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Efficient and Stereoselective Synthesis of J-104,118, A Novel, Potent Inhibitor of Squalene Synthase

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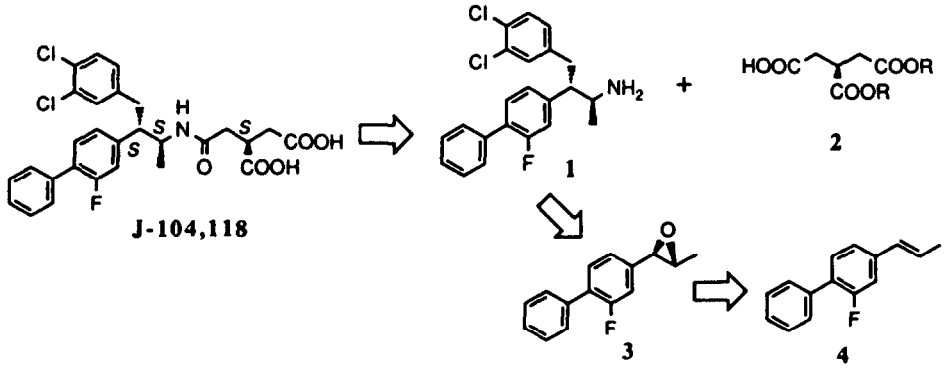
Abstract: J-104,118, a novel and potent inhibitor of squalene synthase, was synthesized stereoselectively. The chiral amine **1** was efficiently synthesized by Sharpless asymmetric dihydroxylation as a key reaction.

Elevated serum cholesterol has been established as a major risk factor for atherosclerosis. Inhibitors of the enzyme HMG-CoA reductase, a major regulatory enzyme in the cholesterol biosynthetic pathway, effectively lower serum cholesterol in man and are widely used clinically[1]; these drugs include lovastatin, simvastatin and pravastatin. The enzyme squalene synthase (SQS) catalyzes the reductive dimerization of two molecules of farnesyl pyrophosphate to form squalene in the middle stage of the cholesterol biosynthetic pathway. Inhibitors of SQS would be expected to be ideal cholesterol-lowering agents because they do not prevent the biosynthesis of ubiquinone, dolichol, and isopentenyl t-RNA. Some potent inhibitors of SQS have been reported, such as zaragozic acids[2] and squalestatins[3]. We have developed a novel, potent inhibitor of squalene synthase, J-104,118[4], which has a structure different from those of the known SQS inhibitors. J-104,118 has hydrophobic fluorobiphenyl and dichlorophenyl groups on the left side and a hydrophilic dicarboxylic acid function on the right side that are connected by an amide bond. J-104,118 has three asymmetric carbons; the isomer having a 3*S*,7*S*,8*S* configuration showed the most potent inhibitory activity against SQS. Herein we describe a highly efficient and stereoselective synthetic method of J-104,118 using the Sharpless asymmetric dihydroxylation reaction as the key step.

