Synthesis of Novel 4,1-Benzoxazepine Derivatives as Squalene Synthase Inhibitors and Their Inhibition of Cholesterol Synthesis

Takashi Miki,*,† Masakuni Kori,† Hiroshi Mabuchi,† Ryu-ichi Tozawa,† Tomoyuki Nishimoto,† Yasuo Sugiyama,‡ Koichiro Teshima,† and Hidefumi Yukimasa†

Pharmaceutical Research Division, Takeda Chemical Industries, Ltd., 2-17-85, Juso-Honmachi, Yodogawa-ku, Osaka 532-8686, Japan, and Strategic Product Planning Department, Takeda Chemical Industries, Ltd., 4-1-1, Doshomachi, Chuo-ku, Osaka 540-8645, Japan

Received May 29, 2002

Modification of the carboxyl group at the 3-position and introduction of protective groups to the hydroxy group of the 4,1-benzoxazepine derivative **2** (metabolite of **1**) were carried out, and the inhibitory activity for squalene synthase and cholesterol synthesis in the liver was investigated. Among these compounds, the glycine derivative **3a** and *β*-alanine derivative **3f** exhibited the most potent inhibition of squalene synthase prepared from HepG2 cells (IC_{50} = 15 nM). On the other hand, the piperidine-4-acetic acid derivative **4a**, which was prepared by acetylation of **3j**, was the most effective inhibitor of cholesterol synthesis in rat liver (ED_{50} = 2.9 mg/kg, po). After oral administration, **4a** was absorbed and rapidly hydrolyzed to deacylated **3j**. Compound **3j** was detected mainly in the liver, but the plasma level of **3j** was found to be low. Compounds **3j** and **4a** were found to be competitive inhibitors with respect to farnesyl pyrophosphate. Further evaluation of **4a** as a cholesterol-lowering and antiatherosclerotic agent is underway.

Introduction

Squalene synthase [EC 2.5.1.21] catalyzes the formation of squalene from farnesyl pyrophosphate (FPP) in cholesterol biosynthesis. This enzymatic reaction takes place after the pathway branches to other isoprene derivatives such as dolichol, ubiquinones, and isopentenyl t-RNA. Since squalene synthase inhibitors might not interfere with the biosynthesis of these isoprene derivatives, inhibition of this step would arrest only cholesterol biosynthesis and might be useful for the treatment of hyperlipidemia. Several squalene synthase inhibitors,[1] such as cationic intermediate analogues (containing ammonium ions or sulfonium ions), substrate analogues (phosphorus-containing compounds bisphosphonates and α-phosphonosulfonic acids), quinuclidine derivatives, 2,8-dioxabicyclo[3.2.1]octane derivatives[2,3] (squalestatins, zaragozic acids, and TAN-1607A[4]), and others,[5] have been reported.

Previously, we reported the synthesis of a series of 4,1-benzoxazepine derivatives and their inhibitory activity for squalene synthase.[6a−d] Through modification of the skeleton and substituents, we synthesized a novel squalene synthase inhibitor, sodium (3*R*,5*S*)-7-chloro-5-(2,3-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetate (Figure 1, **1**).

Pharmacokinetic studies of compound **1** revealed that **2** was the urinary metabolite of **1** in dogs (Figure 1). Compound **2** exhibited potent inhibitory activity for squalene synthase derived from human hepatoma (HepG2) cells (IC_{50} = 18 nM) similar to **1**. We focused our studies on the modification and the structure−activity relationship of **2**. Modification of the carboxyl group at the 3-position and introduction of protective groups to the hydroxy group were carried out, and the inhibitory activity for squalene synthase and sterol synthesis in the liver was investigated (Figure 1, **3** and **4**). In this paper, we report the synthesis of the 4,1-benzoxazepine derivatives **3** and **4**, which led to the candidate **4a** (Figure 1).

Chemistry

Compounds **2** and **3** were synthesized as follows (Scheme 1). Compound **2** was prepared using the optically active alcohol **5**[6d] as starting material. Compound **5** was treated with 3-hydroxy-2,2-dimethylpropionaldehyde[7] and sodium cyanoborohydride ($NaBH_3$-CN) to obtain alkylated compound **6**. Condensation of **6** and a fumaryl chloride monoethyl ester followed by intramolecular Michael addition of the obtained intermediate **7** afforded the 4,1-benzoxazepine derivative **8**.[6a,b,8] In this cyclization, a thermodynamically stable 3,5-trans compound was obtained.[9] Hydrolysis of the ester **8** gave the carboxylic acid **2**. The enantiomeric purity of compound **2** was 100% ee by HPLC analysis. The optically active alcohol **5** was transformed into compound **2** without racemization. The amide derivative **9** was prepared by condensation of **2** with various amino acid esters using diethylphosphoryl cyanide (DEPC). Then compounds **9a**−**l** were hydrolyzed or hydrogenated to yield acids **3a**−**l**.

Acid **3j** was reacted with acetic anhydride to provide the acetylated compound **4a** (Scheme 2). Compound **3j** was converted to benzyl ester **10**, which was treated with acid chloride or chloromethyl pivalate to afford acylated compounds **11a**−**c** and alkylated compound **11d**. Acids **4b**−**e** were obtained by hydrogenation of compounds **11a**−**d** (Scheme 3).

* To whom correspondence should be addressed. Phone: +81-6-6300-6263. Fax: +81-6-6300-6306. E-mail: Miki_Takashi@takeda.co.jp.
† Pharmaceutical Research Division.
‡ Strategic Product Planning Department.

10.1021/jm020234o CCC: $22.00
Published on Web 08/30/2002

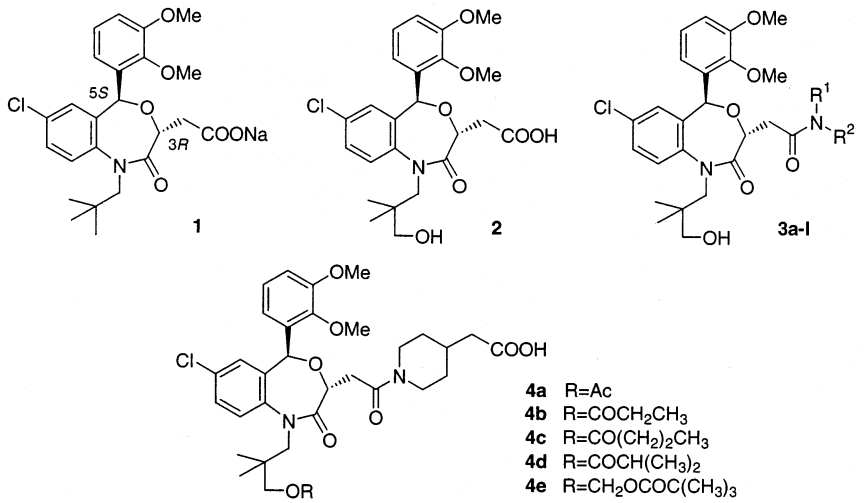
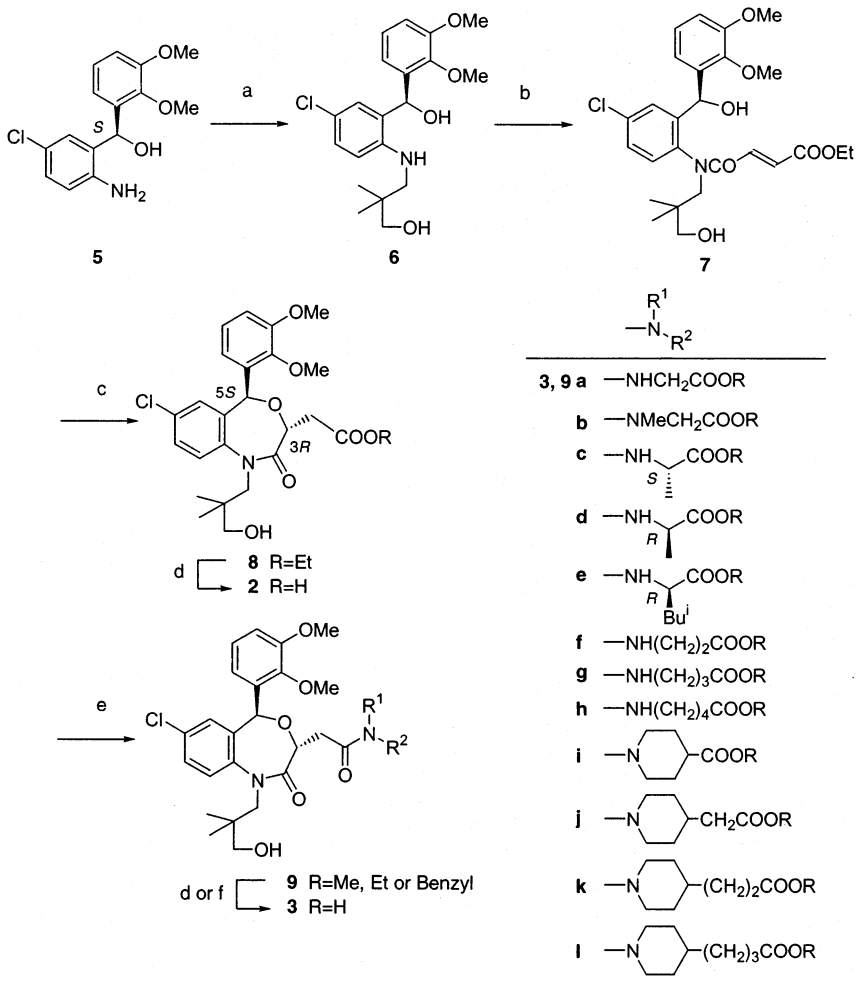


Figure 1. Structures of 4,1-benzoxazepine derivatives.

Scheme 1[a]



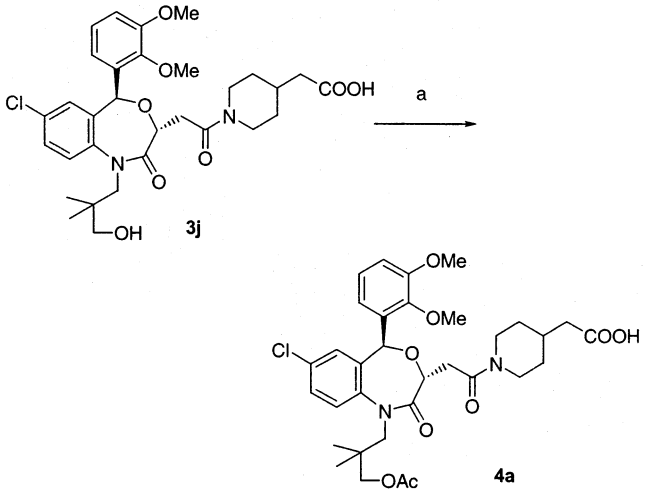
[a] Reagents: (a) 3-hydroxy-2,2-dimethylpropionaldehyde, $NaBH_3CN$, AcOH, MeOH; (b) fumaryl chloride monoethyl ester, $NaHCO_3$, AcOEt; (c) K_2CO_3, EtOH; (d) NaOH, EtOH; (e) amino acid esters, DEPC, NEt_3, DMF; (f) H_2, Pd−C, AcOEt.

