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Dedicated to Full Member of the Russian Academy of Sciences G.A. Tolstikov on his 75th anniversary

An Efficient Procedure for the Synthesis of Esomeprazole Using a Titanium Complex with Two Chiral Ligands

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Abstract—A procedure has been proposed for the selective preparation of Esomeprazole via asymmetric oxidation of the corresponding prochiral sulfide in the presence of a catalytic complex derived from titanium(IV) isopropoxide and two different chiral ligands, diethyl D-tartrate and (*R*)-*N*,*N*-dimethyl-1-phenylethanamine.

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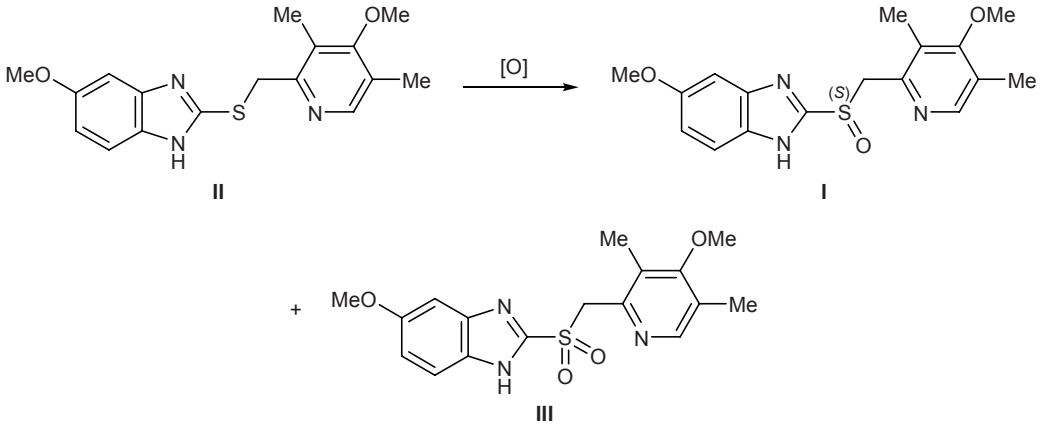
Esomeprazole (**I**) is a modern highly effective antiulcer drug; it is enantiomeric (*S* isomer) to Omeprazole, and it considerably exceeds the latter in clinical effect [1]. The main procedure for the preparation of Esomeprazole (**I**) has long been based on separation of the corresponding racemic mixture [2–4], but most part of the initial Omeprazole was not utilized, which stimulated search for methods for asymmetric oxidation of prochiral sulfide **II**. The oxidation of sulfide **II** with Davis' reagent [5], (3*S*,2*R*)-(−)-*N*-phenylsulfonyl-(3,3-dichlorocamphoryl)oxaziridine, gave optically active sulfoxide **I** with an optical purity of 40% [6] (Scheme 1); however, this procedure required a stoichiometric amount of the expensive oxidant, and it could not be regarded as efficient from the preparative viewpoint.

It seemed to be more promising to use modified Sharpless procedures [7] for asymmetric oxidation, but attempts to obtain Esomeprazole (**I**) according to these procedures were unsuccessful. For example, the oxidation of sulfide **II** following the procedure proposed in [8] [oxidation with organic peroxides at –20 to –40°C in the presence of a catalytic complex consisting of titanium(IV) isopropoxide Ti(OPr-*i*)$_4$, optically active diethyl tartrate, and 1 equiv of water] resulted in the isolation of racemic sulfoxide **I** [9]. Presumably, these

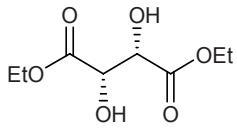
Scheme 1.



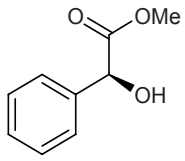
catalytic systems are unsuitable for asymmetric oxidation of sulfides having bulky substituents with comparable sizes.

Oxidation of sulfide **II** could give rise to a number of by-products such as sulfone **III** resulting from profound oxidation of the sulfur atom and decomposition products; these side processes considerably affect the yield of the target product, thus strongly restricting the choice of reagents and oxidation conditions.

In 1996, Larsson et al. [10] proposed a modified procedure for the stereoselective oxidation of sulfide **II** to Esomeprazole (**I**) on the basis of the method described in [8]. The following modifications were made [10]: (1) the catalytic complex was prepared from titanium(IV) isopropoxide, diethyl D-tartrate (**IV**), and water in the presence of sulfide **II**; (2) the complex was preliminary held (before addition of the oxidant) at elevated temperature; (3) the reaction was carried out in the presence of a base, preferably *N*,*N*-diisopropylethanamine. Each modification resulted in increased enantioselectivity, but the best results were obtained when all three modifications were applied simultaneously. 1-Methyl-1-phenylethyl hydroperoxide was used as oxidant, and toluene, as solvent; the amounts of Ti(OPr-*i*)$_4$ and diethyl D-tartrate (**IV**) were 30 and 60 mol %, respectively. After appropriate treatment of the reaction mixture, the crude product with an optical purity of up to 94% was converted into the corresponding sodium salt, and the optical purity of sulfoxide **I** increased to almost 100% (yield 55%).