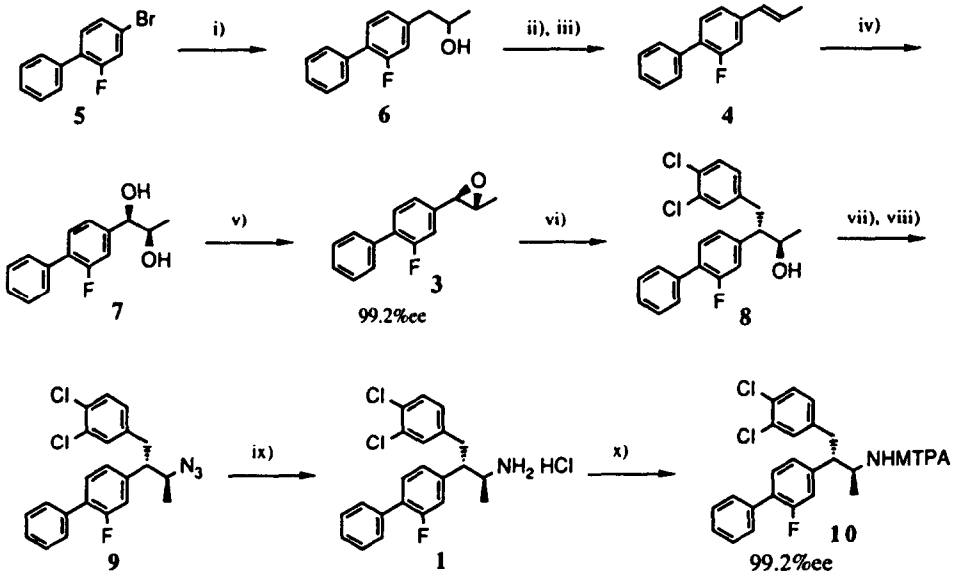
Scheme I



Retrosynthetic analysis indicated that J-104,118 could be synthesized by amide formation of optically active hydrophobic amine **1** with a suitably protected carboxylic acid **2** (Scheme I). Schultz *et al.* reported the synthesis of similar racemic amines by 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 amines produced were a mixture of the *threo-erythro* isomers[5]. We considered that the two neighboring chiral centers of amine **1** could be directly constructed by regioselective reaction of chiral epoxide **3** with a benzylic Grignard reagent followed by amination along with inversion of the stereochemistry. The chiral epoxide would be synthesized by the Sharpless asymmetric dihydroxylation of trans styrene derivative **4**.

Scheme II outlines the synthesis of optically pure amine **1**. The trans olefin **4** was conveniently prepared from commercially available 3-bromo-2-fluorobiphenyl **5**. Thus, **5** was treated with n-butyllithium in ether followed by propylene oxide to produce hydroxy derivative **6** in an 84% yield. This was converted to the methanesulfonate in the usual manner and then treated with sodium ethoxide in refluxing ethanol, which gave trans olefin **4** in an 89% yield. This trans olefin was converted to chiral diol **7** according to the Sharpless procedure[6]. Vigorous stirring of **4** with AD-mixß at 0°C in a mixture of t-BuOH and water in the presence of methanesulfonamide for 24 hours gave the desired diol **7** in an excellent yield. This diol **7** was converted to epoxide **3** in a one-pot manner according to the Sharpless procedure[7] in a 92% yield. The optical purity was determined to be 99.2% by HPLC analysis using chiralcel® OD. The Grignard reagent prepared

Scheme II

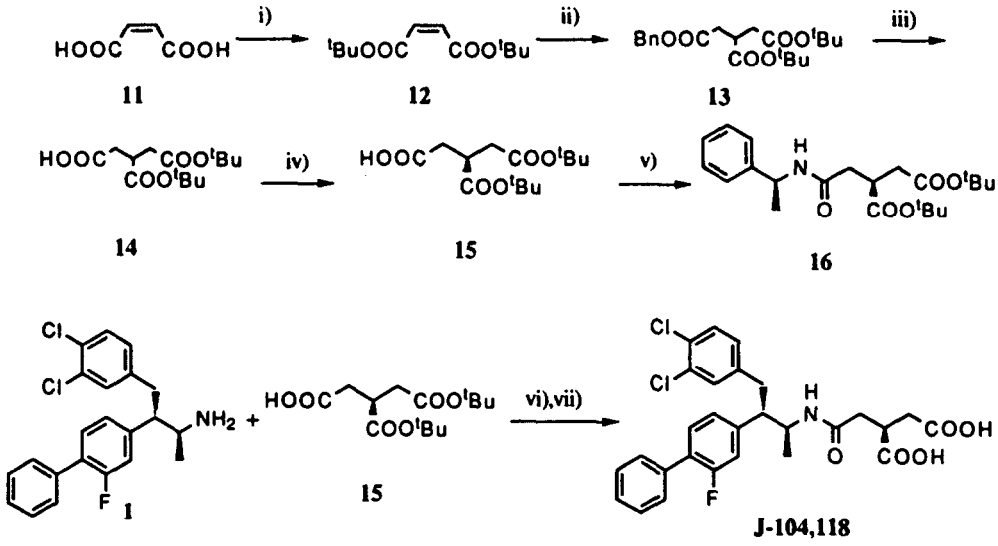


Reagents: i) n-BuLi, Et_2O, 0°C, 1h then propylene oxide, -78°C, 1h, 84% ii) MsCl, Et_3N, AcOEt, 0°C, 1h iii) NaOEt, EtOH, reflux, 4h, 89% iv) AD-mixβ, methanesulfonamide, t-BuOH, H_2O, 0°C, 24h, 99% v) TMSCl, trimethyl orthoacetate, CH_2Cl_2, rt, 1.5h then K_2CO_3, MeOH, rt, 1.5h, 92% vi) 3,4-dichlorobenzylbromide, Mg, ether, 0°C, 1h then **3**, 2h, 99% vii) MsCl, Et_3N, EtOAc, rt, 0.5h viii) NaN_3, DMF, 80°C, 3h, 83% ix) PPh_3, THF, H_2O, 80°C, 8h then HCl, 89% x) R-(-)-MTPCl, Et_3N, CH_2Cl_2, rt, 1h, 90%.

