-5-olide (δ 4.80).[26] Comparing the PMR spectra of the stereoisomers, the signal due to C_5-H in the *trans* isomer usually appears at lower field (0.3—0.5 ppm) than that in the *cis* form. This seems to be an important indicator of the stereochemistry. It has been generally assumed that halolactonization proceeds by a polar mechanism involving a halogen to yield a cyclic halonium cation[27-30] or a charge-transfer complex,[31] which reacts intramolecularly with a carboxylate anion to form a halolactone. In acyclic γ,δ-unsaturated acids, γ-lactones have usually been obtained in preference to δ-ones, as exemplified by the iodolactonization of 4-pentenoic acid derivatives,[32,33] whereas in our system, the mode of cyclization is reversed. This suggests participation of the hydroxy group.

In view of the above assumption, we tentatively propose the following mechanism. In the approach of bromine to the double bond, bromine gives a cyclic bromonium cation asso-

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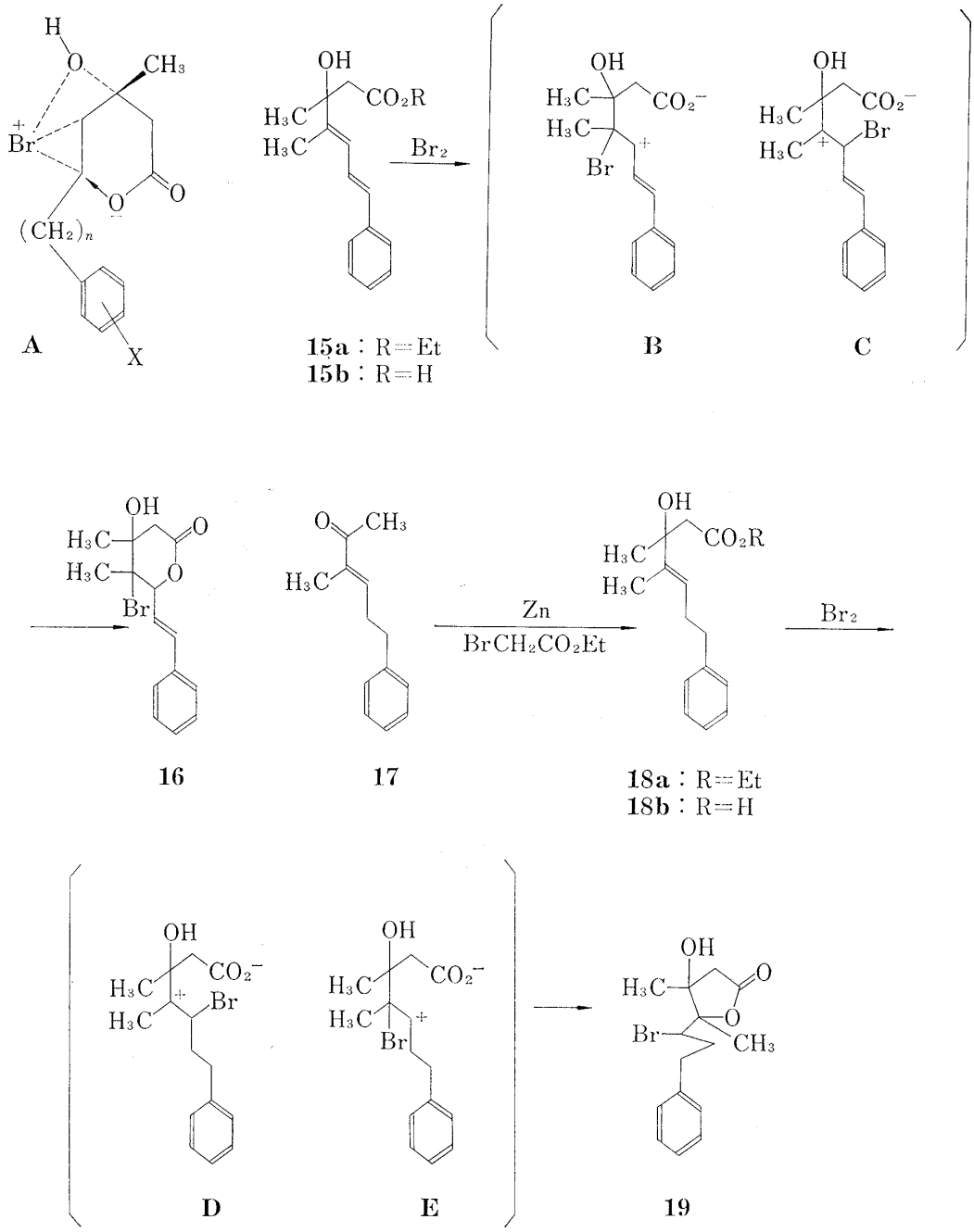

Chart 5

ciated with the hydroxy group as shown in **A**, which functions as a carrier for bormine, and attack of bromine on the double bond is favored from the same side as the hydroxy substituent, concurrent with the intramolecular attack of the carboxyl group from the opposite side. Such an effect has been invoked to account for the steric course of bromine addition to 2-ethoxy-5,6-dihydro-2*H*-pyran.[34] In the case of an acid having a diene system, for example, **15b** was exposed to bromine at −35° to afford a single γ-bromo-δ-lactone (**16**); ν_{max}^{Nujol}: 1735 cm^{-1}, in 63% yield. The depression of the yield may possibly be attributed to the attack of bromine on the other double bond. The excellent regioselectivity can be explained by the consideration

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that the carbonium cation (**B**) is more stable than (**C**), since a double bond stabilizes a carbonium cation more than a methyl group does. Similar results were observed for **4g** (X=*p*-OCH_2Ph, $n=0$) and **4n** (X=*p*-$O(CH_2)_3Ph$, $n=0$). Actually, on the bromolactonization of **18b**, in which no double bond resonance stabilization is expected, the δ-bromo-γ-lactone (**19**); ν_{max}^{Nujol}: 1760 cm^{-1}, was obtained alone in 74% yield; it has been generally assumed that the disubstituted cation (**D**) is more stable than the monosubstituted one (**E**) in addition to the greater stability of γ- over δ-lactones. Putting the above results together, it is clear that the stability of the carbonium cation is one of the important factors controlling regioselectivity.

TABLE I. Inhibitory Potencies of Mevalonolactone Derivatives against Cholesterol Biosynthesis in Mouse L cells (929)

Compound	X	n	$ID_{50}(\times 10^{-5}$ mol/l)
1a	H	2	4.2
1a′	H	2	N.E.[a]
1b	*p*-CH_3	2	N.E.
1c	*p*-Cl	2	3.0
1d	*o*-OCH_2Ph	2	5.0
1e	*m*-OCH_2Ph	2	12.0
1f	*p*-OCH_2Ph	2	0.6
1f′	*p*-OCH_2Ph	2	6.2
1g	*p*-OCH_2Ph	0	14.0
1g′	*p*-OCH_2Ph	0	N.E.
1h	*p*-OCH_2Ph	1	3.4
1i	*p*-OCH_2Ph	3	0.7
1j	*p*-OCH_2Ph	4	2.3
1k	*p*-OCH_2Ph(*p*-Cl)	2	1.9
1l	*p*-OCH_2Ph(*p*-F)	2	5.0
1m	*p*-$OCH_2CH_2CH_2Ph$	2	1.4
1n	*p*-$OCH_2CH_2CH_2Ph$	0	4.4
1n′	*p*-$COH_2CH_2CH_2Ph$	0	N.E.
1o	*p*-OCH_2CH=$CHPh$	2	0.5
1p	*p*-OCH_2COPh(p-Cl)	2	1.1
1q	*p*-OH	2	N.E.
1r	*p*-OCH_3	2	N.E.
1s	*p*-$OCO(CH_2)_6CH_3$	2	10.0
1t	*p*-OCOPh	2	1.4
1u	*p*-OCH_2Ph(*p*-Cl)	2	7.5
1v	*p*-Nicotinyloxy	2	2.5
1w	*p*-Ph	2	1.9
1x	*p*-Ph	0	16.0
1y	*p*-OCH_2Ph-*o*,*o′*-$(CH_3)_2$	2	0.5
1z	*p*-OCH_2Ph-*m*-OCH_3	2	0.6
21	*p*-$OCOPh$-*o*,*o′*$(CH_3)_2$	2	0.6
23	*p*-OCH_2Ph	2	3.1
24	*p*-OCH_2Ph	2	7.3
25	*p*-OCH_2Ph	2	7.0
5a	H	2	N.E.
5a′	H	2	N.E.
5c	*p*-Cl	2	N.E.
5d	*o*-OCH_2Ph	2	8.8
5f	*p*-OCH_2Ph	2	3.0
5g+5g′	*p*-OCH_2Ph	0	N.E.
5i	*p*-OCH_2Ph	3	8.5
5j	*p*-OCH_2Ph	4	1.4
5l	*p*-OCH_2Ph(*p*-F)	2	11.0
5w	*p*-Ph	2	2.6
5x	*p*-Ph	0	N.E.

a) "N.E." indicates that cholesterol biosynthesis was inhibited by less than 50% at a concentration over 50 μg/ml.

On the other hand, in the case of **4a**—**z**, with no such resonance contribution, the above discussion is unsatisfactory. It has been shown that in the electrophilic addition reactions of 3-methoxycyclohexene[35-37] and 2-methoxy-[38] and 2-ethoxy-5,6-dihydro-2*H*-pyran[34] with bromine or NBA, nucleophiles such as bromide, methoxide or hydroxide anions attack the cyclic bromonium cation preferentially at the carbon atom distant from the alkoxy substituent because of the inductive and steric effects of the alkoxy group. These results can account for the regioselectivity. Accordingly, it seems likely that in our plausible intermediate (**A**), the carboxyl group prefers to attack the C-5 carbon, favored by the inductive effect of the hydroxy group, rather than the C-4 carbon adjacent to the crowded tertiary carbon at C-3, to yield the mevalonolactone derivatives.

Thus, the hydroxy group plays an important part in controlling the stereo- and regioselectivities in the bromolactonization.

c) Biological Activity

The results of *in vitro* inhibitory potency tests with HMG CoA reductase are summarized in Table I, in which inhibitory activities (ID_{50}) are shown in terms of the concentration (mol/l) required for 50% inhibition of cholesterol biosynthesis in biossay using cultivated cells.[39,40] It is apparent that the mevalonolactone derivatives having an additional aromatic ring, such as phenyl (**1w**), benzyloxy (**1f**, **1i**, **1y**, and **1z**), benzoyloxy (**1t** and **21**), phenacyloxy (**1p**), cinnamyloxy (**1o**), and nicotinyloxy (**1v**) substituents, had more potent inhibitory activities. Halogen substituents such as chlorine and fluorine atoms on the aromatic ring did not enhance the inhibitory potency, but often reduced it. The substitution of bromine at C-4 seemed not to increase the inhibitory potency. The hydroxy group at C-3 was shown to be involved in the inhibition, because the acetyl derivative (**24**) and anhydro derivative (**25**) of **1f** were less potent than **1f**. The mevalonolactone derivative (**1f**) possessed inhibitory activity about 10 times greater than that of the analog (**26**) lacking the methyl group. Since the *p*-benzyloxy derivative (**1f**) was one of the most potent enzyme inhibitors, mevalonolactone derivatives carrying a benzyloxy group should be suitable for a detailed discussion of the structure-activity relationship.

