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TETRAHEDRON: *ASYMMETRY*

Asymmetric synthesis of esomeprazole

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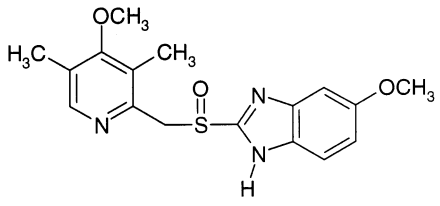
Abstract

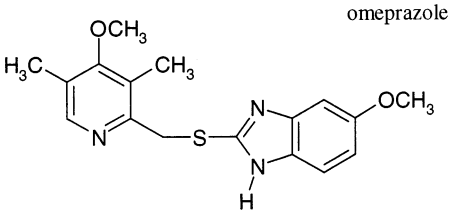
A highly efficient synthesis of esomeprazole—the (*S*)-enantiomer of omeprazole—via asymmetric oxidation of prochiral sulphide **1** is described. The asymmetric oxidation was achieved by titanium-mediated oxidation with cumene hydroperoxide (CHP) in the presence of (*S*,*S*)-diethyl tartrate [(*S*,*S*)-DET]. The enantioselectivity was provided by preparing the titanium complex in the presence of **1** at an elevated temperature and/or during a prolonged preparation time and by performing the oxidation of **1** in the presence of an amine. An enantioselectivity of >94% ee was obtained using this method.

1. Introduction

5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulphinyl]-1*H*-benzimidazole, which has the generic name omeprazole, is the prototypical compound of a class of highly potent gastric acid secretion inhibitors.[1] Omeprazole—a racemic mixture—is successfully used against acid-related diseases. Unlike the histamine H_2-receptor antagonists, such as cimetidine and ranitidine, omeprazole acts as an inhibitor of the gastric H^+, K^+-ATPase, the gastric acid pump.[2]



omeprazole



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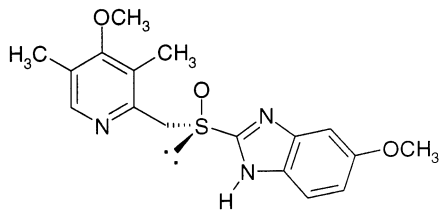

esomeprazole

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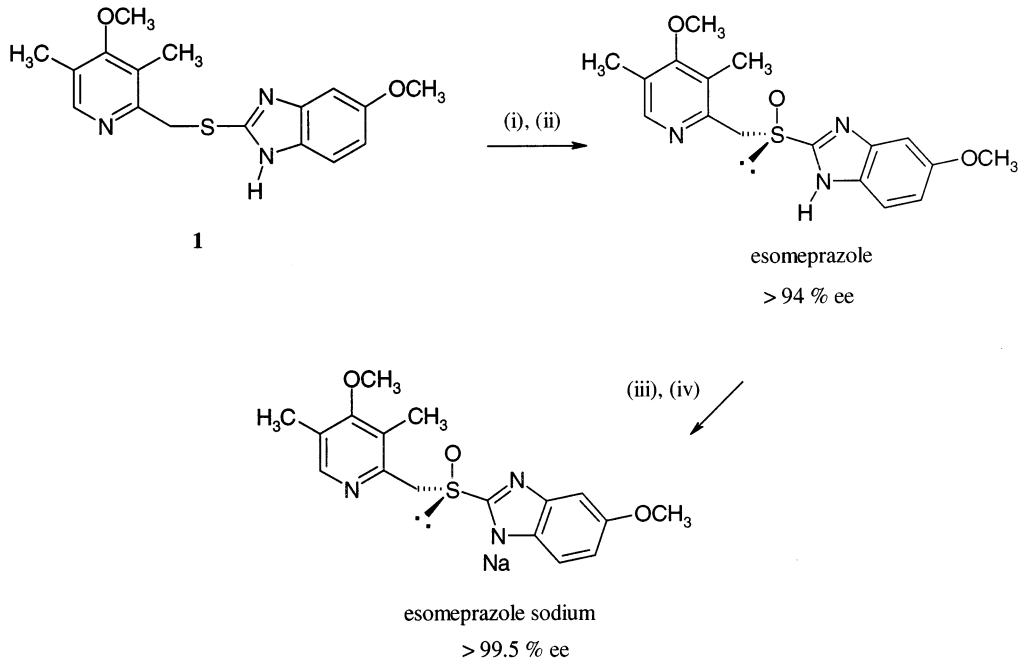
Esomeprazole—the generic name of the (*S*)-enantiomer[3] of omeprazole—is currently under registration as Nexium™, a new proton pump inhibitor. Consequently, we required an efficient synthesis of esomeprazole which could be used on a large scale.[4] Having considered different synthetic alternatives, we soon realised that the most attractive approach should be based on an enantioselective oxidation of sulphide **1**.[5] We also considered that asymmetric sulphoxidation would be even more desirable if a catalytic amount of a chiral catalyst could be employed rather than a stoichiometric amount of a chiral oxidant such as one of the Davis chiral oxaziridines.[6] We were however, able to oxidise sulphide **1** and obtained 40% ee using such a reagent[7] and the enantiomeric excess could be further enhanced to over 94% ee by a crystallisation method.[8] In spite of this we did not consider the oxaziridines to be applicable in production scale.