Biological Results and Discussion

The compounds synthesized were evaluated for their inhibitory activity for squalene synthase prepared from HepG2 cells. Inhibitory activity was measured according to the method of L. H. Cohen et al. with slight modification.[6a,10] The compounds were also evaluated for their ability to inhibit the incorporation of [^{14}C]-acetate into sterols in the Wistar rat liver at 1 h after oral dosing. The results are shown in Tables 1 and 2.

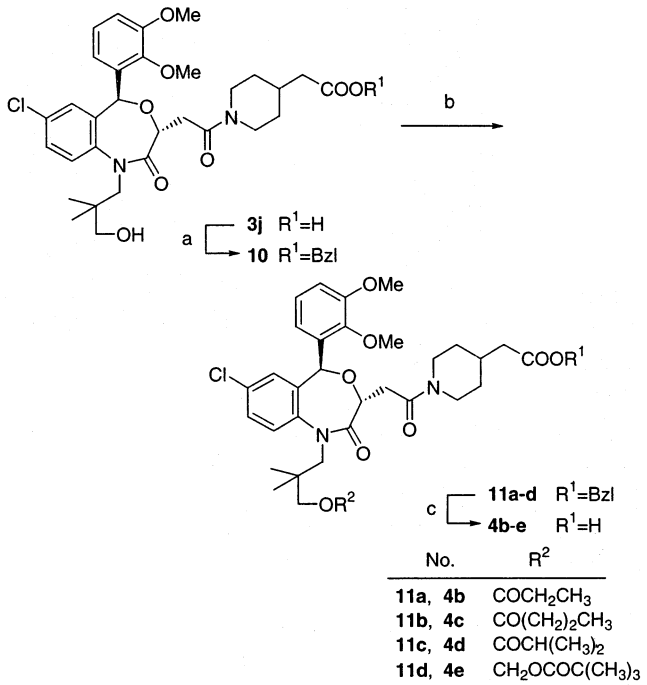
In a previous paper,[6b] we described that elongation of the tether length and the conversion to carboxamide of the 3-acetic acid moiety decreased the activity. We then found that the inhibitory activity of glycine derivative **3a** for squalene synthase was as potent as that of

Scheme 2[a]



[a] Reagents: (a) Ac_2O, DMAP, pyridine.

Scheme 3[a]



No.	R^2
11a, 4b	$COCH_2CH_3$
11b, 4c	$CO(CH_2)_2CH_3$
11c, 4d	$COCH(CH_3)_2$
11d, 4e	$CH_2OCOC(CH_3)_3$

[a] Reagents: (a) benzyl bromide, K_2CO_3, DMF; (b) R^2Cl, NEt_3, DMAP, THF or R^2Cl, NaH, DMF; (c) H_2, Pd−C, AcOEt.

2 (Table 1, entry 1). Both the carbamoyl group and carboxyl group were assumed to play important roles in exerting the inhibitory activity. The N-methylated compound **3b** also achieved the same extent of inhibition (Table 1, entry 2). This result indicated that the hydrogen atom on the nitrogen did not affect the inhibition.

The L-alanine derivative **3c** was found to be as potent as the D-alanine derivative **3d**. The stereochemistry of the side chain was not essential for the inhibition (Table 1, entries 3 and 4). Conversion of D-alanine to D-leucine resulted in a slight decrease in activity (Table 1, entry 5). Modification of the tether length between the carbamoyl group and carboxyl group gave the following results. The β-alanine derivative **3f** exhibited the same level of activity as the glycine derivative **3a**. Further elongation resulted in a slight loss of activity (Table 1, entries 6−8). Bulky substituents at the 3-position were found to be undesirable for the inhibition.

Although compounds **3a**−**f**, which have methylene or ethylene between the carboxyl group and carbamoyl group, are potent inhibitors of squalene synthase, they only weakly inhibit the synthesis of sterols in rat liver (<31% inhibition at 10 mg/kg, po) (Table 1, entries 1−6). On the other hand, adding methylene groups to **3f** improved the inhibitory activity (butyric acid derivative **3g** and pentanoic acid derivative **3h** showed 59% and 50% inhibition at 10 mg/kg, po, respectively) (Table 1, entries 7 and 8). Since we had much success in improving the oral activity through elongation of the chain, we added methylene groups to the piperidine-4-carboxylic acid derivative **3i**. Although the acetic acid, propionic acid, and butyric acid derivatives **3j**−**l** showed a 3- to 4-fold reduced activity than **3i** at the enzyme level, their inhibition of sterol synthesis increased significantly (Table 1, entries 9−12). In consideration of the balance between in vitro inhibitory activity for the human enzyme and de novo synthesis of sterols in rats, we selected compound **3j** for further pharmacological investigation.

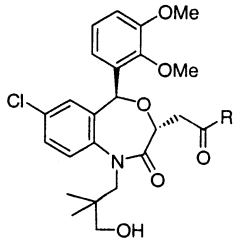
The dose that achieved 50% inhibition of sterol synthesis in rat liver after oral administration (ED_{50}) of **3j** was 6.8 mg/kg, po (Wistar rats). This compound was approximately 2-fold less active than **1** (ED_{50} = 3.0 mg/kg, po, Wistar rats). Compounds **4a**−**e** having protective groups added to the hydroxy group were prepared, and their activity to inhibit squalene synthase and sterol synthesis was investigated. Their inhibitory effect for the enzyme was 2- to 10-fold weaker than that of **3j** (Table 2). Acetylated **4a** showed the most potent inhibition of sterol synthesis with an ED_{50} of 2.9 mg/kg, po, which was almost equal to that of **1**. The propionyl, butyryl, and isobutyryl derivatives **4b**−**d** showed 30−40% inhibition at 10 mg/kg, po ($p > 0.05$). Although the pivaloyloxymethyl derivative **4e** reduced sterol synthesis by 43% at 10 mg/kg, po ($p < 0.01$), the activity was weaker than that of **3j** and **4a**.

Lineweaver−Burk analysis of the inhibitory effect on the HepG2 enzyme revealed compounds **3j** and **4a** to be competitive inhibitors with respect to FPP ($K_m = 5.9 \times 10^{-7}$ M). Dixon plot analysis showed that the K_i values for compounds **3j** and **4a** were 3.4×10^{-9} and 9.4×10^{-9} M, respectively.

The pharmacokinetic profile of compound **4a** in rats was evaluated. After oral administration, **4a** was absorbed and rapidly hydrolyzed to deacylated **3j**. Compound **3j** was detected mainly in the liver, but the plasma level of **3j** was found to be low. Thus, it was assumed that **4a** would be distributed mainly to the liver as deacylated **3j**. The ratio of the area under curve (AUC) (liver/plasma) of compound **3j** (injected as **4a**) was 3-fold higher than that of compound **1**. Because the target organ of squalene synthase is the liver, we believe that **4a** has a good profile compared to **1**.

Compound **4a** significantly reduced plasma non-HDL-cholesterol and triglyceride levels in marmosets and Watanabe heritable hyperlipidemic (WHHL) rabbits.[11] Thus, **4a** (TAK-475) is a promising candidate for an antihyperlipidemic and antiatherosclerotic drug.

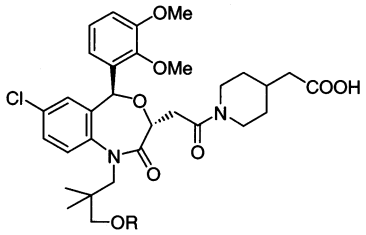
Table 1. Inhibition of Squalene Synthase and Sterol Synthesis in Rat Liver by 4,1-Benzoxazepine Derivatives **3a**−**l**



entry	compound	R (configuration)	enzyme IC_{50} [a] (nM)	sterol synthesis[b] % inhibition (10 mg/kg, po)
1	**3a**	−$NHCH_2COOH$	15	14 ± 26
2	**3b**	−$N(Me)CH_2COOH$	18	−1 ± 43
3	**3c**	−NHCH(Me)COOH (*S*)	21	14 ± 48
4	**3d**	−NHCH(Me)COOH (*R*)	18	31 ± 16
5	**3e**	−$NHCH(Bu^i)COOH$ (*R*)	28	14 ± 30
6	**3f**	−$NHCH_2CH_2COOH$	15	19 ± 24
7	**3g**	−$NHCH_2CH_2CH_2COOH$	32	59 ± 13**
8	**3h**	−$NHCH_2CH_2CH_2CH_2COOH$	38	50 ± 16*
9	**3i**	4-(carboxy)piperidin-1-yl	18	26 ± 23
10	**3j**	4-(carboxymethyl)piperidin-1-yl	45	77 ± 11**
11	**3k**	4-(2-carboxyethyl)piperidin-1-yl	61	76 ± 11**
12	**3l**	4-(3-carboxypropyl)piperidin-1-yl	70	87 ± 5**

[a] IC_{50} values were determined by a single experimental run in duplicate. [b] Test compounds (10 mg/kg) as a 0.5% MC solution were administered to 6-week-old male Wistar rats. Animals were intravenously injected with [^{14}C]acetate (50 μCi/kg) 1 h after the drug administration. They were sacrificed 1 h after the injection, and the radioactivity of the digitonin-precipitable sterols in the tissues was measured. Values are the mean ± SD (n = 6−10). (*) $p \le 0.05$, (**) $p \le 0.01$ (vs control), by Dunnett's test.

Table 2. Inhibition of Squalene Synthase and Sterol Synthesis in Rat Liver by 4,1-Benzoxazepine Derivatives **3j** and **4a**−**e**



entry	compound	R	enzyme IC_{50} [a] (nM)	sterol synthesis[b] ED_{50} (mg/kg, po)	% inhibition 1 mg/kg, po	% inhibition 3 mg/kg, po	% inhibition 10 mg/kg, po
1	**3j**	H	45	6.8	11 ± 69	20 ± 47	64 ± 15**
2	**4a**	$COCH_3$	78	2.9	31 ± 20*	42 ± 21**	81 ± 9**
3	**4b**	$COCH_2CH_3$	87				40 ± 18
4	**4c**	$COCH_2CH_2CH_3$	93				30 ± 32
5	**4d**	$COCH(CH_3)_2$	89				34 ± 26
6	**4e**	$CH_2OCOC(CH_3)_3$	471				43 ± 19**
7	**1**			3.0[c]			

[a] IC_{50} values were determined by a single experimental run in duplicate. [b] Test compounds (10 mg/kg) as a 0.5% MC solution were administered to 6-week-old male Wistar rats. Animals were intravenously injected with [^{14}C]acetate (50 μCi/kg) 1 h after the drug administration. They were sacrificed 1 h after the injection, and the radioactivity of the digitonin-precipitable sterols in the tissues was measured. Values are the mean ± SD (n = 6−10). (*) $p \le 0.05$, (**) $p \le 0.01$ (vs control), by Dunnett's test. [c] See ref 6b.

