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Davis Oxaziridine-Mediated Asymmetric Synthesis of Proton Pump Inhibitors Using DBU Salt of Prochiral Sulfide

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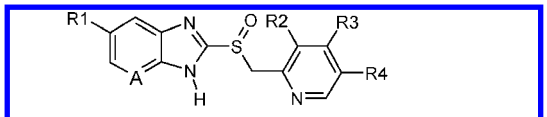
Abstract:

A simple and clean asymmetric synthesis of proton pump inhibitors using inexpensive 10-camphorsulfonyl oxaziridine is described. Here, we report the activation of prochiral sulfide by making the DBU salt that is capable of enhancing the reactivity and enantioselectivity.

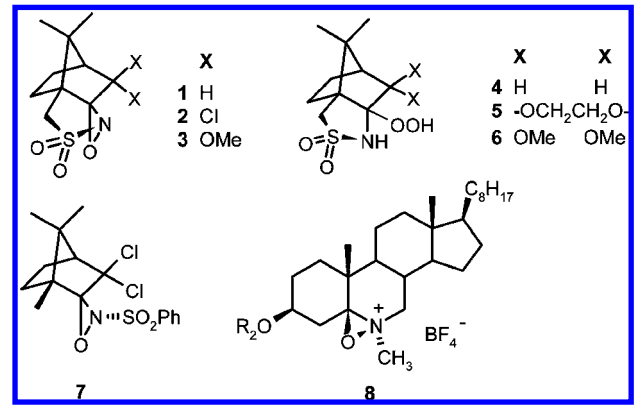
Introduction

Optically pure sulfoxides are not only utilized as chiral auxiliaries in asymmetric synthesis but they also constitute part of the structure of a group of proton pump inhibitors (PPI).[1−3] Although these drugs contain a chiral center, they are introduced in the racemic forms. However, the omeprazole has subsequently been marketed in the *S*-form as Esomeprazole which was the second largest selling drug in 2008 ($5.9 billions in US dollars).[4] Recently, the US Food and Drug Administration (USFDA) approved Kapidex (name changed to Dexilant in April 2010 by the FDA), which is the *R*-form of lansoprazole. Other prazoles in their chiral forms are either under development or have been approved.



Although, several synthetic methods[5−14] have appeared in the literature for asymmetric oxidation of pro-chiral sulfides, the most widely used method is undoubtedly the metal-catalyzed enantioselective sulfoxidation developed by Kagan et al. and Modena et al.[5−7] von Unge et al. suitably modified Kagan's method and successfully extended this methodology to prepare esomeprazole with 55% yield.[15] However, there are intrinsic issues with this method, the foremost being the formation of sulfone. The complex formation involving sulfide, titanium isopropoxide, water, and (*S*,*S*)-diethyl tartrate and oxidation in the presence of *N*,*N*-diisopropylethylamine are crucial steps. The author clearly mentions that enantioselectivity is dramatically decreased when DBU is used as the base. Several metal-catalyzed methods are also reported for the synthesis of PPIs.[16−19]

The first report on the asymmetric oxidation of sulfides with moderate ee using camphor-based (10-camphorsulfonyl)oxaziridine, **1**, was published by Davis et al.[20,21] The only way to improve enantioselectivity is by modifying the stereochemical and electronic environment of the oxaziridine molecule, which increases the cost of production.[22−26] Bulman Page et al. made an interesting observation that α-hydroperoxyamines **4**−**6** are more effective regents for asymmetric sulfoxidation than the corresponding oxaziridines.[27,28] α-Hydroperoxyamines are synthesized from (camphorsulfonyl)imine using H_2O_2 and DBU. However, it is pertinent to note that the above-mentioned methods are mainly accessed with unfunctionalized sulfides having no base labile hydrogen.



von Unge also discloses asymmetric oxidation for esomeprazole using **7** in carbon tetrachloride solvent and triethylamine with 22% yield.[29] Bohe et al[30] describes asymmetric synthesis