Having contemplated the different metal-catalysed chiral oxidations described in the literature[9] we regarded a modification[10] of the Sharpless reagent[11] to be a good candidate for the ideal chiral catalyst. However, asymmetric sulphoxidation using the modified Sharpless reagent has previously been associated with two fundamental limitations. Firstly, most of the highly enantioselective reactions so far reported in the literature employ stoichiometric amounts or near stoichiometric amounts of a chiral Ti-complex.[12] Secondly, oxidation of sulphides substituted at sulphur with two large groups which is the case of sulphide **1** generally gives little or no asymmetric induction.[13] Indeed, our first attempt at applying a titanium-mediated oxidation to our specific case, following Kagan's original method,[10a] gave very nearly racemic omeprazole.[14] We persevered with the modified Sharpless reagent despite the lack of success in the initial experiments. Eventually we were rewarded with a breakthrough when an amine was added to the oxidising system and the method for preparing the chiral titanium complex was altered as compared to state of the art.[10]

2. Results and discussion

Three alterations were introduced to the original procedures,[10] which taken together enabled an oxidation of sulphide **1** in over 94% ee[15] (Scheme 1). Firstly, the preparation of the titanium complex—including $Ti(O\text{–}iPr)_4$, (*S*,*S*)-DET and water—was performed in the presence of sulphide **1**. Secondly, the solution of titanium complex was equilibrated at an elevated temperature and/or for a prolonged time.[16] Thirdly, the oxidation was performed in the presence of an amine, such as *N*,*N*-diisopropylethylamine. Each of the modifications enhances the enantioselectivity on their own. However, in order to ensure a very high enantiomeric excess of formed sulphoxide it was necessary to introduce all of the three alterations. The enantiomeric excess of the product could then be further enhanced by preparing a metal salt of crude esomeprazole and subsequently crystallising the salt from a suitable solvent.[4c]

Several striking features of the oxidation reaction are in very sharp contrast to what has been reported previously in the literature for titanium-mediated asymmetric sulphoxidations in general. One is that the enantiomeric excess of formed sulphoxide can still be high, in spite of the fact that the sulphur atom of sulphide **1** bears two seemingly similar-size groups.[13] Another feature is that we were able to obtain a high enantioselectivity even when catalytic quantities of titanium complex were employed.[12] Esomeprazole with over 91% ee can be obtained when 4 mol% catalyst is being used. We have observed however, that when using such a low amount of titanium complex the enantioselectivity occasionally is not reproducible and thus it is more

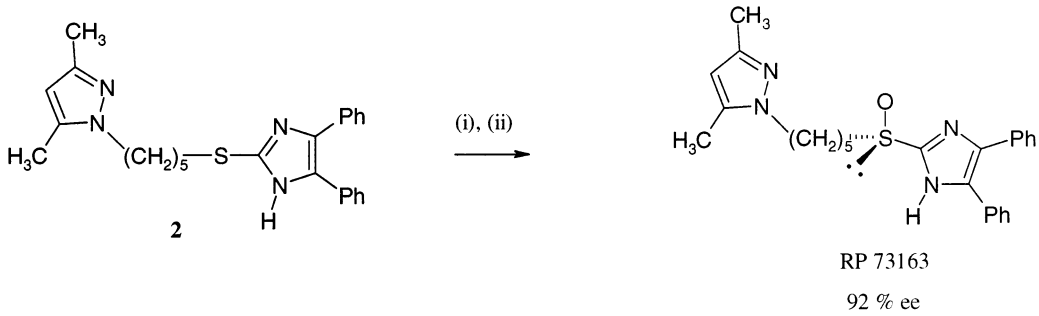


Scheme 1. Reagents and conditions: (i) Ti(O–*i*Pr)$_4$/(*S*,*S*)-DET/H_2O (0.3:0.6:0.1), $PhCH_3$ Δ; (ii) (*i*Pr)$_2$NEt/$PhC(CH_3)_2OOH$ (0.3:1), 30°C; (iii) NaOH (0.7), MIBK; (iv) crystallisation from MIBK and MeCN

preferable to use for instance 30 mol% of catalyst on a large scale. Still another feature of the method is that neither the choice of solvent[17] nor oxidation reaction temperature[18] affected the enantioselectivity dramatically. The oxidation reaction may thus be readily performed in non-chlorinated solvents, for instance toluene or ethyl acetate rather than dichloromethane (chlorinated solvents are less desirable with respect to environmental aspects), at or above room temperature with a high enantiomeric excess of esomeprazole still being obtained.

