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An efficient asymmetric approach to the R-enantiomer impurity of esomeprazole

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Abstract: Esomeprazole {(S)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl) sulfinyl]-1*H*-benzimidazole} is a proton pump inhibitor used as an antiulcer drug. Its R-enantiomer **3** was synthesized with high enantioselectivity by asymmetric oxidation of prochiral sulfide **2** using the oxaziridinium salt **4**. Product **3**, useful as a reference for the quality control of esomeprazole, was characterized by ^{1}H and ^{13}C NMR, IR, and HRMS. The enantiomeric excess was determined by HPLC.

Keywords: asymmetric synthesis; impurity; quality control; R-enantiomer of esomeprazole.

Introduction

Safety and efficacy of pharmaceuticals are two fundamental issues of importance in drug therapy. The safety of a drug is determined by its pharmacological toxicological profile and the adverse effects caused by impurities. Therefore, the products intended for human consumption must be characterized completely. The quality and safety of a drug is generally assured by monitoring and controlling the impurities effectively. Esomeprazole (Figure 1) is a strong proton pump inhibitor used in the treatment of dyspepsia, peptic ulcer disease, gastroesophageal reflux disease and Zollinger-Ellison syndrome [1]. The drug suppresses gastric acid secretion by specific inhibition of the H^+/K^+-ATPase in the gastric parietal cells. It was launched as Nexium® in 2000 by AstraZeneca to improve the pharmacokinetic profile and potency of the racemic product. Only the S-enantiomer shows high biological activity.

Many synthetic routes [2–7] have been developed for the synthesis of esomeprazole in recent years. Impurities, including the R-enantiomer of esomeprazole, are generally formed during the synthesis. In order to enhance the safety of esomeprazole and effectively control drug quality, a facile preparation of the optically pure R-enantiomer of esomeprazole is desired. So far, several tedious methods [8–12] for the preparation of the R-enantiomer have been reported, including asymmetric synthesis and enantiomeric separation. In this report, we describe a facile synthetic approach to the R-enantiomer of esomeprazole.

Results and discussion

Our efficient approach is based on the work of Del Rio [13] of highly enantioselective asymmetric oxidation of prochiral sulfides using the oxaziridinium salt **4**.

As shown in Scheme 1, treatment of 5-methoxybenzimidazol-2(1*H*)-thione (**1**) with 2-(chloromethyl)-4-methoxy-3,5-dimethylpyridine hydrochloride gave the sulfanyl derivative **2** in a 95% yield [14, 15]. The highly enantioselective oxidation reaction of **2** by the oxaziridinium salt **4** proceeded smoothly in dichloromethane and furnished the desired product **3** with excellent enantioselectivity (98% ee). The chemical yield was 86%. The structure was fully supported by analysis of ^{1}H NMR, ^{13}C NMR, IR, and HRMS data.

Conclusion

A highly enantioselective synthesis of the R-enantiomer of esomeprazole has been developed using oxidation of prochiral sulfide **2** with the asymmetric oxaziridinium salt **4**.

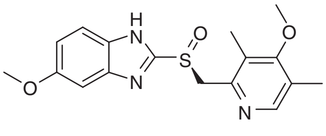

Figure 1 Chemical structure of esomeprazole (S-enantiomer). The R-enantiomer differs in absolute stereochemistry around the sulfur atom.

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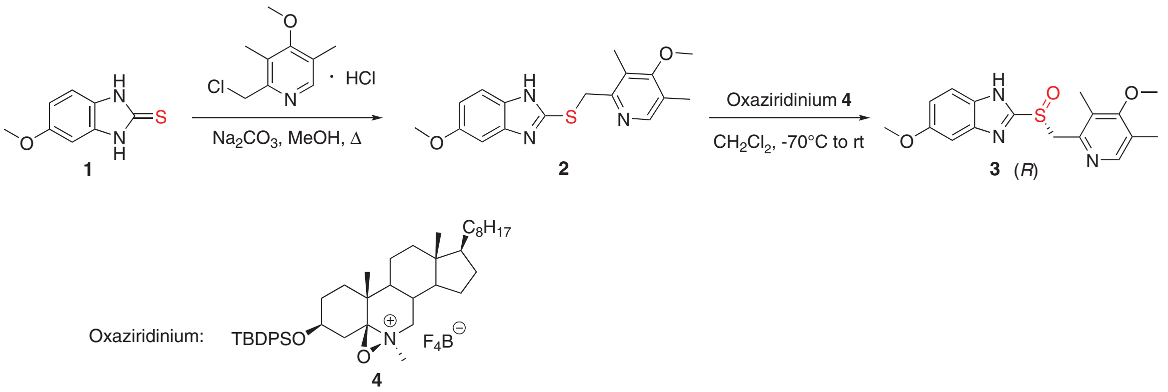

Scheme 1 Asymmetric synthesis of the R-enantiomer of esomeprazole.

