

A practical asymmetric synthesis of LTD₄ antagonist

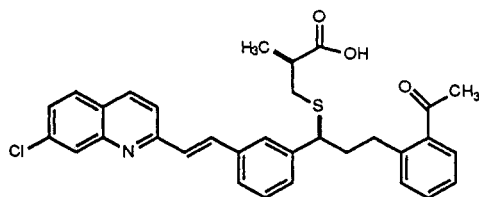
I. Shinkai, A.O. King and R.D. Larsen

Merck Research Laboratories
Process Research & Development
Rahway, New Jersey, 07065, U.S.A.

The asymmetric synthesis of L-699,392, a leukotriene antagonist, is reported. The main framework of the molecule is formed *via* a Heck reaction. The introduction of the asymmetric center was accomplished by the chiral reduction of prochiral ketone using *B*-chlorodiisopinocampheylborane. A very high asymmetric amplification was observed in which 95% ee product can be obtained from 70% optically pure α -pinene. A new reagent, which is prepared *in situ* from methylmagnesium chloride and lithium-hexamethyldisilazide, is used to convert the methyl ester to the methyl ketone in one step with essentially no impurities formed under the reaction conditions.

Introduction

As part of an ongoing program for the development of specific leukotriene antagonists¹ for the treatment of asthma and other associated diseases, L-699,392 [3-[(1*S*)-[3(*E*)[2-(7-chloroquinolinyl)ethenyl]phenyl]-3-(acetylphenyl)propylthio]-2(*S*)-methylpropionic acid was identified as a potent, orally active agent. This new class of compounds is an extension of the dithioacetal series, MK-0571/MK-0679. The 3-thiopropionamide 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.

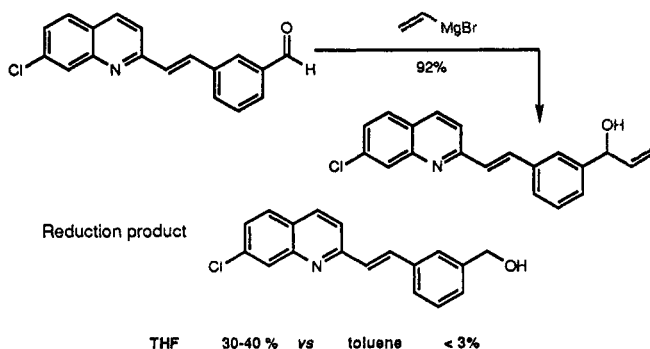


L-699,392

Results and Discussion

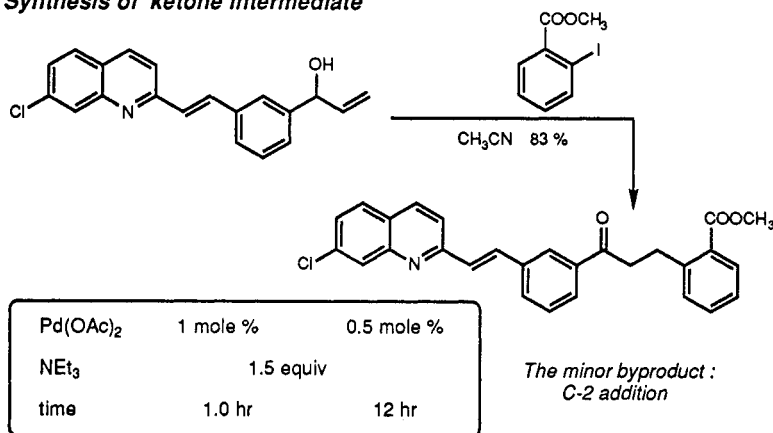
A number of new applications of the Heck coupling have appeared in literature². The addition of vinylmagnesium bromide to the aldehyde gave the desired allylic alcohol in 92% yield. Under the reaction conditions in THF 30-40% of the benzyl alcohol was

produced. The use of toluene as the solvent minimized the amount of reduction product to less than 3%.² The quality of vinylmagnesium bromide also affected the yield and purity of the product.