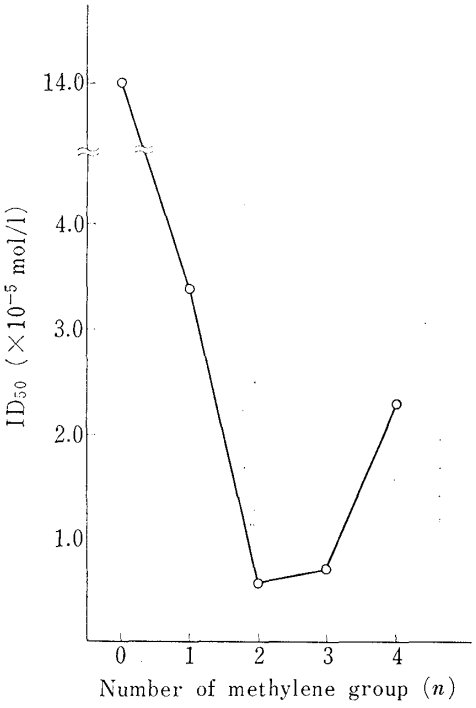

Fig. 1. Relationship between *in Vitro* Inhibitory Potency against HMG CoA Reductase and Alkylene Chain Length

Comparing the inhibitory activities of positional isomers on the benzene ring, the *para*-isomer (**1f**) was more potent than the others (**1d** and **1e**). In the case of stereoisomers, the *trans* isomer (**1f**) was 10 times more potent than the *cis* alternative (**1f'**). A similar tendency was also observed in other pairs of stereoisomers (**1g**, **1g'**, and **1n**, **1n'**). In addition, it is interesting that the distance

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between the δ-lactone and the aromatic ring greatly influenced the inhibitory activity. As shown in Fig. 1, a plot of the activities versus the number of methylene groups gave a distorted parabola, which clearly shows the activity to be highest in the case of an ethylene ($n=2$) or trimethylene linkage ($n=3$). The results indicate that the activity is only enhanced in a compound where the δ-lactone moiety, which may be a reaction site, is kept at an appropriate distance from the *p*-benzyloxy substituent, which is presumably a binding site. However, the distance between the aromatic rings did not always affect the inhibitory activity.

Experimental

Melting points were measured on a Yamato capillary melting point apparatus or on a Yanagimoto hot stage apparatus and are uncorrected. The PMR spectra were measured with tetramethylsilane as a standard on Varian A-60 and HA-100 instruments. The IR spectra were determined on a JASCO IRA-2 spectrophotometer. The UV spectra were measured in 99% EtOH using a Hitachi 624 digital spectrophotometer.

General Procedure for the Synthesis of 2——a) A solution of 10.0 mmol of an aldehyde and 12.0 mmol of acetylmethylenetriphenylphosphorane in 20—30 ml of dry benzene or THF was refluxed for several hours. After removal of the solvent by evaporation, *n*-hexane or ether was added to the residue and the resulting crystalline solid was filtered off. The filtrate was concentrated to dryness. The product was purified by recrystallization, by distillation, or, if necessary, by chromatography.

b) A solution of 11.0 mmol of dimethyl 2-oxopropylphosphonate and 10.0 mmol of the aldehyde in 20—30 ml of dry THF was added to a stirred suspension of 12.0 mmol of 50% NaH in 20 ml of dry THF under cooling at −20°. The reaction mixture was kept at this temperature for 1—2 hr, then warmed up to ambient temperature, poured into ice-water, and extracted with ethyl acetate. The ethyl acetate layer was washed with water and dried over Na_2SO_4. After removal of the solvent, the product was purified by recrystallization, by distillation, or, if necessary, by chromatography.

The physical data and yields of novel α,β-unsaturated ketones prepared by the methods mentioned above are given below.

6-Phenyl-*trans*-3-hexen-2-one (2a)[17]——68.0% yield. bp 98—100°/0.5 mmHg. IR $\nu_{max}^{liq.}$ cm^{-1}: 1660, 1590. PMR ($CDCl_3$) δ: 2.17 (3H, s), 2.4—3.0 (4H, m), 6.10 (1H, br d, $J=16.0$ Hz), 6.84 (1H, td, $J=6.0$ and 16.0 Hz), 7.20 (5H, s). *Anal.* Calcd for $C_{12}H_{14}O$: C, 82.76, H, 8.05. Found: C, 82.79; H, 8.00.

6-(*p*-Tolyl)-*trans*-3-hexen-2-one (2b)——65.6% yield. bp 98—101°/0.5 mmHg. IR $\nu_{max}^{liq.}$ cm^{-1}: 1660, 1585. PMR ($CDCl_3$) δ: 2.19 (3H, s), 2.33 (3H, s), 2.4—3.0 (4H, m), 6.09 (1H, br d, $J=16.0$ Hz), 6.86 (1H, td, $J=6.0$ and 16.0 Hz), 7.0—7.3 (4H, m). *Anal.* Calcd for $C_{13}H_{16}O$: C, 82.98; H, 8.51. Found: C, 83.04; H, 8.48.

6-(*p*-Chlorophenyl)-*trans*-3-hexen-2-one (2c)——66.4% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 1660, 1585. PMR ($CDCl_3$) δ: 2.18 (3H, s), 2.4—3.0 (4H, m), 6.10 (1H, br d, $J=16.0$ Hz), 6.85 (1H, td, $J=6.0$ and 16.0 Hz), 7.1—7.3 (4H, m). *Anal.* Calcd for $C_{12}H_{13}ClO$: C, 69.03; H, 6.23; Cl, 17.07. Found: C, 68.89; H, 6.25; Cl, 17.14.

6-(*o*-Benzyloxyphenyl)-*trans*-3-hexen-2-one (2d)——91.2% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 1660, 1620, 1590. PMR ($CDCl_3$) δ: 2.20 (3H, s), 2.4—3.0 (4H, m), 5.09 (2H, s), 6.10 (1H, br d, $J=16.0$ Hz), 6.7—7.9 (10H, m). *Anal.* Calcd for $C_{19}H_{20}O_2$: C, 81.43; H, 7.14. Found: C, 81.70; H, 7.34.

6-(*m*-Benzyloxyphenyl)-*trans*-3-hexen-2-one (2e)——90.2% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 1660, 1610, 1590. PMR ($CDCl_3$) δ: 2.20 (3H, s), 2.4—3.0 (4H, m), 5.08 (2H, s), 6.10 (1H, br d, $J=16.0$ Hz), 6.7—7.9 (10H, m). *Anal.* Calcd for $C_{19}H_{20}O_2$: C, 81.43; H, 7.14. Found: C, 81.59; H, 7.38.

6-(*p*-Benzyloxyphenyl)-*trans*-3-hexen-2-one (2f)——93.4% yield. mp 70—72° (from *n*-hexane–ether). IR ν_{max}^{Nujol} cm^{-1}: 1665, 1620, 1590, 1510. PMR ($CDCl_3$) δ: 2.22 (3H, s), 2.4—2.9 (4H, m), 5.08 (2H, s), 6.10 (1H, br d, $J=16.0$ Hz), 6.7—7.9 (10H, m). *Anal.* Calcd for $C_{19}H_{20}O_2$: C, 81.43; H, 7.14. Found: C, 81.19; H, 6.95.

4-(*p*-Benzyloxyphenyl)-*trans*-3-buten-2-one (2g)——83.4% yield. mp 106—107° (from ether). IR ν_{max}^{Nujol} cm^{-1}: 1660, 1620, 1605, 1575, 1510. PMR ($CDCl_3$) δ: 2.32 (3H, s), 5.10 (2H, s), 6.62 (1H, d, $J=16.0$ Hz), 7.00 (2H, d, $J=9.0$ Hz), 7.42 (5H, s), 7.52 (2H, d, $J=9.0$ Hz), 7.53 (1H, d, $J=16.0$ Hz). *Anal.* Calcd for $C_{17}H_{16}O_2$: C, 77.27; H, 6.06. Found: C, 77.20; H, 6.04.

5-(*p*-Benzyloxyphenyl)-*trans*-3-penten-2-one (2h)——64.5% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 1670, 1615, 1600, 1510. PMR ($CDCl_3$) δ: 2.25 (3H, s), 3.45 (2H, d, $J=5.5$ Hz), 5.05 (2H, s), 7.02 (4H, q, $J=9.0$ Hz), 7.48 (5H, s). *Anal.* Calcd for $C_{18}H_{18}O_2$: C, 81.20; H, 6.77. Found: C, 81.30; H, 6.65.

7-(*p*-Benzyloxyphenyl)-*trans*-3-hepten-2-one (2i)——80.5% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 1680, 1630, 1610, 1515. PMR ($CDCl_3$) δ: 2.20 (3H, s), 1.5—2.8 (6H, m), 5.07 (2H, s), 6.10 (1H, br d, $J=16.0$ Hz), 6.6—7.6 (10H, m). *Anal.* Calcd for $C_{20}H_{22}O_2$: C, 81.63; H, 7.48. Found: C, 81.90; H, 7.66.

8-(*p*-Benzyloxyphenyl)-*trans*-3-octen-2-one (2j)——63.9% yield. mp 56—58° (from *n*-hexane-ether). IR ν_{max}^{Nujol} cm^{-1}: 1680, 1610, 1580, 1515. PMR ($CDCl_3$) δ: 1.5—1.8 (4H, m), 2.20 (3H, s), 2.0—2.8 (4H, m),

5.03 (2H, s), 6.10 (1H, br d, J=16.0 Hz). 6.5—7.6 (10H, m). *Anal.* Calcd for $C_{21}H_{24}O_2$: C, 81.82; H, 7.79. Found: C, 81.99; H, 7.80.

6-{*p*-(*p'*-Fluorobenzyloxy)phenyl}-*trans*-3-hexen-2-one (21)——53.5% yield. mp 70.5—71.5° (from ether). IR ν_{max}^{Nujol} cm^{-1}: 1680, 1640, 1605, 1590, 1520. PMR ($CDCl_3$) δ: 2.18 (3H, s), 2.3—3.0 (4H, m), 5.02 (2H, s), 6.08 (1H, br d, J=16.0 Hz), 6.6—7.6 (9H, m). *Anal.* Calcd for $C_{19}H_{19}FO_2$: C, 76.51; H, 6.38; F, 6.38. Found: C, 76.41; H, 6.44; F, 6.40.

6-{*p*-(3'-Phenylpropoxy)phenyl}-*trans*-3-hexen-2-one (2m)——84.8% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 1680, 1640, 1525, 1520. PMR ($CDCl_3$) δ: 2.19 (3H, s), 1.9—2.3 (2H, m), 2.4—3.0 (6H, m), 3.96 (2H, t, J=6.5 Hz), 6.15 (1H, br d, J=16.0 Hz), 6.6—7.2 (4H, m), 7.25 (5H, s). *Anal.* Calcd for $C_{21}H_{24}O_2$: C, 81.82; H, 7.79, Found: C, 81.99; H, 7.65.

4-{*p*-(3'-Phenylpropoxy)phenyl}-*trans*-3-buten-2-one (2n)——82.4% yield. mp 92—92.5° (from ether). IR ν_{max}^{Nujol} cm^{-1}: 1660, 1630, 1600, 1510. PMR ($CDCl_3$) δ: 1.4—1.8 (2H, m), 2.32 (3H, s), 2.7—3.0 (2H, m), 4.00 (2H, t, J=6.5 Hz), 6.62 (1H, d, J=16.0 Hz), 6.92 (2H, d, J=9.0 Hz), 7.27 (5H, s), 7.51 (2H, d, J=9.0 Hz), 7.53 (1H, d, J=16.0 Hz). *Anal.* Calcd for $C_{19}H_{20}O_2$: C, 81.42; H, 7.14. Found: C, 81.55; H, 7.07.

6-(*p*-Biphenylyl)-*trans*-3-hexen-2-one (2w)——89.4% yield. mp 73—75° (from *n*-hexane-ether). IR ν_{max}^{Nujol} cm^{-1}: 1675, 1640, 1625, 1600, 1590. PMR ($CDCl_3$) δ: 2.04 (3H, s), 2.4—3.1 (4H, m), 6.13 (1H, br d, J=16.0 Hz), 6.88 (1H, td, J=6.0 and 16.0 Hz), 7.2—7.8 (9H, m). *Anal.* Calcd for $C_{18}H_{18}O$: C, 86.40; H, 7.20. Found: C, 86.26; H, 7.42.

