Total synthesis of 5-hydroxyomeprazole

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Abstract

A convenient synthetic route for preparation of 5-hydroxyomeprazole (metabolite of omeprazole) was developed. During this work synthetic possibilities to attain the crucial precursor - [6-(chloromethyl)-4-methoxy-5-methylpyridin-3-yl]methanol - were studied and evaluated.

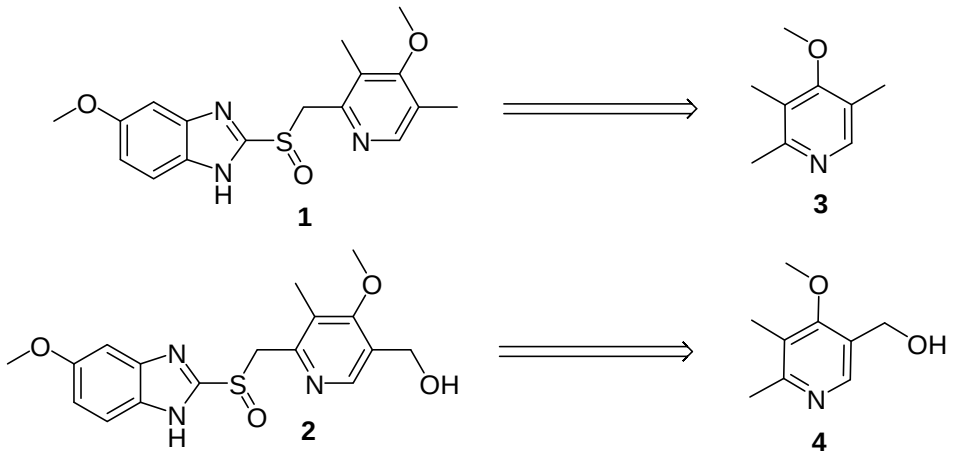
Keywords: Omeprazole, 5-hydroxyomeprazole, 5-methoxy-2-[[(4-methoxy-3-methyl-5-hydroxymethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, omeprazole metabolite, pyridine, total synthesis

Introduction

Omeprazole (**1**) and its analogues, so-called proton pump inhibitors that inhibit gastric acid secretion by interacting with the (H^+/K^+)-ATPase, is a class of compounds widely used in the treatment of dyspepsia, peptic ulcer disease, gastroesophageal and laryngopharyngeal reflux. The investigation of Omeprazole has disclosed many another useful properties. It was applied for the treatment of gastric ulcer caused by infection with *Helicobacter pylori*. It is known[1,2] that in liver omeprazole is metabolized by several cytochrome P-450 (CYP) isoenzymes to products of oxidation - omeprazole sulphone and 5-hydroxyomeprazole (**2**). Omeprazole and its metabolites are widely used in search for new applications of these compounds, in routine blood analysis,[3] studies of specific cases of metabolism[4] or pharmacokinetics,[5] in investigation of reactions with enzymatic catalysis.[6,7]

Although synthesis of omeprazole (**1**) and its analogues is well known,[8-10] to the best of our knowledge no data on the chemical synthesis of its primary metabolite 5-hydroxyomeprazole (**2**) is published. Present work introduces one of possible routes for a total synthesis of compound **2**. Since the structures of 5-hydroxyomeprazole (**2**) and omeprazole (**1**) differs only by substituent at 5-position of pyridine ring, we have decided to use the same synthetic strategy, i.e. conversion

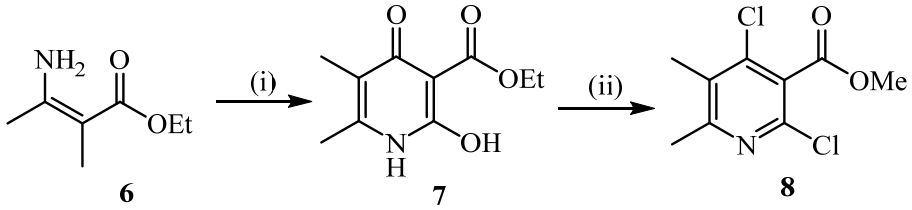
of 2-methyl group to 2-chloromethyl group in pyridines **3** and **4** and coupling of obtained intermediates with 5-methoxy-1*H*-benzimidazolethiol (**5**) (Scheme 1). While 5-methoxy-1*H*-benzimidazolethiol (**5**) is commercially available, to the best of our knowledge no literature data on the synthesis of pyridine **4** is published.