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Table 1. **Effect of base and solvent on asymmetric sulfoxidation of rabeprazole sulfide using 1[a]**

entry	base	solvent	time (h)	% sulfoxide[b]	% ee (conf.)[34]
1	no base	carbon tetrachloride	78	0.9	–
2	no base	dichloromethane	27	19.2	43.41 (*S*)
3	no base	isopropyl alcohol	15	11.96	12.28 (*R*)
4	triethylamine	carbon tetrachloride	22	39.9	9.04 (*S*)
5	triethylamine	dichloromethane	22	25.0	22.12 (*S*)[c]
6	triethylamine	isopropyl alcohol	18	38.38	22.08 (*R*)

[a] Reaction condition: stochiometric quantity of sulfide, **1**, and base were stirred at 25−30 °C in specified solvent and time. [b] Reaction mixture was analyzed, and results were based on HPLC area %, conf.: configuration. [c] % *R* isomer was more in comparison to entry 2.

Table 2. **Effect of different bases on asymmetric sulfoxidation of rabeprazole sulfide using 1[a]**

entry	base	solvent	time (h)	% sulfoxide[b]	% ee (conf.)[34]
1	hexamine	isopropyl alcohol	18	42.07	19.1 (*R*)
2	sodium hydroxide	isopropyl alcohol	18	89.66	25.15 (*R*)
3	dicyclohexylamine	isopropyl alcohol	18	49.39	29.3 (*R*)
4	diisopropylethylamine	isopropyl alcohol	18	9.21	30.66 (*R*)
5	quinaldine	isopropyl alcohol	18	[c]	25.92 (*R*)
6	Triton-B	isopropyl alcohol	18	[c]	30.04 (*R*)
7	(*S*)-α-methylbenzylamine	isopropyl alcohol	18	47.0	40.34 (*R*)
8	DABCO	isopropyl alcohol	18	[c]	16.0 (*R*)
9	DBU	isopropyl alcohol	16	85.25	75.52 (*R*)

[a] Reaction condition: Stochiometric quantity of sulfide, **1** and base were stirred at 25 to 30 °C in specified solvent and time. [b] Reaction mixture was analyzed, and results are based on HPLC area %. [c] Incomplete conversion on TLC.

of lansoprazole with 97% ee and 60% yield by using **8** as the oxidizing agent. However, the basic issue in this methodology is the number of steps required for the synthesis of **8**.

The above-reported methods show that there is still a need to develop a simple, mild, inexpensive, and high-yielding process for commercial production of optically pure PPIs. As per the literature, it is observed that (10-camphorsulfonyl)oxaziridine, **1**, is least preferred for enantioselective sulfoxidation. The basic premise of our work is to develop a simple protocol for the asymmetric synthesis of PPIs by using (10-camphorsulfonyl)oxaziridine.

Results and Discussion

We prepared oxaziridine **1**[31−33] and used it for asymmetric sulfoxidation of rabeprazole sulfide using literature conditions,[22−24] i.e. reaction in dichloromethane or carbon tetrachloride. We noted almost no conversion in carbon tetrachloride and poor conversion and enantioselectivity in dichloromethane. In order to check the role of base on the above reactions, we repeated the same experiments in the presence of triethylamine, and the results are described in Table 1. We observed better conversion in comparison to the reactions without base. This study provided us with a clue to explore the role of base in sulfoxidation reactions. We also observed better yield and ee when IPA was used as the solvent. This intrigued us to carry out experiments with different bases (Table 2) and solvents (Table 3).

As per the results in Table 2 (entries 2 and 9), strong bases like sodium hydroxide and DBU gave better results with respect

Table 3. **Solvent screening for asymmetric sulfoxidation of rabeprazole sulfide using DBU and 1[a]**

entry	solvent	time (h)	% sulfoxide[b]	% ee (conf.)[34]
1	water	18	62.54	40.91 (*R*)
2	acetonitrile	14	93.11	50.79 (*R*)
3	methanol	20	87.86	58.84 (*R*)
4	ethylacetate	18	88.3	59.41 (*R*)
5	dichloromethane	27	86.31	62.37 (*R*)
6	DMF	18	91.92	66.08 (*R*)
7	acetone	18	90.5	66.28 (*R*)
8	THF	18	90.98	69.98 (*R*)
9	carbon tetrachloride	22	78.91	70.48 (*R*)
10	DME	18	86.93	71.8 (*R*)
11	polyethylene glycol	30	90.81	72.5 (*R*)
12	toluene	16	91.08	73.8 (*R*)
13	isopropyl alcohol	16	85.25	75.52 (*R*)

[a] Reaction condition: Stochiometric quantity of sulfide, **1** and base are stirred at 25 to 30 °C in specified solvent and time. [b] Reaction mixture was analyzed, and the results are based on HPLC area %. [c] Incomplete conversion on TLC.

