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TETRAHEDRON: *ASYMMETRY*

Enzymatic resolution of benzothiazepine for the preparation of squalene synthetase inhibitors

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Abstract

A key intermediate with a 4,1-benzothiazepine skeleton, useful for the synthesis of potent squalene synthetase inhibitors, has been prepared via enzymatic resolution providing excellent yield and enantiomeric purity. © 2000 Elsevier Science Ltd. All rights reserved.

Over the last decade, industrial as well as academic investigators have intensified their research efforts toward the discovery of squalene synthetase (SQS) inhibitors. This focus on SQS inhibitors derives from their potential as anti-atherosclerotic and hypocholesterolemic agents:[1,2] SQS is a key enzyme in the cholesterol biosynthetic pathway that catalyzes the reductive dimerization of farnesyl diphosphate to squalene, the first compound committed toward sterol production. The position of SQS in the cascade offers potential advantages over HMG-CoA reductase inhibitors, such as pravastatin, lovastatin and simvastatin, in that the biosynthesis of isoprenoid products and isoprenylated protein are not affected.[1,2] Therefore, the hope for SQS inhibitors becoming the next generation of cholesterol-lowering drugs[1,2] is high.

CP-340868 **10**, a 5-(1-naphthyl)-4,1-benzothiazepine derivative, was discovered at Pfizer as a potent SQS inhibitor;[2b] however, its enantiomer was an almost four-fold less active SQS inhibitor (90 nM versus 23 nM, Scheme 1). CP-340868 was derived from the 5-(1-naphthyl)-4,1-benzothiazepine carboxylic acid **9**. Therefore, an efficient preparation of enantiomerically pure compound **9** was crucial for the synthesis of this series of SQS inhibitors for further evaluation. Recently hydrolytic enzymes as tools for enantiomeric resolution have been utilized more frequently as demand for pure enantiomers in pharmaceuticals and agrochemicals[3,4] has increased. In addition, mild and environmentally friendly reaction conditions, as well as recoverable and inexpensive biocatalysts used in the reactions, have made the enzymatic resolution an attractive alternative to other traditional chemical resolutions. Here we report the use of lipases to prepare the enantiomeric pure compound **9** providing excellent yield and

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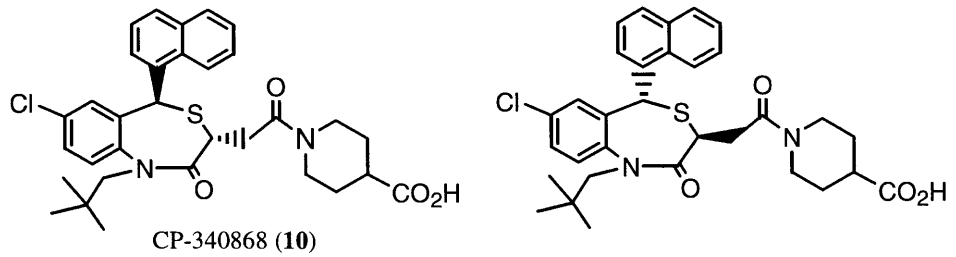
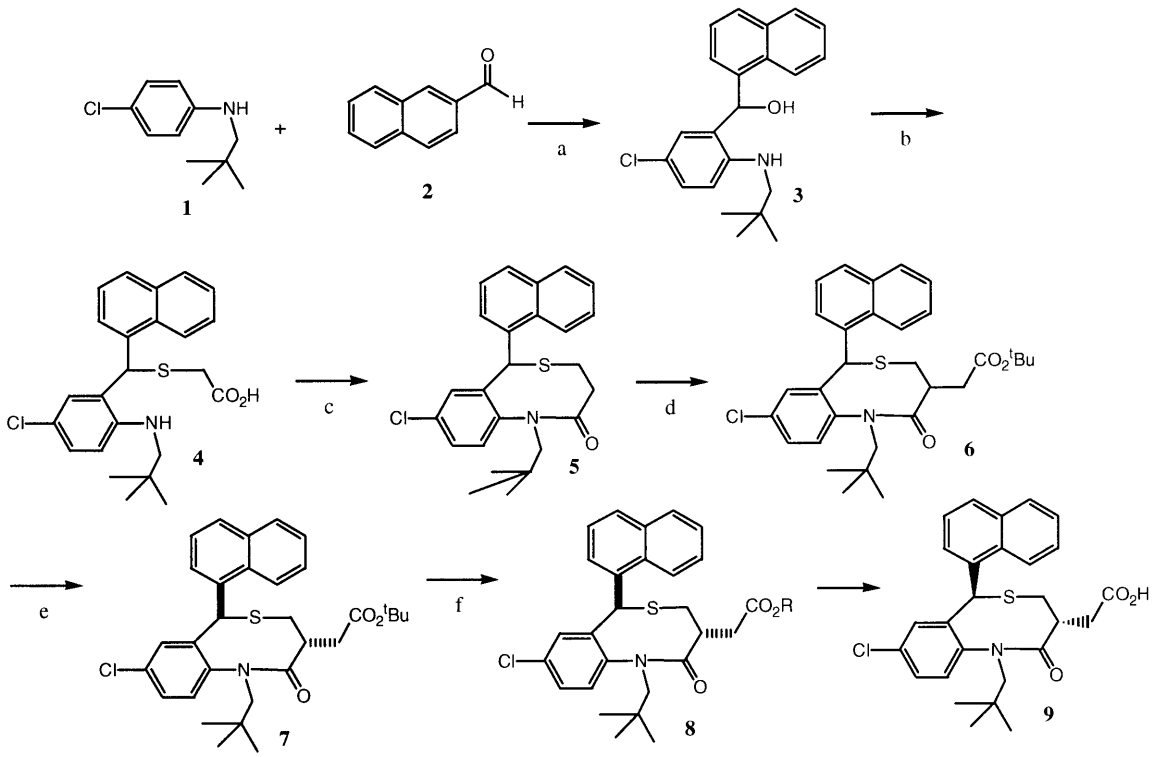
enantiomeric excess. This is the first time that a compound with 4,1-benzothiazepine structure has been resolved successfully through the use of lipases.