The reaction mechanism of the presented titanium mediated asymmetric oxidation of **1** is not understood in detail. The fact that catalytic quantities of titanium complex can be used without a dramatic decrease in enantioselectivity suggests a reaction mechanism involving a catalytic intermediate formed between the sulphide and the catalyst. Also in support of such a mechanism is the importance of equilibrating the titanium complex in the presence of the prochiral sulphide **1**. Furthermore, we believe that the N–H group of the imidazole moiety is important for the enantioselectivity. Hitherto we have not been able to demonstrate any enhancement of enantioselectivity using our new method for sulphide substrates containing an *N*-alkylated benzimidazole or when the substrate simply lacks a benzimidazole or an imidazole moiety. Interestingly, we have been able to demonstrate that the ACAT enzyme inhibitor RP 73163—an imidazole derivative—can be synthesised in 92% ee by treating the prochiral sulphide **2** with CHP using our new method (Scheme 2). It has previously been reported[13b,c] that treatment of sulphide **2** with Kagan's modified Sharpless reagent affords the corresponding sulphoxide as a racemic mixture.

The role of *N*,*N*-diisopropylethylamine in the oxidising system is unclear. Although other amines, such as triethylamine and 4-methylmorpholine, could be used these generally gave lower enantioselectivity. We do not believe that the effect of the added amine on the enantioselectivity



Scheme 2. Reagents and conditions: (i) $Ti(O–iPr)_4/(S,S)$-DET/H_2O (1:2.5:0.6), $PhCH_3$, Δ; (ii) $(iPr)_2NEt/PhC(CH_3)_2OOH$ (1:1), rt

is due to a simple proton abstraction from the N–H group of the benzimidazole moiety. We have observed that if a stronger base, such as DBU or 1,1,3,3-tetramethylguanidine, is used the enantiomeric excess of formed sulphoxide is dramatically decreased. In the presence of such strong bases the (*R*)-enantiomer of omeprazole unexpectedly dominates in the sulphoxide product in spite of the fact that (*S*,*S*)-DET is being used. One possibility that should not be excluded is that *N*,*N*-diisopropylethylamine and/or the N–H group of the benzimidazole moiety may participate in the chiral titanium complex. Interestingly, a titanium mediated asymmetric oxidation of methyl *p*-tolyl sulphide has recently been developed where the titanium complex being used contains chiral trialkanolamines as ligands.[19] When the peroxotitanium complex is formed in situ it has been suggested that titanium coordinates to four oxygen atoms as well as to the nitrogen atom of the alkanolamine.

Enantiomers of seven omeprazole analogues have also been prepared by the present method in our laboratories[15] (enantiomeric excess of crude sulphoxide is generally close to or above 90%).

3. Conclusions

A highly efficient synthesis of esomeprazole has been developed. The synthesis, which is based upon a titanium mediated asymmetric oxidation of the corresponding prochiral sulphide, is suitable for large-scale production. Our present finding, that a benzimidazole or an imidazole group adjacent to sulphur seems to steer the stereochemistry of formed sulphoxide, suggests that this type of functionality could be utilised as directing groups when synthesising chiral sulphoxides as templates in asymmetric synthesis.

4. Experimental

4.1. General

All commercially available reagents and solvents were employed without prior purification. The toluene, which in the experiment uses 4 mol% of titanium complex and is considered to

be the source of water, had an analyzed water content of 0.047% (w/w). The ^{1}H NMR spectrum was recorded on a Bruker AC-P 300 spectrometer (300.13 MHz). The optical rotation was determined with a Perkin–Elmer 241 polarimeter (D line). Enantiomeric excess, the conversion of sulphide **1** and the sulphoxide:sulphone ratio were all determined by HPLC analysis on a Chiralpak® AD column (50×4.6 mm), *iso*-hexane/ethanol/acetic acid (10:10:1) as eluent, UV detection at 302 nm, and a flow rate of 0.5 ml/min.

