Pure & Appl. Chem., Vol. 69, No. 3, pp. 453–458, 1997.
Printed in Great Britain.

Design and development of practical asymmetric syntheses of drug candidates

Ichiro Shinkai

Merck Research Laboratories,
PO Box 2000, Rahway, New Jersey, U.S.A.

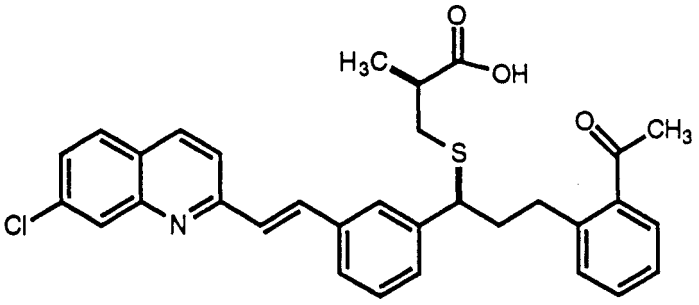
Abstract: Recent progress in asymmetric syntheses has made a significant impact on strategies for drug development in the pharmaceutical industry. Under the recent guidelines by the Food and Drug Administration (FDA), many drug firms are no longer considering the development of racemic forms of chiral drugs. This lecture presents a few examples of highly practical stereoselective syntheses of drug candidates, shown below, discovered and developed at Merck Research Laboratories.

Introduction

Until recently, most drug firms have been developing racemic forms of chiral drugs. In contrast, Merck has been synthesizing a non-racemic isomer of α-methyldopa, Aldomet™, on a multi-ton scale since the 1960's. The trend now is shifting as firms attempt to develop many of their chiral drugs as single enantiomers according to the recent guidelines published by the Food and Drug Administration (FDA). The extra steps and chemicals required for making single enantiomeric drugs in bulk quantity clearly result in much higher production costs. The establishment of practical stereoselective syntheses has therefore become an important goal for synthetic organic chemists, especially in the pharmaceutical industry.

Results and Discussion

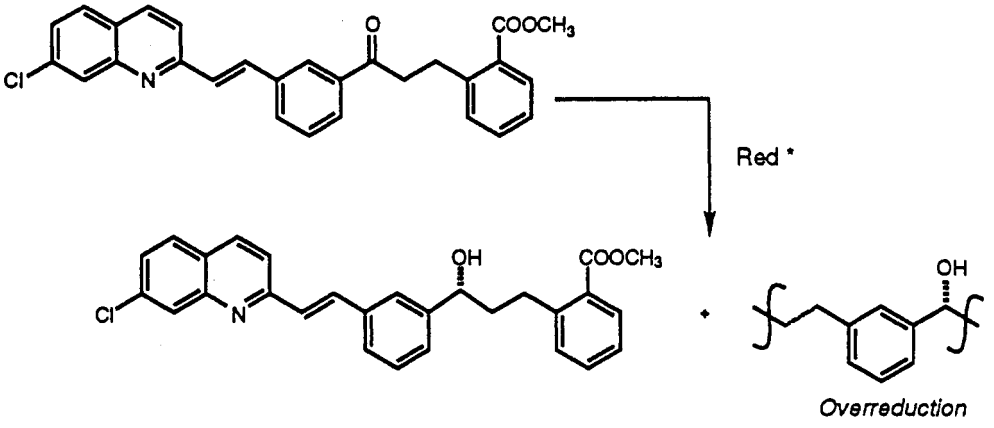
As part of an ongoing program for the development of specific leukotriene antagonists for the treatment of asthma and other associated diseases, L-699,392 [3-[(1S)-[3(E)[2-(7-chloroquinolinyl)ethenyl]phenyl]-3-(acetylphenyl)propylthio]-2(S)-methylpro-pionic acid was identified as a potent, orally active agent. This new class of compounds is an extention of the dithioacetal series, MK-0571/MK-0679. The 3-thiapropionamide side chain has been replaced with a 2-arylethyl group. In order to carry out further studies, an efficient synthesis of this drug candidate was developed. The key diarylpropanone building block was prepared using the Heck coupling of the allylic alcohol. The ketone was then converted to the chiral hydroxy group by a *B*-chlorodiisopinocampheylborane. A novel reagent prepared from lithiumhexamethyldisilazide and methylmagnesium chloride was utilized for the one step conversion of the ester to methyl ketone derivative. The introduction of the chiral mercapto side chain with inversion of the benzyl center was achieved *via* the mesylate activation of the chiral alcohol.