Scheme 1.

The racemic key intermediate **8** was prepared as shown in Scheme 2.[2b,c] The synthesis started with the Friedel–Crafts hydroxyalkylation of 4-chlorophenyl-2,2-dimethylpropyl amine **1**, prepared by reductive amination of *p*-chloroaniline and trimethylacetaldehyde ($NaBH_4$, HOAc, 96%), with 1-naphthaldehyde **2**. The resulting compound **3** was treated with mercaptoacetic acid to produce the corresponding thiacarboxylic acid **4**. Subsequently, carbodiimide (morpho-CDI) was employed for the intramolecular amidation to provide the 4,1-benzothiazepine derivative **5**.

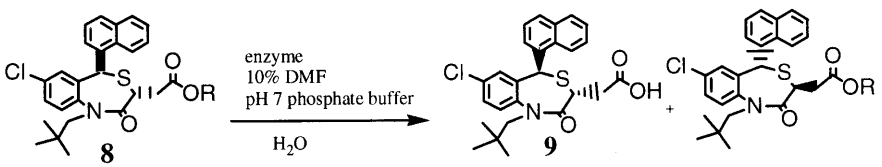


Scheme 2. (a) BCl_3, CH_2Cl_2, benzene, Et_3N, 80%; (b) mercaptoacetic acid, 6N HCl, 100°C, 90%; (c) morpho-CDI (CMC metho-*p*-toluenesulfonate), CH_2Cl_2, 75%; (d) LDA, THF, *t*-butyl bromoacetate, 85%; (e) K_2CO_3, MeOH, 65°C, 80%; (f) i. CF_3COOH, CH_2Cl_2, 95%. ii. H^+, ROH, 80–95%

Compound **5** was then reacted with *t*-butyl bromoacetate to yield the alkylated product, **6**. The pure *trans*-isomer, **7**, was obtained after recrystallization. To prepare the enantiomerically pure **9**, compound **7** was transesterified to a variety of esters, **8**, to investigate their enzymatic resolution.

The asymmetric hydrolysis of the various esters by a variety of lipases and esterases was investigated at three different temperatures (25, 37 and 45°C), with or without organic co-solvents (THF, acetone, dioxane and DMF). Due to the poor solubility and high crystallinity of compound **9**, elevated temperatures, adequate stirring and an organic co-solvent were required in order for the enzymatic reaction to proceed with a reasonable rate and yield. Among the different reaction conditions that were tried, the optimal condition for enzyme-catalyzed hydrolysis was at 37°C in 10% DMF as the co-solvent. In general, lipases produced better results than esterases; therefore, we directed our efforts toward lipase-catalyzed hydrolysis. Because of the slow lipase-catalyzed hydrolysis that we observed with the methyl ester, we investigated esters such as chloromethyl and trifluoromethyl esters, which are more susceptible to hydrolysis but stable in an aqueous solution. Two lipases, rhizopus arrhizus and FAP-15, provided promising results when the chloromethyl ester was used as the substrate (Table 1). These two reactions were then scaled up to gram scale: 45% yield (90% theoretical yield) and 98% e.e.[5] of **9** was obtained when lipase FAP-15 was used; 36% yield (72% theoretical yield) and 99.3% e.e. of **9** was obtained with the lipase from rhizopus arrhizus. Because of the reproducible results from this large scale reaction, compound **9** was prepared efficiently through the lipase FAP-15[6] catalyzed resolution and was used for making other SQS inhibitors by modifying the carboxylic acid functionality for further structure–activity relationship studies.

Table 1
Enzymatic resolution of benzothiazepine



Enzyme	Conversion (%)	E.e.$_p$ (%)	E.e.$_s$ (%)
	OR=OCH_2CH_2Cl		
Lipase from rhizopus arrhizus	36	99	50
Lipase FAP-15	45	98	72
	OR=OMe		
Lipase MAP-10	30	85	20
Lipase (mucor javanicus)	40	90	60
	OR=Obu		
Lipase (rhizopus arrhizus)	36	90	55
	OR=OCH_2CF_3		
Lipase N	20	92	31
Lipase (rhizopus arrhizus)	30	90	30

*E.e. = enantiomeric excess (see reference 5 for details).

In summary, we have found an efficient enzymatic resolution for the preparation of a key intermediate with the 4,1-benzothiazepine skeleton providing excellent yield and enantiomeric excess. We believe that this mild enzyme-catalyzed ester hydrolysis can be applied to other compounds with similar structures for enantiomeric resolution purposes.

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5. (a) The absolute configuration of **9** is determined according to reference 2c; (b) Chiralpak AD (4.6×250) HPLC column was used to analyze the e.e. of **9**. Mobil phase: 950 ml of hexane, 50 ml of 2-propanol and 1 ml of trifluoroacetic acid. Flow rate: 1.0 ml/min; rt; wavelength: 220 nm. The retention time for **8b** is 20 min and its enantiomer is 15.9 min.
6. Lipases were purchased from Amano Co Japan.