from 3,4-dichloro-benzylbromide and magnesium in ether attacked the benzylic carbon of the epoxide **3** at 0°C to give exclusively the desired alcohol **8** having 2*R*, 3*S* stereochemistry in a 99% yield. The hydroxy group of **8** was converted to the methanesulfonate, which was treated with sodium azide in DMF at 80°C to give azide **9**. Finally, reduction of the azide function of **9** with triphenylphosphine in the presence of water followed by treatment with hydrogen chloride gave the desired amine hydrochloride **1** as a crystalline powder. The optical purity of **1** was determined to be 99.2% by HPLC analysis of the MTP amide **10**. The overall yield was 49.8% in 9 steps starting from compound **5**.

Next, we tried to synthesize the hydrophilic part of J-104,118. Because alkaline hydrolysis of the dimethyl ester derivative of J-104,118 produced an isomeric mixture as a result of cyclic imide formation[8], t-butyl esters were selected as suitable protective groups of the carboxylic functions. Unsymmetrical di-t-butyl tricarballylate was successfully synthesized as outlined in Scheme III. Yamaguchi *et al.* reported a simple method of synthesis of glutarate by Michael reaction of ester enolates to α,β-unsaturated esters[9]. We applied this method; thus, Michael reaction of lithium enolate generated from benzyl acetate with di-t-butyl maleate produced the desired compound **13** in a 90% yield. Debenzylation under the usual hydrogenation conditions gave racemic di-t-butyl tricarballylate **14**. Optical resolution of this racemic acid was carried out by recrystallization of the cinchonidine salt of **14** from carbon tetrachloride. The optical purity was measured as 99.5% by HPLC analysis of its phenylethylamide derivative.

Scheme III



Reagents: i) isobutene, H_2SO_4, rt, 48h, 60% ii) benzyl acetate, LDA, THF, -78°C, 2h then **12**, -78°C, 1h, 90% iii) H_2, Pd-C, dioxane, rt, 12h, 80% iv) cinchonidine, recryst. from CCl_4, 30%, 98%ee v) (+)-α-phenylethylamine, EDC•HCl, CH_2Cl_2, rt, 2h, quant. vi) EDC•HCl, DMAP, CH_2Cl_2, rt, 4h, 98% vii) TFA, CH_2Cl_2, rt, 18h, 87%.

Finally, a coupling reaction of amine **1** with acid **15** in the presence of EDC gave an amide derivative in a 98% yield. Deprotection of t-butyl esters was smoothly conducted by stirring with trifluoroacetic acid at room temperature for 18 hours. J-104,118 was obtained as fine plates by recrystallization from dichloromethane and hexane. The absolute configuration of J-104,118 was confirmed to be 3*S*, 7*S* and 8*S* by X-ray analysis[4].

We have developed a highly efficient, stereoselective method of synthesizing J-104,118. This synthetic method is applicable to large-scale operations.

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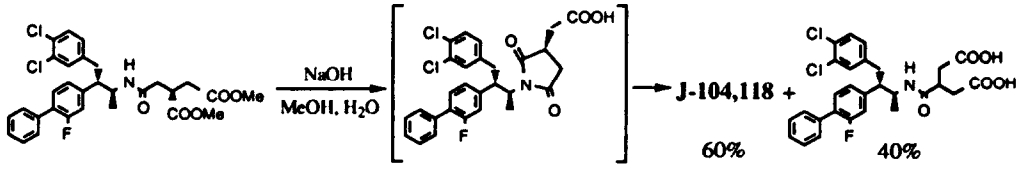
8. 

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10. All new compounds shown exhibited satisfactory spectroscopic data. J-104,118: ^{1}H NMR (CD_3OD, 300MHz) 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.; mp 170~171°C; $[\alpha]^{20}_D$ +124° (c = 1.0, MeOH).

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