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Stereoselective Synthesis of J-104,118 and J-104,123, Novel, Potent Inhibitors of Squalene Synthase

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Abstract: A novel class of squalene synthase inhibitors (J-104,118 and J-104,123) were synthesized efficiently. An amine intermediate **1** was synthesized using two distinct methods. First, the racemic amine **1** was synthesized diastereoselectively using a key reaction consisting of the stereo-controlled reduction of the ketone **7** by L-Selectride®. Second, the optically active amine **1** was synthesized efficiently and enantioselectively using Sharpless dihydroxylation as a key reaction. A stereo-controlled method for synthesizing J-104,123 was developed starting from a commercially available methyl (*R*)-3-hydroxybutyrate.

Introduction

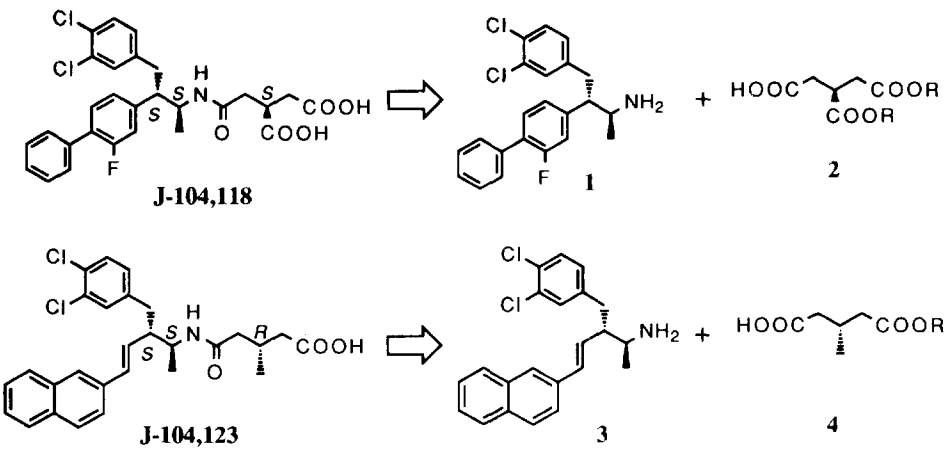
Elevated serum cholesterol is considered a major risk factor for atherosclerosis. Inhibitors of the enzyme HMG-CoA reductase, a major regulatory enzyme in the cholesterol biosynthetic pathway, are widely used because they effectively lower serum cholesterol in humans. A recent clinical study (the Scandinavian Simvastatin Survival Study) showed that long-term treatment with simvastatin improved survival rates in patients with coronary artery disease.[1] The enzyme squalene synthase (SQS) is another key enzyme in the cholesterol biosynthetic pathway and catalyzes the reductive dimerization of two molecules of farnesyl pyrophosphate to form squalene. Inhibition of this step to cholesterol should leave unhindered biosynthetic pathways to ubiquinone, dolicol, and isopentenyl t-RNA. Therefore, inhibitors of SQS would be expected to be ideal cholesterol-lowering agents.

We have studied novel, potent inhibitors of squalene synthase (J-104,118 and J-104,123, Scheme I),[2,3,4] which structures are different from those of known SQS inhibitors.[5] J-104,118 and J-104,123 have a hydrophobic arylalkyl group on the left side and a hydrophilic carboxylic acid moiety on the right side, which are connected with an amide linkage. These inhibitors have three asymmetric carbons. Among the eight possible stereoisomers, the isomer with the 3*S*, 7*S*, 8*S* (J-104,118) / 3*R*, 7*S*, 8*S* (J-104,123) configurations had the most potent inhibitory activity.[2,4] Here, we report the details of the study of the synthesis of J-104,118 and J-104,123.

Results and Discussion

Retrosynthetic analysis indicated that both J-104,118 and J-104,123 could be synthesized by the amide formation of an optically active hydrophobic amine **1** or **3** with a suitably protected carboxylic acid **2** or **4**, followed by deprotection (Scheme I).

Scheme I

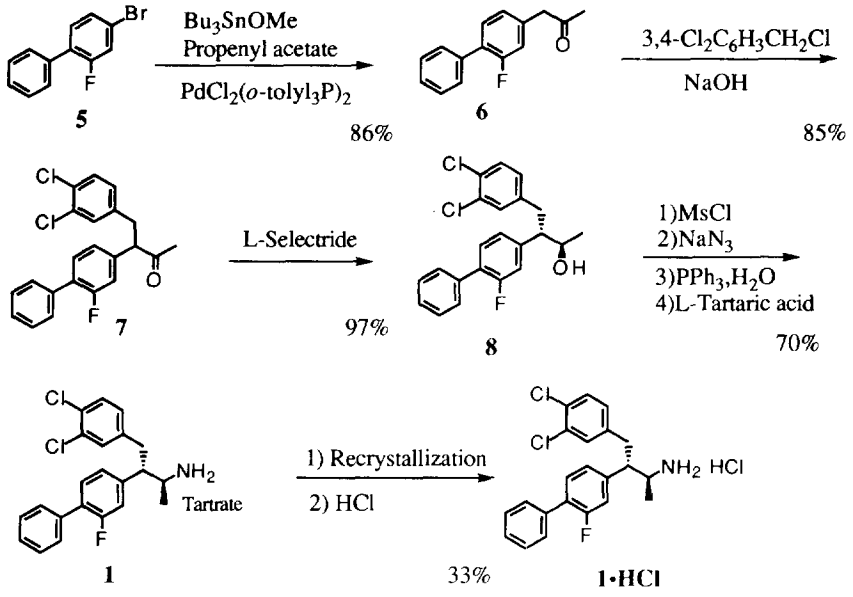


Preparation of the amine intermediate 1 (Route A)

A key issue for the synthesis of the amine intermediate **1** was to control the stereochemistry of the two neighboring chiral carbons (2*S*, 3*S*).

First, we developed a diastereo-controlled synthetic method for this molecule as outlined in Scheme II. (2-Fluoro-4-biphenylyl)acetone **6** was synthesized according to the method reported by Kosugi *et al.*[6] An alkylation of **6** with 3,4-dichlorobenzyl chloride in the presence of sodium hydroxide gave an 85% yield of racemic ketone **7**. Schultz *et al.* reported the synthesis of similar racemic amines using various procedures, such as (1) the Leuckart reaction on an appropriate ketone, (2) catalytic hydrogenation of a corresponding ketoxime, and (3) catalytic hydrogenation of a corresponding ketimine. In each case, the produced amine was a mixture of the *threo* and *erythro* isomers.[7] To control the stereochemistry, we tried to convert the ketone **7** to an amine through the alcohol intermediate **8**. It is well-recognized that the alcohol having (2*R**,3*S**) stereochemistry could be synthesized by the diastereoselective reduction with L-Selectride®.[8] Thus, the reduction of **7** with L-Selectride® gave an excellent yield of Cram isomer **8** with complete diastereoselectivity. Next, the hydroxy group of **8** was converted to methanesulfonate, which was subsequently treated with sodium azide in DMF at 120°C to give an azide derivative. The rduction of the azide function with triphenylphosphine in the presence of water, followed by the treatment with L-tartaric acid gave the desired amine **1** tartrate as a crystalline powder. Recrystallizing the tartrate twice from ethanol gave an optically active compound in 33% yield. HPLC analysis of the MTP amide showed that the optical purity of the amine **1** was higher than 99% ee. Most of the analogues of J-104,118 were synthesized using this method.