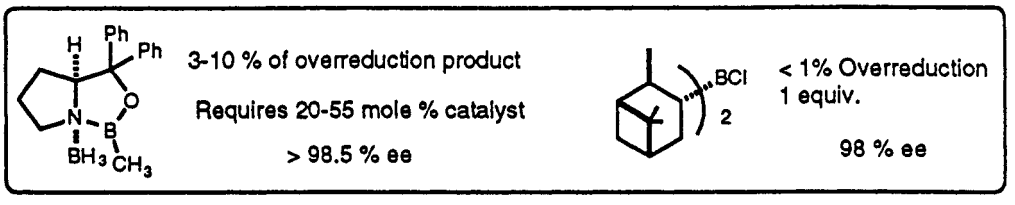


L-699,392

Two reagents for the chiral reduction of the ketone to the desired (R)-hydroxy ester were used: the oxazaborolidine·boranecomplex and *B*-chlorodiisopinocampheylborane. Although the former reagent provided exceptional enantioselectivity in the reduction (98.5% ee), the overreduction to the ethane-bridged by-product was a problem. The latter borane reducing reagent, although used stoichiometrically, can be prepared cheaply and easily from α-pinene and borane. The reagent showed no propensity for reduction of the C=C bond (< 1%) and gave only a slightly lower enantiomeric excess (98%).

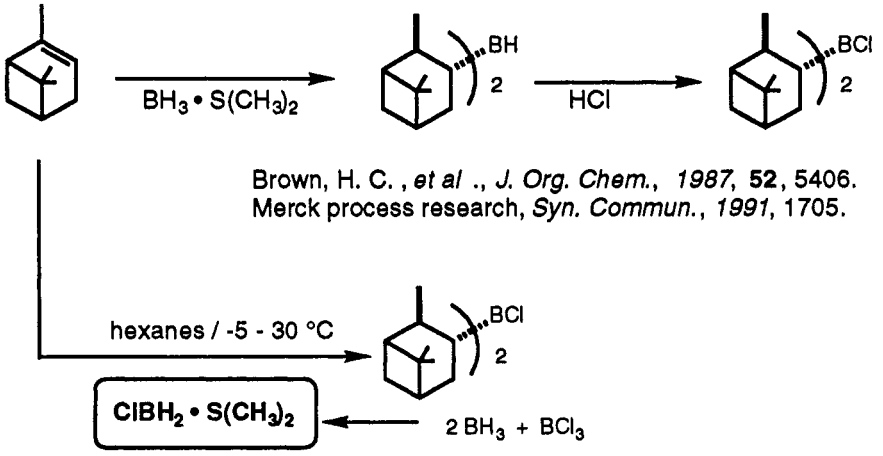
Chiral reduction





During the development of this reduction we have further improved on the use of this reagent. The reducing reagent can be prepared from 98% optically pure (-) α-pinene and

