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Preparation of Optically Pure Esomeprazole and Its Related Salt[#]

Satya V. N. Raju, Koilkonda Purandhar,* Padi Pratap Reddy, Ghanta Mahesh Reddy, Lekkala Amarnath Reddy, Kikkuri Srirami Reddy, Keshaboina Sreenath, Kagga Mukkanti, and Ganji Santhi Reddy

Research and Development, Dr. Reddy's Laboratories Ltd., Integrated Product Development, Unit-III, Plot No. 116, S.V. Co-Op. Ind. Estate, Bollaram, Jinnaram, Medak District 502 - 325, A.P, India

Abstract:

The magnesium salt of (*S*)-isomer of omeprazole, with a trade name of Nexium, is the first proton-pump inhibitor developed as a single isomer for the treatment of acid-related diseases. A process for the preparation of the optically pure (*S*)-isomer of omeprazole through transition metal complex is described.

Introduction

Esomeprazole, the (*S*)-isomer of omeprazole, with a trade name of Nexium, is the first proton-pump inhibitor developed as a single isomer for the treatment of acid-related diseases. Because its activity is decreasing the amount of acid produced in the stomach, it is used for the treatment of ulcers, gastroesophagal reflux disease (GERD or heart burn), erosive esophagitis, and other dysfunctions following from excessive stomach acid production. It may be used in combination with two antibiotics to treat *Helicobacter pylori* (H. pylori) infection and duodenal ulcers.

It is chemically known as (T-4)-bis[5-methoxy-2-[(*S*)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazolato]magnesium (Figure 1).

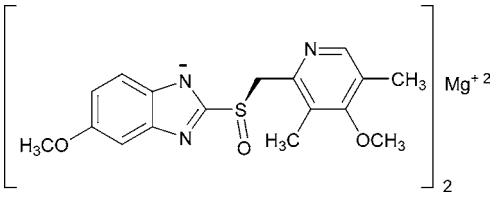

Figure 1.

However, most of the sulfinylation methods available today permit the introduction of a racemic sulfoxide group into a molecule. Methods available for the preparation of optically active sulfoxides are either optical resolution or asymmetric oxidation of the corresponding sulfides. Different methods giving access to esomeprazole have been described. The enantiomers of omeprazole and some of its analogues have been separated on a chiral stationary phase comprising trisphenylcarbamoyl cellulose coated on 3-aminopropyl silica. The racemisation half-life of omeprazole was estimated to be 1.5−2 h at 37 °C, but the nature of the supporting silica showed a crucial effect on the separations obtained.[1] Chankvetadze et al. reported the HPLC enantioseparation of selected chiral sulfoxides studied with the use of cellulose and amylose phenylcarbamate derivatives as chiral stationary phases (CSPs). The importance of various functional groups of chiral analytes as well as of the polysaccharide derivatives was evaluated for chiral recognition. A very high enantioseparation factor exceeding 110 was observed in the enantioseparation of 2-(benzylsulfinyl)benzamide (BSBA) on cellulose tris(3,5-dichlorophenylcarbamate) (CDCPC) using 2-propanol as a mobile phase. The enantiomer elution order was opposite that on cellulose and amylose phenylcarbamates.[2]

Asymmetric oxidations of sulfides by optically active peracids were also investigated, but in general, the yields were poor. A closely related process is the oxidation of an enantiomeric excess of sulfides in the presence of a chiral catalyst, which can be (−)-menthol or a substituted chiral succinate, or with optically active substituted *N*-halocaprolactam, but the enantiomeric excess is still very poor.[3] Another method for the preparation of (*S*)-omeprazole proceeds through inclusion of a complex with cyclodextrin from an enriched aqueous solution of the benzimidazole derivative or a pharmaceutically acceptable salt. This was followed by isolating the inclusion complex thus formed, but the complex formed is unstable, leading to a close monitoring throughout the process, and the compound thus formed was obtained with a purity between 90 and 95%.[4]

Larsson et al.[5] disclosed the asymmetric oxidation of sulfides by using cumene hydroperoxide with $TI(O\text{-}^{i}Pr)_4$, diethyl-D-tartrate, water in the ratio of (1:2:1) in methylene chloride at −23 °C. The product was isolated from this process, suffering from an undesirable amount of sulfone and an uncontrollable *R*-isomer content (more than 6%). A highly efficient synthesis of esomeprazole via asymmetric oxidation of prochiral sulphide is described.[6] The asymmetric oxidation was achieved by titanium-mediated oxidation with cumene hydroperoxide (CHP) in the presence of (*S*,*S*)-diethyl tartrate [(*S*,*S*)-DET] and a base. Another method is disclosed for the synthesis of esomeprazole using titanium as the catalyst together with a chiral auxiliary such as tartaric acid esters in the presence of water and a base such as diisopropylethylamine leading to prochiral sulfide pyridinemethazole

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* Corresponding author. E-mail: kpurandhar@drreddys.com. Fax: +91-8458 279619. Telephone: +91-0939 2481747.