Scheme 1. Synthetic strategy of Omeprazole (**1**) and 5-Hydroxyomeprazole (**2**).

Results and Discussion

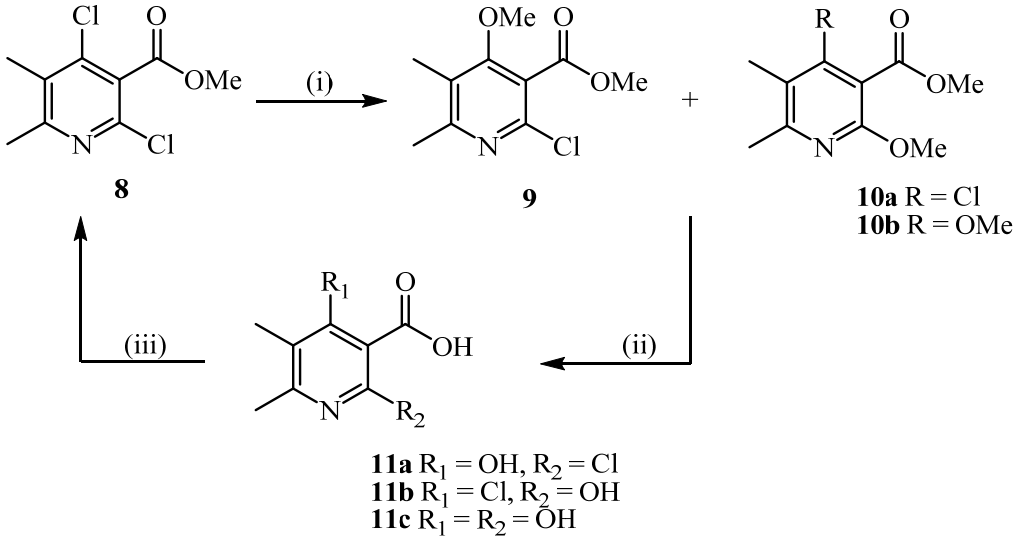
The analysis of the available literature data have suggested that the pyridone **7**, which can be easily obtained by reaction of β-aminocrotonates **6** with diethylmalonate[11] (Scheme 2), could be used as a synthetic precursor en route to pyridine **4**.



Scheme 2. (i): $NaOC_3H_7$, 1,3-diethyl propanedioate, toluene, 2-propanol, Ar, 81 °C. (ii): 1. $POCl_3$, 106 °C; 2. MeOH, 0 °C.

Methyl 2,4-dichloro-5,6-dimethylnicotinate (**8**) was synthesized using the modified procedure reported by Seeman.[12] Conversion of pyridones to chloropyridines is typically performed by reaction with phosphorus oxychloride and often requires the use of a sealed tube, which both limits the scale of a reaction and causes risk of explosion. In our hands deoxygenative chlorination of ethyl dioxonicotinate **7** could be performed at atmospheric

pressure under mild conditions. The substitution of chlorine at 4-position to methoxy group using 2 equiv. of sodium methoxide in dry methanol at 30 °C yielded methoxypyridine **9** in good yield (87%). Only small amount of isomer **10a** (10%) and dimethoxyderivative **10b** (3%) has formed (Scheme 3). By performing the same reaction without cooling (up to 65 °C), the content of compounds **9**, **10a** and **10b** has changed to 28%, 5.5% and 65%, respectively.