IV



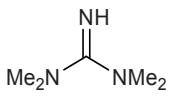
V

An essential disadvantage of the above procedure is formation of an appreciable amount (about 4%) of sulfone **III** which is fairly difficult to separate [11]. If the concentration of **III** exceeds 1%, preparation of pharmaceutically pure compound **I** is strongly complicated [11]. Further studies in this field were focused mainly on variation of procedures for the treatment of the reaction mixture with a view to increase purity of the target product, while the stage of enantioselective oxidation fell out of the scope of these studies [12, 13].

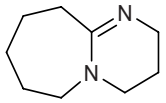
In 2003, Thennati et al. [11] modified the procedure proposed in [10] via replacement of diethyl D-tartrate by a unidentate ligand, (*S*)-(+)-mandelic acid methyl ester (**V**). Compound **V** was added in a large excess with respect to both Ti(OPr-*i*)$_4$ (740 mol %) and sulfide **II** (250 mol %). The yield of Esomeprazole (**I**) was lower (40%) than in [10], but the concentration of sulfone **III** in the product was less than 1%.

The above data show that no perfect procedure has been developed so far for the synthesis of Esomeprazole (**I**) with a high yield and low (<1%) concentration of sulfone **III**.

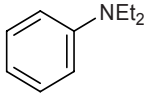
As we already noted, an important factor affecting the optical purity of Esomeprazole (**I**) obtained according to the procedure proposed in [10] is the presence of a base (*N*,*N*-diisopropylethanamine). The role of *N*,*N*-diisopropylethanamine remains so far unclear, but the use of other amines, such as triethylamine, 4-methylmorpholine, 1,1,3,3-tetramethylguanidine (**VI**), or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, **VII**) resulted in sharp decrease of the optical purity of the product [10]. We found that aromatic *N*,*N*-diethylaniline (**VIII**) as a base gives rise to a complex mixture of products. Thus the amine structure strongly affects both reaction direction and product purity. Presumably, *N*,*N*-diisopropylethanamine directly participates in the formation of chiral catalytic complex. Therefore, we expected that proper choice of an optically active amine as ligand for complex formation with Ti(OPr-*i*)$_4$ and diethyl tartrate could enhance the enantioselectivity of the oxidation and process and/or the chemical purity of Esomeprazole (**I**).



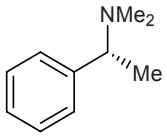
VI



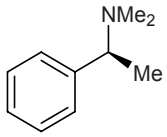
VII



VIII



IX



X

In fact, the oxidation of sulfide **II** with 1-methyl-1-phenylethyl hydroperoxide in the presence of a catalytic complex derived from titanium(IV) isopropoxide (46 mol %), diethyl D-tartrate (**IV**, 70 mol %), and (*S*)-*N*,*N*-dimethyl-1-phenylethanamine (**IX**, 49 mol %) gave 57% of Esomeprazole sodium salt with an optical purity of no less than 99.5%, and the impurity of sulfone **III** did not exceed 0.3%. Replacement of compound **IX** by its enantiomer, (*R*)-*N*,*N*-dimethyl-1-phenylethanamine (**X**) allowed us to raise the yield of

Esomeprazole sodium salt to 64%, the optical purity and the concentration of sulfone **III** remaining almost the same.

Appreciable differences in the optical purities of the crude products (84% using compound **X** against 79% using amine **IX**) and in the yields of Esomeprazole sodium salt suggest considerable effect of the absolute configuration of *N*,*N*-dimethyl-1-phenylethanamine on the reaction stereoselectivity. Amine **IX** or **X** is likely to act as the second chiral ligand. We have found no published data on the use of metal complexes with two different chiral ligands in asymmetric oxidation of sulfides.

The oxidation of sulfide **II** in the presence of the complex derived from ligands **IV** and **X** occurs at a much lower rate (reaction time 4.5 h) than the reactions performed according to the procedures described in [10, 11] (1.5 and 2 h, respectively). Presumably, the high yield of Esomeprazole (**I**) according to our procedure is largely determined by high chemoselectivity of the process; this is confirmed, e.g., by the low concentration of sulfone **III**.

To conclude, we have developed a procedure for highly selective synthesis of Esomeprazole (**I**) via asymmetric oxidation of prochiral sulfide **II** in the presence of a catalytic complex derived from titanium(IV) isopropoxide and two different chiral ligands, diethyl D-tartrate (**IV**) and (*R*)-*N*,*N*-dimethyl-1-phenylethanamine (**X**).