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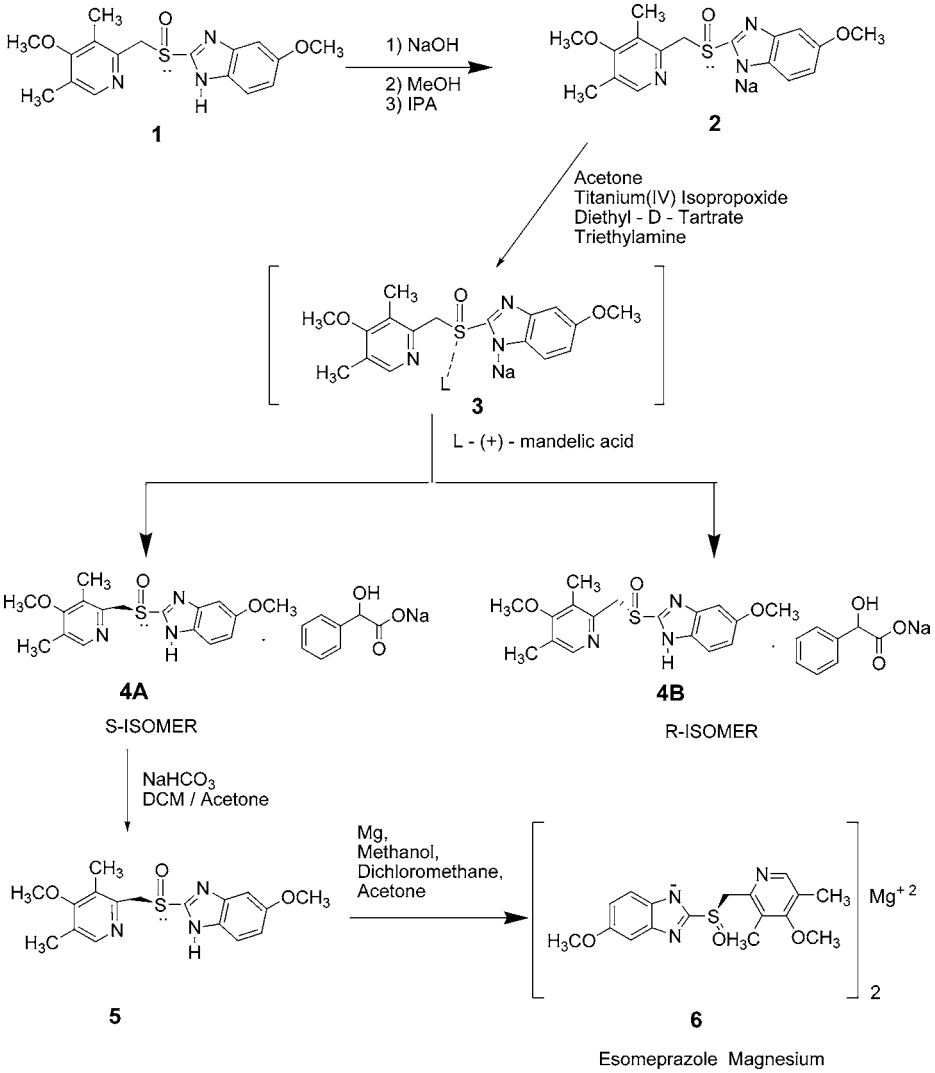
Scheme 1



with cumene hydroperoxide (CHP) at room temperature [7] with another catalytic asymmetric sulfide oxidation leading to the corresponding (*S*)-sulfoxide and also chromatographic separation of the mixture of sulfoxide diastereomers.[8]

The (*S*)-enantiomer of omeprazole was prepared via asymmetric oxidation of prochiral sulphide as 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] and a base.[9,10] The synthesis of esomeprazole was effected by using both asymmetric and racemic processes.[11]

Our approach lead us to separate the enantiomers with the help of transition metal complexes such as *trans*-dichloro-[ethyl-*p*-tolylsulfoxide][α-methylbenzylamine]platinum (II), bis(5-(2-aminoethyl)imidazole-N_3)tetrakis(isothiocyanato)-nickel (II), dichloro-bis(5,7-diphenyl-1,2,4-triazolo[1,5-*a*] pyrimidine)cobalt (II) (**2**), titanium (IV) isopropoxide, and some of the platinum and iron complexes with high purity and yields. In this paper we describe the process for the separation of the *S*-(−) enantiomer of racemic omeprazole, referred to as esomeprazole, with a purity of 99.97% (*S*-isomer) (Scheme 1).

