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LARGE SCALE ASYMMETRIC SYNTHESIS OF A BIOLOGICALLY ACTIVE SULFOXIDE

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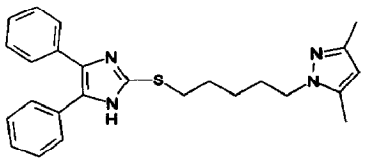
Key words: Asymmetric sulfoxidation; Optically pure sulfoxides; Modified Sharpless reagent

Abstract: *The asymmetric synthesis of sulfoxide RP 73163 is described. The synthetic strategy is based on the enantioselective oxidation of a suitably designed prochiral methyl sulfide, followed by α alkylation of the resulting sulfoxide.*

Sulfide **1** is a potent systematically available ACAT inhibitor[1] which is rapidly metabolised into the corresponding sulfoxide. Of the two sulfoxide enantiomers, only one - RP 73163 - exhibits useful biological activity, hence the need for a simple asymmetric synthesis of this compound which could be suitable for scale up.



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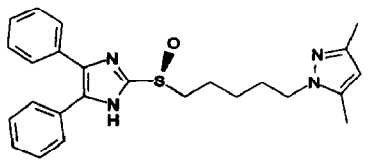
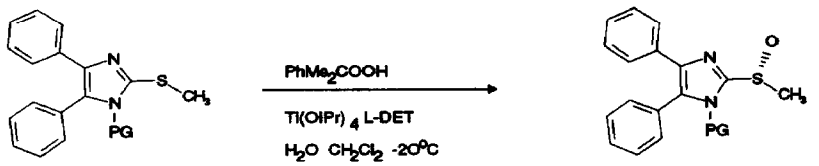


RP 73163

Among the possible routes to RP 73163, we elected to start our investigations with syntheses based on the enantioselective oxidation of sulfides such as **1** mediated by chiral titanium alcoholates. This asymmetric oxidation reaction was based on key modifications to the Sharpless reagent used for asymmetric epoxidation of allylic alcohols. Indeed, whereas the Sharpless reaction requires the use of one mole equivalent of $Ti(OiPr)_4$ per mole of diethyl tartrate (DET)[2] and gives little or no asymmetric induction in the oxidation of prochiral sulfides, it was discovered in Kagan's group[3] that very high levels of asymmetric induction could be achieved by addition of one mole equivalent of water ($Ti(OiPr)_4$:DET:H_2O, 1:1:1), or, in anhydrous conditions, 1 extra mole equivalent of DET ($Ti(OiPr)_4$:DET, 1:2) or the addition of both one mole equivalent of water and one mole equivalent of DET ($Ti(OiPr)_4$:DET:H_2O, 1:2:1) to the Sharpless reagent. Independently, Modena et al. reported similar results using a larger excess of DET in anhydrous condition ($Ti(OiPr)_4$:DET, 1:4).[4]

It must be pointed out that in the above titanium tartrate mediated reactions, the highest enantioselectivities have always been reported in the case of rigid (e.g. cyclic) sulfides or sulfides bearing two substituents of very different size (e.g. aryl methyl sulfides).[3-5] Unlike allylic alcohols which can actually form a chiral titanium alcoholate with the Sharpless reagent, thus leading to a conformationally restricted transition state,[6] sulfides can be considered as "non functional" substrates and the enantioselectivity is therefore mainly governed by steric effects. Indeed, when applying Kagan's optimised reaction conditions ($Ti(OiPr)_4$:DET:H_2O 1:2:1)[7] to the oxidation of sulfide **1**, the desired sulfoxide was obtained in good chemical yield but as *a racemic mixture*. We therefore decided to investigate the asymmetric oxidation of diphenylimidazolyl *methyl* sulfides and to take advantage of the relatively low pKa of the protons α to the resulting sulfoxide to subsequently elaborate the side chain.[8] This strategy would offer the following advantages: a) anticipated high enantioselectivity for the reasons mentioned above, b) a rigid - and probably solid - methyl sulfoxide intermediate, thus giving the possibility of enhancing the optical purity by recrystallisation if needed, c) the possibility of predicting the sulfoxide absolute configuration,[9] and d) the possibility of modifying the size and flexibility of the imidazole protecting group. Sulfides **2** to **7** were prepared by conventional methods from commercially available 4,5-diphenyl-2-imidazolethiol and subjected to asymmetric oxidation under the same conditions used with **1**.[10,7]

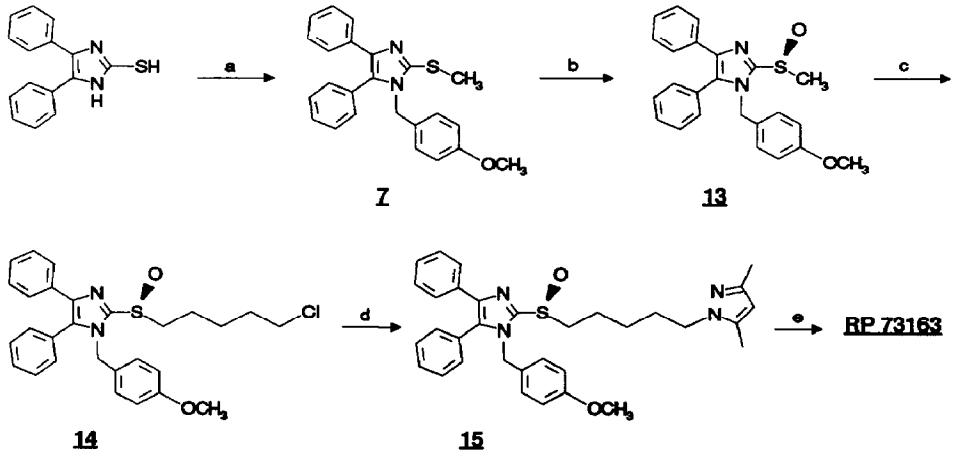


PG	sulfide[a]	sulfoxide[a]	% yield	% ee[b]
H	2	8	52[c]	65
Ac	3	8[f]	38[c]	95
$CH_2O(CH_2)_2OCH_3$	4	9	64[c]	93
$CH_2O(CH_2)_2OSiMe_3$	5	10	90[c]	90
CH_2Ph	6	11	66[d]	>99[e]
$CH_2C_6H_4$-*p*-OMe	7	13	71[d]	98-99[e]