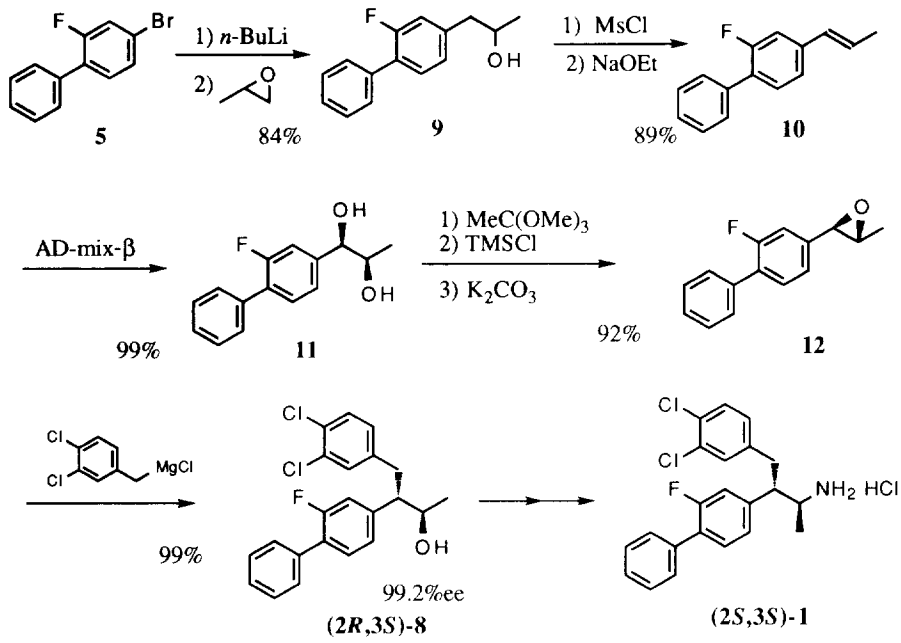
Scheme II



Preparation of optically-active amine 1 using Sharpless dihydroxylation (Route B)

Next, we developed an enantioselective method for synthesizing the amine **1** (Scheme III). The trans olefin **10** was efficiently prepared from commercially available 4-bromo-2-fluorobiphenyl **5**. Thus, **5** was treated with *n*-butyllithium in ether followed by propylene oxide to produce the hydroxy derivative **9** in 84% yield. This compound was converted to its methanesulfonate in the usual manner and treated with sodium ethoxide in refluxing ethanol, giving trans olefin **10** in 89% yield. This trans olefin was converted to the chiral diol **11** using Sharpless asymmetric dihydroxylation.[9] Vigorous stirring of **10** with AD-mix ß at 0°C in a mixture of *t*-BuOH and water in the presence of methanesulfonamide for 24 hours gave an excellent yield of **11**. **11** was converted to the epoxide **12** in a one-pot manner according to the literature[10] in 92% yield. The optical purity was 99.2% based on HPLC analysis using chiralcel® OD. The Grignard reagent prepared from 3,4-dichlorobenzylchloride and magnesium in ether reacted with **12** at 0°C to give the desired alcohol **8** having 2*R*, 3*S* stereochemistry in 99% yield. This compound was converted to the optically active **1** by the same procedure described in Scheme II. The optical purity of **1** was determined to be 99.2% ee based on HPLC analysis of the MTP amide. The overall yield was 49.8% in 9 steps starting from **5**.

Scheme III

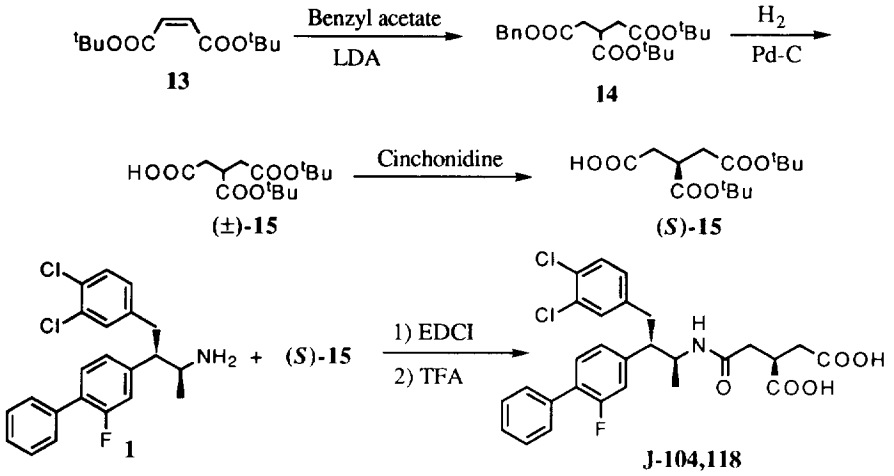


Synthesis of carboxylic acid 15 and J-104,118

At first, we used an acid chloride derived from tricarballylic anhydride as a building block of the carboxylic acid part. However, reaction of **22** with **1** in the presense of triethyl amine, followed by hydrolysis with aqueous sodium hydroxide solution gave a mixture of the desired compound **23** and its isomer **24**.[11] On the otherhand, an alkaline hydrolysis of the dimethyl ester derivative of J-104,118 also produced an isomeric mixture of J-104,118 and its isomer **24**.[11] The isomer **24** was thought to be produced via cyclic imide intermediate **25** formed under the alkaline condition. These data suggested that the deprotection should be operated under neutral or acidic conditions to avoid the production of the isomer. We chose the *t*-butyl ester as a suitable protecting group of the carboxylic functions. Unsymmetrical di-*t*-butyl tricarballylate was successfully synthesized as outlined in Scheme IV. Yamaguchi *et al.* reported a simple method for the synthesis of glutarate using the Michael reaction of the ester enolates to α,β-unsaturated esters.[12] We applied this method. Thus, the lithium enolate generated from benzyl acetate was reacted with di-*t*-butyl maleate (**13**) to produce the desired compound **14** in 90% yield. Hydrogenolysis gave racemic di-t-butyl tricarballylate (**15**). The optical resolution of this racemic acid was carried out by recrystallization of the cinchonidine salt of **15** from carbon tetrachloride. The optical purity was determined to be 98% ee based on HPLC analysis of its *N*-(α-methylbenzyl) amide derivative.

Finally, the coupling reaction of amine **1** with acid **15** in the presence of EDCI gave the amide derivative in 98% yield. Deprotection was performed smoothly by mixing the *t*-butyl esters with trifluoroacetic acid in dichloromethane at room temperature for 18 hours. J-104,118 was obtained in fine plates by recrystallization from dichloromethane and hexane. Absolute configuration of J-104,118 was determined to be 3*S*, 7*S* and 8*S* by X-ray analysis.[2]