4-(*p*-Biphenylyl)-*trans*-3-buten-2-one (2x)[41]——86.3% yield. mp 131—132° (from ether). IR ν_{max}^{Nujol} cm^{-1}: 1665, 1640, 1620, 1605, 1490. PMR ($CDCl_3$) δ: 2.38 (3H, s), 6.18 (1H, d, J=16.0 Hz), 7.4—7.8 (10H, m). *Anal.* Calcd for $C_{16}H_{14}O$: C, 86.49; H, 6.31. Found: C, 86.61; H, 6.33.

6-(*p*-Benzyloxy-*o*,*o'*-dimethylphenyl)-*trans*-3-hexen-2-one (2y)——84.1% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 1675, 1630, 1610, 1565. PMR ($CDCl_3$) δ: 2.22 (3H, s), 2.28 (6H, s), 2.2—2.9 (4H, m), 5.03 (2H, s), 6.15 (1H, br d, J=16.0 Hz), 6.92 (1H, td, J=6.5 and 16.0 Hz), 7.42 (5H, s). *Anal.* Calcd for $C_{21}H_{24}O_2$: C, 81.82; H, 7.79. Found: C, 81.55; H, 7.60.

6-(*p*-Benzyloxy-*m*-methoxyphenyl)-*trans*-3-hexen-2-one (2z)——58.9% yield. mp 59.5—60.5° (from *n*-hexane-ether). IR ν_{max}^{Nujol} cm^{-1}: 1675, 1640, 1630, 1590. PMR ($CDCl_3$) δ: 2.18 (3H, s), 2.3—2.9 (4H, m), 3.87 (3H, s), 5.13 (2H, s), 6.12 (1H, br d, J=16.0 Hz), 6.6—7.1 (4H, m), 7.3—7.6 (5H, m). *Anal.* Calcd for $C_{20}H_{22}O_3$: C, 77.42; H, 7.10. Found: C, 77.19; H, 6.95.

3-Methyl-6-phenyl-*trans*-3-hexen-2-one (17)——95% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 1670, 1640, 1605, 1495. PMR ($CDCl_3$) δ: 1.72 (3H, br s), 2.25 (3H, s), 2.4—2.9 (4H, m), 6.63 (1H, br t, J=6.0 Hz), 7.25 (5H, s). *Anal.* Calcd for $C_{13}H_{16}O$: C, 82.98; H, 8.51. Found: 82.85; H, 8.44.

General Procedure for the Synthesis of 3 and 4——A solution of 10.0 mmol of the α,β-unsaturated ketone (2) and 1.84 ml of ethyl bromoacetate in 20—30 ml of dry benzene was added to 0.80 g of granular zinc in 5 ml of boiling benzene. After the addition was complete, the reaction mixture was refluxed for a further one hour, then cooled with ice-water, and washed successively with cold dil. HCl and water. The organic layer was dried over Na_2SO_4 and concentrated to dryness. The ester (3) was subjected to silica gel chromatography and hydrolyzed to the corresponding acid (4) with aqueous NaOH in MeOH or EtOH. The ester, when the corresponding acid was crystalline, was hydrolyzed without purification by chromatography.

The physical data and yields obtained by the Reformatsky reaction described above are given below.

Ethyl 3-Hydroxy-3-methyl-7-phenyl-*trans*-4-heptenoate (3a)——79.4% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 3550, 1720, 1610, 1500. PMR ($CDCl_3$) δ: 1.23 (3H, t, J=7.0 Hz), 1.28 (3H, s), 2.50 (2H, s), 2.2—2.9 (4H, m), 3.75 (1H, br s), 4.16 (2H, q, J=7.0 Hz), 5.3—6.1 (2H, m), 7.22 (5H, s). *Anal.* Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.36; H, 8.46.

Ethyl 3-Hydroxy-3-methyl-7-(*p*-tolyl)-*trans*-4-heptenoate (3b)——92.3% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 3500, 1720, 1600, 1515. PMR ($CDCl_3$) δ: 1.23 (3H, t, J=7.0 Hz), 1.29 (3H, s), 2.32 (3H, s), 2.52 (2H, s), 2.2—2.9 (4H, m), 3.80 (1H, br s), 4.18 (2H, q, J=7.0 Hz), 5.4—5.9 (2H, m), 7.12 (5H, s). *Anal.* Calcd for $C_{17}H_{24}O_3$: C, 73.91; H, 8.70. Found: C, 73.55; H, 8.90.

Ethyl 7-(*p*-Chlorophenyl)-3-hydroxy-3-methyl-*trans*-4-heptenoate (3c)——66.4% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 3500, 1720, 1495, 1200. PMR ($CDCl_3$) δ: 1.23 (3H, t, J=7.0 Hz), 1.26 (3H, s), 2.2—2.8 (6H, m), 3.80 (1H, s), 4.10 (2H, q, J=7.0 Hz), 5.2—6.0 (2H, m), 6.9—7.4 (4H, m). *Anal.* Calcd for $C_{17}H_{21}ClO_3$: C, 66.13; H, 6.81; Cl, 11.51. Found: C, 65.95; H, 6.74; Cl, 11.36.

Ethyl 7-(*o*-Benzyloxyphenyl)-3-hydroxy-3-methyl-*trans*-4-heptenoate (3d)——91.2% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 3500, 1720, 1600, 1590. PMR ($CDCl_3$) δ: 1.20 (3H, t, J=7.0 Hz), 1.26 (3H, s), 2.0—3.0 (4H, m), 2.50 (2H, s), 4.13 (2H, q, J=7.0 Hz), 5.10 (2H, s), 5.2—6.1 (2H, m), 6.7—7.6 (9H, m). *Anal.* Calcd for $C_{23}H_{28}O_4$: C, 75.00; H, 7.61. Found: C, 74.84; H, 7.64.

Ethyl 7-(*m*-Benzyloxyphenyl)-3-hydroxy-3-methyl-*trans*-4-heptenoate (3e)——92.8% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 3500, 1720, 1605, 1510. PMR ($CDCl_3$) δ: 1.22 (3H, t, J=7.0 Hz), 1.26 (3H, s), 2.51 (2H, s), 2.1—2.8 (4H, m), 3.82 (1H, s), 4.14 (2H, q, J=7.0 Hz), 5.00 (2H, s), 5.3—6.1 (2H, m), 6.5—7.7 (9H, m). *Anal.* Calcd for $C_{23}H_{28}O_4$: C, 75.00; H, 7.61. Found: C, 74.84; H, 7.73.

41) R. Trave and G. Bianchetti, *Chem. Abstr.*, **49**, 2381*h* (1950).

Ethyl 7-(*p*-Benzyloxyphenyl)-3-hydroxy-3-methyl-*trans*-4-heptenoate (3f)——96.6% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 3500, 1720, 1615, 1585, 1515. PMR ($CDCl_3$) δ: 1.21 (3H, t, J=7.0 Hz), 1.27 (3H, s), 2.50 (2H, s), 2.0—2.8 (4H, m), 3.80 (1H, s), 4.15 (2H, q, J=7.0 Hz), 5.05 (2H, s), 5.3—6.1 (2H, m), 7.00 (4H, q, J=9.0 Hz), 7.40 (5H, s). *Anal.* Calcd for $C_{23}H_{28}O_4$: C, 75.00; H, 7.61. Found: C, 74.72; H, 7.80.

Ethyl 5-(*p*-Benzyloxyphenyl)-3-hydroxy-3-methyl-*trans*-4-pentenoate (3g)——90% yield. mp 52—53° (from *n*-hexane–ether). IR ν_{max}^{Nujol} cm^{-1}: 3500, 1705, 1605, 1580, 1510. PMR ($CDCl_3$) δ: 1.21 (3H, t, J=7.0 Hz), 1.40 (3H, s), 2.63 (2H, s), 3.92 (1H, s), 4.16 (2H, q, J=7.0 Hz), 5.07 (2H, s), 6.60 (1H, d, J=16.0 Hz), 6.67 (1H, d, J=16.0 Hz), 7.14 (4H, q, J=9.0 Hz), 7.40 (5H, s). *Anal.* Calcd for $C_{21}H_{24}O_4$: C, 74.11; H, 7.06. Found: C, 74.00; H, 7.19.

Ethyl 6-(*p*-Benzyloxyphenyl)-3-hydroxy-3-methyl-*trans*-4-hexenoate (3h)——73.7% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 3500, 1720, 1600, 1580, 1510. PMR ($CDCl_3$) δ: 1.20 (3H, t, J=7.0 Hz), 1.32 (3H, s), 2.55 (2H, s), 3.33 (2H, d, J=5.5 Hz), 3.83 (1H, s), 4.15 (2H, q, J=7.0 Hz), 5.08 (2H, s), 5.5—6.2 (2H, m), 7.03 (4H, q, J=9.5 Hz), 7.43 (5H, s). *Anal.* Calcd for $C_{22}H_{26}O_4$: C, 74.58; H, 7.34. Found: C, 74.79; H, 7.15.

Ethyl 8-(*p*-Benzyloxyphenyl)-3-hydroxy-3-methyl-*trans*-4-octenoate (3i)——96.6% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 3520, 1720, 1615, 1585, 1515. PMR ($CDCl_3$) δ: 1.23 (3H, t, J=7.0 Hz), 1.32 (3H, s), 1.4—2.8 (6H, m), 2.55 (2H, s), 3.80 (1H, s), 4.18 (2H, q, J=7.0 Hz), 5.08 (2H, s), 5.5—5.8 (2H, m), 7.05 (4H, q, J=9.0 Hz), 7.73 (5H, s). *Anal.* Calcd for $C_{24}H_{30}O_4$: C, 75.39; H, 7.85. Found: C, 75.01; H, 7.68.

Ethyl 9-(*p*-Benzyloxyphenyl)-3-hydroxy-3-methyl-*trans*-4-nonenoate (3j)——74.3% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 3500, 1715, 1610, 1585, 1510. PMR ($CDCl_3$) δ: 1.20 (3H, t, J=7.0 Hz), 1.30 (3H, s), 1.2—2.2 (8H, m), 2.52 (2H, s), 3.76 (1H, s), 4.13 (2H, q, J=7.0 Hz), 5.03 (2H, s), 5.3—5.8 (2H, m), 7.01 (4H, q, J=9.0 Hz), 7.40 (5H, s). *Anal.* Calcd for $C_{25}H_{32}O_4$: C, 75.76; H, 8.08. Found: C, 75.44; H, 8.15.

Ethyl 7-{*p*-(*p'*-Fluorobenzyloxy)phenyl}-3-hydroxy-3-methyl-*trans*-4-heptenoate (3l)——94.3% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 3530, 1720, 1615, 1590, 1520. PMR ($CDCl_3$) δ: 1.23 (3H, t, J=7.0 Hz), 1.28 (3H, s), 2.1—2.8 (4H, m), 2.50 (2H, s), 3.74 (1H, s), 4.16 (2H, q, J=7.0 Hz), 5.00 (2H, s), 5.3—6.1 (2H, m), 6.8—7.6 (9H, m). *Anal.* Calcd for $C_{23}H_{27}FO_4$: C, 71.50; H, 6.99. Found: C, 71.69; H, 7.24.

Ethyl 3-Hydroxy-3-methyl-7-{*p*-(3'-phenylpropoxy)phenyl}-trans-4-heptenoate (3m)——85.4% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 3530, 1720, 1615, 1585, 1520. PMR ($CDCl_3$) δ: 1.23 (3H, t, J=7.0 Hz), 1.28 (3H, s), 1.9—3.0 (8H, m), 2.52 (2H, s), 3.75 (1H, s), 3.96 (2H, t, J=6.5 Hz), 4.17 (2H, q, J=7.0 Hz), 5.4—5.9 (2H, m), 6.98 (4H, q, J=8.0 Hz), 7.27 (5H, s). *Anal.* Calcd for $C_{25}H_{32}O_4$: C, 75.76; H, 8.08. Found: C, 75.89; H, 8.13.