Conclusion

We performed chemical modifications of 4,1-benzoxazepine derivatives and evaluated the inhibitory activitiy for microsomal squalene synthase and for in vivo hepatic sterol synthesis. Among these compounds, the piperidine-4-acetic acid derivative **4a** was the most effective inhibitor of cholesterol synthesis in rat liver (ED_{50} = 2.9 mg/kg, po). A pharmacokinetic study showed that **4a** was deacylated to **3j** (major active metabolite) with distribution to the liver. Pharmacological studies on this new squalene synthase inhibitor **4a** will be reported in due course.

Experimental Section

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian GEMINI-200 (200 MHz) spectrometer (with tetramethylsilane as an internal standard). Infrared absorption spectra were recorded on a JASCO IR-810. $[\alpha]_D$ values were determined in the indicated solvents on a JASCO DIP-370 polarimeter. TLC analyses were carried out on Merck Kieselgel 60 F_{254} plates. Elemental analyses were carried out by Takeda Analytical Laboratories, Ltd. and are within ±0.4% of the theoretical values. For column chromatography, Merck Kieselgel 60 (70−230 mesh ASTM) was used. Yields were not

maximized. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m multiplet, br = broad.

(*S*)-5-Chloro-α-(2,3-dimethoxyphenyl)-2-(3-hydroxy-2,2-dimethylpropyl)aminobenzyl Alcohol (6). 3-Hydroxy-2,2-dimethylpropionaldehyde (21 g, 0.206 mol) and acetic acid (12.4 g, 0.206 mol) were added to a solution of (*S*)-2-amino-5-chloro-α-(2,3-dimethoxyphenyl)benzyl alcohol (**5**, 55 g, 0.187 mol) in MeOH (500 mL). After the mixture was stirred for 1 h at 60 °C, sodium cyanoborohydride (12.8 g, 0.206 mol) was added to this solution with ice-cooling. The mixture was stirred for 2 h at 60 °C and diluted with AcOEt (500 mL). The solution was washed with 1 N NaOH, water, and brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was subjected to column chromatography [eluent: hexane−AcOEt (2:1)] to give **6** (62 g, 0.163 mol, 87%) as a colorless oil. $[\alpha]^{22}_D$ −37.9° (*c* 0.453, MeOH). IR ν_{max}(neat), cm^{-1}: 3400 (br, OH, NH). ^1H NMR ($CDCl_3$): δ 0.91 (3H, s), 0.93 (3H, s), 2.95 (2H, s), 3.37 (2H, s), 3.83 (3H, s), 3.88 (3H, s), 5.99 (1H, s), 6.63 (1H, d, J = 8.8 Hz), 6.77 (1H, dd, J = 1.6, 7.6 Hz), 6.90 (1H, dd, J = 1.6, 7.6 Hz), 7.03 (1H, d, J = 2.6 Hz), 7.03 (1H, t, J = 7.6 Hz), 7.13 (1H, dd, J = 2.6, 8.8 Hz).

Ethyl (*S*)-3-[*N*-[4-Chloro-2-(α-hydroxy-2,3-dimethoxybenzyl)phenyl]-*N*-(3-hydroxy-2,2-dimethylpropyl)carbamoyl]acrylate (7). A solution of fumaryl chloride monoethyl ester (**3**, 29 g, 0.179 mol) in AcOEt (50 mL) was added to a stirred mixture of **6** (62 g, 0.163 mol) and $NaHCO_3$ (21 g, 0.245 mol) in AcOEt (500 mL). After being stirred for 30 min at room temperature, the reaction mixture was washed with water, dried over Na_2SO_4, and then concentrated under reduced pressure to give **7** (82 g, 0.163 mol, quantitative) as a colorless oil. IR ν_{max}(neat), cm^{-1}: 3400 (br, OH), 1715, 1650 (C=O), 1620 (C=C). ^1H NMR ($CDCl_3$): δ 0.73 (1/2 × 3H, s), 0.74 (1/2 × 3H, s), 0.87 (1/2 × 3H, s), 1.01 (1/2 × 3H, s), 1.18−1.30 (3H, m), 2.87 (1/2 × 1H, d, J = 14.6 Hz), 3.05−3.41 (2H + 1/2 × 1H, m), 3.70 (1/2 × 3H, s), 3.73 (1/2 × 3H, s), 3.79 (1/2 × 3H, s), 3.89 (1/2 × 3H, s), 4.04−4.22 (2H, m), 4.32−4.55 (2H, m), 6.01−7.85 (10H, m).

Ethyl (3*R*,5*S*)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetate (8). A mixture of **7** (82 g, 0.163 mol) and K_2CO_3 (22.5 g, 0.163 mol) in EtOH (500 mL) was stirred overnight at room temperature. The reaction mixture was diluted with AcOEt (1 L). This solution was washed with water (500 mL) and brine (500 mL), dried over Na_2SO_4, and then concentrated under reduced pressure. The solid residue was recrystallized from EtOH to give **8** (65.2 g, 0.129 mol, 79%) as colorless needles. Mp 188−190 °C (EtOH). $[\alpha]^{22}_D$ −205° (*c* 0.318, MeOH). IR ν_{max}(KBr), cm^{-1}: 3430 (br, OH), 1720, 1650 (C=O). ^1H NMR ($CDCl_3$): δ 0.64 (3H, s), 1.05 (3H, s), 1.25 (3H, t, J = 7.4 Hz), 2.77 (1H, dd, J = 5.8, 16.8 Hz), 3.07 (1H, dd, J = 8.0, 16.8 Hz), 3.09−3.20 (1H, m), 3.39 (1H, d, J = 14.4 Hz), 3.58−3.65 (1H, m), 3.62 (3H, s), 3.89 (3H, s), 4.13 (2H, dq, J = 1.8, 7.4 Hz), 4.12−4.20 (1H, br), 4.38 (1H, dd, J = 5.8, 8.0 Hz), 4.49 (1H, d, J = 14.4 Hz), 6.16 (1H, s), 6.61 (1H, s), 6.96−7.36 (5H, m). Anal. ($C_{26}H_{32}NO_7Cl\cdot0.5H_2O$) C, H, N.

(3*R*,5*S*)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic Acid (2). An aqueous solution (100 mL) of NaOH (10.3 g, 0.258 mol) was added to a solution of **8** (65.2 g, 0.129 mmol) in EtOH (400 mL). After being stirred for 2 h at 60 °C, the reaction mixture was diluted with water (500 mL), acidified, and then extracted with AcOEt (500 mL, twice). The combined organic extracts were washed with brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The solid residue was recrystallized from AcOEt−hexane (1:2) to give **2** (58.2 g, 0.122 mol, 94%) as colorless needles. Mp 199−202 °C (AcOEt−hexane). $[\alpha]^{22}_D$ −223° (*c* 0.193, MeOH). IR ν_{max}(KBr), cm^{-1}: 3600−2400 (br, COOH, OH), 1710, 1650 (C=O). ^1H NMR ($CDCl_3$): δ 0.65 (3H, s), 1.04 (3H, s), 2.76 (1H, dd, J = 5.4, 16.8 Hz), 3.08 (1H, dd, J = 8.0, 16.8 Hz), 3.11−3.17 (1H, m), 3.39 (1H, d, J = 14.6 Hz), 3.57−3.64 (1H, m), 3.61 (3H, s), 3.89 (3H, s), 4.37 (1H, dd, J = 5.4, 8.0 Hz), 4.48 (1H, d, J = 14.6 Hz), 6.15 (1H, s), 6.61 (1H, s), 6.96−7.01 (1H, m), 7.18−7.22 (2H, m), 7.36−7.37 (2H, m). Anal. ($C_{24}H_{28}NO_7Cl$) C, H, N. 100% ee [HPLC analysis; Sumichiral-OA (4.6 i.d. × 250 mm; Sumitomo Chemical Analysis Center, Ltd.); eluent, 50 mM ammonium acetate methanol solution; flow rate, 1.0 mL/min; retention time, 14.27 min for **2**, 14.36 and 19.09 min for racemic compound].

Ethyl 1-[[(3*R*,5*S*)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]piperidine-4-acetate (9j). To a stirred mixture of **2** (0.6 g, 1.26 mmol) and ethyl piperidine-4-acetate hydrochloride[12] (0.27 g, 1.29 mmol) in DMF (6 mL) was added diethylphosphoryl cyanide (DEPC) (0.23 g, 1.39 mmol) at room temperature, followed by the addition of NEt_3 (0.28 g, 2.97 mmol). The mixture was stirred for 30 min at room temperature. The mixture was diluted with AcOEt (50 mL) and washed with 5% $KHSO_4$, saturated $NaHCO_3$, and brine and was then dried over Na_2SO_4. The solvent was removed under reduced pressure. The residue was subjected to column chromatography [eluent: hexane−AcOEt (1:2)] to give **9j** (0.45 g, 0.713 mmol, 57%) as a colorless amorphous powder. $[\alpha]^{22}_D$ −163° (*c* 0.213, MeOH). IR ν_{max} (KBr), cm^{-1}: 3440 (br, OH), 1730, 1640 (C=O). ^1H NMR ($CDCl_3$): δ 0.63 (3H, s), 1.05 (3H, s), 1.26 (3H, t, J = 7.2 Hz), 1.54−1.80 (4H, m), 2.19−2.28 (2H, m), 2.50−2.75 (2H, m), 2.96−3.23 (3H, m), 3.39 (1H, d, J = 14.2 Hz), 3.58−3.67 (1H, m), 3.62 (3H, s), 3.89 (3H, s), 3.91−3.98 (1H, m), 4.13 (2H, q, J = 7.2 Hz), 4.43−4.53 (3H, m), 6.16 (1H, s), 6.60 (1H, s), 6.96−7.01 (1H, m), 7.18−7.41 (4H, m). Anal. ($C_{33}H_{43}ClN_2O_8$) C, H, N.