Scheme IV

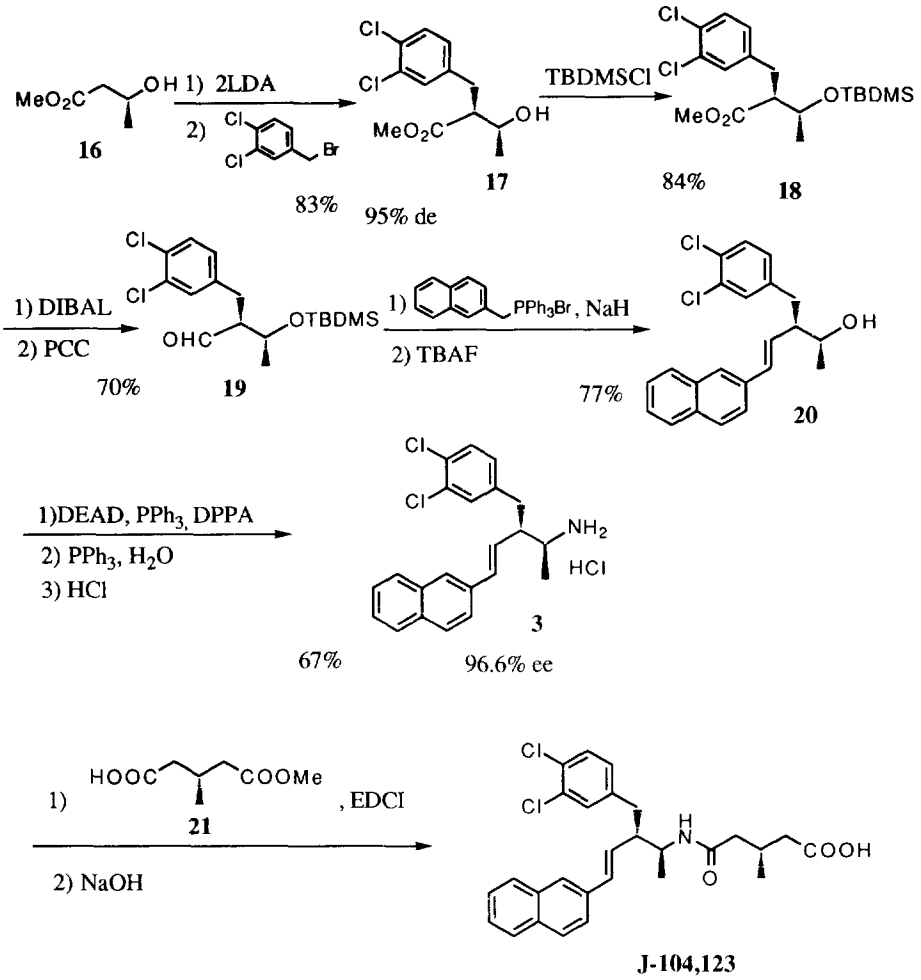


Synthesis of J-104,123

Optically active amine **3** was synthesized starting from commercially available methyl (*R*)-3-hydroxybutyrate **16** as described in Scheme V.[13] We employed the method reported by Frater[14] to construct the neighboring chiral carbons. Thus, the dianion generated from **16** by the treatment with 2 equivalents of LDA was alkylated stereoselectively to afford methyl (2*S*,3*R*)-2-(3,4-dichlorobenzyl)-3-hydroxybutyrate **17** in 83% yield. The hydroxy group was protected with TBDMS. Then, the ester moiety was converted to aldehyde by reduction with DIBAL, followed by oxidation with PCC. A subsequent Wittig reaction followed by deprotection gave a trans olefin derivative **20**. The hydroxy group of **20** was converted to an azide derivative under Mitsunobu conditions. Finally, reducing the azide by triphenylphosphine gave the desired amine **3**. The optical purity was determined to be 96.6% ee based on HPLC analysis of the MTP amide derivative.

The optically active methyl (*R*)-3-methylglutarate **21** was synthesized according to the reported procedure using pig liver esterase.[15] J-104,123 was easily obtained using the coupling reaction of the amine **3** and carboxylic acid **21** in the presence of EDCI followed by alkaline hydrolysis. In this case, no cyclic-imide was formed during the alkaline hydrolysis.

Scheme V



Conclusions

We have developed stereoselective synthetic method of J-104,118 by two distinct strategies. First, racemic amine **1** was synthesized diastereoselectively using stereo-controlled reduction of the ketone **7** with L-Selectride as a key reaction. Second, optically active amine **1** was synthesized efficiently and enantioselectively using Sharpless dihydroxylation as a key reaction. We also developed a stereo-controlled synthetic method of J-104,123 from commercially available methyl (*R*)-3-hydroxybutyrate. These synthetic methods can be used to prepare large amounts of J-104,118 and J-104,123.

Experimental Section

General. IR spectra were measured on Horiba FT-200 spectrometer. ^{1}H NMR spectra were measured on Gemini-300 or Jeol JNM-EX 400 spectrometers. High-resolution mass spectra (HRMS) were recorded on a Jeol JMS-SX 102A instrument. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. Melting points were measured with a Yanaco hot-stage apparatus. Analytical high pressure liquid chromatography (HPLC) was performed on a Hitachi D-6100 instrument equipped with a Senshu Pak column (Silica-1201-N, 4.6 ϕ X 200 mm). Reactions were conducted in a nitrogen atmosphere, if necessary. For thin-layer chromatography (TLC) analysis, Merck precoated TLC plates(silica gel 60 GF_{254}, 0.25 mm) were used. The products were purified by column chromatography on silica gel (Wakogel C-100 and C-200).

4–(3,4-Dichlorophenyl)-3-(2-fluoro-4-biphenylyl)butan-2-one (7). 2–Fluoro-4-biphenylylacetone (**6**) was prepared according to the procedure reported by Kosugi *et al.*[6] A stirred mixture of 2-fluoro-4-biphenylylacetone (**6**) (45.1 g, 198 mmol) and 3,4-dichlorobenzyl chloride (50.3 g, 257 mmol) was warmed to 40 °C. Powdered NaOH (15.8 g, 395 mmol) was added to this homogenous solution. The mixture was stirred for 6 h at 100°C, then allowed to cool to room temperature. The resulting mixture was poured into water and extracted with AcOEt. The organic phase was washed with 1 N HCl and brine, dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (hexane : AcOEt = 50 : 1, then 20 : 1) to give **7** (65.0 g, 168 mmol, 85%) as colorless oil. IR (film) 1712, 1483, 1417, 1130, 768, 698. ^{1}H NMR ($CDCl_3$) δ = 2.11 (s, 3H), 2.88 (dd, J = 13.9, 7.6 Hz, 1H), 3.39 (dd, J = 13.9, 7.6 Hz, 1H), 3.91 (t, J = 7.6 Hz, 1H), 6.91 (dd, J = 7.8, 1.8 Hz, 1H), 6.97-7.50 (m, 2H), 7.20 (d, J = 1.8 Hz, 1H), 7.30 (d, J = 7.8 Hz, 1H), 7.52-7.58 (m, 2H), 7.35-7.50 (m, 4H). HRMS Calcd. for $C_{22}H_{17}Cl_2FO$ 386.0640, Found 386.0652.

(2*R,3*S**)-4-(3,4-Dichlorophenyl)-3-(2-fluoro-4-biphenylyl)butan-2-ol (8).**

L-Selectride® (1 M solution in THF, 61.4 ml) was added to a solution of ketone **7** (21.6 g, 55.8 mmol) in dry THF (210 ml) under N_2 at -78 °C. The mixture was stirred at -78°C for 1.5 h and warmed to -40 °C. 3 N NaOH (61.4 ml, 184 mmol) and 30% H_2O_2 (31 ml) was added slowly and stirred vigorously for 2 h at 0 °C. The reaction mixture was diluted with AcOEt, and the organic phase was separated. The organic phase was washed with water, saturated $Na_2S_2O_3$, and brine, and dried over $MgSO_4$. After evaporation, the residue was purified using column chromatography on silica gel (hexane : AcOEt = 4 : 1) to give **8** (21.2 g, 97%) as colorless oil. IR (film) 2972, 1483, 1471, 1417, 1396, 1130, 1030, 905. ^{1}H NMR ($CDCl_3$) δ = 1.19 (d, J = 6.4 Hz, 3H), 2.77-2.86 (dd, J = 13.4, 8.8 Hz, 2H), 3.15 (dd, J = 13.4, 6.7 Hz, 1H), 3.95-4.06 (m, 1H), 6.92 (dd, J = 8.4, 2.3 Hz, 1H), 7.00-7.07 (m, 2H), 7.21 (d, J = 2.3 Hz, 1H), 7.28 (d, J = 8.4 Hz, 1H), 7.32-7.47 (m, 4H), 7.51-7.57 (m, 2H). HRMS Calcd. for $C_{22}H_{19}Cl_2FO$ 388.0797, Found 388.0792.

(1*S*,2*S*)-3-(3,4-Dichlorophenyl)-2-(2-fluoro-4-biphenylyl)-1-methylpropylamine (1). Methanesulfonyl chloride (13.2 ml, 171 mmol) was added to a solution of triethylamine (25.6 ml, 185 mmol) and alcohol **8** (60.1 g, 154 mmol) in AcOEt (420 ml) at 0 °C. The mixture was stirred for 30 min at the same temperature. Saturated $NaHCO_3$ was added to the mixture and vigorously stirred at room temperature for 1 h. The organic phase was separated, dried over $MgSO_4$ and concentrated. The residue was dissolved in DMF (210 ml) and was added NaN_3 (50.0 g, 769 mmol). The mixture was stirred at 120 °C for 45 min, then allowed to cool to the ambient temperature. The mixture was poured into water and extracted with Et_2O. The organic layer was washed with water, dried over $MgSO_4$ and evaporated. The residue was dissloved in THF (400 ml) - H_2O (40 ml), and PPh_3 (40.3 g, 154 mmol) was added. The mixture was refluxed for 8 h, and the solvents were removed in vacuo. The residue was dissolved in isopropyl ether (200 ml) and added a solution

of L-tartaric acid (23.1 g, 154 mmol) in MeOH (200 ml). After standing at room temperature for 24 h, the resulting precipitate was collected to give the tartrate salt of **1** (58.0 g, 70%).