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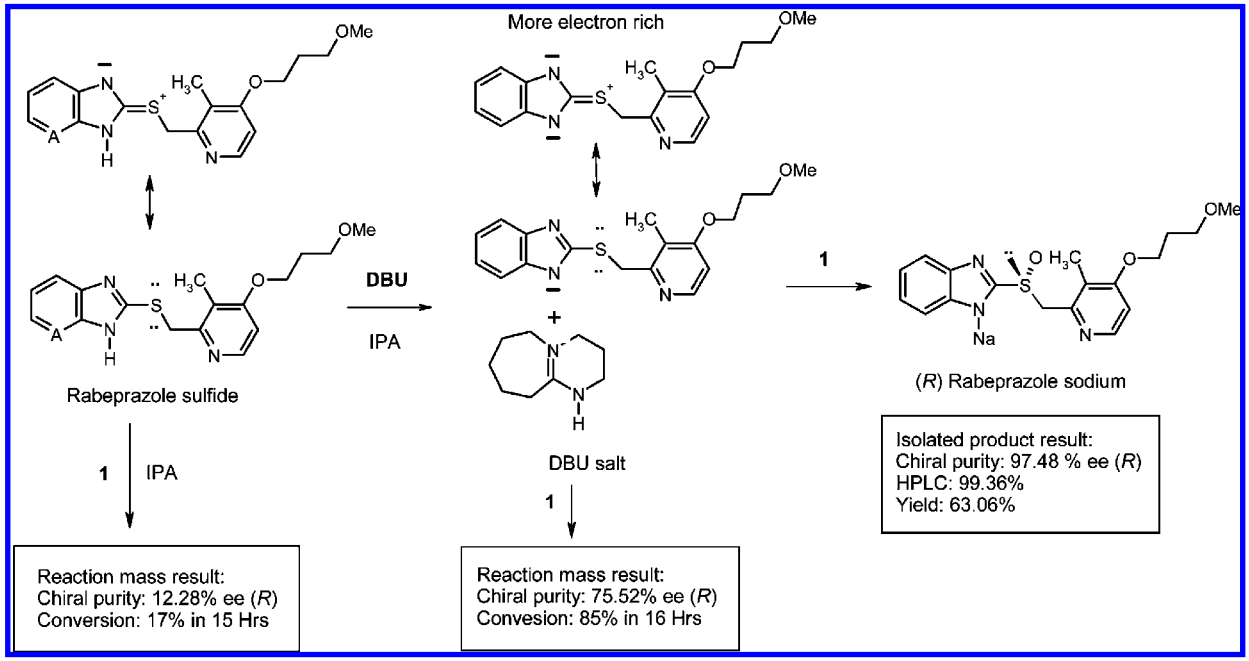
Scheme 1. **Diversity in enantioselective sulfoxidation due to the DBU salt of sulfide**



to conversion (89.66% and 85.25%, respectively) of sulfide to sulfoxide. However, DBU gave better enhancement in ee (75.52%) in comparison to sodium hydroxide (25.15%). The above results clearly demonstrated an important role of DBU in sulfoxidation reaction. We assume this high reactivity in case of strong bases like DBU and sodium hydroxide could be because of greater availability of the lone pair of electrons on sulfur to abstract the oxygen from oxaziridine (Scheme 1) in comparison to less basic amines (table 2).

As shown in Table 3, most of the solvents used gave good conversion to sulfoxide, but there were differences in enantioselectivity. Solvents as shown in entries 9−13 produced better enantioselectivity. We have chosen IPA over the other solvents as it is a class 3 solvent as per ICH guidelines.