Methyl *N*-[[(3*R*,5*S*)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]glycinate (9a). Compound **9a** (1.15 g, 2.09 mmol, quantitative) was prepared from **2** (1.0 g, 2.09 mmol) and methyl glycinate hydrochloride (0.28 g, 2.20 mmol) in the same manner as described for the preparation of **9j**. Colorless prisms. Mp 83−84 °C (AcOEt−hexane). $[\alpha]^{22}_D$ −197° (*c* 0.155, MeOH). IR ν_{max} (KBr), cm^{-1}: 3600−3200 (br, OH, NH), 1749, 1658 (C=O). ^1H NMR ($CDCl_3$): δ 0.64 (3H, s), 1.05 (3H, s), 2.72 (1H, dd, J = 5.8, 14.6 Hz), 2.96 (1H, dd, J = 7.2, 14.6 Hz), 3.06−3.22 (1H, br), 3.38 (1H, d, J = 14.0 Hz), 3.62 (3H, s), 3.62 (1H, d, J = 11.2 Hz), 3.75 (3H, s), 3.89 (3H, s), 4.01−4.03 (2H, m), 4.40 (1H, dd, J = 5.8, 7.2 Hz), 4.47 (1H, d, J = 14.0 Hz), 6.17 (1H, s), 6.32−6.42 (1H, br), 6.61 (1H, s), 6.97−7.36 (5H, m). Anal. ($C_{27}H_{33}N_2O_8Cl$) C, H, N.

Benzyl *N*-[[(3*R*,5*S*)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]-*N*-methylglycinate (9b). Compound **9b** (1.1 g, 1.72 mmol, 82%) was prepared from **2** (1.0 g, 2.09 mmol) and benzyl sarcosinate *p*-toluenesulfonate (0.74 g, 2.11 mmol) in the same manner as described for the preparation of **9j**. A colorless amorphous powder. $[\alpha]^{22}_D$ −177° (*c* 0.136, MeOH). IR ν_{max} (KBr), cm^{-1}: 3600−3200 (br, OH), 1736, 1680, 1651 (C=O). ^1H NMR ($CDCl_3$): δ 0.64 (3H, s), 1.02 (3H, s), 2.60 (1/5 × 1H, dd, J = 4.2, 15.0 Hz), 2.79 (4/5 × 1H, dd, J = 4.2, 16.4 Hz), 2.94 (1/5 × 3H, s), 3.12 (4/5 × 3H, s), 3.09 (1/5 × 1H, dd, J = 8.4, 15.0 Hz), 3.24 (4/5 × 1H, dd, J = 8.4, 16.4 Hz), 3.19 (1H, d, J = 10.6 Hz), 3.55 (1H, d, J = 14.2 Hz), 3.61 (3H, s), 3.63 (1H, d, J = 10.6 Hz), 3.89 (3H, s), 4.41−4.60 (4H, m), 5.14 (4/5 × 2H, s), 5.19 (1/5 × 2H, s), 6.26 (1/5 × 1H, s), 6.27 (4/5 × 1H, s), 6.64 (1H, s), 6.96−7.36 (10H, m). Anal. ($C_{34}H_{39}N_2O_8Cl$) C, H, N.

Ethyl *N*-[[(3*R*,5*S*)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]-L-alaninate (9c). Compound **9c** (0.62 g, 1.07 mmol, quantitative) was prepared from **2** (0.5 g, 1.05 mmol) and ethyl L-alaninate hydrochloride (0.18 g, 1.15 mmol) in the same manner as described for the preparation of **9j**. Colorless prisms. Mp 130−132 °C (AcOEt−hexane). $[\alpha]^{22}_D$ −191° (*c* 0.171, MeOH). IR ν_{max} (KBr), cm^{-1}: 3600−3200 (br, OH, NH), 1739, 1655 (C=O). ^1H NMR ($CDCl_3$): δ 0.64 (3H, s), 1.04 (3H, s), 1.26 (3H, t, J = 7.4 Hz), 1.40 (3H, d, J = 7.4 Hz), 2.70 (1H, dd, J = 5.6, 14.8 Hz), 2.90 (1H, dd, J = 7.4, 14.8 Hz), 3.14 (1H, d, J = 11.6 Hz), 3.37 (1H, d, J = 14.6 Hz), 3.61 (3H, s), 3.61 (1H, d, J = 11.6 Hz), 3.89 (3H, s), 4.18 (2H, q, J = 7.4 Hz), 4.38−4.55 (3H, m), 6.16 (1H, s), 6.27 (1H, d, J

= 6.6 Hz), 6.61 (1H, s), 6.96−7.35 (5H, m). Anal. ($C_{29}H_{37}N_2O_8$-Cl·H_2O) C, H, N.

Methyl *N*-[[(3*R*,5*S*)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]-D-alaninate (9d). Compound **9d** (0.61 g, 1.08 mmol, quantitative) was prepared from **2** (0.5 g, 1.05 mmol) and methyl D-alaninate hydrochloride (0.16 g, 1.15 mmol) in the same manner as described for the preparation of **9j**. A colorless amorphous powder. $[\alpha]^{22}_D$ −174° (*c* 0.268, MeOH). IR ν_{max} (KBr), cm^{-1}: 3600−3200 (br, OH, NH), 1743, 1660 (C═O). ^1H NMR ($CDCl_3$): δ 0.64 (3H, s), 1.05 (3H, s), 1.41 (3H, t, *J* = 7.4 Hz), 2.68 (1H, dd, *J* = 6.6, 14.8 Hz), 2.89 (1H, dd, *J* = 6.8, 14.8 Hz), 3.15 (1H, d, *J* = 10.8 Hz), 3.38 (1H, d, *J* = 14.6 Hz), 3.57−3.66 (1H, br), 3.62 (3H, s), 3.74 (3H, s), 3.89 (3H, s), 4.38 (1H, dd, *J* = 6.6, 6.8 Hz), 4.48 (1H, d, *J* = 14.6 Hz), 4.56 (1H, t, *J* = 7.4 Hz), 6.17 (1H, s), 6.43 (1H, d, *J* = 7.8 Hz), 6.61 (1H, s), 6.96−7.35 (5H, m). Anal. ($C_{28}H_{35}N_2O_8Cl$·0.5H_2O) C, H, N.

Methyl *N*-[[(3*R*,5*S*)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]-D-leucine (9e). Compound **9e** (1.9 g, 3.14 mmol, quantitative) was prepared from **2** (1.5 g, 3.13 mmol) and methyl D-leucinate hydrochloride (0.63 g, 3.47 mmol) in the same manner as described for the preparation of **9j**. A colorless powder. Mp 110−111 °C (Et_2O). IR ν_{max} (KBr), cm^{-1}: 3600−3200 (br, OH, NH), 1749, 1658 (C═O). ^1H NMR ($CDCl_3$): δ 0.64 (3H, s), 0.92 (3H, d, *J* = 3.0 Hz), 0.95 (3H, d, *J* = 1.6 Hz), 1.05 (3H, s), 1.42−1.85 (3H, s), 2.69 (1H, dd, *J* = 6.0, 14.6 Hz), 2.91 (1H, dd, *J* = 6.6, 14.6 Hz), 3.28 (1H, d, *J* = 14.4 Hz), 3.05−3.22 (1H, m), 3.62 (3H, s), 3.72 (3H, s), 4.35−4.68 (3H, m), 6.18 (1H, s), 6.28−6.42 (1H, m), 6.61 (1H, d, *J* = 1.6 Hz), 6.94−7.42 (5H, m). Anal. ($C_{31}H_{41}N_2O_8Cl$) C, H, N.

Methyl *N*-[[(3*R*,5*S*)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]-*β*-alaninate (9f). Compound **9f** (1.80 g, 3.20 mmol, 77%) was prepared from **2** (2.0 g, 4.18 mmol) and methyl *β*-alaninate hydrochloride (0.64 g, 4.59 mmol) in the same manner as described for the preparation of **9j**. A colorless amorphous powder. $[\alpha]^{22}_D$ −208 (*c* 0.114, MeOH). IR ν_{max} (KBr), cm^{-1}: 3600−3200 (br, OH, NH), 1738, 1650 (C═O). ^1H NMR ($CDCl_3$): δ 0.64 (3H, s), 1.05 (3H, s), 2.51 (2H, t, *J* = 6.2 Hz), 2.66 (1H, dd, *J* = 5.8, 14.2 Hz), 2.83 (1H, dd, *J* = 7.4, 14.2 Hz), 3.14 (1H, t, *J* = 11.0 Hz), 3.50 (2H, q, *J* = 6.2 Hz), 3.38 (1H, d, *J* = 14.0 Hz), 3.58−3.68 (1H, br), 3.61 (3H, s), 3.67 (3H, s), 3.89 (3H, s), 4.13−4.25 (1H, br), 4.40 (1H, dd, *J* = 5.8, 7.4 Hz), 4.46 (1H, d, *J* = 14.0 Hz), 6.15 (1H, s), 6.30−6.40 (1H, br), 6.61 (1H, d, *J* = 1.4 Hz), 6.97−7.44 (5H, m). Anal. ($C_{28}H_{35}N_2O_8Cl$) C, H, N.

Methyl 4-[[[(3*R*,5*S*)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]amino]butyrate (9g). Compound **9g** (1.59 g, 2.76 mmol, 66%) was prepared from **2** (2.0 g, 4.18 mmol) and methyl 4-aminobutyrate hydrochloride (0.71 g, 4.60 mmol) in the same manner as described for the preparation of **9j**. A colorless powder. Mp 78−80 °C (AcOEt−hexane). $[\alpha]^{22}_D$ −202° (*c* 0.149, MeOH). IR ν_{max} (KBr), cm^{-1}: 3600−3200 (br, OH, NH), 1738, 1651 (C═O). ^1H NMR ($CDCl_3$): δ 0.64 (3H, s), 1.05 (3H, s), 1.4 (2H, quintet, *J* = 7.2 Hz), 2.36 (2H, t, *J* = 7.2 Hz), 2.63 (1H, dd, *J* = 5.8, 14.2 Hz), 2.83 (1H, dd, *J* = 7.4, 14.2 Hz), 3.14 (1H, t, *J* = 10.8 Hz), 3.23−3.34 (2H, m), 3.38 (1H, d, *J* = 14.6 Hz), 3.58−3.67 (1H, br), 3.61 (3H, s), 3.67 (3H, s), 3.89 (3H, s), 4.14−4.22 (1H, br), 4.40 (1H, dd, *J* = 5.8, 7.4 Hz), 4.46 (1H, d, *J* = 14.6 Hz), 5.96−6.03 (1H, br), 6.15 (1H, s), 6.61 (1H, d, *J* = 1.4 Hz), 6.97−7.40 (5H, m). Anal. ($C_{29}H_{37}N_2O_8Cl$·0.5H_2O) C, H, N.