A solution of the salt **1** (50.8 g, 94.4 mmol) in hot MeOH (920 ml) was cooled to room temperature. Seed crystal was added, and the mixture was left to stand for 24 h. The crystalline precipitate was filtered off and recrystallized again to give the tartrate salt of (1*S*, 2*S*)-amine **1** (16.7 g, 33%). $[\alpha]_D^{20}$ + 129° (*c* 0.75, MeOH). The tartrate salt of **1** was converted to its free amine by treatment with 1 N NaOH followed by extraction with Et_2O. After removal of the solvent, the residue was dissloved in Et_2O and added to 4 N HCl-dioxane. The resulting precipitate was collected to give (1*S*, 2*S*)-**1** hydrochloride (12.5 g, 85%) as a white crystalline powder. $[\alpha]_D^{20}$ +173° (c 0.965, MeOH). Mp. 242-247°C. IR (film) 3405, 2915, 1519, 1419, 1133, 767, 698. ^{1}H NMR ($CDCl_3$) δ = 1.33 (d, *J* = 6.6 Hz, 3H), 2.80 (t, *J* = 12.9 Hz, 1H), 3.07-3.25 (m, 1H), 3.43 (dd, *J* = 12.9, 3.7 Hz, 1H), 3.58-3.70 (m, 1H), 6.75 (dd, *J* = 7.9, 1.9 Hz, 1H), 6.82-6.90 (m, 2H), 7.08 (d, *J* = 7.9Hz, 1H), 7.18 (d, *J* = 1.9 Hz, 1H), 7.28-7.55 (m, 6H). Anal. Calcd. for $C_{22}H_{21}NCl_3F$: C, 62.2; H, 4.98; N, 3.30. Found: C, 62.4; H, 4.69; N, 3.29.

The optical purity of **1** was determined to be 99.2% ee by HPLC analysis after conversion to the amide of (*R*)-(-)-MTPA: t_R = 12.8 min, isomer: t_R = 10.6 min (hexane : AcOEt = 10 : 1).

3-(2-Fluoro-4-biphenylyl)-2-propanol (9). A 1.6 M hexane solution of *n*-BuLi (75 ml, 120 mmol) was added dropwise to a solution of 4-bromo-2-fluorobiphenyl **5** (30.0 g, 119 mmol) in dry Et_2O (300 ml) at -70 °C under N_2. The mixture was allowed to warm to 0 °C, then propylene oxide (9.1 ml, 130 mmol) was added at 0 °C. The resulting mixture was stirred at the same temperature for 1 h, poured into water and extracted with AcOEt. The organic layer was washed with water, dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (hexane : AcOEt = 50 : 1, then 7 : 1) to give 3-(2-fluoro-4-biphenylyl)-2-propanol **9** (23.3 g, 85%) as a colorless oil. IR (film) 3354, 1490, 1417, 1128, 767, 698. ^{1}H NMR ($CDCl_3$) δ = 1.31 (d, *J* = 6.0 Hz, 3H). 2.75 (dd, *J* = 13.2, 7.8 Hz, 1H), 2.84 (dd, *J* = 13.2, 4.8 Hz, 1H), 4.03-4.15 (m, 1H), 7.03-7.10 (m, 2H), 7.34-7.49 (m, 4H), 7.53-7.58 (m, 2H). Anal. Calcd. for $C_{15}H_{15}FO$: C, 78.2; H, 6.57. Found: C, 78.1; H, 6.68.

(1*E*)-1-(2-Fluoro-4-biphenylyl)-1-propene (10). Methanesulfonylchloride (1.6 g, 14 mmol) was added to a solution of **9** (3.0g, 13 mmol) and triethylamine (2.1g, 21 mmol) in AcOEt (20 ml). The mixture was stirred at room temperature for 0.5 h. The insoluble material was filtered off and evaporated. The residue was dissolved in a solution of sodium ethoxide (6.3 g, 93 mmol) in ethanol (50 ml) and refluxed for 5 h. The mixture was poured into brine (100 ml), extracted with ether (100 ml x 2), dried over $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography to afford compound **10** as a colorless oil (2.5 g, 90%). IR (film) 3030, 1481, 1417, 962. ^{1}H NMR ($CDCl_3$) δ = 1.91 (d, *J* = 5.2 Hz, 3H), 6.29 (dq, *J* = 15.8, 5.2 Hz, 1H), 6.39 (d, *J* = 15.8 Hz, 1H), 7.07-7.18 (m, 2H), 7.31-7.47 (m, 4H), 7.51-7.58 (m, 2H). Anal. Calcd. for $C_{15}H_{13}F$: C, 84.9; H, 6.17. Found: C, 89.1; H, 6.38.

(1*R*,2*R*)-1-(2-Fluoro-4-biphenylyl)propan-1,2-diol (11). A solution of AD-mix-β[9] (4.2 g) and methanesulfonamide (285 mg, 3.0 mmol) in 30 ml of 1:1 *tert*-butyl alcohol-water was cooled to 0°C, and **10** (636 mg, 3.0 mmol) was added. The mixture was stirred at 0°C for 24 h, then 4.5 g of Na_2SO_3 was added and stirring continued at room temperature for 30 min. The *tert*-butanol layer was separated and the aqueous layer was further extracted with ethyl acetate. The combined extracts were washed with 4 N NaOH, dried over Na_2SO_4. After evaporation, the residue was chromatographed on silica gel (hexane : AcOEt = 5 : 1, then 1 : 1) to afford compound **11** (795 mg, 99%) as a white powder. Mp 78-79 °C. $[\alpha]_D^{20}$ -14.2° (*c* 0.99, EtOH). IR (film) 3270, 1483, 1417, 1147, 1035. ^{1}H NMR ($CDCl_3$) δ = 1.16 (d, *J* = 6.3 Hz, 3H), 3.83-3.95 (m, 1H),

4.43 (dd, J = 3.8, 7.0 Hz, 1H), 7.15-7.22 (m, 2H), 7.37 (tt, J = 1.6, 7.5 Hz, 1H), 7.40-7.48 (m, 3H), 7.51-7.57 (m, 2H). Anal. Calcd. for $C_{15}H_{15}FO_2$: C, 73.2; H, 6.14. Found: C, 72.9; H, 6.28.

(1*R*,2*R*)-1-(2-Fluoro-4-biphenylyl)-2-methyloxirane (12). Compound **12** was prepared in a 92% yield from **11** according to the procedure reported by Kolb *et al.*[10] Enantiomeric excess was determined to be 99.2% ee by HPLC analysis (CHIRALCEL® OD column, hexane : 2-propanol = 400 : 1, 1ml/min). Mp 50-51 °C. $[\alpha]_D^{20}$ +44.3°(*c* 0.99, EtOH). IR (film) 2989, 1625, 1581, 1484, 1411, 1280, 1124, 1020, 919, 825. ^{1}H NMR ($CDCl_3$) δ = 1.47 (d, J = 5.1 Hz, 3H), 3.05 (dq, J = 1.6, 5.1 Hz, 1H), 3.60 (d, J = 1.6 Hz, 1H), 7.05 (dd, J = 1.7, 11.2 Hz, 1H), 7.13 (dd, J = 1.7, 7.8 Hz, 1H), 7.33-7.47 (m, 3H), 7.50-7.56 (m, 2H). Anal. Calcd. for $C_{15}H_{13}FO$: C, 78.93; H, 5.74. Found: C, 78.95; H, 5.37.