We further studied the structural effect of various oxaziridines in our reactions. We found that the antipode of oxaziridine **2** gave rabeprazole with 85.71% ee (*S*), **3** gave rabeprazole with 37.95% ee (*S*). More surprisingly, oxaziridine **7** gave omeprazole with only 19.3% ee (*R*). It is to be noted that in our new approach, the increasing order of enantioselectivity observed with oxaziridines is in the direction **7** < **3** < **1** < **2** which is not in exact agreement with the literature i.e **1** < **2** < **3** < **7.**[23−25]

Conclusion

In summary, we have developed a simple, clean, and metal free protocol for preparation of PPI using Davis oxaziridine **1**. This process is also cost-effective as the imine after oxidation is recoverable and can be reused.

Experimental Section

We prepared oxaziridines **3** and **7** as per the procedure developed by Davis and Page.[23,32,33] Antipode of **2** was purchased from Sigma Aldrich. As shown in the experiments, initial ee obtained during reaction monitoring was further improved during work up to 97−99%. In the scale-up experiments conducted to establish the protocol, we have deliberately used substoichiometric quantities (0.97−0.99 equiv) of oxaziridine in order to minimize over-oxidation without compromising yield and ee.

(*S*)-Omeprazole Sodium. To a solution of omeprazole sulfide (800 g, 2.42 mol) and DBU (369.8 g, 2.43 mol) in isopropyl alcohol (5.6 L) was added (1*R*)-(−)-(10-camphorsulfonyl)oxaziridine (529 g, 2.3 mol) at 10−15 °C. The reaction mixture was stirred at 25−30 °C for 18 h. The precipitated (camphorsulfonyl)imine was filtered, washed with isopropyl alcohol (800 mL), and dried (466 g, 94.7% recovery). The filtrate was concentrated under vacuum, water (6.4 L) was added to the residue, and pH was adjusted to 8.2 by using 50% aqueous acetic acid. The sulfoxide was extracted with ethyl acetate (3.2 L); the organic layer was washed with brine solution (1.6 L) and concentrated under vacuum. A solution of sodium hydroxide (92.3 g) in water (4 L) was added to the residue. The aqueous solution was washed with dichloromethane (1.6 L) and was concentrated under vacuum. The purification step for chiral purity enrichment: Acetone (1.6 L) and toluene (3.2 L) were added to the residue to get a suspension. The solid was filtered, washed with solution of acetone (533 mL) in toluene (1.0 L), and dried under vacuum to obtain 600 g of (*S*)-omeprazole sodium (67.26% yield) with 99.02% ee, HPLC purity 99.84, $[\alpha]^{25}_{D} = +27.12°$ ($c = 0.01$ g/mL, H_2O), ^{1}H NMR (400 MHz, CD_3OD): δ 6.7−8.17 (m, 4H), 4.9 (s, 1H, H_2O), 4.55−4.86 (ABq, 2H), 3.8 (s, 3H), 3.62 (s, 3H), 2.2 (s, 3H), 2.06 (s, 3H), 1.88 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 180.5, 166.0, 159.5, 156.6, 151.1, 151.0, 150.1, 147.3, 141.7, 129.0, 127.6, 118.6, 112.4, 100.0, 60.5, 60.4, 56.0, 24.2, 13.3, 11.5. Enantiomeric excess was determined by chiral HPLC on a chiral AG-P (4.0 mm × 150 mm, 5 μ) column eluting with acetonitrile/buffer mixture (130 mL:870 mL) at 0.8 mL/min flow rate and $\lambda = 302$ nm. Buffer was prepared from 3.55 g of

(34) For chiral purity, sulfoxides were isolated by selective extraction with aqueous sodium hydroxide solution from the reaction mixture, (washed with dichloromethane when isopropyl alcohol was used), the aqueous layer was neutralized with acetic acid, and the products were extracted into dichloromethane; after evaporation, the residue was analyzed on chiral HPLC.

disodium hydrogen phosphate in 1000 mL of water, and pH 7.5 was adjusted with orthophosphoric acid. Retention times were 4.42 and 6.12 min for (*R*)- and (*S*)-omeprazole, respectively.