3-Hydroxy-3-methyl-5-{*p*-(3'-phenylpropoxy)phenyl}-*trans*-4-pentenoic Acid (4n)——49.2% yield. mp 89.5—90.5° (from *n*-hexane–ether). IR ν_{max}^{Nujol} cm^{-1}: 3550, 3000, 1690, 1605, 1580. PMR ($CDCl_3$) δ: 1.42 (3H, s), 1.9—2.3 (2H, m), 2.68 (2H, s), 2.6—3.0 (2H, m), 3.95 (2H, t, J=6.5 Hz), 6.13 (1H, d, J=16.0 Hz), 6.63 (1H, d, J=16.0 Hz), 6.85 (2H, d, J=9.0 Hz), 7.25 (5H, s), 7.32 (2H, d, J=9.0 Hz). *Anal.* Calcd for $C_{21}H_{24}O_4$: C, 74.11; H, 7.06. Found: C, 74.24; H, 7.11.

Ethyl 7-(*p*-Biphenylyl)-3-hydroxy-3-methyl-*trans*-4-heptenoate (3w)——94.8% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 3500, 1710, 1600, 1520, 1480. PMR ($CDCl_3$) δ: 1.21 (3H, t, J=7.0 Hz), 1.28 (3H, s), 2.50 (2H, s), 2.2—2.9 (4H, m), 4.13 (2H, q, J=7.0 Hz), 5.4—5.9 (2H, m), 7.1—7.8 (9H, m). *Anal.* Calcd for $C_{22}H_{26}O_3$: C, 78.11; H, 7.69. Found: C, 78.52; H, 7.96.

5-(*p*-Biphenylyl)-3-hydroxy-3-methyl-*trans*-4-pentenoic Acid (4x)——67.9% yield. mp 128—130° (from *n*-hexane–ether). IR ν_{max}^{Nujol} cm^{-1}: 3530, 3000, 1690, 1580, 1560, 1485. PMR (d_6-acetone) δ: 1.48 (3H, s), 2.71 (2H, s), 6.52 (1H, d, J=16.0 Hz), 6.87 (1H, d, J=16.0 Hz), 7.3—7.8 (9H, m). *Anal.* Calcd for $C_{18}H_{18}O_3$: C, 76.59; H, 6.38. Found: C, 76.77; H, 6.27.

Ethyl 7-(*p*-Benzyloxy-*o,o'*-dimethylphenyl)-3-hydroxy-3-methyl-*trans*-4-heptenoate (3y)——71.2% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 3530, 1715, 1605, 1585. PMR ($CDCl_3$) δ: 1.25 (3H, t, J=7.0 Hz), 1.32 (3H, s), 2.28 (6H, s), 1.9—2.9 (4H, m), 2.54 (2H, s), 3.79 (1H, s), 4.19 (2H, q, J=7.0 Hz), 5.03 (2H, s), 5.4—6.2 (2H, m), 6.70 (2H, s), 7.58 (5H, s). *Anal.* Calcd for $C_{25}H_{32}O_4$: C, 75.56; H, 8.08. Found: C, 75.39; H, 8.40.

Ethyl 7-(*p*-Benzyloxy-*m*-methoxyphenyl)-3-hydroxy-3-methyl-*trans*-4-heptenoate (3z)——73.5% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 3500, 1720, 1600, 1590, 1515. PMR ($CDCl_3$) δ: 1.23 (3H, t, J=7.0 Hz), 1.29 (3H, s), 2.1—2.9 (4H, m), 2.53 (2H, s), 3.78 (1H, s), 3.88 (3H, s), 4.17 (2H, q, J=7.0 Hz), 5.14 (2H, s), 5.5—5.9 (2H, m), 6.6—7.0 (3H, m), 7.3—7.6 (5H, m). *Anal.* Calcd for $C_{24}H_{30}O_5$: C, 72.36; H, 7.54. Found: C, 72.19; H, 7.72.

Ethyl 3-Hydroxy-3,4-dimethyl-7-phenyl-*trans,trans*-4,6-heptadienoate (15a)——96.3% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 3500, 1720, 1640, 1600, 1590. PMR ($CDCl_3$) δ: 1.23 (3H, t, J=7.0 Hz), 1.35 (3H, s), 1.90 (3H, d, J=1.0 Hz), 2.68 (2H, q, J=16.0 Hz), 4.00 (1H, s), 4.16 (2H, q, J=7.0 Hz), 6.3—7.1 (3H, m), 7.2—7.6 (5H, m). *Anal.* Calcd for $C_{17}H_{22}O_3$: C, 74.45; H, 8.03. Found: C, 74.63; H, 7.85.

Ethyl 3-Hydroxy-3,4-dimethyl-7-phenyl-*trans*-4-heptenoate (18a)——96.3% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 3530, 1720, 1610, 1500. PMR ($CDCl_3$) δ: 1.22 (3H, t, J=7.0 Hz), 1.30 (3H, s), 1.58 (3H, br s), 2.1—2.9 (4H, m), 3.28 (1H, br s), 4.13 (2H, q, J=7.0 Hz), 5.62 (1H, br t, J=7.0 Hz), 7.23 (5H, s). *Anal.* Calcd for $C_{17}H_{24}O_3$: C, 73.91; H, 8.70. Found: C, 73.62; H, 8.80.

General Procedure for the Synthesis of the Bromolactone (5)——A solution of 10.0 mmol of **4** and 12.0 mmol of $NaHCO_3$ in 30—50 ml of MeOH was treated with 13.0 mmol of bromine under cooling at −70°. After the addition was complete, the reaction mixture was stirred at this temperature for a further one hour, and warmed gradually up to 0° by addition of saturated $NaHCO_3$ solution. The mixture was extracted with

ethyl acetate and the extract was washed with water and dried over Na_2SO_4. After removal of the solvent, the products were purified by recrystallization.

The physical data and yields of the bromolactones prepared by the above method are given below.

5*H*-*r*,*cis*-4-Bromo-*cis*-3-hydroxy-*trans*-3-methyl-7-phenylheptan-5-olide (5a)——70% yield. mp 156—158° (from *n*-hexane–acetone). IR ν_{max}^{Nujol} cm^{-1}: 3450, 1710, 1600, 1490. PMR ($CDCl_3$) δ: 1.42 (3H, s), 1.9—3.2 (6H, m), 4.00 (1H, d, J=10.0 Hz), 4.73 (1H, ddd, J=3.0, 7.0 and 10.0 Hz), 7.27 (5H, s). *Anal.* Calcd for $C_{14}H_{17}BrO_3$: C, 53.67; H, 5.43. Found: C, 53.55; H, 5.28.

5*H*-*r*,*cis*-4-Bromo-7-(*p*-Chlorophenyl)-cis-3-hydroxy-*trans*-3-methylheptan-5-olide (5c)——51.9% yield. (in aqueous MeOH at 0°). mp 116—119° (from *n*-hexane–acetone). IR ν_{max}^{Nujol} cm^{-1}: 3600, 1720, 1500. PMR ($CDCl_3$) δ: 1.43 (3H, s), 1.8—3.2 (6H, m), 4.03 (1H, d, J=10.0 Hz), 4.70 (1H, ddd, J=3.0, 7.0 and 10.0 Hz), 7.4—7.8 (4H, m). *Anal.* Calcd for $C_{14}H_{16}BrClO_3$: C, 48.35; H, 4.60. Found: C, 48.39; H, 4.61.

5*H*-*r*,7-(*o*-Benzyloxyphenyl)-*cis*-4-bromo-*cis*-3-hydroxy-*trans*-3-methylheptan-5-olide (5d)——79.9% yield. mp 124—125° (from *n*-hexane–ethyl acetate). IR ν_{max}^{Nujol} cm^{-1}: 3480, 1710, 1600, 1590, 1500. PMR ($CDCl_3$) δ: 1.35 (3H, s), 2.0—3.2 (6H, m), 3.96 (1H, d, J=10.0 Hz), 4.73 (1H, ddd, J=3.0, 7.0 and 10.0 Hz), 5.11 (2H, s), 6.7—7.6 (9H, m).

5*H*-*r*,7-(*p*-Benzyloxyphenyl)-*cis*-4-bromo-*cis*-3-hydroxy-*trans*-3-methylheptan-5-olide (5f)——79.5% yield. mp 159—160°. IR ν_{max}^{Nujol} cm^{-1}: 3480, 1720, 1615, 1585, 1515. PMR (d_6-acetone) δ: 1.43 (3H, s), 1.8—3.2 (6H, m), 4.2—4.9 (3H, m), 5.11 (2H, s), 7.10 (4H, q, J=9.0 Hz), 7.4—7.8 (5H, m). *Anal.* Calcd for $C_{21}H_{23}BrO_4$: C, 60.14; H, 5.49; Br, 19.07. Found: C, 60.01, H, 5.45; Br, 19.15.

5-(*p*-Benzyloxyphenyl)-4-bromo-3-hydroxy-3-methylpentan-5-olide (5g and 5g′)——68.0% yield. mp 157—162°. IR ν_{max}^{Nujol} cm^{-1}: 3450, 1720, 1595, 1520. PMR (d_6-acetone) δ: 1.50, 1.53 (3H, s), 2.98 (2H, s), 4.57, 4.69 (1H, d, J=10.0 Hz), 5.16 (2H, s), 5.43, 5.65 (1H, d, J=10.0 Hz), 7.0—7.7 (9H, m). *Anal.* Calcd for $C_{19}H_{19}BrO_4$: C, 58.31; H, 4.86. Found: C, 58.42; H, 5.06.

5*H*-*r*,8-(*p*-Benzyloxyphenyl)-*cis*-4-bromo-*cis*-3-hydroxy-*trans*-3-methyloctan-5-olide (5i)——81.2% yield. mp 100—101° (from ether). IR ν_{max}^{Nujol} cm^{-1}: 3480, 1720, 1615, 1590, 1520. PMR (d_6-DMSO) δ: 1.28 (3H, s), 1.5—2.1 (4H, m), 2.4—2.7 (2H, m), 2.74 (2H, q, J=17.5 Hz), 4.33 (1H, d, J=10.5 Hz), 4.58 (1H, m), 5.10 (2H, s), 7.08 (4H, q, J=9.0 Hz), 7.45 (5H, m). *Anal.* Calcd for $C_{22}H_{25}BrO_4$: C, 60.97; H, 5.77. Found: C, 60.66; H, 5.68.

5*H*-*r*,9-(*p*-Benzyloxyphenyl)-*cis*-4-bromo-*cis*-3-hydroxy-*trans*-3-methylnonan-5-olide (5j)——79.0% yield. mp 100—102° (from ether–ethyl acetate). IR ν_{max}^{Nujol} cm^{-1}: 3380, 1700, 1605, 1585. PMR (d_6-acetone) δ: 1.37 (3H, s), 1.2—2.8 (6H, m), 2.90 (2H, q, J=18.0 Hz), 3.94 (1H, d, J=10.0 Hz), 4.67 (1H, m), 5.05 (2H, s), 7.02 (4H, q, J=9.0 Hz), 7.40 (5H, s). *Anal.* Calcd for $C_{23}H_{27}BrO_4$: C, 61.74; H, 6.04. Found: C, 61.38; H, 6.34.

5*H*-*r*,*cis*-4-Bromo-7-{*p*-(*p*′-fluorobenzyloxy)phenyl}-*cis*-3-hydroxy-*trans*-3-methylheptan-5-olide (51)——56.7% yield. mp 160—163° (from ether–acetone). IR ν_{max}^{Nujol} cm^{-1}: 3460, 1715, 1610, 1580, 1515, 1500. PMR (d_6-acetone) δ: 1.39 (3H, s), 2.2—3.0 (4H, m), 2.82 (2H, s), 4.36 (1H, d, J=10.0 Hz), 4.73 (1H, m), 5.10 (2H, s), 6.9—7.6 (8H, m). *Anal.* Calcd for $C_{21}H_{22}BrFO_4$: C, 57.67; H, 5.03. Found: C, 57.40; H, 4.85.