Methyl 5-[[[(3*R*,5*S*)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]amino]pentanoate (9h). Compound **9h** (2.57 g, 4.35 mmol, quantitative) was prepared from **2** (2.0 g, 4.18 mmol) and methyl 5-aminopentanoate hydrochloride (0.77 g, 4.60 mmol) in the same manner as described for the preparation of **9j**. Colorless prisms. Mp 84−85 °C (AcOEt−hexane). $[\alpha]^{22}_D$ −191° (*c* 0.126, MeOH). IR ν_{max}(KBr), cm^{-1}: 3600−3200 (br, OH, NH), 1738, 1660 (C═O). ^1H NMR ($CDCl_3$): δ 0.64 (3H, s), 1.05 (3H, s), 1.45−1.68 (4H, m), 2.34 (2H, t, *J* = 7.0 Hz), 2.63 (1H, dd, *J* = 5.6, 14.4 Hz), 2.84 (1H, dd, *J* = 7.4, 14.4 Hz), 3.14 (1H, t, *J* = 11.2 Hz), 3.24 (2H, q, *J* = 6.2 Hz), 3.38 (1H, d, *J* = 14.2 Hz), 3.61 (3H, s), 3.61 (1H, dd, *J* = 4.4, 11.2 Hz), 3.67 (3H, s), 3.89 (3H, s), 4.20 (1H, dd, *J* = 4.4, 11.2 Hz), 4.40 (1H, dd, *J* = 5.6, 7.4 Hz), 4.46 (1H, d, *J* = 14.2 Hz), 5.88−5.94 (1H, br), 6.15 (1H, s), 6.60 (1H, s), 6.96−7.36 (5H, m). Anal. ($C_{30}H_{39}N_2O_8Cl$·H_2O) C, H, N.

Methyl 1-[[(3*R*,5*S*)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]piperidine-4-carboxylate (9i). Compound **9i** (1.0 g, 1.66 mmol, 79%) was prepared from **2** (1.0 g, 2.09 mmol) and methyl piperidine-4-carboxylate hydrochloride (0.38 g, 2.09 mmol) in the same manner as described for the preparation of **9j**. A colorless powder. Mp 121−124 °C (AcOEt−hexane). $[\alpha]^{22}_D$ −180° (*c* 0.418, MeOH). IR ν_{max} (KBr), cm^{-1}: 3600−3300 (br, OH), 1730, 1645 (C═O). ^1H NMR ($CDCl_3$): δ 0.63 (3H, s), 1.04 (3H, s), 1.56−1.73 (4H, m), 2.30−2.55 (1H, m), 2.65−2.82 (2H, m), 3.06−3.24 (3H, m), 3.39 (1H, d, *J* = 14.2 Hz), 3.61 (3H, s), 3.66−3.72 (4H, m), 3.878 (3H, s), 4.25−4.40 (1H, m), 4.45−4.48 (2H, m), 6.16 (1H, s), 6.61 (1H, s), 6.96−7.40 (5H, m). Anal. ($C_{31}H_{39}N_2O_8Cl$) C, H, N.

Ethyl 1-[[(3*R*,5*S*)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]piperidine-4-propionate (9k). Compound **9k** (1.1 g, 1.70 mmol, 81%) was prepared from **2** (1.0 g, 2.09 mmol) and ethyl piperidine-4-propionate hydrochloride[13] (0.49 g, 2.21 mmol) in the same manner as described for the preparation of **9j**. A colorless amorphous powder. $[\alpha]^{22}_D$ −189° (*c* 0.248, MeOH). IR ν_{max} (KBr), cm^{-1}: 3600−3300 (br, OH), 1732, 1645 (C═O). ^1H NMR ($CDCl_3$): δ 0.63 (3H, s), 1.05 (3H, s), 1.26 (3H, t, *J* = 7.2 Hz), 0.88−1.20 (2H, m), 1.43−1.80 (4H, m), 2.37−2.40 (2H, m), 2.46−2.58 (1H, m), 2.67−2.77 (1H, m), 2.90−3.03 (1H, m), 3.11−3.23 (2H, m), 3.39 (1H, d, *J* = 14.0 Hz), 3.61 (3H, s), 3.65 (1H, d, *J* = 12.0 Hz), 3.89 (3H, s), 3.85−3.95 (1H, m), 4.13 (2H, q, *J* = 7.2 Hz), 4.30−4.53 (4H, m), 6.16 (1H, s), 6.60 (1H, s), 6.97−7.36 (5H, m). Anal. ($C_{34}H_{45}N_2O_8Cl$) C, H, N.

Ethyl 1-[[(3*R*,5*S*)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]piperidine-4-butyrate (9l). Compound **9l** (1.0 g, 1.52 mmol, 73%) was prepared from **2** (1.0 g, 2.09 mmol) and ethyl piperidine-4-butyrate hydrochloride[14] (0.52 g, 2.21 mmol) in the same manner as described for the preparation of **9j**. A colorless amorphous powder. $[\alpha]^{22}_D$ −182° (*c* 0.152, MeOH). IR ν_{max} (KBr), cm^{-1}: 3600−3300 (br, OH), 1732, 1645 (C═O). ^1H NMR ($CDCl_3$): δ 0.63 (3H, s), 1.04 (3H, s), 0.88−1.80 (9H, m), 1.26 (3H, t, *J* = 7.4 Hz), 2.24−2.31 (2H, m), 2.46−2.57 (1H, m), 2.65−2.78 (1H, m), 2.90−3.03 (1H, m), 3.08−3.24 (2H, m), 3.39 (1H, d, *J* = 14.0 Hz), 3.61 (3H, s), 3.64 (1H, dd, *J* = 3.0, 11.4 Hz), 3.89 (3H, s), 3.85−3.97 (1H, m), 4.12 (2H, q, *J* = 7.4 Hz), 4.32−4.53 (4H, m), 6.16 (1H, s), 6.59 (1H, s), 6.96−7.36 (5H, m). Anal. ($C_{35}H_{47}N_2O_8Cl$) C, H, N.

1-[[(3*R*,5*S*)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]piperidine-4-acetic Acid (3j). To a solution of **9k** (0.45 g, 0.713 mmol) in EtOH (4 mL), 1 N NaOH (1 mL) was added. The mixture was stirred for 30 min at 60 °C. The reaction mixture was diluted with water (50 mL), acidified, and then extracted with AcOEt (50 mL × 3). The organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The solid residue was crystallized with Et_2O−hexane (1:1) to give **3k** (0.30 g, 0.497 mmol, 70%) as a colorless powder. Mp 135−140 °C (Et_2O−hexane). $[\alpha]^{22}_D$ −191° (*c* 0.179, MeOH). IR ν_{max} (KBr), cm^{-1}: 3600−2400 (br, COOH, OH), 1730, 1640 (C═O). ^1H NMR ($CDCl_3$): δ 0.63 (3H, s), 1.03 (3H, s), 1.70−1.85 (4H, m), 1.96−2.10 (1H, m), 2.24−2.33 (2H, m), 2.50−2.78 (2H, m), 3.01−3.22 (3H, m), 3.39 (1H, d, *J* = 15.4 Hz), 3.58−3.67 (1H, m), 3.61 (3H, s), 3.891 (3H, s), 3.92−3.97 (1H, m), 4.46−4.57

(3H, m), 6.149 (1H, s), 6.60 (1H, s), 6.96−7.40 (5H, m). Anal. ($C_{31}H_{39}N_2O_8Cl$) C, H, N.

***N*-[[(3*R*,5*S*)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]glycine (3a).** Compound **3a** (0.94 g, 1.76 mmol, 97%) was prepared from **9a** (1.0 g, 1.82 mmol) in the same manner as described for the preparation of **3j**. Colorless prisms. Mp 122−123 °C (AcOEt−hexane). $[\alpha]^{22}_D$ −191° (*c* 0.332, MeOH). IR ν_{max} (KBr), cm^{-1}: 3600−2400 (br, COOH, OH, NH), 1736, 1657 (C=O). ^1H NMR ($CDCl_3$): δ 0.65 (3H, s), 1.03 (3H, s), 2.72 (1H, dd, *J* = 5.2, 14.6 Hz), 2.97 (1H, dd, *J* = 7.8, 14.6 Hz), 3.18 (1H, d, *J* = 11.6 Hz), 3.39 (1H, d, *J* = 14.2 Hz), 3.61 (3H, s), 3.61 (1H, d, *J* = 11.6 Hz), 3.89 (3H, s), 4.03 (2H, t, *J* = 3.6 Hz), 4.38 (1H, dd, *J* = 5.2, 7.8 Hz), 4.45 (1H, d, *J* = 14.2 Hz), 6.16 (1H, s), 6.61 (1H, s), 6.64−6.74 (1H, br), 6.96−7.35 (5H, m). Anal. ($C_{26}H_{31}N_2O_8Cl$) C, H, N.

***N*-[[(3*R*,5*S*)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]-*N*-methylglycine (3b).** 10% Pd−C catalyst (100 mg) was added to a stirred solution of **9b** (0.95 g, 1.49 mmol) in AcOEt (20 mL) at room temperature. The reaction mixture was stirred under H_2 atmosphere for 30 min at room temperature. The catalyst was removed by filtration and the solvent was removed under reduced pressure to give **3b** (0.86 g, 1.57 mmol, quantitative) as a colorless amorphous powder. $[\alpha]^{22}_D$ −194° (*c* 0.201, MeOH). IR ν_{max} (KBr), cm^{-1}: 3600−2400 (br, COOH, OH), 1734, 1653 (C=O). ^1H NMR ($CDCl_3$): δ 0.63 (3H, s), 1.04 (3H, s), 2.63 (1/5 × 1H, dd, *J* = 4.0, 15.2 Hz), 2.80 (4/5 × 1H, dd, *J* = 4.4, 16.4 Hz), 2.95 (1/5 × 3H, s), 3.13 (4/5 × 3H, s), 3.17 (1H, d, *J* = 11.0 Hz), 3.25 (1H, dd, *J* = 9.2, 16.4 Hz), 3.40 (1H, d, *J* = 14.4 Hz), 3.61 (3H, s), 3.63 (1H, d, *J* = 11.0 Hz), 3.79 (1/5 × 3H, s), 3.89 (4/5 × 3H, s), 4.31−4.52 (4H, m), 6.13 (1/5 × 1H, s), 6.16 (4/5 × 1H, s), 6.61 (1H, s), 6.95−7.37 (5H, m). Anal. ($C_{27}H_{33}N_2O_8Cl\cdot 0.3H_2O$) C, H, N.