Results and Discussions

Conversion of racemic omeprazole (**1**) to its corresponding sodium salt with sodium hydroxide in a mixture of methanol and isopropyl alcohol (IPA), which is further reacted with a chelating agent such as titanium (IV) isopropoxide and diethyl-D-tartarate in acetone yields a transition metal complex. Without isolating the transition metal complex thus obtained in a solution, it is further reacted with L(+)-mandelic acid into its diastereomeric salts, and the diastereomeric complex (**4A**) precipitates are filtered. The diastereomer (**4A**) is suspended in dichloromethane in the presence of aqueous sodium bicarbonate solution, providing the free species of sulfoxide with the desired configuration at the sulphur atom. The free species that is obtained is converted into its desired salt by treatment with the corresponding metal ion such as magnesium. As our main target is the (*S*)-isomer, the (*S*)-isomer was obtained having an

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optical purity of 99.97% by chiral HPLC (Chiral pack AD 50 mm × 4.6 mm or equivalent, flow rate 0.5 mL/min with a UV detector at 280 nm, load 20 μl, runtime 30 min at 25−30 °C), with SOR $[\alpha]^{25}_{D}$ −132° (c = 0.5 in methanol).

Experimental Section

The ^{1}H NMR spectra were measured in $CDCl_3$, using a 400 MHz spectrometer on Varian Gemini spectrometer; the chemical shifts are reported in δ (ppm) relative to TMS.

5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole Sodium. Mixtures of sodium hydroxide (12.8 g, 0.32 mol) flakes were dissolved in 100 mL of methanol and 920 mL of IPA maintaining the temperature at 25−30 °C. The solution was then filtered through Celite followed by washing the Celite with 116 mL of IPA. To the resultant filtrate, omeprazole (**1**, 100 g, 0.28 mol) was added at ambient temperature followed by stirring for 1−2 h. The product thus obtained was isolated by filtration, and the solid obtained was washed with 100 mLof IPA, followed by 225 mL of cyclohexane. The wet salt obtained was stirred for 1−2 h in a mixture of cyclohexane (500 mL) and water (9 mL), followed by filtration, and the obtained solid was washed with cyclohexane (250 mL). The solid obtained was dried at atmospheric pressure to afford 101 g, 95% yield of sodium salt of omeprazole **2**.

(*S*)-5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole Mandelate Salt (3). Omeprazole sodium (**2**, 200 g, 0.544 mol) was suspended into 2.4 L of acetone, diethyl-D-tartrate (112 g, 0.543 mol). Titanium (IV) isopropoxide (47.24 g, 0.272 mol) and triethylamine (164 g, 1.623 mol) were added consecutively at a temperature of 35−40 °C. A homogeneous solution thus formed in situ to which was added L-(+)-mandelic acid (94.73 g, 0.623 mol) followed by stirring for about 1−2 h. The separated solid was filtered, and the solid obtained was washed with acetone (1.0 L) to afford the compound of formula **4A**.

(*S*)-5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole (4A). Mandelic acid salt of esomeprazole (**4A**, 75 g) was suspended in a mixture of dichloromethane (800 mL) and 5% sodium bicarbonate solution (800 mL) followed by stirring for 15−30 min. The organic phase was separated from the aqueous phase, and the organic phase was distilled under reduced pressure to afford 73 g (yield: 77.6%) of the *S*-(−) form of omperazole (**5**) in crude form with a chiral purity of 99.84%.

Bis(5-methoxy-2-[(*S*)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-yl)magnesium Salt (6). Magnesium turnings (1.31 g, 0.054 mol) and dichloromethane (5 mL) were added to methanol (150 mL) and stirred under nitrogen atmosphere for 2−3 h. The magnesium methoxide solution formed at 40−45 °C was cooled to a temperature of 5−10 °C. Then, to a mixture of esomeprazole (**5**, 42.0 g, 0.121 mol) and methanol (150.0 mL) was added the resulting solution with simultaneous stirring for 2−3 h. Water (2.0 mL) was added to the reaction medium followed by stirring for about 45−60 min and then by filtering. The filtrate was distilled under reduced pressure at 35 °C. Traces of the methanol were completely removed by repeated distillation in the presence of acetone; subsequently, acetone (400 mL) was added to the above residue and stirred for about 45−60 min at a temperature of 25−35 °C. The solid mass thus obtained was filtered and washed with acetone (200 mL). The resulting compound was dissolved in methanol (222 mL) and water (8 mL) followed by stirring for 15−30 min at 25−30 °C. The resultant solution was filtered, and the filtrate was suspended into the water with constant stirring at a temperature of 0−5 °C for about 30−45 min. The solid thus obtained was filtered, followed by washing with water (300 mL) and drying at a temperature below 35 °C to yield 18 g of the desired amorphous form of white-colored esomeprazole magnesium, **6**, having an optical purity 99.97% with specific optical rotation (SOR) $[\alpha]^{25}_{D}$ −132° (c = 0.5 in methanol), ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (1H, br s), 6.94 (1H, br s), 7.90 (1H), 4.75 (2H, m), 8.18 (1H, s), 3.69 (3H, s), 2.22 (1H, s), 3.83 (1H, s), 2.22 (1H, s).

Acknowledgment

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Supporting Information Available

This material is available free of charge via the Internet at http://pubs.acs.org.

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