5*H*-*r*,*cis*-4-Bromo-*cis*-3-hydroxy-*trans*-3-methyl-7-{*p*-(3′-phenylpropoxy)phenyl}heptan-5-olide (5m)——62.1% yield. mp 142—144° (from ether–ethyl acetate). IR ν_{max}^{Nujol} cm^{-1}: 3480, 1715, 1615, 1605, 1585, 1515. PMR (d_6-acetone) δ: 1.44 (3H, s), 1.9—3.0 (8H, m), 4.03 (2H, t, J=6.3 Hz), 4.68 (1H, m), 6.93 (2H, d, J=9.0 Hz), 7.07 (2H, d, J=9.0 Hz), 7.33 (5H, s). *Anal.* Calcd for $C_{23}H_{27}BrO_4$: C, 61.45; H, 6.04; Br, 17.90. Found: C, 61.64; H, 6.09; Br, 17.73.

4-Bromo-3-hydroxy-3-methyl-5-{*p*-(3′-phenylpropoxy)phenyl}pentan-5-olide (5n and 5n′)——85.2% yield. mp 128—130° (from ether–acetone). IR ν_{max}^{Nujol} cm^{-1}: 3440, 1720, 1610, 1515. PMR (d_6-DMSO) δ: 1.37, 1.42 (3H, s), 1.8—2.4 (2H, m), 2.6—3.1 (4H, m), 4.02 (2H, t, J=6.3 Hz), 4.53, 4.74 (1H, d, J=11.0 Hz), 5.42, 5.55 (1H, d, J=11.0 Hz), 6.98 (2H, d, J=9.0 Hz), 7.28 (5H, s), 7.47 (2H, d, J=9.0 Hz). *Anal.* Calcd for $C_{21}H_{23}BrO_4$: C, 60.14; H, 5.50; Br, 19.09. Found: C, 60.01; H, 5.31; Br, 18.90.

5*H*-*r*,7-(*p*-Biphenylyl)-*cis*-4-bromo-*cis*-3-hydroxy-*trans*-3-methylheptan-5-olide (5w)——64.5% yield (at 0° in 50% aqueous MeOH). mp 156—159° (from *n*-hexane–acetone). IR ν_{max}^{Nujol} cm^{-1}: 3450, 1720, 1620, 1600, 1580, 1565, 1520. PMR ($CDCl_3$) δ: 1.40 (3H, s), 1.9—2.3 (6H, m), 4.00 (1H, d, J=11.0 Hz), 4.77 (1H, ddd, J=3.0, 6.7 and 11.0 Hz), 7.2—7.8 (9H, m). *Anal.* Calcd for $C_{20}H_{21}BrO_3$: C, 61.70; H, 5.40; Br, 20.57. Found: C, 61.70; H, 5.48; Br, 20.78.

5*H*-*r*,5-(*p*-Biphenylyl)-*cis*-4-bromo-*cis*-3-hydroxy-*trans*-3-methylpentan-5-olide (5x)——63.5% yield (at 0° in 50% aqueous MeOH). mp 173—176° (from *n*-hexane–acetone). IR ν_{max}^{Nujol} cm^{-1}: 3460, 1700, 1600, 1480. PMR (d_6-acetone) δ: 1.52 (3H, s), 3.04 (2H, q, J=17.0 Hz), 4.72 (1H, s), 4.78 (1H, d, J=10.5 Hz), 5.73 (1H, d, J=10.5 Hz), 7.4—7.9 (9H, m). *Anal.* Calcd for $C_{18}H_{17}BrO_3$: C, 59.83; H, 4.71; Br, 22.13. Found: C, 59.91; H, 4.54; Br, 22.44.

4-Bromo-3-hydroxy-3,4-dimethyl-7-phenyl-*trans*-6-hepten-5-olide (16)——A stirred solution of 1.09 g of **15b** and 0.70 g of $NaHCO_3$ in 40 ml of 50% aqueous MeOH was treated with 0.34 ml of bromine with cooling at −35°. After the addition was complete, the resulting colorless crystals were separated and dried. Recrystallization from *n*-hexane–ethyl acetate gave 0.75 g of the desired compound. mp 121—123°. IR ν_{max}^{Nujol} cm^{-1}: 3350, 1735, 1660. PMR (d_6-DMSO) δ: 1.37 (3H, s), 1.78 (3H, s), 2.88 (2H, q, J=18.0 Hz), 5.67 (1H, d, J=6.0 Hz), 6.51 (1H, dd, J=6.0 and 15.0 Hz), 6.91 (1H, d, J=15.0 Hz), 7.3—7.7 (5H, m). UV λ_{max} nm:

250 (ε 22000). *Anal.* Calcd for $C_{15}H_{17}BrO_3$: C, 55.38; H, 5.23; Br, 24.61. Found: C, 55.49; H, 5.19; Br, 24.57.

5-Bromo-3-hydroxy-3,4-dimethyl-7-phenylheptan-4-olide (19)——A stirred solution of 0.875 g of **18b** in 20 ml of water containing 0.900 g of $NaHCO_3$ was treated with 0.4 ml of bromine at 0°. After usual work-up, recrystallization from *n*-hexane–benzene gave 0.850 g of the desired compound. mp 143—144°. IR ν_{max}^{Nujol} cm^{-1}: 3440, 1760, 1605, 1495. PMR (d_6-DMSO) δ: 1.42 (3H, s), 1.46 (3H, s), 1.8—3.4 (7H, m), 4.41 (1H, dd, J=3.0 and 10.0 Hz), 7.15 (5H, s). *Anal.* Calcd for $C_{15}H_{19}BrO_3$: C, 55.05; H, 5.86; Br, 24.46. Found: C, 55.23; H, 5.93; Br, 24.20.

General Procedure for the Synthesis of 1——A mixture of 5.0 mmol of the bromolactone (**5**) and 15.0 mmol of tri-*n*-butyltin hydride was refluxed in 10—20 ml of dry THF for several hours, or stirred at ambient temperature overnight. After removal of the solvent, the residue was washed with *n*-hexane and the *n*-hexane extract was decanted. The portion insoluble in *n*-hexane was purified by recrystallization or, if necessary, by silica gel chromatography. The physical data and yields of **1** prepared by the above method are given below.

5*H*-*r*,*cis*-3-Hydroxy-trans-3-methyl-7-phenylheptan-5-olide (1a)——83.0% yield. mp 69—70° (from *n*-hexane–ether). IR ν_{max}^{Nujol} cm^{-1}: 3440, 1710, 1600, 1495. PMR ($CDCl_3$) δ: 1.35 (3H, s), 1.5—2.2 (6H, m), 3.30 (3H, br s), 4.73 (1H, m), 7.10 (5H, s). *Anal.* Calcd for $C_{14}H_{18}O_3$: C, 73.28; H, 8.40. Found: C, 73.50; H, 8.35.

5*H*-*r*,*cis*-3-Hydroxy-*trans*-3-methyl-7-(*p*-tolyl)heptan-5-olide (1b)——75.9% yield. mp 70.5—72° (from *n*-hexane–ether). IR ν_{max}^{Nujol} cm^{-1}: 3430, 1695, 1515. PMR ($CDCl_3$) δ: 1.33 (3H, s), 1.5—2.1 (4H, m), 2.32 (3H, s), 2.5—3.0 (4H, m), 4.73 (1H, m), 7.15 (4H, s). *Anal.* Calcd for $C_{15}H_{20}O_3$: C, 72.58; H, 8.06. Found: C, 72.54; H, 8.01.

5*H*-*r*,7-(*p*-Chlorophenyl)-*cis*-3-hydroxy-*trans*-3-methylheptan-5-olide (1c)——57.5% yield. mp 61—64° (from *n*-hexane–benzene). IR ν_{max}^{Nujol} cm^{-1}: 3450, 1700, 1490. PMR ($CDCl_3$) δ: 1.37 (3H, s), 1.5—2.3 (4H, m), 2.5—3.0 (4H, m), 4.70 (1H, m), 7.0—7.4 (4H, m), *Anal.* Calcd for $C_{14}H_{17}ClO_3$: C, 62.57; H, 6.33; Cl, 13.22. Found: C, 63.00; H, 6.30; Cl, 13.08.

5*H*-*r*,7-(*o*-Benzyloxyphenyl)-*cis*-3-hydroxy-*trans*-3-methylheptan-5-olide (1d)——75.6% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 3500, 1710, 1600, 1500, 1485. PMR ($CDCl_3$) δ: 1.28 (3H, s), 1.5—2.2 (4H, m), 2.3—3.1 (4H, m), 4.77 (1H, m), 5.17 (2H, s), 6.8—7.7 (9H, m). *Anal.* Calcd for $C_{21}H_{24}O_4$: C, 74.12; H, 7.06. Found: C, 74.25; H, 7.09.

5*H*-*r*,7-(*m*-Benzyloxyphenyl)-*cis*-3-hydroxy-*trans*-3-methylheptan-5-olide (1e)——79.5% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 3480, 1710, 1600, 1515, PMR ($CDCl_3$) δ: 1.30 (3H, s), 1.5—2.2 (4H, m), 2.3—3.0 (4H, m), 4.78 (1H, m), 5.10 (2H, s), 6.7—7.6 (9H, m). *Anal.* Calcd for $C_{21}H_{24}O_4$: C, 74.11; H, 7.06. Found: C, 74.38; H, 7.29.

5*H*-*r*,7-(*p*-Benzyloxyphenyl)-*cis*-3-hydroxy-*trans*-3-methylheptan-5-olide (1f)——88.7% yield. mp 82—85° (from *n*-hexane-ethyl acetate). IR ν_{max}^{Nujol} cm^{-1}: 3440, 1700, 1615, 1585, 1520. PMR (d_6-acetone) δ: 1.30 (3H, s), 1.6—2.1 (4H, m), 2.4—3.0 (4H, m), 4.60 (1H, m), 5.10 (2H, s), 7.09 (4H, q, J=9.0 Hz), 7.3—7.6 (5H, m). *Anal.* Calcd for $C_{21}H_{24}O_4$: C, 74.11; H, 7.06. Found: C, 74.25; H, 7.18.

5*H*-*r*,5-(*p*-Benzyloxyphenyl)-*cis*-3-hydroxy-*trans*-3-methylpentan-5-olide (1g)——88.1% yield (**1g**+**1g′**). mp 128—129° (from *n*-hexane–acetone). IR ν_{max}^{Nujol} cm^{-1}: 3480, 1730, 1620, 1590, 1520. PMR ($CDCl_3$) δ: 1.38 (3H, s), 1.8—3.1 (4H, m), 3.37 (1H, br s), 5.17 (2H, s), 5.72 (1H, dd, J=4.5 and 10.0 Hz), 7.17 (4H, q, J=8.5 Hz), 7.42 (5H, s). *Anal.* Calcd for $C_{19}H_{20}O_4$: C, 73.08; H, 6.41. Found: C, 73.20; H, 6.50.

5*H*-*r*,5-(*p*-Benzyloxyphenyl)-*trans*-3-hydroxy-*cis*-3-methylpentan-5-olide (1g′)——mp146—148° (from *n*-hexane–acetone). IR ν_{max}^{Nujol} cm^{-1}: 3410, 1710, 1610, 1580, 1515. PMR ($CDCl_3$) δ: 1.48 (3H, s), 2.19 (1H, d, J=9.0 Hz), 2.21 (1H, d, J=7.0 Hz), 2.55 (2H, s), 3.54 (1H, br s), 5.09 (2H, s), 5.24 (1H, dd, J=7.0 and 9.0 Hz), 7.18 (4H, q, J=8.5 Hz), 7.42 (5H, s). *Anal.* Calcd for $C_{19}H_{20}O_4$: C, 73.08; H, 6.41. Found: C, 73.05; H, 6.45.

5*H*-*r*,6-(*p*-Benzyloxyphenyl)-*cis*-3-hydroxy-*trans*-3-methylhexan-5-olide (1h)——71.4% yield from **4h**. mp 136—138° (from *n*-hexane–ethyl acetate). IR ν_{max}^{Nujol} cm^{-1}: 3360, 1720, 1605, 1580, 1515. PMR (d_6-DMSO) δ: 1.18 (3H, s), 1.5—1.8 (2H, m), 2.40 (2H, s), 2.91 (2H, d, J=6.5 Hz), 3.32 (1H, s), 4.80 (1H, m), 5.13 (2H, s), 7.14 (4H, q, J=8.5 Hz), 7.47 (5H, s). *Anal.* Calcd for $C_{20}H_{22}O_4$: C, 73.62; H, 6.75. Found: C, 73.85; H, 6.75.