(2*R*,3*S*)-4-(3,4-Dichlorophenyl)-3-(2-fluoro-4-biphenylyl)butan-2-ol (8).

Dibromoethane (15 mg) was added to a suspension of magnesium (256 mg, 10.5 mmol) in dry ether (5 ml) under N_2 and stirred for 10 min at room temperature. A solution of 3,4-dichlorobenzylchloride (1.95 g, 10 mmol) in dry ether (5 ml) was added to the above mixture dropwise at temperatures below 5 °C. The Grignard reagent was added to a solution of oxirane **12** (361 mg, 1.58 mmol) in ether (4 ml) and the mixture was stirred for 3 h under ice-cooling. The mixture was poured into a saturated NH_4Cl (20 ml), and extracted with ether. The organic layer was washed with brine and dried over Na_2SO_4. After evaporation, the residue was chromatographed on silica gel (hexane : AcOEt = 20 : 1, then 5 : 1) to afford compound **8** (607 mg, 99%) as a colorless oil. $[\alpha]_D^{20}$ +148° (*c* 1.00, $CHCl_3$). IR (film) 2966, 1483, 1396, 1130, 767, 698, 501. ^{1}H NMR ($CDCl_3$) δ = 1.19 (d, J = 6.4 Hz, 3H), 2.77-2.86 (dd, J = 13.4, 8.8 Hz, 2H), 3.15 (dd, J = 13.4, 6.7 Hz, 1H), 3.95-4.06 (m, 1H), 6.92 (dd, J = 8.4, 2.3 Hz, 1H), 7.00-7.07 (m, 2H), 7.21 (d, J = 2.3 Hz, 1H), 7.28 (d, J = 8.4 Hz, 1H), 7.32-7.47 (m, 4H), 7.51-7.57 (m, 2H). HRMS Calcd. for $C_{22}H_{19}Cl_2FO$ 388.0797, Found 388.0786.

(1*R*,2*S*)-3-(3,4-Dichlorophenyl)-2-(2-fluoro-4-biphenylyl)-1-methylpropylamine (1) hydrochloride. The optically active amine **1** was prepared from alcohol **8** using the same procedure described in the synthesis of racemic amine **1**. Mp 240-248°C (dec.). $[\alpha]_D^{20}$ +173° (*c* 0.97, MeOH). IR (film) 3405, 2915, 1519, 1419, 1133, 767, 698. ^{1}H NMR ($CDCl_3$) δ = 1.33 (d, J = 6.6 Hz, 3H), 2.80 (t, J = 12.9 Hz, 1H), 3.07-3.25 (m, 1H), 3.43 (dd, J = 12.9, 3.7 Hz, 1H), 3.58-3.70 (m, 1H), 6.75 (dd, J = 7.9, 1.9 Hz, 1H), 6.82-6.90 (m, 2H), 7.08 (d, J = 7.9Hz, 1H), 7.18 (d, J = 1.9 Hz, 1H), 7.28-7.55 (m, 6H). Anal. Calcd. for $C_{22}H_{21}NCl_3F$: C, 62.2; H, 4.98; N, 3.30. Found: C, 62.0; H, 5.11; N, 3.15.

Di-*tert*-butyl carboxymethylsuccinate (15). A 1.5 M cyclohexane solution of lithium diisopropylamide (35.1 ml, 52.6 mmol) was diluted with THF (33 ml), and a solution of benzyl acetate (7.89 g, 52.6 mmol) in THF (33 ml) was added dropwise at -70 °C. The mixture was stirred at the same temperature for 1 h. Then, a solution of di-*tert*-butyl maleate (**13**) (10 g, 43.8 mmol) in THF (22 ml) was added dropwise at the same temperature. The resulting mixture was stirred at the same temperature for 1 h, poured into water and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was dissolved in dioxane (185 ml), and then 10% Pd-C (1.85 g) was added. The mixture was stirred at room temperature under H_2 for 20 h. The catalyst was separated by filtration through a Celite and washed with AcOEt. Evaporation of solvents and crystallization of the residue gave a racemic **15** as a white crystalline powder (10.5 g, 83%). Mp 55-57 °C. IR (film) 2975, 1727, 1367, 503. ^{1}H NMR ($CDCl_3$) δ = 1.43 (s, 9H), 1.45 (s, 9H), 2.49 (dd, J = 16.5, 6.6 Hz, 1H), 2.59 (dd, J = 16.8, 6.0 Hz, 1H), 2.64 (dd, J = 16.8, 6.9 Hz, 1H), 2.76 (dd, J = 17.1, 7.2 Hz, 1H), 3.10 (quintet, J = 6.9 Hz, 1H). HRMS Calcd. for $C_{14}H_{25}O_6$ 289.1651, Found 289.1673.

Optical resolution of 15. The carboxylic acid **15** (12.97 g, 45 mmol) and cinchonidine (13.24 g, 45 mmol) were dissolved in hot CCl_4 (1 L). Seed crystals were added, and the mixture was left to stand at room temperature for 24 h. The crystals were collected by filtration. The recrystallization was repeated twice to obtain a cinchonidine salt of a (*S*)-**15** as white needles (6.66 g, 25%). Mp 98.5-99.5 °C. $[\alpha]_D^{20}$ -62.7 ° (*c* 1.0, $CHCl_3$)). IR (film) 3230, 2970, 1722, 1589, 1402, 1350. ^1H NMR ($CDCl_3$) δ = 1.13-1.23 (1H, m), 1.39 (9H, s), 1.42 (9H, s), 1.67-1.80 (1H, m), 1.86-2.11 (3H, m), 2.40-2.71 (5H, m), 2.93-3.04 (1H, m), 3.09-3.41 (4H, m), 4.21-4.35 (1H, m), 4.95 (1H, d, *J* = 10.2 Hz), 5.01 (1H, d, *J* = 17.1 Hz), 5.55 (1H, ddd, *J* = 17.1, 10.2, 6.6 Hz), 6.26 (1H, d, *J* = 2.4 Hz), 7.51 (1H, t, *J* = 8.1 Hz), 7.66 (1H, t, *J* = 8.1 Hz), 7.71 (1H, d, *J* = 1.5 Hz), 7.94 (1H, d, *J* = 8.1 Hz), 8.09 (1H, d, *J* = 8.1 Hz), 8.90 (1H, d, *J* = 1.5 Hz).

The cinchonidine salt was dissolved in a liquid mixture of ether and 1 N HCl under cooling with ice. The organic layer was separated and dried over $MgSO_4$. Evaporation of the solvent gave a (*S*)-**15** as a colorless oil. $[\alpha]_D^{20}$ +4.44 ° (*c* 0.92, $CHCl_3$). IR (film) 2980, 1730, 1360, 1286, 1247, 846. ^1H NMR ($CDCl_3$) δ = 1.43 (s, 9H), 1.45 (s, 9H), 2.49 (dd, *J* = 16.5, 6.6 Hz, 1H), 2.59 (dd, *J* = 16.8, 6.0 Hz, 1H), 2.64 (dd, *J* = 16.8, 6.9 Hz, 1H), 2.76 (dd, *J* = 17.1, 7.2 Hz, 1H), 3.10 (quintet, *J* = 6.9 Hz, 1H). HRMS Calcd. for $C_{14}H_{25}O_6$ 289.1651, Found 289.1664.

The optical purity of the carboxylic acid was established to be >98% ee by HPLC analysis after conversion to the amide of (*R*)-(+)-α-methylbenzylamine: *R*-isomer, t_R = 8.4 min; *S*-isomer, t_R = 9.0 min (hexane : AcOEt = 3 : 1, 1.0 ml/min).

The fraction containing a large amount of another enantiomer (obtained by the above optical resolution operation) was converted to free acid, and the same operation was conducted in isopropyl ether by means of quinine to obtain a (*R*)-**15**.