(*R*)-Lansoprazole Sodium. To a solution of lansoprazole sulfide (2.5 kg, 7.07 mol) and DBU (1.07 kg, 7.07 mol) in isopropyl alcohol (17.5 L) was added (1*S*)-(+)-(10-camphorsulfonyl)oxaziridine (1.57 kg, 6.85 mol) at 10 to 15 °C. The reaction mixture was stirred at 25−30 °C for 18 h. The precipitated (camphorsulfonyl)imine was filtered, washed with isopropyl alcohol (2.5 L), and dried (1.3 kg, 89% recovery). The filtrate was concentrated under vacuum, and water (25 L) was added to the residue. The reaction mixture pH was adjusted to 9.25 by using 50% aqueous acetic acid (755 mL). The precipitated solid was filtered and washed with water (5 L). The wet solid was suspended in a solution of methanol (7.5 L) and sodium hydroxide (283 g) in water (26 L). The mixture was washed with dichloromethane (2 × 7.5 L). The purification step for chiral purity enrichment: The aqueous layer was concentrated under vacuum up to 17 L and stirred for 1 h at 25−30 °C. The precipitated solid was filtered, washed with water (1 L) and dried at 45 to 50 °C under vacuum to obtain 1.59 kg (*R*)-lansoprazole sodium (57.8% yield) with 97.45% ee, HPLC purity 99.73% and $[\alpha]^{25}_{D} = +81.6°$ ($c = 0.999\%$ in methanol). ^{1}H NMR (400 MHz, DMSO): δ 8.35 (d, 1H), 7.5 (m, 2H), 7.07 (d, 1H), 6.93 (m, 2H), 4.89 (m, 2H), 4.5 and 4.7 (ABq, 2H), 2.2 (s, 3H). ^{13}C NMR (100 MHz, DMSO): δ 161.9, 160.4, 152.7, 148.7, 145.3, 125.6, 122.8, 120.4, 117.8, 107.3, 65.7, 65.3, 65, 64.6, 59.6, 11.1. Enantiomeric excess was determined by chiral HPLC on Chiralpak AD-H, (4.6 mm × 250 mm, 5 μ) column eluting with *n*-hexane/isopropyl alcohol/ethanol/dibutylamine (760:120:120:0.5 v/v) mixture (1 mL/min., $\lambda = 285$ nm). Retention times 13.75 and 16.0 min for (*R*)- and (*S*)-lansoprazole, respectively.

(*R*)-Rabeprazole Sodium. To a solution of rabeprazole sulfide (1.0 kg, 2.91 mol) and DBU (0.45 kg, 2.95 mol) in isopropyl alcohol (7.0 L) was added (1*S*)-(+)-(10-camphorsulfonyl)oxaziridine (0.65 kg, 2.83 mol) at 10 to 15 °C. The reaction mixture was stirred at 25−30 °C for 18 h. The precipitated (camphorsulfonyl)imine was filtered, washed with isopropyl alcohol (2 L), and dried (574 g, 94.9% recovery). The filtrate was concentrated under vacuum; residue was dissolved in water (5 L) and filtered. The filtrate was washed with toluene (2 × 3 L). The aqueous layer pH was adjusted to 8.8 at 10−15 °C using dilute acetic acid, and the sulfoxide was extracted in ethyl acetate (9 L). The ethyl acetate layer was washed with brine (2.0 L) and concentrated under vacuum to obtain the residue. The residue was dissolved in a solution of sodium hydroxide (128 g) in water (5.0 L), and the aqueous solution thus obtained was washed with dichloromethane (2 × 2.5 L). The aqueous layer pH was adjusted to 9.5 by using dilute acetic acid at 10−15 °C, and the precipitated sulfoxide was filtered and washed with water (3 L). The purification step for chiral purity enrichment: Wet solid was dissolved in a solution of sodium hydroxide (128 g) in water (5.0 L). The reaction mixture pH was adjusted to 9.5 using dilute acetic acid at 10−15 °C. The precipitated sulfoxide was filtered and washed with water (3 L). The above purification step was repeated for four times to obtain wet solid (1.234 kg) with 98% ee (water content 43.3%). The wet solid was dissolved in dichloromethane (2.1 L), and the water layer was separated. Toluene (5.0 L) was added to the dichloromethane layer and concentrated under vacuum up to 5 L. A solution of sodium hydroxide (85.8 g) in water (136.5 mL) was added to the above concentrated mass, stirred for 8 h, and filtered. The wet solid was washed with toluene (2 × 1.0 L) and dried under vacuum at 40 °C to yield 700 g (*R*)-rabeprazole sodium (63.06% yield) with 97.48% ee, HPLC purity 99.36, $[\alpha]^{25}_{D} = +90.93°$ ($c = 0.5\%$ in methanol) on anhydrous basis, water content 8.25%. ^{1}H NMR (400 MHz, CD_3OD): δ 6.88−8.23 (m, 6H), 4.9 (s, 1H, H_2O), 4.59−4.88 (ABq, 2H), 4.1 (t, 2H), 3.51 (t, 2H), 3.3 (s, 3H), 2.07 (s, 3H) 2.0 (p, 2H). ^{13}C NMR (100 MHz, CD_3OD): δ 165.3, 160.1, 151.2, 149.0, 146.4, 124.5, 121.7, 118.3, 107.3, 69.8, 66.3, 60.1, 58.9, 30.0, 11.04. Enantiomeric excess was determined by chiral HPLC on a chiral AG-P (4.0 mm × 150 mm, 5 μ) column eluting with acetonitrile/buffer (14:86 v/v) mixture (0.5 mL/min., $\lambda = 210$ nm). Buffer was prepared from 3.56 g of disodium hydrogen phosphate in 1000 mL of water, and pH 7.0 was adjusted with orthophosphoric acid. Retention times 4.68 and 6.33 min for (*R*)- and (*S*)-rabeprazole, respectively.