5*H*-*r*,8-(*p*-Benzyloxyphenyl)-*cis*-3-hydroxy-*trans*-3-methyloctan-5-olide (1i)——83.3% yield. mp 80—81° (from ether-acetone). IR ν_{max}^{Nujol} cm^{-1}: 3450, 1710, 1610, 1580, 1510. PMR ($CDCl_3$) δ: 1.32 (3H, s), 1.4—2.2 (6H, m), 2.2—2.8 (4H, m), 4.70 (1H, m), 5.07 (2H, s), 7.03 (4H, q, J=9.0 Hz), 7.12 (5H, s). *Anal.* Calcd for $C_{22}H_{26}O_4$: C, 74.58; H, 7.34. Found: C, 74.43; H, 7.29.

5*H*-*r*,9-(*p*-Benzyloxyphenyl)-*cis*-3-hydroxy-*trans*-3-methylnonan-5-olide (1j)——60.2% yield. mp 88—89° (from isopropylether–ethyl acetate). IR ν_{max}^{Nujol} cm^{-1}: 3420, 1700, 1610, 1580, 1515. PMR ($CDCl_3$) δ: 1.30 (3H, s), 1.4—2.0 (6H, m), 2.47 (2H, s), 2.4—2.7 (2H, m), 4.70 (1H, m), 5.05 (2H, s), 7.02 (4H, q, J=9.0 Hz), 7.40 (5H, s). *Anal.* Calcd for $C_{23}H_{28}O_4$: C, 75.00; H, 7.61. Found: C, 75.20; H, 7.55.

5*H*-*r*,7-{*p*-(*p′*-Fluorobenzyloxy)phenyl}-*cis*-3-hydroxy-*trans*-3-methylheptan-5-olide (1l)——60.4% yield. mp 143.5—144.5° (from ether–acetone). IR ν_{max}^{Nujol} cm^{-1}: 3450, 1700, 1615, 1605, 1585, 1520. PMR

($CDCl_3$) δ: 1.33 (3H, s), 1.5—3.0 (8H, m), 4.70 (1H, m), 5.03 (2H, s), 6.8—7.6 (8H, m). *Anal.* Calcd for $C_{21}H_{23}FO_4$; C, 70.39; H, 6.42. Found: C, 71.02; H, 6.70.

5*H*-*r*,*cis*-3-Hydroxy-*trans*-3-methyl-7-{*p*-(3′-phenylpropoxy)phenyl}heptan-5-olide (1m)——64.7% yield. mp 80—81.5° (from *n*-hexane–acetone). IR ν_{max}^{Nujol} cm^{-1}: 3430, 1690, 1615, 1580, 1515, 1500. PMR ($CDCl_3$) δ: 1.32 (3H, s), 1.5—2.3 (6H, m), 3.95 (2H, t, J=6.3 Hz), 4.71 (1H, m), 7.00 (4H, q, J=9.0 Hz), 7.26 (5H, s). *Anal.* Calcd for $C_{23}H_{28}O_4$: C, 75.00; H, 7.61. Found: C, 75.20; H, 7.65.

5*H*-*r*,*cis*-3-Hydroxy-*trans*-3-methyl-5-{*p*-(3′-phenylpropoxy)phenyl}pentan-5-olide (1n)——85.5% yield (**1n**+**1n′**). mp 84.5° (from ether–acetone). IR ν_{max}^{Nujol} cm^{-1}: 3440, 1720, 1615, 1585, 1515. PMR ($CDCl_3$) δ: 1.37 (3H, s), 1.8—2.4 (4H, m), 2.6—3.0 (4H, m), 3.97 (2H, t, J=6.3 Hz), 5.69 (1H, dd, J=4.5 and 11.0 Hz), 6.90 (2H, d, J=9.0 Hz), 7.31 (2H, d, J=9.0 Hz), 7.27 (5H, s). *Anal.* Calcd for $C_{21}H_{24}O_4$: C, 74.11; H, 7.06. Found: C, 73.90; H, 7.08.

5*H*-*r*,*trans*-3-Hydroxy-*cis*-3-methyl-5-{*p*-(3′-phenylpropoxy)phenyl}pentan-5-olide (1n′)——mp 107—109.5° (from ether–acetone). IR ν_{max}^{Nujol} cm^{-1}: 3410, 1730, 1610, 1585, 1515. PMR ($CDCl_3$) δ: 1.45 (3H, s), 1.8—2.2 (4H, m), 2.3—3.0 (4H, m), 3.97 (2H, t, J=6.3 Hz), 5.20 (1H, dd, J=7.0 and 9.0 Hz), 6.89 (2H, d, J=9.0 Hz), 7.27 (5H, s), 7.33 (2H, d, J=9.0 Hz). *Anal.* Calcd for $C_{21}H_{24}O_4$: C, 74.11; H, 7.06. Found: C, 73.86; H, 7.07.

5*H*-*r*,7-(*p*-Biphenylyl)-*cis*-3-hydroxy-*trans*-3-methylheptan-5-olide (1w)——58.8% yield. mp 118—120° (from *n*-hexane–acetone). IR ν_{max}^{Nujol} cm^{-1}: 3440, 1700, 1615, 1600, 1580, 1565, 1490. PMR ($CDCl_3$) δ: 1.32 (3H, s), 1.9—3.1 (8H, m), 4.74 (1H, m), 7.1—7.7 (9H, m). *Anal.* Calcd for $C_{20}H_{22}O_3$: C, 77.42; H, 7.10. Found: C, 77.28; H, 7.09.

5*H*-*r*,5-(*p*-Biphenylyl)-*cis*-3-hydroxy-*trans*-3-methylpentan-5-olide (1x)——48.6% yield. mp 151—153° (from *n*-hexane–acetone). IR ν_{max}^{Nujol} cm^{-1}: 3450, 1700, 1600, 1570, 1485. PMR (d_6-acetone) δ: 1.41 (3H, s), 2.0—2.4 (2H, m), 2.68 (2H, s), 5.79 (1H, dd, J=6.7 and 9.5 Hz), 7.3—7.9 (9H, m). *Anal.* Calcd for $C_{18}H_{18}O_3$: C, 76.60; H, 6.38. Found: C, 76.43; H, 6.43.

5*H*-*r*,7-(*p*-Benzyloxy-*o*,*o′*-dimethylphenyl)-*cis*-3-hydroxy-*trans*-3-methylheptan-5-olide (1y)——79.0% yield. mp 157—159° (from isopropylether–ethyl acetate). IR ν_{max}^{Nujol} cm^{-1}: 3370, 1700, 1610, 1585. PMR (d_6-DMSO) δ: 1.23 (3H, s), 1.4—2.0 (4H, m), 2.25 (6H, s), 2.2—2.8 (4H, m), 4.67 (1H, m), 5.05 (2H, s), 6.70 (2H, s), 7.42 (5H, s). *Anal.* Calcd for $C_{23}H_{28}O_4$: C, 75.00; H, 7.61. Found: C, 74.69; H, 7.71.

5*H*-*r*,7-(*p*-Benzyloxy-*m*-methoxyphenyl)-*cis*-3-hydroxy-*trans*-3-methylheptan-5-olide (1z)——47.1% yield from **4z**. IR $\nu_{max}^{liq.}$ cm^{-1}: 3450, 1720, 1605, 1590, 1515. PMR ($CDCl_3$) δ: 1.33 (3H, s), 1.5—2.2 (4H, m), 2.4—2.9 (4H, m), 3.88 (3H, s), 4.75 (1H, m), 5.15 (2H, s), 6.7—7.5 (8H, m). *Anal.* Calcd for $C_{22}H_{26}O_5$: C, 71.35; H, 7.03; Found: C, 71.70; H, 7.29.

5*H*-*r*,*cis*-3-Hydroxy-7-(*p*-hydroxyphenyl)-*trans*-3-methylheptan-5-olide (1q)——A solution of 5.65 g of **1f** and 2.0 g of 5% Pd-C in 50 ml of ethyl acetate was shaken under H_2. After usual work-up, recrystallization from *n*-hexane–acetone afforded 3.92 g of the desired compound. mp 135—137°. IR ν_{max}^{Nujol} cm^{-1}: 3300, 1700, 1615, 1595. PMR (d_6-acetone) δ: 1.33 (3H, s), 1.6—2.2 (4H, m), 2.5—2.9 (4H, m), 4.40 (1H, br s), 4.88 (1H, m), 6.80 (2H, d, J=9.0 Hz), 7.12 (2H, d, J=9.0 Hz), 8.00 (1H, br s). *Anal.* Calcd for $C_{14}H_{18}O_4$: C, 67.20; H, 6.60. Found: C, 67.25; H, 6.55.

5*H*-*r*,*cis*-3-Hydroxy-7-(*p*-hydroxy-*o*,*o′*-dimethylphenyl)-*trans*-3-methylheptan-5-olide (20)——From 0.500 g of **1y** and 0.500 g of 5% Pd-C, 0.219 g of the desired compound was obtained by the same method described for the preparation of **1q**. mp 181—183° (from *n*-hexane–ethyl acetate). IR ν_{max}^{Nujol} cm^{-1}: 3460, 3280, 1675, 1615, 1595. PMR (d_6-DMSO) δ: 1.20 (3H, s), 1.5—1.9 (4H, m), 2.20 (6H, s), 2.3—2.9 (4H, m), 4.65 (1H, m), 4.90 (1H, s), 6.47 (2H, s), 8.82 (1H, s). *Anal.* Calcd for $C_{16}H_{22}O_4$: C, 69.06; H, 7.93. Found: C, 69.15; H, 7.91.

5*H*-*r*,*cis*-3-Hydroxy-7-(*p*-hydroxy-*m*-methoxyphenyl)-*trans*-3-methylheptan-5-olide (22)——From 0.140 g of **1z** and 0.140 g of 5% Pd-C, 0.075 g of the desired compound was obtained. mp 162—164° (from isopropyl-ether–acetone). IR ν_{max}^{Nujol} cm^{-1}: 3430, 3350, 1680, 1600, 1520. PMR (d_6-DMSO) δ: 1.20 (3H, s), 1.5—2.1 (4H, m), 2.4—2.9 (4H, m), 3.78 (3H, s), 4.58 (1H, m), 6.7—7.0 (3H, m), 8.58 (1H, s). *Anal.* Calcd for $C_{15}H_{20}O_5$: C, 64.29; H, 7.14. Found: C, 64.50; H, 7.33.

5*H*-*r*,7-{*p*-(*p′*-Chlorobenzyloxy)phenyl}-*cis*-3-hydroxy-*trans*-3-methylheptan-5-olide (1k)——A solution of 0.100 g of **1q**, 0.100 g of *p*-chlorobenzyl chloride and 0.100 g of K_2CO_3 in 5 ml of dry DMF was heated at 100—110° for 2 hr. After usual work-up, recrystallization from *n*-hexane–acetone gave 0.095 g of the desired compound. mp 160—163°. IR ν_{max}^{Nujol} cm^{-1}: 3500, 1710, 1600, 1585, 1510. PMR (d_6-DMSO) δ: 1.38 (3H, s), 1.5—2.1 (4H, m), 2.4—2.9 (4H, m), 4.58 (1H, m), 5.08 (2H, s), 6.93 (2H, d, J=9.0 Hz), 7.03 (2H, d, J=9.0 Hz), 7.47 (4H, m). *Anal.* Calcd for $C_{21}H_{23}ClO_4$: C, 67.29; H, 6.14. Found: C, 67.65; H, 5.92.