(3*S*,7*S*,8*S*)-*N*-[3-(3,4-Dichlorophenyl)-2-(2-fluoro-4-biphenylyl)-1-methyl-propyl]-carbamoylmethylsuccinic acid (J-104,118). To a mixture of (1*S*, 2*S*)-**1** hydrochloride (1.67 g, 3.92 mmol) and (*S*)-**15** in CH_2Cl_2 (75 ml) was added 4-dimethylaminopyridine (575 mg, 4.70 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) (901 mg, 4.70 mmol) at 0 °C. The mixture was stirred at room temperature for 4 h, poured into 1 N HCl, and extracted with CH_2Cl_2. The organic layer was washed with saturated $NaHCO_3$, brine and dried over $MgSO_4$. Evaporation and purification of the residue by column chromatography on silica gel (hexane : AcOEt = 4 : 1, then 2 : 1) gave amide (2.52 g, 98%). ^1H NMR ($CDCl_3$) δ = 1.03 (d, *J* = 6.6 Hz, 3H), 1.44 (s, 9H), 1.45 (s, 9H), 2.34 (dd, *J* = 14.8, 5.6 Hz, 1H), 2.60 (d, *J* = 6.4 Hz, 2H), 2.64 (dd, *J* = 14.8, 7.8 Hz, 1H), 2.79-3.20 (m, 4H), 4.22-4.41 (m, 1H), 5.67 (d, *J* = 8.8 Hz, 1H), 6.78-6.93 (m, 3H), 7.11-7.55 (m, 8H).

To a solution of amide (2.52 g, 3.83 mmol) in CH_2Cl_2 (10 ml) was added trifluoroacetic acid (20 ml) at room temperature. The mixture was stirred at same temperature for 18 h. The solvents were concentrated under reduced pressure, and trifluoroacetic acid was removed by codistillation from benzene. Recrystallization of the residue from $CHCl_3$ - MeOH - hexane (40 ml - 2 ml - 50 ml) gave J-104,118 (1.82 g, 87%) as white plates. $[\alpha]_D^{20}$ +124° (*c* 1.0, MeOH). Mp 170-171 °C. IR (KBr) 3317, 1726, 1668, 1540, 1419, 1365,1149, 696. ^1H NMR (CD_3OD) δ = 0.99 (d, *J* = 6.9 Hz, 3H), 2.53 (dd, *J* = 6.9, 15.9 Hz, 1H), 2.61 (dd, *J* = 6.0, 17.1 Hz, 1H), 2.69 (dd, *J* = 6.9, 15.6 Hz, 1H), 2.74 (dd, *J* = 7.5, 17.1 Hz, 1H), 2.82 (dd, *J* = 11.7, 12.6 Hz, 1H), 2.89-2.96 (m, 1H), 3.21-3.28 (m, 1H), 3.17 (dd, *J* = 3.3, 12.6 Hz, 1H), 4.23 (dq, *J* = 8.7, 6.9 Hz, 1H), 6.91 (dd, J = 1.8, 8.0 Hz, 1H), 6.93-7.00 (m, 2H), 7.16 (d, *J* = 1.8 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.29-7.43 (m, 4H), 7.46-7.51 (m, 2H); Anal. Calcd. for $C_{28}H_{26}NO_5FCl_2$: C, 61.55; H, 4.80; N, 2.56. Found: C, 61.46; H, 4.77; N, 2.53.

Methyl (2*R*,3*R*)-2-(3,4-Dichlorobenzyl)-3-hydroxybutyrate (17). To a solution of Methyl (*R*)-3-hydroxybutyrate (**16**) (21.2 g, 180 mmol) in THF (200 ml) was added lithium diisopropylamide (189 ml, 2 M solution in cyclohexane, 378 mmol) below -60 °C dropwise over 40 min under N_2. The reaction mixture was warmed to -25 °C. 3,4-Dichlorobenzyl bromide (47.5 g, 198 mmol) in HMPA (79 ml) was added dropwise over 1.5 h below -20 °C, and the mixture was allowed to warm to room temperature. Saturated NH_4Cl was added, the mixture was poured into water and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel (hexane : AcOEt = 10 : 1, then 3 : 1) to give **17** (39.1 g, 141 mmol, 78%) as colorless oil. $[\alpha]_D^{20}$ +37.2 ° (*c* 1.0, EtOH). ^1H NMR ($CDCl_3$) δ = 1.22 (d, *J* = 6.1 Hz, 3H), 2.60-2.70 (m, 1H), 2.90-3.00 (m, 2H), 3.64 (s, 3H), 3.80-3.90 (m, 1H), 7.03 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.28 (d, *J* = 1.6 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 1H). Anal. Calcd. for $C_{12}H_{15}O_3C_{12}$: C, 52.0; H, 5.09. Found: C, 52.0; H, 5.40.

Methyl (2*R*,3*R*)-3-*tert*-Butyldimethylsilyloxy-2-(3,4-dichlorobenzyl)butyrate (18). To a stirred solution of alcohol **17** (39.1 g, 141 mmol) and imidazole (14.4 g, 211 mmol) in DMF (220 ml) was added *tert*-butyldimethylsilyl chloride (25.5 g, 169 mmol) at 0 °C. The mixture was stirred at room temperature for 11 h and saturated aqueous $NaHCO_3$ was added. The mixture was poured into water and extracted with Et_2O. The organic layer was washed with water, brine and dried over $MgSO_4$. Evaporation and purification of the residue by column chromatography on silica gel (hexane : AcOEt = 50 : 1, then 20 : 1) to give **18** (50.4 g, 129 mmol, 91%) as colorless oil. IR (film) 2952, 1736, 1473, 1378, 831. ^1H NMR ($CDCl_3$) δ = 0.06 (s, 3H), 0.08 (s, 3H), 0.88 (s, 9H), 1.21 (d, *J* = 6.3 Hz, 3H), 2.65-2.72 (m, 1H), 2.75-2.85 (m, 2H), 3.56 (s, 3H), 4.05-4.18 (m, 1H), 6.99 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.25 (d, *J* = 1.7 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H). HRMS Calcd. for $C_{18}H_{29}Cl_2O_3Si$ 391.1280, Found 391.1280.

(2*R*,3*R*)-3-*tert*-Butyldimethylsilyloxy-2-(3,4-dichlorobenzyl)butyraldehyde (19). A solution of **18** (12.6 g, 32.2 mmol) in toluene (100 ml) under N_2 was cooled to -78 °C. Diisobutylaluminum hydride (79 ml, 1.02 M solution in toluene, 80.5 mmol) was added dropwise. The mixture was stirred at the same temperature for 1 h. The mixture was poured into 1 N HCl and extracted with AcOEt. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. The crude alcohol was dissolved in CH_2Cl_2 (70 ml). PCC (13.9 g, 64.4 mmol) was added to the solution at room temperature. The resulting mixture was stirred for 2 h, diluted with Et_2O and filtered through a Celite. The filtrate was concentrated and the residue was chromatographed on silica gel (hexane : AcOEt = 50 : 1) to afford **19** (8.15 g, 70%) as colorless oil. IR (film) 2927, 1705, 1471, 829. ^1H NMR ($CDCl_3$) δ = 0.08 (s, 6H), 0.90 (s, 9H), 1.27 (d, *J* = 6.3 Hz, 3H), 2.52-2.63 (m, 1H), 2.76 (dd, *J* = 5.7, 14.1 Hz, 1H), 3.05 (dd, *J* = 14.4, 8.6 Hz, 1H), 4.08-4.15 (m, 1H), 6.98 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.26 (d, *J* = 1.9 Hz, 1H), 7.33 (d, *J* = 8.2 Hz, 1H), 9.77 (d, *J* = 2.5 Hz, 1H).