***N*-[[(3*R*,5*S*)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]-L-alanine (3c).** Compound **3c** (0.44 g, 0.801 mmol, 89%) was prepared from **9c** (0.52 g, 0.901 mmol) in the same manner as described for the preparation of **3j**. A colorless powder. Mp 133−135 °C (AcOEt−hexane). $[\alpha]^{22}_D$ −189° (*c* 0.226, MeOH). IR ν_{max} (KBr), cm^{-1}: 3600−2400 (br, COOH, OH, NH), 1732, 1651 (C=O). ^1H NMR ($CDCl_3$): δ 0.65 (3H, s), 1.04 (3H, s), 1.43 (3H, t, *J* = 7.4 Hz), 2.73 (1H, dd, *J* = 6.2, 14.6 Hz), 2.89 (1H, dd, *J* = 6.6, 14.6 Hz), 3.16 (1H, d, *J* = 12.0 Hz), 3.39 (1H, d, *J* = 14.2 Hz), 3.60 (1H, d, *J* = 12.0 Hz), 3.60 (3H, s), 3.88 (3H, s), 4.37−4.55 (3H, m), 6.16 (1H, s), 6.48 (1H, d, *J* = 6.6 Hz), 6.62 (1H, d, *J* = 1.6 Hz), 6.96−7.36 (5H, m). Anal. ($C_{27}H_{33}N_2O_8Cl$) C, H, N.

***N*-[[(3*R*,5*S*)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]-D-alanine (3d).** Compound **3d** (0.37 g, 0.674 mmol, 74%) was prepared from **9d** (0.51 g, 0.906 mmol) in the same manner as described for the preparation of **3j**. A colorless powder. Mp 130−132 °C (AcOEt−hexane). $[\alpha]^{22}_D$ −174° (*c* 0.358, MeOH). IR ν_{max} (KBr), cm^{-1}: 3600−2400 (br, COOH, OH, NH), 1732, 1658 (C=O). ^1H NMR ($CDCl_3$): δ 0.65 (3H, s), 1.04 (3H, s), 1.44 (3H, t, *J* = 7.4 Hz), 2.69 (1H, dd, *J* = 5.8, 14.6 Hz), 2.93 (1H, dd, *J* = 7.0, 14.6 Hz), 3.18 (1H, d, *J* = 12.2 Hz), 3.39 (1H, d, *J* = 14.2 Hz), 3.61 (1H, d, *J* = 12.2 Hz), 3.61 (3H, s), 3.89 (3H, s), 4.33−4.58 (3H, m), 6.16 (1H, s), 6.61 (1H, s), 6.66 (1H, d, *J* = 7.0 Hz), 6.96−7.35 (5H, m). Anal. ($C_{27}H_{33}N_2O_8Cl$) C, H, N.

***N*-[[(3*R*,5*S*)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]-D-leucine (3e).** Compound **3e** (1.2 g, 2.03 mmol, 94%) was prepared from **9e** (1.3 g, 2.15 mmol) in the same manner as described for the preparation of **3j**. A colorless amorphous powder. IR ν_{max} (KBr), cm^{-1}: 3600−2400 (br, COOH, OH, NH), 1736, 1657 (C=O). ^1H NMR ($CDCl_3$): δ 0.65 (3H, s), 0.93 (6H, d, *J* = 5.6 Hz), 1.03 (3H, s), 1.45−1.82 (3H, m), 2.69 (1H, dd, *J* = 5.4, 14.5 Hz), 2.95 (1H, dd, *J* = 7.4, 14.5 Hz), 3.18 (1H, d, *J* = 11.8 Hz), 3.40 (1H, d, *J* = 14.2 Hz), 3.61 (3H, s), 3.61 (3H, s), 3.61 (1H, d, *J* = 11.8 Hz), 4.07 (3H, s), 4.36 (1H, dd, *J* = 5.4, 7.2 Hz), 4.45 (1H, d, *J* = 14.2 Hz), 4.52−4.66 (1H, m), 6.16 (1H, s), 6.57−6.66 (2H, m). Anal. ($C_{30}H_{39}N_2O_8Cl$) C, H, N.

***N*-[[(3*R*,5*S*)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]-*β*-alanine (3f).** Compound **3f** (1.1 g, 2.00 mmol, 76%) was prepared from **9f** (1.49 g, 2.65 mmol) in the same manner as described for the preparation of **3j**. A colorless amorphous powder. $[\alpha]^{22}_D$ −232° (*c* 0.133, MeOH). IR ν_{max} (KBr), cm^{-1}: 3600−2200 (br, COOH, OH, NH), 1716, 1651 (C=O). ^1H NMR ($CDCl_3$): δ 0.64 (3H, s), 1.04 (3H, s), 2.53 (2H, t, *J* = 5.4 Hz), 2.65 (1H, dd, *J* = 5.2, 14.2 Hz), 2.84 (1H, dd, *J* = 7.4, 14.2 Hz), 3.16 (1H, t, *J* = 11.2 Hz), 3.43−3.56 (2H, m), 3.38 (1H, d, *J* = 14.2 Hz), 3.60 (3H, s), 3.60 (1H, d, *J* = 11.2 Hz), 3.89 (3H, s), 4.43 (1H, dd, *J* = 5.2, 7.4 Hz), 4.47 (1H, d, *J* = 14.2 Hz), 6.15 (1H, s), 6.60 (1H, d, *J* = 1.8 Hz), 6.82−6.92 (1H, br), 6.96−7.36 (5H, m). Anal. ($C_{27}H_{33}N_2O_8Cl$) C, H, N.

4-[[[(3*R*,5*S*)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]amino]butyric Acid (3g). Compound **3g** (1.1 g, 1.95 mmol, 76%) was prepared from **9g** (1.49 g, 2.58 mmol) in the same manner as described for the preparation of **3j**. Colorless prisms. Mp 111−113 °C (AcOEt−hexane). $[\alpha]^{22}_D$ −203° (*c* 0.106, MeOH). IR ν_{max}(KBr), cm^{-1}: 3600−2200 (br, COOH, OH, NH), 1716, 1651 (C=O). ^1H NMR ($CDCl_3$): δ 0.64 (3H, s), 1.04 (3H, s), 1.84 (2H, quintet, *J* = 6.8 Hz), 2.37 (2H, t, *J* = 6.8 Hz), 2.65 (1H, dd, *J* = 5.4, 14.2 Hz), 2.84 (1H, dd, *J* = 7.6, 14.2 Hz), 3.16 (1H, t, *J* = 10.8 Hz), 3.25−3.33 (2H, m), 3.39 (1H, d, *J* = 14.6 Hz), 3.60 (3H, s), 3.60 (1H, d, *J* = 10.8 Hz), 3.89 (3H, s), 4.37−4.48 (2H, m), 6.15 (1H, s), 6.22−6.30 (1H, br), 6.61 (1H, d, *J* = 1.4 Hz), 6.96−7.36 (5H, m). Anal. ($C_{28}H_{35}N_2O_8Cl\cdot 0.5H_2O$) C, H, N.

5-[[[(3*R*,5*S*)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]amino]pentanoic Acid (3h). Compound **3h** (2.1 g, 3.64 mmol, 94%) was prepared from **9h** (2.3 g, 3.89 mmol) in the same manner as described for the preparation of **3j**. A colorless amorphous powder. $[\alpha]^{22}_D$ −191° (*c* 0.237, MeOH). IR ν_{max}(KBr), cm^{-1}: 3600−2200 (br, COOH, OH, NH), 1714, 1651 (C=O). ^1H NMR ($CDCl_3$): δ 0.64 (3H, s), 1.04 (3H, s), 1.45−1.75 (4H, m), 2.36 (2H, t, *J* = 7.0 Hz), 2.63 (1H, dd, *J* = 5.6, 14.4 Hz), 2.85 (1H, dd, *J* = 7.6, 14.4 Hz), 3.16 (1H, t, *J* = 12.0 Hz), 3.23−3.28 (2H, m), 3.38 (1H, d, *J* = 14.4 Hz), 3.60 (3H, s), 3.60 (1H, dd, *J* = 12.0 Hz), 3.89 (3H, s), 4.40 (1H, dd, *J* = 5.6, 7.6 Hz), 4.45 (1H, d, *J* = 14.4 Hz), 6.02−6.14 (1H, br), 6.14 (1H, s), 6.60 (1H, s), 6.96−7.36 (5H, m). Anal. ($C_{29}H_{37}N_2O_8Cl\cdot H_2O$) C, H, N.

1-[[(3*R*,5*S*)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]piperidine-4-carboxylic Acid (3i). Compound **3i** (0.54 g, 0.917 mmol, 79%) was prepared from **9i** (0.7 g, 1.16 mmol) in the same manner as described for the preparation of **3j**. A colorless powder. Mp 162−165 °C (AcOEt−hexane). $[\alpha]^{22}_D$ −193° (*c* 0.378, MeOH). IR ν_{max} (KBr), cm^{-1}: 3600−2400 (br, OH, COOH), 1720, 1640 (C=O). ^1H NMR ($CDCl_3$): δ 0.63 (3H, s), 1.04 (3H, s), 1.60−1.90 (4H, m), 2.40−2.59 (1H, m), 2.60−2.83 (2H, m), 3.0−3.3 (2H, m), 3.15 (1H, d, *J* = 13.0 Hz), 3.39 (1H, d, *J* = 15.2 Hz), 3.61 (3H, s), 3.65 (1H, d, *J* = 13.0 Hz), 3.77−3.97 (1H, m), 3.89 (3H, s), 4.43−4.51 (3H, m), 6.16 (1H, s), 6.61 (1H, s), 6.96−7.42 (5H, m). Anal. ($C_{30}H_{37}N_2O_8Cl\cdot 0.3H_2O$) C, H, N.

1-[[(3*R*,5*S*)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]piperidine-4-propionic Acid (3k). Compound **3k** (0.60 g, 0.972 mmol, 90%) was prepared from **9k** (0.7 g, 1.08 mmol) in the same manner as described for the preparation of **3j**. A colorless powder. Mp 152−154 °C (AcOEt−hexane). $[\alpha]^{22}_D$ −186° (*c* 0.185, MeOH). IR ν_{max} (KBr), cm^{-1}: 3600−2400 (br, OH, COOH), 1732, 1651 (C=O). ^1H NMR ($CDCl_3$): δ 0.63 (3H, s), 1.04 (3H, s), 0.95−1.14 (2H, m), 1.54−1.78 (4H, m), 2.34−2.40 (2H, m), 2.48−2.56 (1H, m), 2.67−2.77 (1H, m), 2.89−3.08 (1H, m), 3.12−3.21 (2H, m), 3.39 (1H, d, *J* = 14.0 Hz), 3.61 (3H, s), 3.65 (1H, d, *J* = 12.0 Hz),

3.89 (3H, s), 3.85−3.97 (1H, m), 4.47−4.55 (3H, m), 6.15, 6.16 (total 1H, each s), 6.59 (1H, s), 6.97−7.39 (5H, m). Anal. ($C_{32}H_{41}N_2O_8Cl$) C, H, N.