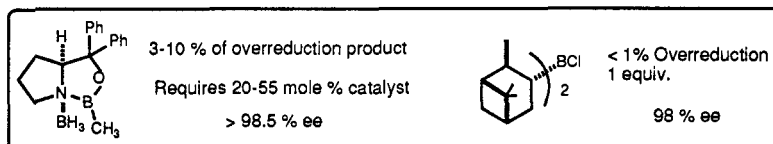
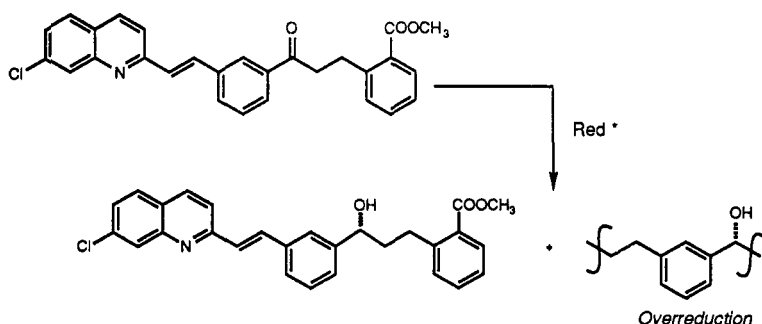
Although allylic alcohol was obtained in 92% yield, its isolation was not necessary. The product mixture was used directly in the next reaction. The Heck coupling of the allylic alcohol and methyl iodobenzoate was carried out in refluxing CH_3CN in the presence of triethylamine and 1 mol % of palladium acetate. On cooling to 22°C , the keto ester crystallized cleanly from the reaction mixture in 83% yield.

Synthesis of ketone intermediate



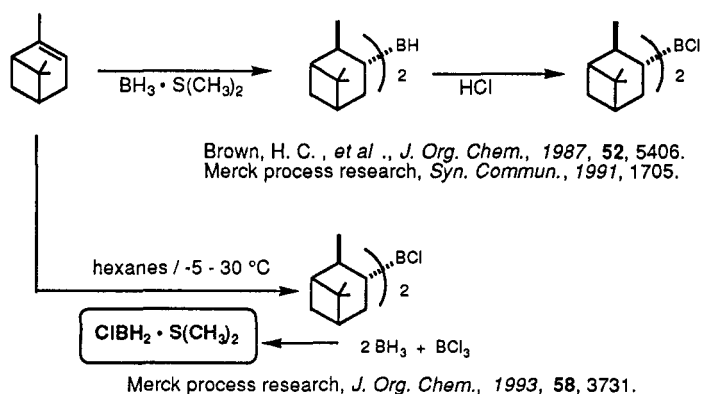
Two reagents for the chiral reduction³ of the ketone to the desired (R)-hydroxy ester were used: the oxazaborolidine-borane complex and *B*-chlorodiisopinocampheylborane. Although the former reagent provided exceptional enantioselectivity in the reduction (98.5% ee), the overreduction to the ethane-bridged by-product was a problem. The latter borane reducing reagent⁴, although used stoichiometrically, can be prepared cheaply and easily from α -pinene and borane. The reagent showed no propensity for reduction of the $\text{C}=\text{C}$ bond (< 1%) and gave only a slightly lower enantiomeric excess (98%).

Chiral reduction

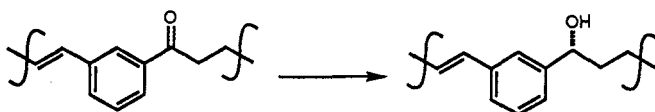


During the development of this reduction we have further improved on the use of this reagent. The reducing reagent can be prepared from 98% optically pure (-)- α -pinene and

Catalyst preparation

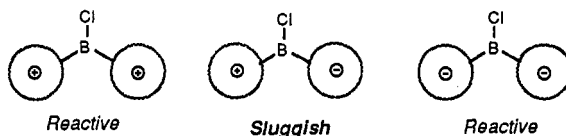


commercially available chloroborane-methylsulfide complex or, alternatively, a 2:1 mixture of borane and boron trichloride-methyl sulfide. Although dihaloboranes or alkylhaloboranes have been used before to prepare dialkylhaloboranes,⁵ this is the first application of this method to this reducing reagent. 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

(-) α -pinene (98 %ee)	$\xrightarrow{-20\text{ }^{\circ}\text{C}; 4\text{ hr}}$	97 % ee
(-) α -pinene (racemic)	$\xrightarrow{-20\text{ }^{\circ}\text{C}; 6\text{ hr}}$	52% conversion
(-) α -pinene (70%ee)	$\xrightarrow{-20\text{ }^{\circ}\text{C}; 4\text{ hr}}$	95 % ee

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

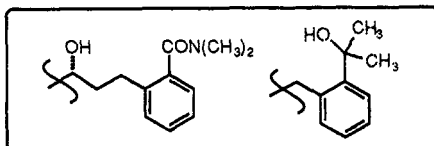
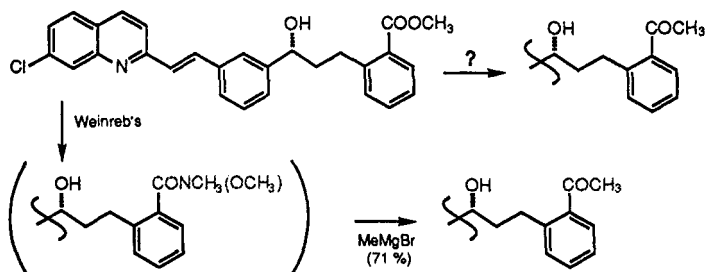
Asymmetric amplification