4.2. Large scale asymmetric synthesis of esomeprazole

Water (44 ml, 2.4 mol), (*S*,*S*)-diethyl tartrate (2.35 kg, 11.4 mol) and titanium tetraisopropoxide (1.60 kg, 5.6 mol) were added to a suspension of **1**[5] (6.2 kg, 18.8 mol) in toluene (25 L) at 54°C. The mixture was stirred for 50 minutes at 54°C, the temperature was then adjusted to 30°C and subsequently *N*,*N*-diisopropylethylamine (0.72 kg, 5.6 mol) and cumene hydroperoxide (84% in cumene, 3.30 kg, 18.2 mol) were added. After one hour at 30°C the conversion of sulphide **1** was 92%, the sulphoxide:sulphone ratio was 76:1 and the enantiomeric excess of crude sulphoxide was over 94%. The solution was extracted three times with aqueous ammonium hydroxide (12.5% of NH_3, 3×20 L). Subsequently, methyl isobutyl ketone (9 L) was added to the combined aqueous extracts. Then the aqueous phase was pH-adjusted with acetic acid, separated and extracted with an additional portion of methyl isobutyl ketone (9 L). To the combined organic solutions were added an aqueous solution of sodium hydroxide (49.6% of NaOH, 1.07 kg, 13.2 mol) and acetonitrile (70 L). The solution was concentrated during which the product gradually precipitated. There was obtained 3.83 kg of esomeprazole sodium as a white solid: enantiomeric excess = >99.5%; $[\alpha]_D^{20} = +30.5$ (*c* 0.01 g/mL, H_2O); ^{1}H NMR (DMSO-d_6) δ 2.15 (s, 3H), 2.20 (s, 3H), 3.68 (s, 3H), 3.71 (s, 3H), 4.41 and 4.58 (AB-system, $J = 12.9$ Hz, 2H), 6.56 (dd, $J = 8.5$ and 2.4 Hz, 1H), 7.00 (d, $J = 2.4$ Hz, 1H), 7.34 (d, $J = 8.5$ Hz), 8.30 (s, 1H).

4.3. Asymmetric oxidation of sulphide **1** using 4 mol% of catalyst

(*S*,*S*)-Diethyl tartrate (171 μL, 1.0 mmol) and titanium tetraisopropoxide (145 μL, 0.5 mmol) were added to a suspension of **1**[5] (4.0 g, 12.1 mmol) in toluene (12 mL) at 50°C. The mixture was stirred for 45 minutes at 50°C, the temperature was then adjusted to 25°C and subsequently *N*,*N*-diisopropylethylamine (85 μL, 0.5 mmol) and cumene hydroperoxide (84% in cumene, 2.1 mL, 12 mmol) were added. After 15 minutes the conversion of sulphide **1** was 96%, the sulphoxide:sulphone ratio was 35:1 and the enantiomeric excess of crude sulphoxide was over 91%. The product was not isolated.