8

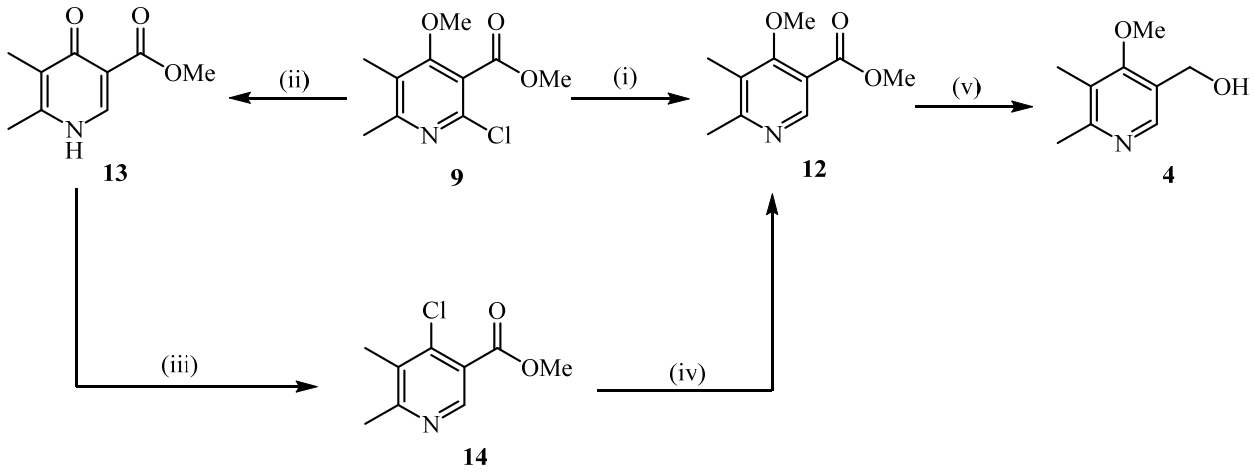
9

10a R = Cl
10b R = OMe

11a R_1 = OH, R_2 = Cl
11b R_1 = Cl, R_2 = OH
11c R_1 = R_2 = OH

Scheme 3. (i): NaOMe, MeOH, 20 °C – 30 °C. (ii): conc. HBr, 122 °C. (iii): 1. $POCl_3$, 106 °C; 2. MeOH, 0 °C – 20 °C.

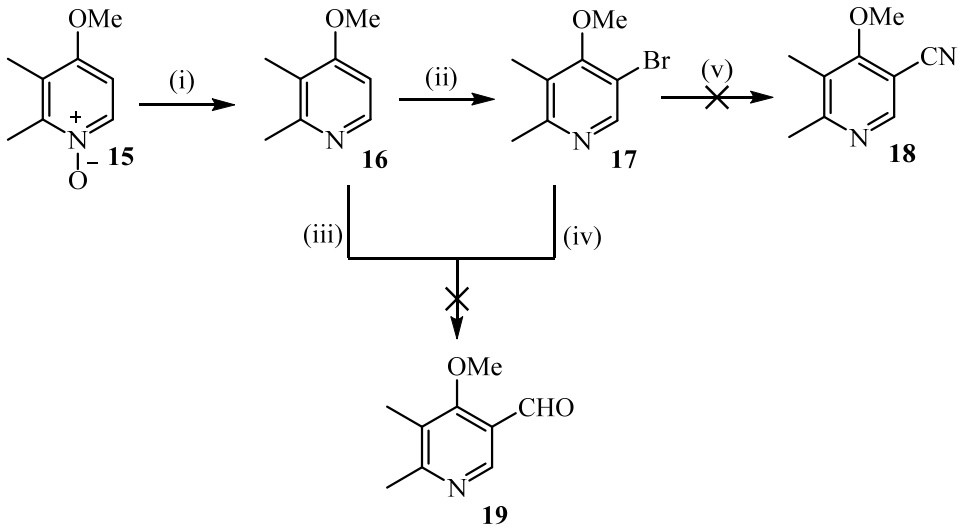
Synthesis under controlled reaction conditions was reproducible on large scale (500-1000 g) and afforded pyridine **9** in 80% yield. The mixture of compounds **9**, **10a** and **10b**, recovered from filtrates after recrystallization of compound **9**, could be recycled to compound **8** in two steps. The mixture was first hydrolyzed by refluxing in concentrated hydrobromic acid to yield pyridines **11a-c**, which were treated with $POCl_3$ and then with methanol to form dichloropyridine **8** in good overall yield (60% of total weight of the mixture of compounds **9**, **10a** and **10b**) (Scheme 3).The hydrogenative dehalogenation of compound **9** with Zn in acetic acid[13] was unsuccessful, whereas hydrogenative dehalogenation using 10% Pd/C – H_2 at atmospheric pressure yielded pyridine **12** (Scheme 4) in low yield (27%). Reduction of **9** at increased pressure (80 atm) has led to the formation of compound **13**, apparently as a result of hydrolysis of methoxy group at 4-position of pyridine ring by HCl, released during hydrogenative dehalogenation. Nevertheless, target methoxyderivative **12** could be synthesized in good overall yield (60%) by heating pyridine **13** with $POCl_3$ and subsequent treatment of obtained chloroderivative **14** with sodium methoxide (Scheme 4). Reduction of pyridine **12** with $LiAlH_4$ under standard conditions[14] led to inseparable mixture of products. Gratifyingly, the reduction of pyridine **12** was successful by using $NaBH_4$ – MeOH system in THF to afford the crucial intermediate, hydroxymethyl derivative **4** in 55% yield.