Pinene (racemic)	1	2	1
Pinene (70% ee)	72	26	2

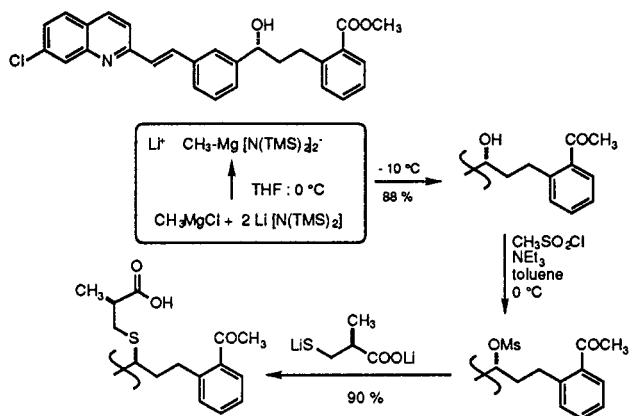
The key ratio = 72 : 2 (97 : 3)

"Predicted % ee = 94 % : Observed % ee = 95%"

The final stage of the synthesis of the main framework involved the selective conversion of the ester to the methyl ketone. Methods for the clean transformation of esters to ketones usually require the preparation of some intermediate esters or amides observed in Weinreb's procedure⁶. Isolation of the intermediate N,O-dimethylhydroxamide was not necessary; the methyl ketone was obtained in 71% overall yield from the ester by addition of methylmagnesium bromide.

Ketone formation

A one step method for a similar transformation has been recently developed.⁷ Thus, the reagent was prepared from lithiumhexamethyldisilazide and methylmagnesium chloride (2:1) in THF. Treatment of the ester with this reagent gave a 88% yield of the methyl ketone in one step. The suppression of the formation of tertiary alcohol was complete. This occurs by enolization of the methyl ketone with the lithium amide. Not unexpectedly, no racemization was observed at the hydroxy carbon.



The activation of the hydroxyl group for displacement by the mercaptan was best accomplished with methansulfonyl chloride and triethylamine in toluene. The mercaptan can be obtained by saponification of the commercially available S-acetyl ester. The dilithio salt is then reacted with mesylate in toluene gave desired L-699,329 in 88% yield with the inversion of configuration at the reaction center and no racemization was observed.

We would like to thank our colleagues in the Process Research group, especially E.G. Corley, R. K. Anderson, D. J. Mathre, A. S. Thompson, T. R. Verhoeven, and P. J. Reider for their help and R.A. Reamer and L. DiMichele for ¹¹B NMR studies.

References

1. McNamara, J.M.; Leazer, J.L.; Bhupathy, M.; Amato, J.S.; Reamer, R.A.; Reider, P.J.; Grabowski, E.J.J. *J. Org. Chem.* **54**, 3718 (1989). For the preparation of the chiral derivative (MK-679) by lipase-catalyzed asymmetric hydrolysis see: Hughes, D.L., et al., *J. Org. Chem.* **55**, 6252 (1990). LTD antagonists see: Zamboni, R. et al., *J. Med. Chem.* **35**, 3832 (1992). King, A.O.; Corley, E.G.; Anderson, R.K.; Larsen, R.D.; Verhoeven, T.R.; Reider, P.J.; Xiang, Y.B.; Belley, M.; Leblanc, Y.; Labelle, M.; Prasit, P.; and Zamboni, R.J.; *J. Org. Chem.* **58**, 3731 (1993).
2. Cabri, W.; Candiani, L.; Bedeschi, A.; Santi, R. *J. Org. Chem.* **57**, 5358 (1992).
3. Corey, E.J.; Bakshi, R.K.; Shibata, S. *J. Am. Chem. Soc.* **109**, 5551 (1987); Mathre, D.J.; Jones, T.; Xavier, L.C.; Blacklock, T.J.; Reamer, R.A.; Mohan, J.J.; Turner Jones, E.T.; Hoogsteen, K.; Baum, M.W.; Grabowski, E.J.J. *J. Org. Chem.* **56**, 751 (1991).
4. Brown, H.C.; Ravindra, N.; Kulkarni, S. *J. Org. Chem.* **44**, 2417 (1979). Simpson, P.; Tschaen, D.; Verhoeven, T.R. *Synth. Commun.* **21**, 1705 (1991).
5. Brown, H.C.; Srebnik, M.; Ramachandran, P.V.J. *J. Org. Chem.* **54**, 1577 (1989).
6. Weinreb, S.M.; Nahm, S. *Tetrahedron Lett.* **22**, 3815 (1981).

7. Conversion of the methyl ester directly to the isobutyl ketones was carried out by M. Williams, U. Dolling and G. Marchesini of Process Research at Merck Research Labs. The detailed results are forthcoming.

Ketone formation