Acknowledgements

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2. Fellenius, E.; Berglindh, T.; Sachs, G.; Olbe, L.; Elander, B.; Sjöstrand, S.-E.; Wallmark, B. *Nature* (*Lond.*) **1981**, *290*, 159–161.
3. The stereochemical assignment of the enantiomers of omeprazole is described in von Unge, S.; Langer, V.; Sjölin, L. *Tetrahedron: Asymmetry* **1997**, *8*, 1967–1970.
4. The enantiomers of omeprazole have previously been isolated by resolution procedures, see: (a) Erlandsson, P.; Isaksson, R.; Lorentzon, P.; Lindberg, P. *J. Chromatogr.* **1990**, *532*, 305–319. (b) Kohl, B.; Senn-Bilfinger, J. Patent appl. DE 4035455 (Priority date: November 8, 1990). (c) Lindberg, P.; von Unge, S. Patent appl. WO 94/27988 (Priority date: May 28, 1993).
5. Sulphide **1** is a key intermediate in the production of racemic omeprazole. The synthesis of **1** is described in Carlsson, E. I.; Junggren, U. K.; Larsson, H. S.; von Wittken Sundell, G. W. Patent appl. EP 074341. (Priority date: August 13, 1981).
6. (a) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703–5742. (b) Davis, F. A.; Reddy, R. T.; Weismiller, M. C. *J. Am. Chem. Soc.* **1989**, *111*, 5964–5965. (c) Davis, F. A.; Reddy, R. T.; Han, W.; Carroll, P. J. *J. Am. Chem. Soc.* **1992**, *114*, 1428–1437.
7. The chiral oxidant used was (3′*S*,2*R*)-(−)-*N*-(phenylsulphonyl)-(3,3-dichlorocamphoryl)oxaziridine. Its synthesis is described in Ref. 6c.
8. von Unge, S. Patent appl. WO 97/02261 (Priority date: July 3, 1995).
9. For recent reviews see: (a) Kagan, H. B.; Diter, P. *Organosulfur Chem.* **1998**, *2*, 1–39. (b) Kagan, H. B. In *Catalytic Asymmetric Synthesis;* Ojima, I., Ed.; Wiley–VCH: New York, 2000; Chapter 6C, pp. 327–356.
10. Although the Sharpless reagent for asymmetric epoxidation of allylic alcohols (see Ref. 11) affords little or no enantioselectivity when used in the oxidation of prochiral sulphides, two groups have independently developed modifications of the reagent that enantioselectively oxidise certain sulphides. Kagan and co-workers obtained aryl methyl sulphoxides with high enantiomeric excess by employing $Ti(O–iPr)_4$/DET/ROOH (R = *tert*-butyl or cumyl) in a ratio of 1:2:1 in the presence of one crucial equivalent of water; see: (a) Pitchen, P.; Duñach, E.; Deshmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188–8193. (b) Zhao, S. H.; Samuel, O.; Kagan, H. B. *Tetrahedron* **1987**, *43*, 5135–5144. On the other hand, Modena and co-workers achieved comparable results for analogous substrates using $Ti(O–iPr)_4$, DET and *t*-BuOOH in the absence of water but by increasing the amount of DET; see: (c) Di Furia, F.; Modena, G.; Seraglia, R. *Synthesis* **1984**, 325–326.
11. (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976. (b) Rossiter, B. E.; Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 464–465.
12. Kagan and co-workers have for instance demonstrated that the enantiomeric excess for *p*-tolyl methyl sulphoxide is dramatically decreased when less than 50 mol% of Ti-catalyst is being used (see Ref. 10b).
13. As opposed to the allylic alcohols employed in the Sharpless asymmetric epoxidation procedure, prochiral sulphides employed in asymmetric sulphoxidations using a modified Sharpless reagent are considered to be non-functional substrates. Thus, the enantioselectivity in these reactions is regarded to be derived mainly from the steric effects of the prochiral sulphide, i.e. by having a large difference in the size of the substituents attached to sulphur; see: (a) Kagan, H. B.; Rebiere, F. *Synlett* **1990**, 643–650. (b) Pitchen, P.; France, C. J.; McFarlane, I. M.; Newton, C. G.; Thompson, D. M. *Tetrahedron Lett.* **1994**, *35*, 485–488. (c) Pitchen, P. *Chem. Ind.* **1994**, 636–639.
14. Chemists at Hoffmann-La Roche have reported that Kagan's original method indeed could be used for the synthesis of the enantiomers of the omeprazole analogue Ro 18-5364 with a modest enantiomeric excess of the crude product (30%); see: Sigrist-Nelson, K.; Krasso, A.; Müller, R. K. M.; Fischli, A. E. *Eur. J. Biochem.* **1987**, *166*, 453–459. However, we were not able to reproduce this result in this study (see: Ref. 15).
15. For further experimental procedures, see: Larsson, E. M.; Stenhede, U. J.; Sörensen, H.; von Unge, P. O. S.; Cotton, H. K. Patent appl. WO 96/02535 (Priority date: July 15, 1994).
16. Kagan and co-workers have shown that control of temperature as well as the reaction time in the premixing of $Ti(O–iPr)_4$, DET and water is necessary in order to ensure high ee's in asymmetric oxidations of different sulphides; see: (a) Diter, P.; Samuel, O.; Taudien, S.; Kagan, H. B. *Tetrahedron: Asymmetry* **1994**, *4*, 549–552. (b) Brunel, J.-M.; Diter, P.; Duetsch, M.; Kagan, H. B. *J. Org. Chem.* **1995**, *60*, 8086–8088.

17. The choice of solvent has been reported earlier to have a pronounced influence on the enantiomeric excess of sulphoxides obtained by Kagan's original method; see e.g.: Kagan, H. B.; Duñach, E.; Nemecek, C.; Pitchen, P.; Samuel, O.; Zhao, S.-H. *Pure Appl. Chem.* **1985**, *57*, 1911–1916.
18. In general, a temperature lower than −20°C during the asymmetric oxidation of sulphides by Kagan's method has proven to be beneficial for the enantioselectivity (see Ref. 13a).
19. Di Furia, F.; Licini, G.; Modena, G.; Motterle, R. *J. Org. Chem.* **1996**, *61*, 5175–5177.