Catalyst preparation



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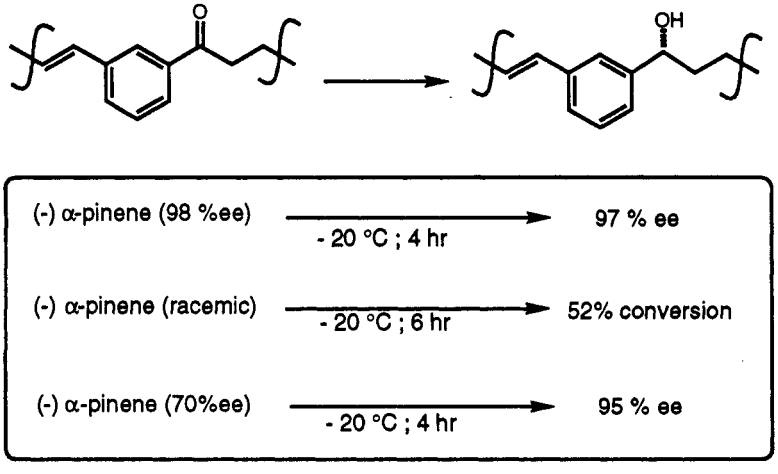
commercially available chloroborane-methylsulfide complex or, alternatively, a 2:1 mixture of borane and boron trichloride-methyl sulfide. Although dihaloboranes or alkylhaloboranes have been used before to prepare dialkylhaloboranes, this is the first application of this method to this reducing reagent. The reduction of the ketone with this reducing reagent gave the hydroxy ester in 97% ee. A tremendous asymmetric amplification resulting from this reagent was evidenced by its generation of 95% ee product from 70% optically pure α-pinene. The isolated yield of hydroxy ester was 80% with > 99.5% ee. The nature of the selectivity of this reagent can be understood. The reactivity of racemic B-chlorodiisopinocampheylborane derived from the racemic pinene was informative. By using 1.0 equivalent of racemic reducing reagent, only 52 % conversion of the ketone to hydroxy ester was observed. The racemic reducing reagent is composed of a statistical mixture of the (+,+),(-,-) and (+,-) species. The first two reagents are relatively active toward reduction, whereas, the last species, formally a mixture of two diastereomers, are relatively inactive or very slow reacting. According to this scenario and assuming a statistical mixture of the reagents was formed, the maximum asymmetric induction that one can obtain with 70% optically pure α-pinene is 94 %. The results match this predicted value closely.

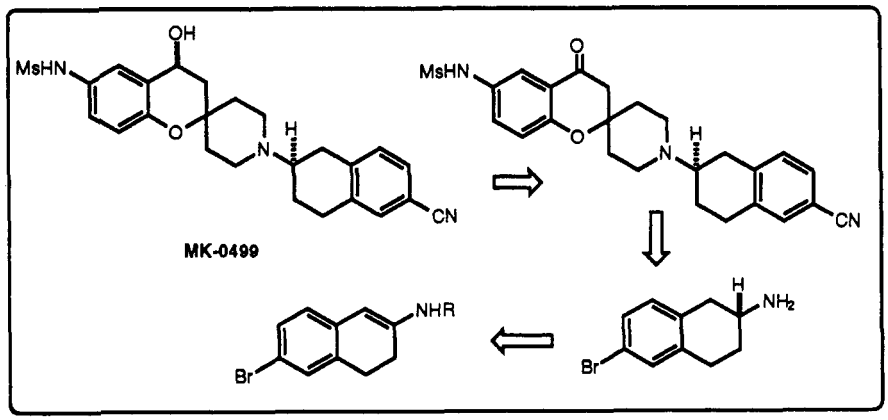
Asymmetric amplification



"(+,+) (-,-) are reactive but (+,-) are very slow reacting"