1-[[(3*R*,5*S*)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]piperidine-4-butyric Acid (3l). Compound **3l** (0.50 g, 0.792 mmol, 75%) was prepared from **9l** (0.7 g, 1.06 mmol) in the same manner as described for the preparation of **3j**. A colorless powder. Mp 133−135 °C (AcOEt−hexane). $[\alpha]^{22}_D$ −187° (*c* 0.108, MeOH). IR ν_{max} (KBr), cm^{-1}: 3600−2400 (br, OH, COOH), 1730, 1651 (C═O). ^1H NMR ($CDCl_3$): δ 0.63 (3H, s), 1.04 (3H, s), 0.95−1.80 (9H, m), 2.29−2.36 (2H, m), 2.46−2.58 (1H, m), 2.65−2.78 (1H, m), 2.91−3.03 (1H, m), 3.11−3.23 (2H, m), 3.39 (1H, d, *J* = 14.0 Hz), 3.61 (3H, s), 3.64 (1H, d, *J* = 11.4 Hz), 3.89 (3H, s), 3.85−3.97 (1H, m), 4.45−4.52 (3H, m), 6.15 (1H, s), 6.59 (1H, s), 6.96−7.36 (5H, m). Anal. ($C_{33}H_{43}N_2O_8Cl$) C, H, N.

1-[[(3*R*,5*S*)-1-(3-Acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]piperidine-4-acetic Acid (4a). A mixture of **3j** (7.2 g, 11.9 mmol), 4-(dimethylamino)pyridine (DMAP) (1.0 mg, 8.19 μmol), acetic anhydride (1.4 g, 14.0 mmol), and pyridine (70 mL) was stiired for 1 h at room temperature. The mixture was concentrated under reduced pressure, and the residue was dissolved in AcOEt (100 mL). The solution was washed with 1 N HCl, saturated $NaHCO_3$, and brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was recrystallized from EtOH−H_2O (1:1) to give **4a** (5.5 g, 9.15 mmol, 77%) as a colorless powder. Mp 194−196 °C. $[\alpha]^{20}_D$ −199° (*c* 1.00, MeOH). IR ν_{max}(KBr), cm^{-1}: 3600−2400 (br, COOH), 1732, 1682 (C═O). ^1H NMR ($CDCl_3$): δ 0.94 (3H, s), 1.02 (3H, s), 1.09−1.39 (2H, m), 1.70−1.85 (2H, m), 1.90−2.10 (1H, m), 2.02 (3H, s), 2.22−2.31 (2H, m), 2.50−2.77 (2H, m), 2.94−3.17 (2H, m), 3.55 (1H, d, *J* = 14.0 Hz), 3.61 (3H, s), 3.72 (1H, d, *J* = 11.0 Hz), 3.85 (1H, d, *J* = 11.0 Hz), 3.89 (3H, s), 3.90−3.98 (1H, m), 4.44−4.60 (3H, m), 6.25 (1/2 × 1H, s), 6.26 (1/2 × 1H, s), 6.62 (1H, s), 6.95−7.33 (5H, m). Anal. ($C_{33}H_{41}N_2O_9Cl$) C, H, N.

Benzyl 1-[[(3*R*,5*S*)-7-Chloro-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-5-(2,3-dimethoxyphenyl)-4,1-benzoxazepin-3-yl]acetyl]piperidine-4-acetate (10). A mixture of **3j** (0.3 g, 0.497 mmol), K_2CO_3 (0.20 g, 1.45 mmol), and benzyl bromide (83 mg, 0.488 mmol) in DMF (3 mL) was stirred for 30 min at 60 °C. The mixture was diluted with AcOEt (50 mL), washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, and brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was recrystallized from AcOEt−hexane (1:3) to give **10** (0.29 g, 0.418 mmol, 84%) as colorless prisms. Mp 115−117 °C. IR ν_{max}(KBr), cm^{-1}: 3600−3200 (br, OH), 1732, 1639 (C═O). ^1H NMR ($CDCl_3$): δ 0.63 (3H, s), 1.04 (3H, s), 1.15−1.30 (2H, m), 1.65−1.80 (2H, m), 1.95−2.10 (1H, m), 2.25−2.34 (2H, m), 2.50−2.78 (2H, m), 3.00−3.23 (4H, m), 3.39 (1H, d, *J* = 13.8 Hz), 3.61 (3H, s), 3.62−3.67 (1H, m), 3.89 (3H, s), 3.85−4.00 (1H, m), 4.30−4.53 (3H, m), 5.11, 5.12 (total 2H, each s), 6.16 (1H, s), 6.60 (1H, s), 6.96−7.39 (10H, m). Anal. ($C_{38}H_{45}N_2O_8Cl$) C, H, N.

Benzyl 1-[[(3*R*,5*S*)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-[2,2-dimethyl-3-(propionyloxy)propyl]-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]piperidine-4-acetate (11a). To a solution of **10** (0.5 g, 0.721 mmol), NEt_3 (0.14 g, 1.42 mmol), and DMAP (9 mg, 0.0709 mmol) in THF (5 mL) was added propionyl chloride (98 mg, 1.06 mmol) at 0 °C. The mixture was stirred for 1 h at room temperature, diluted with AcOEt (50 mL), washed with 5% $KHSO_4$, saturated $NaHCO_3$, and brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel [eluent: hexane−AcOEt (3:2)] to give **11a** (0.46 g, 0.614 mmol, 85%) as a colorless amorphous powder. $[\alpha]^{22}_D$ −167 (*c* 0.221, MeOH). IR ν_{max}(KBr), cm^{-1}: 1736, 1682, 1639 (C═O). ^1H NMR ($CDCl_3$): δ 0.94 (3H, s), 1.02 (3H, s), 1.12 (3H, t, *J* = 7.8 Hz), 0.88−1.26 (2H, m), 1.65−1.80 (2H, m), 1.90−2.10 (1H, m), 2.24−2.36 (4H, m), 2.48−2.61 (1H, m), 2.71 (1H, dd, *J* = 4.0, 15.0 Hz), 2.97−3.17 (2H, m), 3.56 (1H, d, *J* = 14.0 Hz), 3.61 (3H, s), 3.71 (1H, d, *J* = 11.4 Hz), 3.86 (1H, d, *J* = 11.4 Hz), 3.88 (3H, s), 3.88−4.00 (1H, m), 4.45−4.51 (2H, m), 4.56 (1H, d, *J* = 14.0 Hz), 5.11 (2H, s), 6.24 (1H, s), 6.62 (1H, s), 6.98−7.35 (10H, m). Anal. ($C_{41}H_{49}N_2O_9Cl$) C, H, N.

Benzyl 1-[[(3*R*,5*S*)-1-[3-(Butyryloxy)-2,2-dimethylpropyl]-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]piperidine-4-acetate (11b). Compound **11b** (0.12 g, 0.157 mmol, 84%) was prepared from **10** (0.13 g, 0.188 mmol) and butyryl chloride (48 mg, 0.442 mmol) in the same manner as described for the preparation of **11a**. A colorless amorphous powder. $[\alpha]^{22}_D$ −165° (*c* 0.185, MeOH). IR ν_{max}(KBr), cm^{-1}: 1734, 1682, 1639 (C═O). ^1H NMR ($CDCl_3$): δ 0.93 (3H, t, *J* = 7.4 Hz), 0.97 (3H, s), 1.02 (3H, s), 1.10−1.30 (2H, m), 1.55−1.72 (4H, m), 1.95−2.10 (1H, m), 2.23−2.32 (4H, m), 2.48−2.61 (1H, m), 2.72 (1H, dd, *J* = 4.4, 16.0 Hz), 2.92−3.05 (1H, m), 3.11 (1H, dd, *J* = 8.8, 16.0 Hz), 3.56 (1H, d, *J* = 13.8 Hz), 3.61 (3H, s), 3.70 (1H, d, *J* = 11.4 Hz), 3.87 (1H, d, *J* = 11.4 Hz), 3.89 (3H, s), 3.92−4.00 (1H, m), 4.45−4.60 (3H, m), 5.11 (2H, s), 6.24 (1H, s), 6.62 (1H, s), 6.95−7.35 (10H, m). Anal. ($C_{42}H_{51}N_2O_9Cl$) C, H, N.

Benzyl 1-[[(3*R*,5*S*)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-[2,2-dimethyl-3-(isobutyryloxy)propyl]-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]piperidine-4-acetate (11c). Compound **11c** (0.40 g, 0.524 mmol, 73%) was prepared from **10** (0.5 g, 0.721 mmol) and isobutyryl chloride (113 mg, 1.06 mmol) in the same manner as described for the preparation of **11a**. A colorless amorphous powder. $[\alpha]^{22}_D$ −164° (*c* 0.150, MeOH). IR ν_{max}(KBr), cm^{-1}: 1732, 1682, 1639 (C═O). ^1H NMR ($CDCl_3$): δ 0.94 (3H, s), 1.03 (3H, s), 1.15 (3H, d, *J* = 7.0 Hz), 1.17 (3H, d, *J* = 7.0 Hz), 0.88−1.22 (2H, m), 1.55−1.80 (2H, m), 1.90−2.10 (1H, m), 2.24−2.32 (2H, m), 2.47−2.77 (3H, m), 2.98−3.18 (2H, m), 3.57 (1H, d, *J* = 14.0 Hz), 3.61 (3H, s), 3.69 (1H, d, *J* = 11.2 Hz), 3.87 (1H, d, *J* = 11.2 Hz), 3.88 (3H, s), 3.88−3.97 (1H, m), 4.45−4.51 (2H, m), 4.57 (1H, d, *J* = 14.0 Hz), 5.11, 5.12 (total 2H, each s), 6.23 (1H, s), 6.62 (1H, s), 6.96−7.35 (10H, m). Anal. ($C_{42}H_{51}N_2O_9Cl\cdot0.5H_2O$) C, H, N.

Benzyl 1-[[(3*R*,5*S*)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-[2,2-dimethyl-3-(pivaloyloxymethyloxy)propyl]-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]piperidine-4-acetate (11d). To a solution of **10** (0.5 g, 0.721 mmol) and chloromethyl pivalate (0.16 g, 1.06 mmol) in DMF (5 mL) was added NaH (22 mg, 0.922 mmol) at 0 °C. The mixture was stirred overnight at room temperature, diluted with AcOEt, washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, and brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was subjected to column chromatography [eluent: hexane−AcOEt (1:1)] to give **11d** (0.35 g, 0.434 mmol, 60%) as a colorless amorphous powder. $[\alpha]^{22}_D$ −138° (*c* 0.293, MeOH). IR ν_{max}(KBr), cm^{-1}: 1738, 1682, 1643 (C═O). ^1H NMR ($CDCl_3$): δ 0.93 (3H, s), 1.00 (3H, s), 1.17 (9H, s), 1.06−1.26 (2H, m), 1.65−1.80 (2H, m), 1.90−2.10 (1H, m), 2.24−2.32 (2H, m), 2.47−2.60 (1H, m), 2.72 (1H, dd, *J* = 4.4, 15.4 Hz), 2.98−3.35 (4H, m), 3.64 (3H, s), 3.64 (1H, d, *J* = 13.4 Hz), 3.89 (3H, s), 3.89−4.00 (1H, m), 4.41−4.71 (3H, m), 4.69 (1H, d, *J* = 6.2 Hz), 5.11 (2H, s), 5.19 (1H, d, *J* = 6.2 Hz), 6.23 (1H, s), 6.59 (1H, s), 6.95−7.40 (10H, m). Anal. ($C_{45}H_{55}N_2O_{10}Cl\cdot0.5H_2O$) C, H, N.