(*S*)-Pantoprazole Sodium. To a solution of pantoprazole sulfide (2.5 kg, 6.8 mol) and DBU (1.03 kg, 6.77 mol) in isopropyl alcohol (17.5 L) was added (1*R*)-(−)-(10-camphorsulfonyl)oxaziridine (1.55 kg, 6.77 mol) at 10−15 °C. The reaction mixture was stirred at 25−30 °C for 18 h. The precipitated (camphorsulfonyl)imine was filtered, washed with isopropyl alcohol (2.5 L), and dried (1.25 kg, 86.7% recovery). The filtrate was concentrated under vacuum, water (25 L) was added to the residue, pH 7.5 was adjusted using 50% aqueous acetic acid (755 mL), and sulfoxide was extracted in ethyl acetate (17.5 L). The organic layer was washed with water (7.5 L) and concentrated up to 7.5 L volume, and cyclohexane (3.0 L) was added. The suspension thus obtained was stirred at 10−15 °C for 1 h, filtered, and washed with cold ethyl acetate (2.5 L) to obtain 3.6 kg of wet solid. The purification step for chiral purity enrichment: The wet solid was dissolved in ethyl acetate (17.5 L), concentrated up to 7.5 L volume, and cyclohexane (3.0 L) was added. The suspension thus obtained was stirred at 10−15 °C for 1 h, filtered, and washed with cold ethyl acetate (2.5 L) and dried under vacuum to yield 1.48 kg (56.9% yield) of *S*-pantoprazole with 99% ee and 99.76% HPLC purity. *S*-Pantoprazole sodium was prepared by adding aqueous sodium hydroxide to the solution of *S*-pantoprazole in dichloromethane and dried at 50 °C to give a white solid. ^{1}H NMR (400 MHz, DMSO): δ 8.23 (d, 1H) 7.45 (d, 1H) 7.25 (s, 1H) 7.09 (d, 1H) 7.04 (t, 1H) 6.73 (dd, 1H) 4.33 and 4.68 (ABq, 2 H) 3.77 and 3.80 (2s, 6 H). ^{13}C NMR (100 MHz, DMSO): δ 164.6, 159, 147.4, 147.2, 146.6, 145.2, 145.1, 144.9, 115.6, 118.2, 120.7, 111.8, 108.6, 108.2, 61.6, 57.9, 56.6. Enantiomeric excess was determined by chiral HPLC on Chiralcel OJ-RH (4.6 mm × 150 mm, 5 μ) column eluting with acetonitrile/buffer (25:75 v/v) mixture (0.5 mL/min., $\lambda = 290$ nm). Buffer was prepared from 7.02 g of sodium perchlorate in 1000 mL of water. Retention times 11.43 and 13.77 min for (*S*)- and (*R*)-pantoprazole, respectively. $[\alpha]^{25}_{D}$ −109.52° ($c = 1.0$ on anhydrous basis, methanol) for ee = 99.86% (*S*).