(2*R*,3*S*,4*E*)-3-(3,4-Dichlorobenzyl)-5-(2-naphthyl)-4-penten-2-ol (20). To a suspension of 2-naphthylmethyltriphenylphosphonium bromide (16.4 g, 33.9 mmol) in dry THF (80 ml) was added NaH (60% in oil, 1.27 g, 31.6 mmol) at 0 °C. After stirring at room temperature for 30 min, to this orange mixture was added aldehyde **19** (8.15 g, 22.6 mmol) in dry THF (20 ml). The mixture was stirred at the same temperature for 1 h. The mixture was poured into water and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was dissolved in THF (60 ml) and to this solution was added tetrabutylammonium fluoride (45.2 ml, 1 M solution in THF, 45.2 mmol) at room temperature. The mixture was stirred for 3 h, poured into water and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel

(hexane : AcOEt = 10 : 1, then 7 : 1) to give **20** (6.43 g, 17.3 mmol, 77%). $[\alpha]_D^{20}$ +167° (*c* 1.00, EtOH), IR (film) 3400, 1645, 1471, 1130, 1029, 970, 812, 746. ^{1}H NMR ($CDCl_3$) δ = 1.27 (d, *J* = 6.2 Hz, 3H), 2.40-2.50 (m, 1H), 2.73 (dd, *J* = 13.5, 8.5 Hz, 1H), 2.97 (dd, *J* = 13.5, 6.0 Hz, 1H), 3.85-3.90 (m, 1H), 6.22 (dd, *J* = 15.9, 9.0 Hz, 1H), 6.47 (d, *J* = 15.9 Hz, 1H), 7.05 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.25-7.35 (m, 2H), 7.40-7.50 (m, 2H), 7.55 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.65 (s, 1H), 7.73-7.85 (m, 3H). HRMS Calcd. for $C_{22}H_{20}Cl_2O$ 370.0891, Found 370.0906.

(1*S*,2*S*,3*E*)-2-(3,4-Dichlorobenzyl)-1-methyl-4-(2-naphthyl)-3-butenylamine hydrochloride (3). To a stirred mixture of **20** (6.43 g, 17.3 mmol) and triphenylphosphine (6.81 g, 26.0 mmol) in dry THF (80 ml) was added diethyl azodicarboxylate (4.14 ml, 26.0 mmol) under N_2 at 0 °C. To this was added diphenylphosphoryl azide (7.15 g, 26.0 mmol) in dry THF (20 ml) dropwise at the same temperature. The reaction mixture was stirred at ambient temperature for 18 h. THF was removed in vacuo and the residue was chromatographed on silica gel (hexane : AcOEt = 50 : 1) to give the azide derivative (6.50 g, 16.4 mmol, 95%) as colorless oil. ^{1}H NMR ($CDCl_3$) δ = 1.35 (d, *J* = 6.6 Hz, 3H), 2.45-2.60 (m, 1H), 2.68 (dd, *J* = 13.4, 8.7 Hz, 1H), 3.00 (dd, *J* = 13.4, 4.3 Hz, 1H), 3.43-3.55 (m, 1H), 6.02 (dd, *J* = 15.9, 9.3 Hz, 1H), 6.40 (d, *J* = 15.9 Hz, 1H), 6.98 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.25-7.55 (m, 4H), 7.62 (s, 1H), 7.75-7.85 (m, 4H).

A stirred mixture of the azide derivative (6.50 g, 16.4 mmol) and triphenylphosphine (4.30 g, 16.4 mmol) in THF (100 ml) and water (10 ml) was refluxed for 3 h. After removal of the solvent, the residue was dissolved in MeOH (70 ml), and (-)-dibenzoyl-L-tartaric acid (6.17 g, 16.4 mmol) in MeOH (70 ml) was added. After standing at room temperature for 15 h, tartrate of **3** was obtained as a crystalline powder (10.5 g, 87%). The salt was converted to its free amine by treating with aqueous NaOH and extracting with Et_2O. After evaporating the extracts, the residue was dissloved in MeOH, and 10% HCl-MeOH was added. The mixture was concentrated, and the residue was crystallized from CH_2Cl_2 - Et_2O. The resulting precipitate was collected to give **3** (5.0 g, 86%) as a white crystalline powder. Mp 169-171°C. $[\alpha]_D^{20}$ +173° (*c* 0.965, MeOH). IR (film) 3300, 1645, 1441, 1398, 1130, 1029, 972. ^{1}H NMR ($CDCl_3$) δ = 1.16 (d, *J* = 6.9 Hz, 3H), 2.45 (dd, *J* = 12.9, 9.3 Hz, 1H), 2.60-2.95 (m, 3H), 5.80 (dd, *J* = 15.6, 9.3 Hz, 1H), 6.30 (d, *J* = 15.6 Hz, 1H), 6.87 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 7.23 (d, *J* = 1.8 Hz, 1H), 7.35-7.50 (m, 2H), 7.52 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.60 (s, 1H), 7.70-7.80 (m, 3H). Anal. Calcd. for $C_{22}H_{22}NCl_3$: C, 65.0; H, 5.45; N, 3.44. Found: C, 64.7; H, 5.72; N, 3.38.

The optical purity of the amine **3** was established to be 96.6% ee by HPLC analysis after conversion to the amide of (*R*)-(-)-MTPA: t_R = 9.1 min; isomer, t_R = 10.7 min (hexane : AcOEt = 5 : 1).

***N*-[(1*S*,2*S*,3*E*)-2-(3,4-Dichlorobenzyl)-1-methyl-4-naphthyl-3-butenyl]carbamoyl-(3*R*)-3-methylbutyric acid (J-104,123).** To a solution of amine hydrochloride **3** (997 mg, 2.45 mmol) and (3*R*)-methyl hydrogen 3-methylglutarate **21** (432 mg, 2.7 mmol) in CH_2Cl_2 (15 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (564 mg, 2.94 mmol) and 4-dimethylaminopyridine (359 mg, 2.94 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h, poured into 1 N HCl and extracted with CH_2Cl_2. The organic layer was washed with saturated $NaHCO_3$ and brine and dried over $MgSO_4$. Evaporation and purification of the residue by column chromatography on silica gel (hexane : AcOEt = 3 : 2, then 1 : 1) gave amide (1.18 g, 94%). ^{1}H NMR ($CDCl_3$) δ = 1.04 (d, *J* = 6.4 Hz, 3H), 1.20 (d, *J* = 6.8 Hz, 3H), 2.08 (dd, *J* = 13.8, 7.4 Hz, 1H), 2.20-2.30 (m, 2H), 2.38-2.51 (m, 2H), 2.60-2.72 (m, 2H), 2.81-2.90 (m, 1H), 3.61 (s, 3H), 4.12-4.23 (m, 1H), 5.66 (d, *J* = 7.6 Hz, 1H), 6.09 (dd, *J* = 15.8, 8.8 Hz, 1H), 6.39 (d, *J* = 15.8 Hz, 1H), 7.01 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.27 (s, 1H), 7.30 (d, *J* = 6.0 Hz, 1H),

7.41-7.55 (m, 3H), 7.62 (s, 1H), 7.74-7.81 (m, 3H).

To a solution of the amide (1.18 g, 2.3 mmol) in THF (5 ml) - MeOH (5 ml) was added 1 N NaOH (5 ml) at room temperature. The mixture was stirred at the same temperature for 4 h, acidified with 1 N HCl and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and concentrated. Recrystallization of the residue from $CHCl_3$ - hexane (50 ml - 25 ml) gave J-104,123 (1.07 g, 93%) as a white crystalline powder. Mp 146-147 °C. $[\alpha]_D^{20}$ +103° (*c* 1.02, MeOH). IR (film) 3345, 2359, 1727, 1604, 1542, 958, 808, 742, 476. ^1H NMR (CD_3OD) δ = 1.04 (d, *J* = 6.3 Hz, 3H), 1.19 (d, *J* = 6.9 Hz, 3H), 2.11-2.30 (m, 3H), 2.35-2.47 (m, 2H), 2.57-2.68 (m, 2H), 2.94 (d, *J* = 10.2 Hz, 1H), 4.03 (quintet, *J* = 6.6 Hz, 1H), 6.15 (dd, *J* = 15.3, 8.4 Hz, 1H), 6.30 (d, *J* = 15.3 Hz, 1H), 7.10 (d, *J* = 8.1 Hz, 1H), 7.31-7.44 (m, 4H), 7.55 (d, *J* = 8.7 Hz, 1H), 7.62 (s, 1H), 7.73-7.78 (m, 3H). ^{13}C NMR (CD3OD) δ = 18.0, 20.2, 29.5, 38.6, 41.8, 44.0, 49.6, 52.0, 124.5, 126.7, 126.8, 127.2, 128.6, 128.9, 129.1, 130.4, 130.7, 130.8, 131.1, 132.4, 132.8, 134.4, 134.5, 135.1, 136.0, 142.5, 174.1, 176.3. Anal. Calcd. for $C_{28}H_{29}NO_3Cl_2$: C, 67.47; H, 5.86; N, 2.81. Found: C, 67.31; H, 6.13; N, 2.81.