1-[[(3*R*,5*S*)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-[2,2-dimethyl-3-(propionyloxy)propyl]-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]piperidine-4-acetic Acid (4b). 10% Pd−C catalyst (50 mg) was added to a solution of **11a** (0.36 g, 0.480 mmol) in AcOEt (10 mL). The reaction mixture was stirred under H_2 atmosphere for 30 min at room temperature. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was recrystallized from AcOEt−hexane (1:1) to give **4b** (0.27 g, 0.410 mmol, 85%) as a colorless powder. Mp 191−192 °C. $[\alpha]^{22}_D$ −191° (*c* 0.143, MeOH). IR ν_{max}(KBr), cm^{-1}: 3600−2400 (br, COOH), 1732, 1680, 1639 (C═O). ^1H NMR ($CDCl_3$): δ 0.95 (3H, s), 1.02 (3H, s), 1.12 (3H, t, *J* = 7.6 Hz), 0.95−1.26 (2H, m), 1.70−1.85 (2H, m), 1.90−2.10 (1H, m), 2.23−2.37 (4H, m), 2.50−2.77 (2H, m), 2.95−3.20 (2H, m), 3.56 (1H, d, *J* = 13.6

Hz), 3.61 (3H, s), 3.71 (1H, d, J = 11.0 Hz), 3.86 (1H, d, J = 11.0 Hz), 3.89 (3H, s), 3.89−3.99 (1H, m), 4.47−4.53 (2H, m), 4.56 (1H, d, J = 13.6 Hz), 6.24 (1H, s), 6.62 (1H, s), 6.95−7.33 (5H, m). Anal. ($C_{34}H_{43}N_2O_9Cl$) C, H, N.

1-[[(3*R*,5*S*)-1-[3-(Butyryloxy)-2,2-dimethylpropyl]-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]piperidine-4-acetic Acid (4c). Compound **4c** (89 mg, 0.132 mmol, 84%) was prepared from **11b** (0.12 g, 0.157 mmol) in the same manner as described for the preparation of **4b**. A colorless amorphous powder. $[\alpha]^{22}_D$ −182° (*c* 0.171, MeOH). IR ν_{max}(KBr), cm^{-1}: 3600−2400 (br, COOH), 1732, 1680, 1635 (C=O). ^1H NMR ($CDCl_3$): δ 0.89−1.02 (9H, s), 1.10−1.40 (2H, m), 1.57−1.85 (4H, m), 1.90−2.10 (1H, m), 2.22−2.30 (4H, m), 2.50−2.78 (2H, m), 3.00−3.20 (2H, m), 3.57 (1H, d, J = 14.0 Hz), 3.61 (3H, s), 3.70 (1H, d, J = 11.0 Hz), 3.80−3.98 (2H, m), 3.89 (3H, s), 4.45−4.60 (3H, m), 6.24 (1H, s), 6.62 (1H, s), 6.95−7.33 (5H, m). Anal. ($C_{35}H_{45}N_2O_9Cl$) C, H, N.

1-[[(3*R*,5*S*)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-[2,2-dimethyl-3-(isobutyryloxy)propyl]-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]piperidine-4-acetic Acid (4d). Compound **4d** (0.21 g, 0.312 mmol, 79%) was prepared from **11c** (0.3 g, 0.393 mmol) in the same manner as described for the preparation of **4b**. A colorless powder. Mp 200−202 °C (AcOEt−hexane). $[\alpha]^{22}_D$ −181° (*c* 0.120, MeOH). IR ν_{max}(KBr), cm^{-1}: 3600−2400 (br, COOH), 1732, 1680, 1635 (C=O). ^1H NMR ($CDCl_3$): δ 0.95 (3H, s), 1.03 (3H, s), 1.15 (3H, d, J = 7.0 Hz), 1.17 (3H, d, J = 7.0 Hz), 0.90−1.35 (2H, m), 1.70−1.85 (2H, m), 1.90−2.10 (1H, m), 2.22−2.31 (2H, m), 2.47−2.77 (3H, m), 2.95−3.20 (2H, m), 3.57 (1H, d, J = 14.0 Hz), 3.61 (3H, s), 3.69 (1H, d, J = 11.0 Hz), 3.87 (1H, d, J = 11.0 Hz), 3.89 (3H, s), 3.89−3.99 (1H, m), 4.48−4.53 (2H, m), 4.57 (1H, d, J = 14.0 Hz), 6.23 (1H, s), 6.62 (1H, s), 6.99−7.33 (5H, m). Anal. ($C_{35}H_{45}N_2O_9Cl$) C, H, N.

1-[[(3*R*,5*S*)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-[2,2-dimethyl-3-(pivaloyloxymethyloxy)propyl]-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]piperidine-4-acetic Acid (4e). 10% Pd−C catalyst (50 mg) was added to a solution of **11d** (0.25 g, 0.310 mmol) in AcOEt (10 mL). The reaction mixture was stirred under H_2 atmosphere for 30 min at room temperature. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to give **4e** (0.19 g, 0.265 mmol, 85%) as a colorless amorphous powder. $[\alpha]^{22}_D$ −147 (*c* 0.447, MeOH). IR ν_{max}(KBr), cm^{-1}: 3600−2400 (br, COOH), 1732, 1680, 1641 (C=O). ^1H NMR ($CDCl_3$): δ 0.94 (3H, s), 1.00 (3H, s), 1.17 (9H, s), 1.10−1.60 (2H, m), 1.70−1.90 (2H, m), 1.90−2.10 (1H, m), 2.23−2.31 (2H, m), 2.55−2.80 (2H, m), 3.00−3.35 (4H, m), 3.64 (3H, s), 3.64 (1H, d, J = 11.2 Hz), 3.90 (3H, s), 3.90−3.99 (1H, m), 4.33−4.59 (3H, m), 4.70 (1H, d, J = 6.2 Hz), 5.19 (1H, d, J = 6.2 Hz), 6.23 (1H, s), 6.59 (1H, s), 6.97−7.35 (5H, m). Anal. ($C_{38}H_{49}N_2O_{10}Cl\cdot 0.5H_2O$) C, H, N.

Animals and Materials. Animals were purchased from Clea, Japan, Inc. unless otherwise mentioned. Male Wistar rats were allowed access to standard rodent chow (CE-2 in pellet form, Clea Japan). *RS*-[2-^{14}C]Mevalonolactone and [1-^{3}H]-FPP were purchased from New England Nuclear. [2-^{14}C]-Mevalonic acid was synthesized from [2-^{14}C]mevalonolactone by saponification with potassium hydroxide. [2-^{14}C]Sodium acetate was purchased from Amersham. Farnesyl pyrophosphate was synthesized by the method described by V. J. Davisson and co-workers[15] (Nemoto & Co.). HepG2 cells were supplied by ATCC. Fetal bovine serum (FBS) and Dulbecco's modified Eagle's medium (DMEM) were purchased from GIBCO. Human lipoprotein deficient serum (human LPDS) was purchased from Sigma, and all other reagents were purchased from Wako Pure Chemical Industries.

Preparation of Human Squalene Synthase. HepG2 cells (about 1 × 10^9 cells) obtained by incubation (37 °C in the presence of 5% CO_2) in a DMEM contain 10% FBS. Penicillin G (100 units/mL) and streptomycin (10 μg/mL) were suspended in 10 mL of ice-cooled buffer solution [100 mM potassium phosphate buffer (pH 7.4), 30 mM nicotinamide, and 2.5 mM $MgCl_2$]. The cells were crashed by means of ultrasonication (for 30 s, twice). From the sonicate thus obtained, the microsome fraction was obtained by the same procedure as in the preparation of rat-derived enzyme, which was suspended in an ice-cooled 100 mM potassium phosphate buffer (pH 7.4) (about 4 mg/mL protein concentration). This suspension was used as the enzyme preparation.

Assay of Squalene Synthase Inhibitory Activity. Squalene synthase activity was monitored by the formation of [^{3}H]squalene from [1-^{3}H]FPP. Fifty microliters of assay mixture included 5 μM [1-^{3}H]FPP (25 μCi/mol), 1 mM NADPH, 5 mM $MgCl_2$, 6 mM glutathione, 100 mM buffer solution of potassium phosphate (pH 7.4), the test compound dissolved in DMSO (a final concentration of DMSO was 2%), and enzyme solution prepared from rat or HepG2 cells (protein content of 0.8 μg). The assay ran for 45 min at 37 °C and was stopped by adding 150 μL of $CHCl_3$−MeOH (1:2) containing 0.2% cold squalene as carrier. An aqueous solution of 3 N NaOH (50 μM) and $CHCl_3$ (50 μM) was added to the mixture. The chloroform layer containing the reaction mixture having squalene as the principal component and 3 mL of toluene-based liquid scintillator were mixed, and the mixture's radioactivity was determined by means of a liquid scintillation counter. The squalene synthase inhibitory activity was expressed in terms of the concentration of the test compound inhibiting by 50% the radioactivity taken into the chloroform layer (IC_{50}, molar concentration (M)).

Cholesterogenesis in the Liver in Wistar Rats. Six-week-old male Wistar rats were orally administered test compounds (0.5%)−methylcellulose emulsion and were intravenously injected with [^{14}C]acetate (50 μCi/kg) 1 h after administration. Animals were killed 1 h after the injection. The livers were removed, saponified, extracted with petroleum ether, and then dried under nitrogen blowing. The residue was dissolved in the ethanol−acetone (1:1) (3 mL). The 0.5% solution of digitonin in 50% ethanol (2 mL) was added to the solution. After the mixture stood for 4 h at room temperature, the cholesterol fraction was obtained as the digitonin precipitate. The radioactivity taken into the digitonin precipitate was measured.

Acknowledgment. The authors thank Dr. Teruaki Okuda for the pharmacokinetic analysis.

Supporting Information Available: Graphs from Lineweaver−Burk and Dixon analyses of squalene synthase inhibition by compounds **3j** and **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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JM020234O