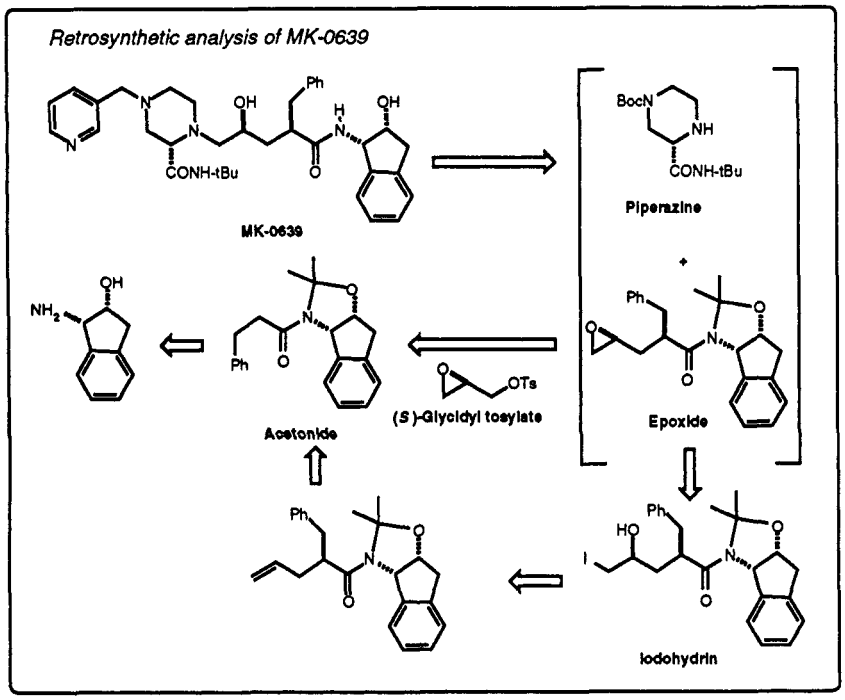
MK-499

MK-499 is a potent potassium channel blocker that mediates repolarization of cardiac tissue and is under investigation for treatment of ventricular arrhythmias and the prevention of sudden cardiac death. A highly convergent route based on the asymmetric reduction of ketone intermediates was developed for its synthesis.



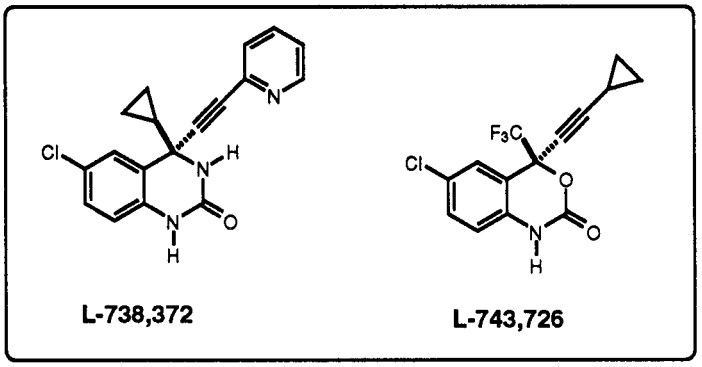
HIV Protease Inhibitor, MK-0639

Numerous HIV protease inhibitors have been reported; however, very few of them have been studied in humans due to their poor oral bioavailability. A potent HIV protease inhibitor, MK-0639 demonstrates excellent oral bioavailability and plasma pharmacokinetic profiles in animals and in man. This compound inhibits the protease-mediated cleavage of viral precursor polyproteins. Inhibition of this cleavage step during the viral replication cycle results in the production of immature, non-infectious viral particles. The HIV protease inhibitor MK-0639 is currently being tested for its effectiveness against AIDS in Phase III clinical trials. A highly diastereoselective synthesis of 2(R)-aryl-4(S)-hydroxy-[1S,2R-1-amino-2-hydroxy-indanamide] hydroxyethylene dipeptide isosteres was established in order to support on-going animal safety studies and large clinical trials.



MK-0639 is derived from an epoxide intermediate, which is prepared in 72% yield by the condensation of the lithium (Z)-enolate of an acetonide with (S)-glycidyl tosylate. An alternate route to the epoxide involves diastereoselective allylation of the lithium (Z)-enolate of acetonide, diastereoselective formation of an iodohydrin and base mediated formation of the desired epoxide. This procedure eliminates (S)-glycidyl tosylate from the process and produces the epoxide in 97:3 diastereoselectivity.