Experimental

Melting points (mp) were determined on a Buchi 535 capillary melting apparatus and are not corrected. The ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in CDCl$_3$ on a Mercury Plus Varian 400 spectrometer. The low-resolution ESI mass spectrum was acquired on a Thermo Scientific LCQ spectrometer and the high-resolution mass spectrum was obtained using a Thermo Fisher Scientific LTQ FT Ultra spectrometer. IR spectra were determined on a Nicolet NEXUS-470 FT-IR spectrometer in KBr pellets.

Analytical TLC was performed on a Merck precoated TLC (silica gel 60 F$_{254}$) plate.

5-Methoxy-2-[3,5-dimethyl-4-methoxy-2-pyridyl]methylsulfanyl-1*H*-benzimidazole (2)

A 500 mL three-necked round bottom flask equipped with an efficient mechanical stirrer was charged with methanol (400 mL), 2-chloromethyl-3,5-dimethyl-4-methoxypyridine hydrochloride (48.6 g, 0.22 mol), 5-methoxybenzimidazol-1*H*-2-thione (**1**, 36.0 g, 0.2 mol) and sodium carbonate (46.6 g, 0.44 mol). The mixture was heated under reflux for 1.5 h while the progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in toluene and the solution was washed with aqueous solution of sodium carbonate and concentrated. The residue was crystallized from toluene to furnish 62.25 g (95%) of **2**; purity 99% (HPLC); mp 120.0–121.8°C; ^{1}H NMR: δ 2.26 (s, 3H), 2.30 (s, 3H), 3.76 (s, 3H), 3.82 (s, 3H), 4.38 (s, 3H), 6.79 (m, 1H), 7.03 (d, 1H, $J = 2.5$), 7.39 (d, 1H, $J = 8.5$), 8.24 (s, 1H); ^{13}C NMR: δ 165.0, 155.9, 150.8, 148.5, 126.3, 125.5, 114.8, 110.9, 97.5, 60.1, 55.8, 35.2, 13.6, 11.3; MS: *m/z* 330.2 [M + H]$^+$; IR: *v* 2958, 1635, 1593, 1456, 1436, 1404, 1344, 1263, 1190, 1155, 1080, 1029, 837, 806, 657cm^{-1}.

(R)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole (3)

A 1000 mL three-necked round bottom flask equipped with an efficient mechanical stirrer, was charged with dichloromethane (500 mL) and compound **2** (8.22 g, 25 mmol). With stirring, the solution was cooled to -70°C under argon and treated with a solution of salt **4** (16.43 g, 25 mmol) in dichloromethane. The temperature of the mixture was allowed to reach slowly room temperature (about 3 h) before work up. The progress of the reaction was monitored by TLC. After the reaction has completed, the mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography to furnish white crystals of the sulfoxide **3**; yield 7.42 g (86%); enantiomeric excess 98%; purity 99.5% (HPLC); mp 154.0–156.0°C; $[\alpha]^{20}_{D}$ +155 (c = 0.5, CHCl$_3$); ^{1}H NMR: δ 2.18 (m, 6H), 3.66 (s, 3H), 3.81 (s, 3H), 4.80 (m, 2H), 6.90 (m, 2H), 7.60 (s, 1H), 8.17 (s, 1H); ^{13}C NMR: δ 164.4, 157.7, 151.2, 149.6, 148.8, 138.2, 135.4, 126.9, 126.4, 120.7, 113.6, 94.6, 60.7, 59.9, 55.7, 13.3, 11.5; HRMS: *m/z* 346.1225 [M + H]$^+$; IR: *v* 2937, 1624, 1589, 1566, 1471, 1431, 1396, 1305, 1269, 1205, 1151, 1076, 1026, 810, 621 cm^{-1}.

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