5*H*-*r*,7-(*p*-Cinnamyloxyphenyl)-*cis*-3-hydroxy-*trans*-3-methylheptan-5-olide (1o)——A solution of 2.50g of **1q**, 3.0 g of cinnamyl bromide and 3.0 g of K_2CO_3 in 50 ml of dry methylethylketone was refluxed for 8 hr. After usual work-up, 2.8 g of the desired compound was obtained. mp 143—144° (from ether–acetone). IR ν_{max}^{Nujol} cm^{-1}: 3390, 1690, 1610, 1580, 1515. PMR ($CDCl_3$) δ: 1.27 (3H, s), 1.4—2.9 (8H, m), 4.59 (2H, d, J=5.5 Hz), 4.60 (1H, m), 6.0—7.5 (11H, m). *Anal.* Calcd for $C_{23}H_{26}O_4$: C, 75.41; H, 7.10. Found: C, 75.40; H, 7.09.

5*H*-*r*,7-{*p*-(*p′*-Chlorophenacyloxy)phenyl}-*cis*-3-hydroxy-*trans*-3-methylheptan-5-olide (1p)——A solution of 0.100 g of **1q** and 0.200 g of *p*-chlorophenacyl bromide in 2 ml of dry methylethylketone was refluxed for

5 hr in the presence of 0.100 g of K_2CO_3 and 0.01 g of NaI. After usual work-up, recrystallization from *n*-hexane–ethyl acetate gave 0.076 g of the desired compound. mp 152.5—153.5°. IR ν_{max}^{Nujol} cm^{-1}: 3500, 1720, 1710, 1620, 1600, 1580, 1520. PMR (d_6-DMSO) δ: 1.38 (3H, s), 1.5—2.1 (4H, m), 2.4—2.9 (4H, m), 4.58 (1H, m), 5.50 (2H, s), 6.93 (2H, d, J=8.7 Hz), 7.20 (2H, d, J=8.7 Hz), 7.66 (2H, d, J=9.0 Hz), 8.11 (2H, d, J=9.0 Hz). *Anal.* Calcd for $C_{22}H_{23}ClO_5$: C, 65.56; H, 5.75; Cl, 8.80. Found: C, 65.29; H, 5.64; Cl, 8.90.

5*H*-*r*,*cis*-3-Hydroxy-7-(*p*-methoxyphenyl)-*trans*-3-methylheptan-5-olide (1r)——A stirred solution of 1.35 g of **1q** in 20 ml of MeOH was treated with an ether solution of diazomethane. Removal of the solvent and recrystallization of the residue from *n*-hexane–acetone gave 1.30 g of the desired compound. mp 76—78°. IR ν_{max}^{Nujol} cm^{-1}: 3410, 1690, 1615, 1590, 1520. PMR ($CDCl_3$) δ: 1.32 (3H, s), 1.5—2.2 (4H, m), 2.4—3.0 (4H, m), 3.78 (3H, s), 4.71 (1H, m), 6.84 (2H, d, J=9.0 Hz), 7.15 (2H, d, J=9.0 Hz). *Anal.* Calcd for $C_{15}H_{20}O_4$: C, 68.18; H, 7.58. Found: C, 68.23; H, 7.59.

5*H*-*r*,*cis*-3-Hydroxy-*trans*-3-methyl-7-(*p*-octanoyloxyphenyl)heptan-5-olide (1s)——A stirred solution of 0.200 g of **1q** and 0.1 ml of dry pyridine in 4 ml of dry CH_2Cl_2 was treated with 0.2 ml of octanoyl chloride under cooling at 0° and was then stirred at ambient temperature for 2 hr. After usual work-up, the residue was purified by thin-layer chromatography with benzene–ethyl acetate (1: 1). Recrystallization from ether gave 0.145 g of the desired compound. mp 73—74°. IR ν_{max}^{Nujol} cm^{-1}: 3550, 3440, 3320, 1755, 1690, 1640, 1515. PMR ($CDCl_3$) δ: 0.92 (3H, br t), 1.33 (13H, m), 1.5—2.3 (4H, m), 2.4—3.0 (6H, m), 4.73 (1H, m), 7.02 (4H, q, J=9.0 Hz). *Anal.* Calcd for $C_{22}H_{32}O_5$: C, 70.21; H, 8.51. Found: C, 70.25; H, 8.61.

5*H*-*r*,7-(*p*-Benzoyloxyphenyl)-*cis*-3-hydroxy-*trans*-3-methylheptan-5-olide (1t)——From 0.150 g of **1q** and 0.08 ml of benzoyl chloride, 0.165 g of the desired compound was obtained by the method described for the preparation of **1s**. mp 118.5—119.5°. IR ν_{max}^{Nujol} cm^{-1}: 3460, 1730, 1695, 1600, 1510. PMR ($CDCl_3$) δ: 1.33 (3H, s), 1.5—2.2 (4H, m), 2.5—3.0 (4H, m), 4.72 (1H, m), 7.0—7.2 (7H, m), 8.1—8.3 (2H, m). *Anal.* Calcd for $C_{21}H_{22}O_5$: C, 71.19; H, 6.21. Found: C, 71.06; H, 6.24.

5*H*-*r*,7-{*p*-(*p'*-Chlorobenzoyloxy)phenyl}-*cis*-3-hydroxy-*trans*-3-methylheptan-5-olide (1u)——From 0.100 g of **1q** and 0.105 g of *p*-chlorobenzoyl chloride, 0.100 g of the desired compound was obtained. mp 168—170° (from *n*-hexane–acetone). IR ν_{max}^{Nujol} cm^{-1}: 3350, 1730, 1700, 1600, 1520. PMR ($CDCl_3$) δ: 1.35 (3H, s), 1.6—3.1 (8H, m), 4.73 (1H, m), 7.1—8.3 (8H, m). *Anal.* Calcd for $C_{21}H_{21}ClO_5$: C, 64.87; H, 5.41; Cl, 9.13. Found: C, 64.51; H, 5.59; Cl, 9.01.

5*H*-*r*,*cis*-3-Hydroxy-*trans*-3-methyl-7-(*p*-nicotinyloxyphenyl)heptan-5-olide (1v)——From 0.100 g of **1q** and 0.100 g of nicotinyl chloride hydrochloride, 0.120 g of the desired compound was obtained. mp 162—163° (from *n*-hexane–acetone). IR ν_{max}^{Nujol} cm^{-1}: 3350, 1740, 1695, 1600, 1520. PMR (d_6-acetone) δ: 1.35 (3H, s), 1.7—2.3 (4H, m), 2.25 (2H, s), 2.7—3.1 (2H, m), 3.53 (1H, br s), 4.75 (1H, m), 7.34 (4H, m), 7.67 (1H, ddd, J=1.0, 5.0 and 8.0 Hz), 8.57 (1H, td, J=2.0 and 8.0 Hz), 8.97 (1H, dd, J=2.0 and 5.0 Hz), 9.42 (1H, dd, J=1.0 and 2.0 Hz). *Anal.* Calcd for $C_{20}H_{21}NO_5$: C, 67.71; H, 5.92; N, 3.94. Found: C, 67.57; H, 5.85; N, 3.99.

5*H*-*r*,7-(*p*-Benzoyloxy-*o*,*o'*-dimethylphenyl)-*cis*-3-hydroxy-*trans*-3-methylheptan-5-olide (21)——From 0.100 g of **20** and 0.18 ml of benzoyl chloride, 0.112 g of the desired compound was obtained. mp 181—183° (from isopropylether–ethyl acetate). IR ν_{max}^{Nujol} cm^{-1}: 3430, 1730, 1700, 1590. PMR (d_6-DMSO) δ: 1.25 (3H, s), 1.5—2.0 (4H, m), 2.35 (6H, s), 2.48 (2H, s), 2.2—3.0 (2H, m), 4.73 (1H, m), 6.98 (2H, s), 7.6—7.9 (3H, m), 8.1—8.4 (2H, m). *Anal.* Calcd for $C_{23}H_{26}O_5$: C, 72.25; H, 6.81. Found: C, 72.20; H, 6.68.

5*H*-*r*,*cis*-3-Acetoxy-7-(*p*-benzyloxyphenyl)-*trans*-3-methylheptan-5-olide (23)——A solution of 0.56 ml of Et_3N in 1 ml of dry CH_2Cl_2 was added to a solution of 0.100 g of **1f**, 0.63 ml of acetic anhydride, and 1.5 mg of N,N-dimethyl-4-pyridineamine in 5 ml of dry CH_2Cl_2 under cooling at 0° and the reaction mixture was stirred at 0° for 4 hr. After usual work-up, 0.068 g of the desired compound was obtained. mp 99—101° (from *n*-hexane–ethyl acetate). IR ν_{max}^{Nujol} cm^{-1}: 1730, 1720, 1610, 1580, 1510. PMR ($CDCl_3$) δ: 1.60 (3H, s), 1.99 (3H, s), 1.5—2.2 (4H, m), 2.3—3.6 (4H, m), 4.50 (1H, m), 5.12 (2H, s), 7.14 (4H, m), 7.3—7.6 (5H, m). *Anal.* Calcd for $C_{23}H_{26}O_5$: C, 72.25; H, 6.81. Found: C, 72.21; H, 6.88.

7-(*p*-Benzyloxyphenyl)-3-methyl-2-hepten-5-olide (24)——A solution of 0.200 g of **1f** in 10 ml of benzene was refluxed in the presence of a catalytic amount of *p*-TsOH for 30 min. After usual work-up, recrystallization from *n*-hexane–ethyl acetate gave 0.215 g of the desired compound. mp 69—70°. IR ν_{max}^{Nujol} cm^{-1}: 1720, 1645, 1610, 1580, 1515. PMR ($CDCl_3$) δ: 1.93 (3H, br s), 1.7—2.5 (4H, m), 2.6—2.9 (2H, m), 4.40 (1H, m), 5.08 (2H, s), 5.83 (1H, br s), 7.08 (4H, q, J=9.0 Hz), 7.44 (5H, s). *Anal.* Calcd for $C_{21}H_{22}O_3$: C, 78.26; H, 6.83. Found: C, 77.92; H, 6.74.

5*H*-*r*,7-(*p*-Benzyloxyphenyl)-*cis*-3-hydroxyheptan-5-olide (25)——A solution of 2.86 g of ethyl acetoacetate in 10 ml of dry THF was added to a suspension of 0.95 g of 50% NaH in 50 ml of dry THF at 0°. When the evolution of hydrogen ceased, 16.9 ml of 15% *n*-BuLi in *n*-hexane was added to the mixture. The mixture was stirred at 0°, then cooled to −70° and a solution of 5.63 g of 3-(*p*-benzyloxyphenyl)propanal in 10 ml of dry THF was added. After stirring at −70° for 2 hr, the reaction mixture was poured into ice-water and extracted with ethyl acetate. After usual work-up, the ethyl acetate extract, without further purification, was dissolved in 20 ml of EtOH and the ethanolic solution was added to a solution of 3.18 g of $NaBH_4$ in 50 ml of EtOH at 0°. After stirring at ambient temperature for 1 hr, the reaction mixture was poured into ice-water and extracted with ethyl acetate. Usual work-up gave 8.5 g of a yellow oil, which was subjected to silica gel chromatography. Elution with benzene–ethyl acetate (5: 1) afforded 5.4 g

of a diastereo mixture, which was hydrolyzed with 1 N NaOH. The aqueous layer was acidified with 1 N HCl and extracted with ethyl acetate. From the ethyl acetate extract the *trans* isomer separated as crystals; this material was recrystallized from *n*-hexane–ethyl acetate to give 1.68 g of the desired compound. mp 82—85°. IR ν_{max}^{Nujol} cm^{-1}: 3460, 1695, 1613, 1585, 1518. PMR ($CDCl_3$) δ: 1.4—2.2 (4H, m), 2.5—3.0 (4H, m), 4.30 (1H, m), 4.75 (1H, m), 5.05 (2H, s), 6.8—7.6 (9H, m). *Anal.* Calcd for $C_{20}H_{22}O_4$: C, 73.62; H, 6.75. Found: C, 73.49; 6.89.