notes: a) all compounds characterised by ^1H NMR, mass spectrometry and microanalysis, b) ee measured by chiral HPLC using a Chiralcel OD column except 8 whose ee was measured by 400 MHz ^1H NMR using (+)-binaphthol phosphoric acid as chiral shift reagent, c) isolated yields after purification by column chromatography, d) isolated yield after crystallisation of the product from the extraction liquors, e) as measured on crystallised material. f) hydrolysis occurred in presence of aqueous NaOH during the work-up.

Sulfide **2** was oxidised in 65 % ee only. Acetylated compound **3** gave as expected a much slower reaction but a dramatic increase in enatioselectivity. In this case, the reaction product was hydrolysed during the work-up giving the de-acetylated product **8** in 95% ee. This result prompted us to screen other protecting groups of the imidazole ring and a very high level of asymmetric induction was obtained

with sulfides 4, 5, 6 and 7. The highest enantioselectivities were achieved using benzyl and p-methoxybenzyl (PMB) protecting groups. The benzyl protecting group proved difficult to remove in the presence of the sulfoxide moiety and sulfoxide 13 was finally selected as the key intermediate for our synthesis. The asymmetric oxidation of sulfide 7 was optimised in order to minimise the use of expensive *D*-DET.[9] In this respect, the best reaction conditions were obtained using 0.5 mole equivalent of $Ti(OiPr)_4$ and 1 equivalent of *D*-DET in anhydrous conditions.[7] Under these conditions, and after crystallising the crude product from a boiling mixture of cyclohexane and ethyl acetate, sulfoxide 13 could routinely be obtained as a white crystalline solid in 75% yield and 98 to 99% ee without chromatography. Lower amounts of titanium tartrate led to reduced enatioselectivities and chemical yields. Alkylation of 13 by 4-chloro-1-iodobutane using LDA as a base required the presence of a polar aprotic co-solvent such as HMPA or 1,3-dimethyl-2-imidazolidinone (DMI) and gave 14 as a viscous oil in quantitative crude yield. After reaction of 14 with dimethylpyrazole, deprotection was achieved without racemisation in refluxing trifluoroacetic acid in the presence of anisole. Recrystallisation of the final product gave RP 73163 in >99% ee.



7 13 14 15

All products characterised by NMR. mass spectrometry and microanalysis. Products isolated by crystallisation except 14. a) one-pot: i. Me_2SO_4 DMI THF RT 30 minutes. ii. t-BuOK p-methoxybenzyl chloride THF reflux 1 hour (87% overall), b) 0.5 eq. $Ti(OiPr)_4$, 1 eq. *D*-DET, cumene hydroperoxide, CH_2Cl_2 -20°C 9 hours (75%)[11] 98-99% ee, c) LDA, $I(CH_2)_4Cl$, DMI, THF -20°C to RT (quantitative crude yield), d) 3,5-dimethylpyrazole, catalytic NaI, NaH, NMP, 80°C 4 hours (50%), e) i. anisole in CF_3COOH reflux 2 hours, ii. recrystallisation from tBuOMe/MeOH 9/1 (81%) >99% ee.

In conclusion, a synthesis of enantiomerically pure RP 73163 was devised, based on the asymmetric oxidation of a suitably designed prochiral sulfide. This synthesis was successfully scaled-up and represents one of the first examples of asymmetric synthesis of a chiral sulfoxide on a multikilogram scale.

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7. Most of the published work on the optimisation of asymmetric sulfoxidation reaction conditions has been based on results obtained with methyl p-tolyl sulfide, where the highest enantioselectivitiy are achieved using cumene hydroperoxide with the system $Ti(OiPr)_4$:DET:H_2O (1:2:1) in dichloromethane at -20°C (see ref. 3d). We have used these conditions to perform the asymmetric oxidation of sulfides **1** to **6** and for the first non optimised oxidation of **7**. *It must be pointed out that what is true for methyl p-tolyl sulfide does not necessarily apply to other sulfides for which the most enantioselective or more practical combination might be different.* See ref 3,4, 5 and Phillips, M. L.; Berry, D. M.; Panetta, J. A. *J. Org. Chem.* **1992**, *57*, 4047.

8. For α-alkylation of sulfoxides, see for instance: Solladie, G. *Synthesis* **1981**, 185. Davis, R.; Kern, L. J.; Pfister, J. R. *J. Am. Chem. Soc.* **1988**, *110*, 7873.

9. The (S) absolute configuration of RP 73163 was first established by this work using the experimental rule for aryl *methyl* sulfides (*L*-DET gives (R)-sulfoxides[3c]) and later confirmed by X-ray crystallography. Unnatural *D*-DET had therefore to be used to get the desired enantiomer.

10. For convenience, the primary screening of protecting groups was done using natural *L*-DET as chiral ligand. The synthesis of RP 73163 was then carried out using *D*-DET (see note 9).

11. The previous procedures published by Kagan *et. al.*[3] describes the hydrolysis of the reaction mixture with water, giving a gel very difficult to filter. We found that using 1N HCl washed out the titanium salts without racemising the sulfoxide **13** left in the organic layer.

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