EXPERIMENTAL

The ^{1}H NMR spectrum was recorded on a Bruker AV-300 spectrometer. The optical rotations were measured on an Optical Activity Polar 3005 polarimeter. The ratios of compounds **I**–**III** were determined by HPLC using a Millikhrom A-02 liquid chromatograph equipped with a 75×2-mm ProntoSIL-120-5-C18 AQ column (grain size 5.0 μm; eluent 0.1% of trifluoroacetic acid in methanol, flow rate 150 μl/min; UV detector, λ 210 nm; temperature 35°C); retention times: 6.9 (**II**), 6.5 (**I**), 6.3 min (**III**). The optical purity of compound **I** was determined by chiral HPLC using a Millikhrom 1 instrument (64×2-mm Kromasil CHI-DMB column, grain size 10 μm; eluent 10% of isopropyl alcohol in hexane, flow rate 100 μl/min; UV detector, λ 210 nm; temperature 35°C); retention times 6.1 and 7.5 min for the (*S*)- and (*R*)-enantiomers of **I**, respectively.

Commercial (*S*)-1-phenylethanamine (Acros, ee > 99%), (*R*)-1-phenylethanamine (Alfa Aesar, ee > 99%), and diethyl (–)-D-tartrate (Alfa Aesar, ee > 99%) were used. Toluene was preliminarily dehydrated by azeotropic distillation. 5-Methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl)methylsulfanyl]-1*H*-benzimidazole (**II**) was synthesized according to the procedure described in [14] from 5-methoxy-1*H*-benzimidazole-2-thiol (Alfa Aesar) and 2-chloromethyl-3,5-dimethyl-4-methoxypyridine hydrochloride (Alfa Aesar). (*S*)-*N*,*N*-Dimethyl-1-phenylethaneamine (**IX**), $[\alpha]_D^{26}$ = –62.7° (*c* = 2.4, $CHCl_3$), and (*R*)-*N*,*N*-dimethyl-1-phenylethanamine (**X**), $[\alpha]_D^{27}$ = +61.9° (*c* = 2.1, $CHCl_3$), were prepared by methylation of the corresponding amines with formaldehyde in aqueous formic acid according to the procedure reported in [15].

Asymmetric synthesis of (*S*)-5-methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl)methylsulfinyl]-1*H*-benzimidazole (I, Esomeprazole) and its sodium salt. *a*. A suspension of 0.545 g (1.66 mmol) of compound **II** in 2.5 ml of toluene was heated to 55°C, 9 μl (0.50 mmol) of water, 0.240 g (1.16 mmol) of diethyl D-tartrate (**IV**), and 0.220 g (0.77 mmol) of titanium(IV) isopropoxide were added, and the mixture was stirred for 1 h at 55°C. The mixture was then cooled to 30°C, 0.120 g (0.81 mmol) of amine **IX** was added, the mixture was stirred for 15 min, 0.270 μl (1.58 mmol) of 1-methyl-1-phenylethyl hydroperoxide (a 86.5% solution in isopropylbenzene) was added, and the mixture was stirred for 4.5 h at 30°C and extracted with 12.5% aqueous ammonia (3×3 ml). The aqueous extracts were combined, 3 ml of methylene chloride was added, the mixture was neutralized with acetic acid, the organic phase was separated, and the aqueous phase was extracted with methylene chloride (2×5 ml). The extracts were combined and evaporated to obtain 0.514 g of a mixture containing (according to the HPLC data) 82.4% of sulfoxide **I**, 9.0% of initial sulfide **II**, and ≤0.3% of sulfone **III**; the optical purity of sulfoxide **I** was 79%.

The product mixture, 0.498 g, was dissolved in 4 ml of acetonitrile, a solution of 0.070 g of sodium hydroxide in 0.075 ml of water was added, and the mixture was stirred for 1 h at room temperature. The precipitate was filtered off, washed with acetone, and dried on a filter. We isolated 0.335 g of (*S*)-5-methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl)-methylsulfinyl]-1*H*-benzimidazole sodium salt. Overall yield 57% (with account taken of the fraction of the crude product converted into sodium salt), optical purity >99.5%, $[\alpha]_D^{24}$ = +36.0° (*c* = 0.3, H_2O). The ^{1}H NMR spectrum of (*S*)-5-methoxy-2-[(4-methoxy-3,5-dimeth-

ylpyridin-2-yl)methylsulfinyl]-1*H*-benzimidazole sodium salt coincided with that reported in [9].

b. Following an analogous procedure, from 0.545 g (1.66 mmol) of compound **II**, 9 μl (0.50 mmol) of water, 0.240 g (1.16 mmol) of diethyl D-tartrate (**IV**), 0.220 g (0.77 mmol) of Ti(OPr-*i*)$_4$, and 0.120 g (0.81 mmol) of amine **X** we obtained 0.537 g of a mixture containing (according to the HPLC data) 82.3% of sulfoxide **I**, 8.8% of initial sulfide **II**, and ≤0.3% of sulfone **III**; the optical purity of crude sulfoxide **I** was 84%.

A 0.440-g portion of the isolated mixture was dissolved in 3.5 ml of acetonitrile, a solution of 0.070 g of sodium hydroxide in 0.075 ml of water was added, and the mixture was stirred for 1 h at room temperature. The precipitate was filtered off, washed with acetone, and dried on a filter. We thus isolated 0.320 g of (*S*)-5-methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl)methylsulfinyl]-1*H*-benzimidazole sodium salt. Overall yield 64% (with account taken of the fraction of the crude product converted into sodium salt), optical purity >99.5%.

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