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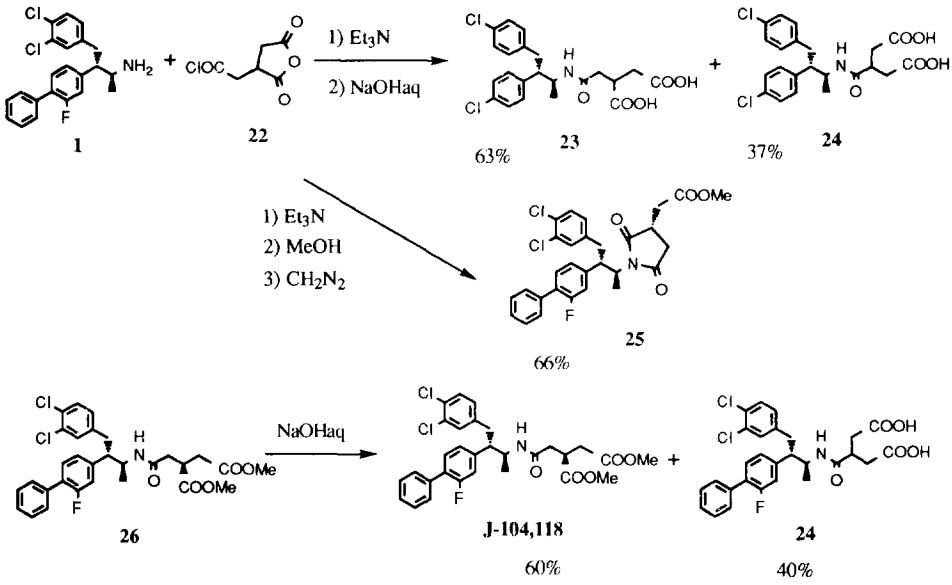
References and Notes

1. Scandinavian Simvastatin Survival Study Group, *Lancet* **1994**, *344*, 1383.
2. Iwasawa, Y.; Hayashi, M.; Nomoto, T.; Shibata, J.; Mitsuya, M.; Hirota, K.; Yonemoto, M.; Kamei, T.; Miura, K.; Tomimoto, K. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1989.
3. Iwasawa, Y.; Nonoshita, K.; Tomimoto, K. *Tetrahedron Lett.* **1995**, *36*, 7459.
4. Iwasawa, Y.; Shibata, J.; Mitsuya, M.; Masaki, H.; Hayashi, M.; Kanno, T.; Sawasaki, Y.; Hisaka, A.; Kamei, T.; Tomimoto, K. *Bioorg. Med. Chem. Lett.*. **1995**, *6*, 463.
5. (a) Oritz de Montellano, P. R.; Wei, J. S.; Castillo, R.; Hsu, C. K.; Boparai, A. *J. Med. Chem.* **1977**, *20*, 243. (b) Biller, S.A.; Sofia, M. J.; DeLange, B.; Forster, C.; Gordon, E. M.; Harrity, T.; Rich, L. C.; Ciosek, C. P., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 8522. (c) Bergstorm, J. D.; Kurtz, M. M.; Rew, D. J.; Amend, A. M.; Karkas, J. D.; Bostedor, R. G. Bansal, V. S.; Dufresne, C.; VanMiddlesworth, F. L.; Hensens, O. D.; Liesch, J. M.; Zink, D. L.; Wilson, K. E.; Onishi, J.; Milligan, J. A.; Bills, G.; Kaplan, L; Nallin Omstead, M.; Jenkins, R. G.; Huang, L; Meinz, M. S.; Quinn, L.; Burg, R. W.; Kong, Y. L.; Mochales, S.; Mojena, M.; Martin, I.; Pelaez, F.; Diez, M. T.; Alberts, A. W. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 80. (d) Baxter, A.; Fitzgerald, B. J.; Hutson, J. L.; McCarthy, A. D.; Motteram, J. M.; Ross, B. C.; Sapra, M.; Snowden, M. A.; Watson, N. S.; Williams, R. J.; Wright, C. *J. Biol. Chem.* **1992**, *267*, 11705. (e) Ciosek, C. P., Jr.; Magnin, D. R.; Harrity, T. W.; Logan, J. V. H.; Dickson, J. K., Jr.; Gordon, E. M.; Hamilton, K. A.; Jolibois, K. G.; Kunselman, L. K.; Lawrence, R. M.; Mookhtiar, K. A.; Rich, L. C.; Slusarchk, D. A.; Sulsky, R. B.; Biller, S. A. *J. Biol. Chem.* **1993**, *268*, 248832. (f) Amin, D.; Cornell, S. A.; Gustafson, S. K.; Needle, S. J.; Ullrich, J. W.; Bilder, G. E.; Perrone, M. H. *J. Lipid Res.* **1992**, *33*, 1657. (g) Corey, E.J.; Volante R. P. *J. Am.*

Chem. Soc. **1976**, *98*, 1291. (h) Poulter, C. D.; Capson, T. L.; Thompson, M. D.; Bard, R. S. *J. Am. Chem.Soc.* **1989**, *111*, 3734. (i) Oehlschlager, A. C.; Singh, S. M.; Sharma, S. *J. Org. Chem.* **1991**, *56*, 3856. (j) Ortitz de Montellano, P. R.; Castillo, R. *Tetrahedron Lett.* **1976**, 4115. (k) Bertolino, A.; Altman, L. J.; Vasak, J.; Rilling, H. C. *Biochim. Biophys. Acta* **1978**, *530*, 17. (l) Prashad, M.; Kathawala, F. G.; Scallen, T. *J. Med. Chem.* **1993**, *36*, 1501.

6. Kosugi, M.; Suzuki, M.; Hagiwara, I.; Goto, K.; Saitoh, K.; Migita, T. *Chem. Lett.* **1982**, 939.
7. Schultz, E. M.; Bolhoffer, W. A.; Augenblick, A.; Bicking, J. B.; Habecker, C. N.; Horner, J. K.; Kwong, S. F.; Pietruszkiewicz, A. M. *J. Med. Chem.* **1967**, *10*, 717.
8. Yamamoto, Y.; Matsuoka, K.; Nemoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 4475.
9. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.; *J. Org. Chem.* **1992**, *57*, 2768.
10. Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515.
11. We isolated cyclic imide **25** after reaction of **1** with **22**, followed by treatment with diazomethane.



12. Yamaguchi, M.; Tsukamoto, M.; Hirao, I. *Chem. Lett.* **1984**, 375.
13. Suzuki et. al reported optically active α-alkyl-β,γ-unsaturated ketones using pinacol-type rearrangement. It might be possible to apply the method to syntesis of **20**. Suzuki K.; Katayama E.; Tsuchihashi G. *Tetrahedron Lett.* **1984**, *25*, 1817.
14. Frater, G. *Helvetica Chimica Acta* **1979**, *62*, 2829.
15. Lam, L. K. P.; Hui, R. A. H. F.; Jones, J. B. *J. Org. Chem.* **1986**, *51*, 2047. Poppe, L.; Novak, L.; Kolonits, P.; Bata, A.; Szantay, C. *Tetrahedron* **1988**, *44*, 1477.
16. McCloskey, A. L.; Fonken, G. S.; Kluiber, R. W.; Johnson, W. S. *Org. Syn. Coll. Vol. IV* **1963**, 261.

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