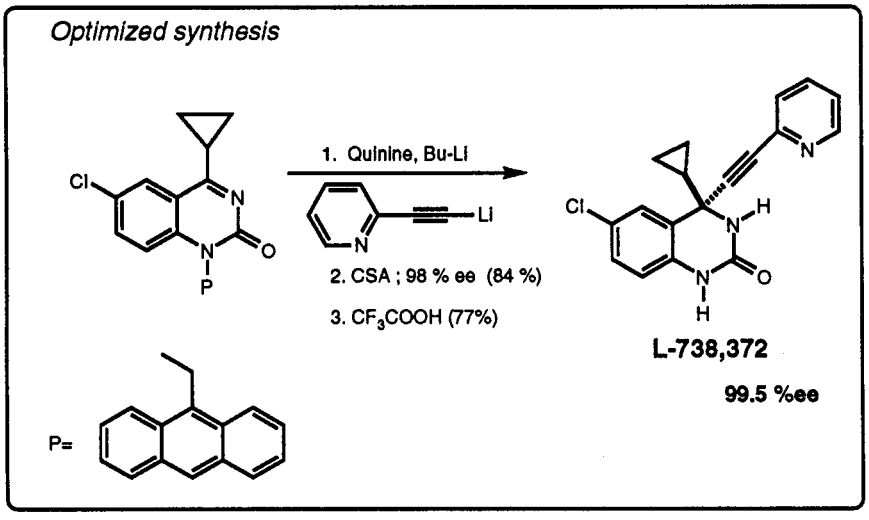
RTI Inhibitors



L-738,372

Ongoing worldwide development of a new non-nucleosidal reverse transcriptase inhibitor, L-738,372 required a practical stereoselective synthesis in order to pursue animal safety studies and clinical trials. Stereocontrolled additions of carbon nucleophiles to aldehydes and aldimines have been developed with chiral auxiliaries on the electrophiles or nucleophiles and noncovalent bound chiral additives [2]. Homogeneous THF solutions of acetylides and alkoxides were more selective than the suspensions obtained with toluene. The chiral additive method appears to be most advantageous since it avoids the auxiliary attachment and removal steps. For practical reasons, the search focused on readily available amino alcohols.

Ephedrine derivatives showed some selectivity, the most promising results were obtained with the cinchona alkaloids. Quinine and dihydroquinine both gave the required S-isomer while quinidine gave the other R-isomer with similar stereoselectivity. We chose quinine for further development due to its availability and cost.

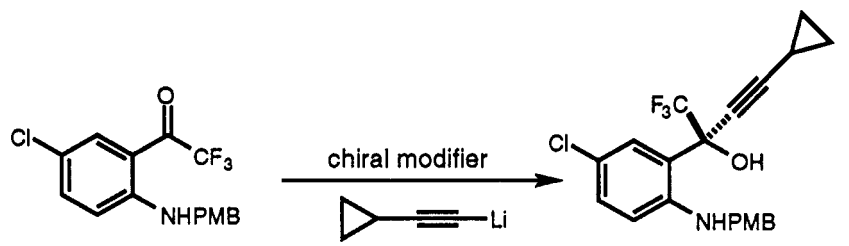


The protecting group on the distal nitrogen also played a key role in stereoselectivity of the addition. There is a substantial electronic influence as well as the effect of steric bulk at this remote position. The selectivity (98% ee) provided by the 9-anthrylmethyl group made it the protecting group of the choice for the synthesis of L-738,372. The scope of the reaction regarding imine variation remains to be explored.

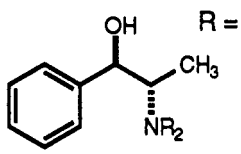
L-743,726

We have developed a highly enantioselective synthesis of L-743,726 based on a lithium cyclopropylacetylide addition to trifluoromethyl ketone intermediate in the presence of an ephedrine alkoxide (96-98 % ee).

Asymmetric approach : chiral modifier



chiral modifier



Norephedrine

R = Methyl : 48 % ee ; R = Ethyl : 65-70 % ee

R = Butyl : 60 % ee ; **R = Pyrrolidinyl : 82 % ee**

R = Piperidinyl : 72 %ee

Effect of deprotonation temperature on ee :

- 50 °C : 80-85 %ee ; **0 °C : 98 %ee**

Since the enantiomeric excess of the product alcohol using lithiated cinchona alkaloids was only in the moderate range of 50 - 60 %, we turned towards ephedrine alkaloids as another class of readily accessible amino alcohols. It was reported[4] that the ephedrine nitrogen substituents can play an important role in the % ee of the product during the asymmetric alkylzinc addition to aldehydes in the presence of amino alcohols. The best ligand we found was 1-phenyl-2-(1-pyrrolidinyl)propan-1-ol. Upon optimizing the reaction conditions with this amino alcohol, we noticed that lithiations performed at 0 °C and cooled to - 50 °C prior to adding the ketone gave desired addition product in high stereoselectivity (96-98 %ee). The optical purity of the product was enhanced to 99.5 % ee by crystallization of the product in 80 % yield. Thus, we have developed a highly enantioselective acetylide addition based on lithiated N-pyrrolidinyl norephedrine. We are currently studying the unusual temperature effect on the stereoselectivity of this reaction.

Acknowledgement

I would like to thank my colleagues in the Process Research group at Merck, especially Dr. Skip Volante, Dr. Ed Grabowski, Dr. Tom Verhoeven and Dr. Paul J. Reider for their scientific and managerial leadership in guiding these projects.