4-Hydroxy-6-phenylhexan-2-one (7)[17]——A stirred solution of 2.20 g of diisopropylamine in 40 ml of dry ether was treated with 20 ml of 15% *n*-BuLi in *n*-hexane under cooling at −10—0° under nitrogen. After the addition was complete, the mixture was stirred at 0° for 30 min, then a solution of 3.06 g of isopropylidenecyclohexylamine in 2 ml of dry ether was added. After 30 min, a solution of 2.66 g of 3-phenylpropanal in 2 ml of dry ether was added to the yellow solution under cooling at −70°. After the addition was complete, the reaction mixture was stirred at this temperature for a further one hour, warmed to 0°, poured into ice-water, and extracted with ether. After usual work-up, the residue was purified by silica gel chromatography to yield 2.02 g of the desired compound as a light yellow oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 3460, 1715, 1610, 1500. PMR ($CDCl_3$) δ: 2.07 (3H, s), 1.4—2.0 (2H, m), 2.3—3.0 (4H, m), 3.49 (1H, br s), 4.04 (1H, m), 7.33 (5H, s). *Anal.* Calcd for $C_{12}H_{16}O_2$: C, 75.00; H, 8.33. Found: C, 74.65; H, 8.54.

4-Acetoxy-6-phenylhexan-2-one (8)——One ml of acetic anhydride was added to a solution of 0.85 g of **7** and 0.8 ml of dry pyridine in 10 ml of dry CH_2Cl_2 under cooling at 0°, and then stirring was continued for a further one hour at ambient temperature. The reaction mixture was poured into water, then the methylene chloride layer was washed with water and dried over Na_2SO_4, and the solvent was evaporated off to afford 1.10 g of the desired compound. IR $\nu_{max}^{liq.}$ cm^{-1}: 1735, 1720, 1615, 1500. PMR ($CDCl_3$) δ: 1.7—2.2 (4H, m), 2.01 (3H, s), 2.07 (3H, s), 2.5—3.0 (4H, m), 4.55 (1H, m), 7.35 (5H, s). *Anal.* Calcd for $C_{14}H_{18}O_3$: C, 72.41; H, 7.76. Found: C, 72.55; H, 7.80.

6-(*p*-Benzyloxyphenyl)-4-hydroxyhexan-2-one (9)——Using the same procedure as in the case of **7**, 2.09 g of **9** was obtained from 3.12 g of 3-(*p*-benzyloxyphenyl)propanal. mp 67—68° (from *n*-hexane–ether). IR ν_{max}^{Nujol} cm^{-1}: 3350, 1720, 1615, 1590, 1520. PMR ($CDCl_3$) δ: 1.5—2.0 (2H, m), 2.14 (3H, s), 2.5—3.1 (4H, m), 4.06 (1H, m), 5.05 (2H, s), 6.91 (2H, d, J=9.0 Hz), 7.16 (2H, d, J=9.0 Hz), 7.40 (5H, s). *Anal.* Calcd for $C_{19}H_{22}O_3$: C, 76.51; H, 7.38. Found: C, 76.45; H, 7.34.

6-(*p*-Benzyloxyphenyl)-4-bromoacetoxyhexan-2-one (11)——A stirred solution of 0.504 g of **9** and 0.500 g of bromoacetic anhydride in 5 ml of dry CH_2Cl_2 was treated with 0.2 ml of dry pyridine at 0°. After two hours, the mixture was poured into ice-water and extracted with ether. After usual work-up, 0.666 g of the desired compound was obtained. IR $\nu_{max}^{liq.}$ cm^{-1}: 1735, 1720, 1610, 1580, 1510. PMR ($CDCl_3$) δ: 1.8—2.2 (2H, m), 2.13 (3H, s), 2.5—2.7 (4H, m), 3.73 (2H, s), 5.06 (2H, s), 5.36 (1H, m), 6.91 (2H, d, J=9.0 Hz), 7.14 (2H, d, J=9.0 Hz), 7.41 (5H, s). *Anal.* Calcd for $C_{21}H_{23}BrO_4$: C, 60.14; H, 5.49; Br, 19.09. Found: C, 60.20; H, 5.51; Br, 19.15.

Ethyl 5-Acetoxy-3-hydroxy-3-methyl-7-phenylheptanoate (12)——A mixture of 1.0 ml of ethyl bromoacetate, 0.620 g of granular zinc and 1.476 g of **8** was refluxed in 5 ml of dry ether. After usual work-up, the residue was purified by chromatography to yield 1.029 g of the desired compound as a light yellow oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 3500, 1735, 1720, 1605, 1500. PMR ($CDCl_3$) δ: 1.26 (3H, t, J=7.0 Hz), 1.26 (3H, s), 1.6—2.2 (4H, m), 2.01 (3H, s), 2.4—2.9 (4H, m), 4.18 (2H, q, J=7.0 Hz), 5.18 (1H, m), 7.23 (5H, s). *Anal.* Calcd for $C_{18}H_{26}O_5$: C, 67.08; H, 8.07. Found: C, 67.06; H, 7.98.

5*H*-*r*,*trans*-3-Hydroxy-*cis*-3-methyl-7-phenylheptan-5-olide (1a′)——A solution of 0.900 g of **12** and 2 ml of 4 N NaOH in 5 ml of MeOH was allowed to stand at ambient temperature for 3 hr. After acidification with 1 N HCl, ethyl acetate was added and the mixture was swirled at ambient temperature for 4 days. After usual work-up, the extract was subjected to thin-layer chromatography, developing twice with *n*-hexane–acetone (2:1), to yield 0.200 g of the desired compound as a colorless oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 3420, 1725, 1600, 1500. PMR ($CDCl_3$) δ: 1.37 (3H, s), 1.7—2.2 (4H, m), 2.59 (2H, s), 2.5—3.0 (2H, m), 4.23 (1H, m), 7.26 (5H, s). *Anal.* Calcd for $C_{14}H_{18}O_3$: C, 71.79; H, 7.69. Found: C, 71.54; H, 7.83.

5*H*-*r*,7-(*p*-Benzyloxyphenyl)-*trans*-3-hydroxy-*cis*-3-methylheptan-5-olide (1f′)——To 0.168 g of granular zinc in 2 ml of dry THF, 0.89 ml of 15% Et_2AlCl in heptane was added at ambient temperature under N_2. After 20 min, the mixture was cooled to 0° and 0.666 g of **11** was added. The reaction mixture was stirred at ambient temperature for 7 hr. After usual work-up, the ethyl acetate extract was subjected to thin-layer chromatography with benzene–ethyl acetate (1:1). Recrystallization from *n*-hexane–acetone gave 0.141 g of the desired compound. mp 131—133°. IR ν_{max}^{Nujol} cm^{-1}: 3425, 1720, 1610, 1580, 1515. PMR (d_6-acetone) δ: 1.35 (3H, s), 1.7—2.2 (4H, m), 2.5—2.9 (4H, m), 3.95 (1H, br s), 4.32 (1H, m), 5.11 (2H, s), 6.95 (2H, d, J=9.0 Hz), 7.23 (2H, d, J=9.0 Hz), 7.4—7.6 (5H, m). *Anal.* Calcd for $C_{21}H_{24}O_4$: C, 74.12; H, 7.11. Found: C, 73.85; H, 7.12.

Methyl 3-Hydroxy-3-methyl-5-oxo-7-phenylheptanoate (13b)——An ether solution of phenethylmagnesium bromide prepared from 2.37 g of phenethyl bromide and 0.31 g of Mg in 20 ml of dry ether was added to a solution of 0.307 g of 3-hydroxy-3-methylglutaric anhydride in 20 ml of dry THF under cooling at −20——10°. When the addition was complete, the reaction mixture was stirred for a further one hour and poured into cold 1 N HCl. The organic layer was washed with satd. $NaHCO_3$ solution. The aqueous layer was acidified with cold 1 N HCl and extracted with ether. The ether extract, after usual work-up, gave

0.253 g of **13a**, which was esterified with diazomethane to yield the desired compound (**13b**). IR $\nu_{max}^{liq.}$ cm^{-1}: 3500, 1735, 1720, 1600, 1500. PMR ($CDCl_3$) δ: 1.26 (3H, s), 2.60 (2H, s), 2.83 (2H, s), 2.8—3.0 (4H, m), 3.65 (3H, s), 7.20 (5H, s). *Anal.* Calcd for $C_{15}H_{20}O_4$: C, 68.18; H, 7.58. Found: C, 67.89; H, 7.49.

Sodium Borohydride Reduction of 13b——A solution of 0.381 g of **13b** in 4 ml of EtOH was added to a solution of 0.060 g of $NaBH_4$ in 6 ml of EtOH under cooling at $-70°$. After usual work-up, 0.285 mg of a 1: 1 mixture of **1a** and **1a′** was obtained. These isomers were separated by thin-layer chromatography, developing twice with benzene–ethyl acetate (2: 1) to yield 0.05 g of **1a** and 0.039 g of **1a′**.

3-Methyl-7-phenyl-3-hepten-5-olide (14)——Compound **4a** (0.400 g) was dissolved in 1 ml of CF_3CO_2H at 0° and the mixture was stirred at ambient temperature for 30 min. Removal of the solvent left 0.350 g of a brown oil, which was subjected to thin-layer chromatography with benzene–ethyl acetate (5: 1), to yield 0.271 g of the desired compound as a colorless oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 1740, 1605, 1500. PMR ($CDCl_3$) δ: 1.77 (3H, br s), 1.8—2.1 (2H, m), 2.3—3.1 (4H, m), 4.92 (1H, m), 5.55 (1H, m), 7.25 (5H, s). UV λ_{max} nm: end absorption. *Anal.* Calcd for $C_{14}H_{16}O$: C, 77.78; H, 7.41. Found: 77.54; H, 7.51.

5*H*-*r*,*trans*-4-Bromo-*cis*-3-hydroxy-*trans*-3-methyl-7-phenylheptan-5-olide (5a′)——A solution of 0.270 g of **14** in 0.5 ml of water and 3 ml of acetone was treated with 0.270 g of NBA at ambient temperature, and the mixture was stirred for 2 hr. After usual work-up, the ethyl acetate extract was subjected to thin-layer chromatography with benzene–ethyl acetate (2: 1). Recrystallization from *n*-hexane–ether afforded 0.161 g of the desired compound. mp 81—82°. IR ν_{max}^{Nujol} cm^{-1}: 3520, 1730, 1600, 1490. PMR ($CDCl_3$) δ: 1.54 (3H, s), 1.8—3.0 (6H, m), 3.15 (1H, s), 4.02 (1H, t, J=2.0 Hz), 4.94 (1H, ddd, J=2.0, 5.5 and 7.5 Hz), 7.24 (5H, s). *Anal.* Calcd for $C_{14}H_{17}BrO_3$: C, 53.67; H, 5.43; Br, 25.56. Found: C, 53.30; H, 5.50; Br, 25.30.

Tri-*n*-butyltin Hydride Reduction of 5a′——Using the general procedure mentioned above, 0.293 g of **1a** was obtained from 0.500 g of **5a′** and 1.25 g of tri-*n*-butyltin hydride.

Cell Culture——Mouse L cells (929) were grown in Eagle's minimum essential medium supplemented with kanamycin (60 μg/ml), 20 mmol of tricine (pH=7.4), 24 mmol of $NaHCO_3$, and 5% (v/v) fetal calf serum. The cells were inoculated (day 0) at about 2.5×10^5 cells per dish into plastic plates (60×15 mm) containing 3 ml of the above medium and incubated in a humidified incubator (5% CO_2) at 37°. On day 3, when the cells were confluent, they were used for experiments.

Incorporation of ^{14}C Acetate into Digitonin-precipitable Sterol——The mevalonolactone derivatives were dissolved in 30 μl of EtOH or DMSO and the solution was added to a portion of cultivated cells. Control cell received 30 μl of EtOH or DMSO. After incubation for 2 hr at 37°, the medium was removed and 2 ml of phosphate buffer saline and 2 ml of 20% ethanolic KOH were added to the cells. The mixture was incubated at 75° for 2 hr and non-saponifiable lipids were extracted with pet. ether; digitonin-precipitable ^{14}C-labeled sterols were isolated from this extract and counted for radioactivity with a liquid scintilation counter.

Acknowledgement The authors are grateful to Mr. Masaaki Kurabayashi for valuable discussions.