(*S*)-Tenatoprazole Sodium. To a solution of tenatoprazole sulfide (420 g, 1.27 mol) and DBU (193.6 g, 1.27 mol) in isopropyl alcohol (5 L) was added (1*R*)-(−)-(10-camphorsulfonyl)oxaziridine (306.6 g, 1.33 mol) at 10−15 °C. The reaction mixture was stirred for 7 h at 10−15 °C followed by 8 h at 25−30 °C. The precipitated (camphorsulfonyl)imine was filtered, washed with isopropyl alcohol (840 mL), and dried (267 g, 93.63% recovery). The filtrate was concentrated under vacuum up to 840 mL, water (8.4 L) was added to the residue, and the pH was adjusted to 7.5 by using 50% aqueous acetic acid (130 mL) at 15−20 °C. The mixture was stirred for 2 h and filtered, and the residue was washed with water (1.26 L). The solid was suspended in water (3.78 L), and a solution of sodium hydroxide (55.86 g) in water (420 mL) was added slowly at 20−25 °C and stirred for 30 min to get a clear solution. The solution was washed with dichloromethane (2 × 840 mL), the pH of the aqueous layer was adjusted to 7.45 using aqueous acetic acid, and sulfoxide was extracted in dichloromethane (2 × 840 mL). The combined dichloromethane layer was washed with water (840 mL) and concentrated to 840 mL. Ethyl acetate (2.94 L) was added to the residual dichloromethane and further concentrated up to 2.52 L. The concentrated mixture was stirred at ambient temperature and filtered, and the residue was washed with ethyl acetate (1260 mL) and dried at 50−55 °C to obtain 340 g of solid. The purification step for chiral purity enrichment: The solid was stirred for 1 h in a solution of sodium hydroxide (38.68 g) in water (1 L). The racemic tenatoprazole obtained was filtered and washed with water (67 mL). Filtrate was washed with dichloromethane (670 mL). The aqueous layer was concentrated to 325 mL under vacuum, and acetone (3350 mL) was added and stirred for 2 h at 10−15 °C. The solid mixture was filtered, washed with acetone (2 × 335 mL), and dried at 50−55 °C to obtain (*S*)-tenatoprazole sodium 190 g (39.58% yield) with 99.2 % ee, 99.65% HPLC purity. $[\alpha]^{25}_{D} = -168°$ ($c = 0.1\%$ in DMF), ^{1}H NMR (400 MHz, CD_3OD): δ 8.22 (s, 1H), 7.68 (d, 1H,), 6.34 (d, 1H), 4.34−4.76 (ABq, 2H), 3.8 (s, 3H), 3.69 (s, 3H), 2.2 (s, 3H) 2.22 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 164, 161.6, 159.3, 156, 151.5, 149.4, 133.3, 128.4, 127.1, 125.8, 103.3, 60.1, 59.9, 53.1, 13.3, 11.61. Enantiomeric excess was determined by chiral HPLC on a chiral AD-H (4.6 mm × 250 mm, 5 μ) column eluting *n*-hexane/isopropyl alcohol/ethanol/dibutylamine (50:25:25:0.05 v/v) mixture (0.5 mL/min., $\lambda = 240$ nm). Retention times 12.0 and 17.4 min for (*S*)- and (*R*)-tenatoprazole, respectively.

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Supporting Information Available

Chiral HPLC chromatograms of reaction mixtures without base, with DBU and isolated (*R*) rabeprazole sodium salt; ^{1}H NMR and ^{13}C NMR spectra for (*S*) omeprazole sodium. This material is available free of charge via the Internet at http://pubs.acs.org.

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