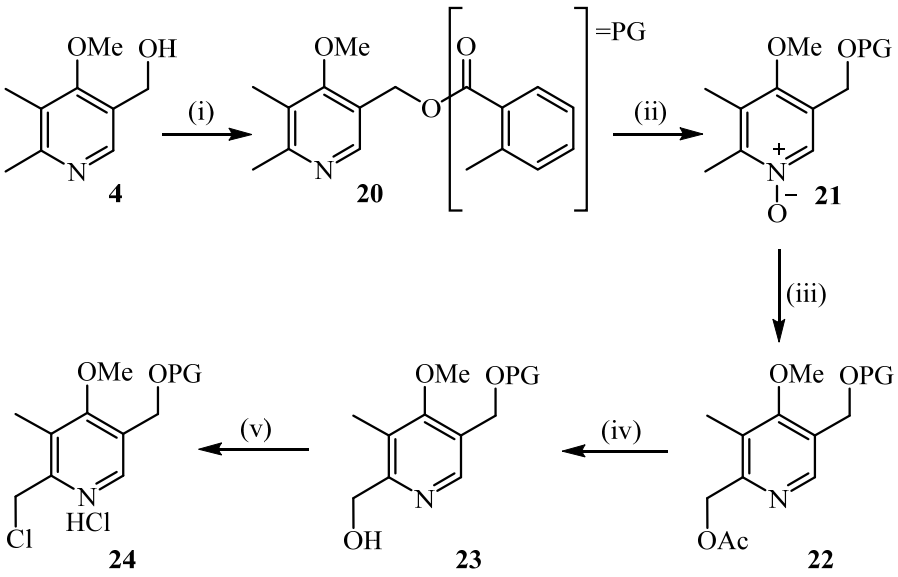
Scheme 4. (i): Pd/C, H_2, MeOH, 1 atm, 20 °C. (ii): Pd/C, H_2, MeOH, 80 atm, 20 °C. (iii): 1. $POCl_3$, Δ; 2. MeOH, 0 °C – 20 °C. (iv): NaOMe, MeOH, 20 °C to reflux. (v): $NaBH_4$-MeOH, THF, Δ.

Low overall yield (3.2%) and long synthetic route (8 steps) prompted us to investigate other synthetic routes to compound **4**. An alternative synthetic strategy involved the use of 2,3-dimethyl-4-methoxypyridine *N*-oxide (**15**) (Scheme 5) as a starting material, which in turn was obtained from 2,3-dimethylpyridine *N*-oxide in 2 steps following the procedure reported by Kuhler.[9] Pyridine *N*-oxide was treated with PCl_3 to afford pyridine **16**. Since the substitution of hydrogen in 5-position using LDA or LTMP did not proceed, we synthesized 2,3-dimethyl-4-methoxy-5-bromopyridine (**17**) (Scheme 5). Surprisingly, however, substitution of bromine to cyano group using CuCN has failed and only unreacted compound **17** could be recovered. The efforts of formylation of bromide **17** using Grignard reaction under various conditions led to the reduction of bromine via Grignard reagent and formation of compound **16** (Scheme 5).

With derivative **4** in hand, we focused on the synthesis of hydroxyomeprazole (**2**). Thus, hydroxy group in pyridine **4** was protected using 2-methylbenzoyl chloride (Scheme 6). The obtained ester **20** was oxidized to N-oxide **21**, which was treated with acetic anhydride to furnish Boekelheide rearrangement product **22**. Hydrolysis of the latter with aqueous NaOH yielded hydroxymethyl pyridine **23**, which was then chlorinated with $SOCl_2$ to yield chloromethyl pyridine **24** in excellent yield. Overall yield of five step synthesis was 55% (Scheme 6).



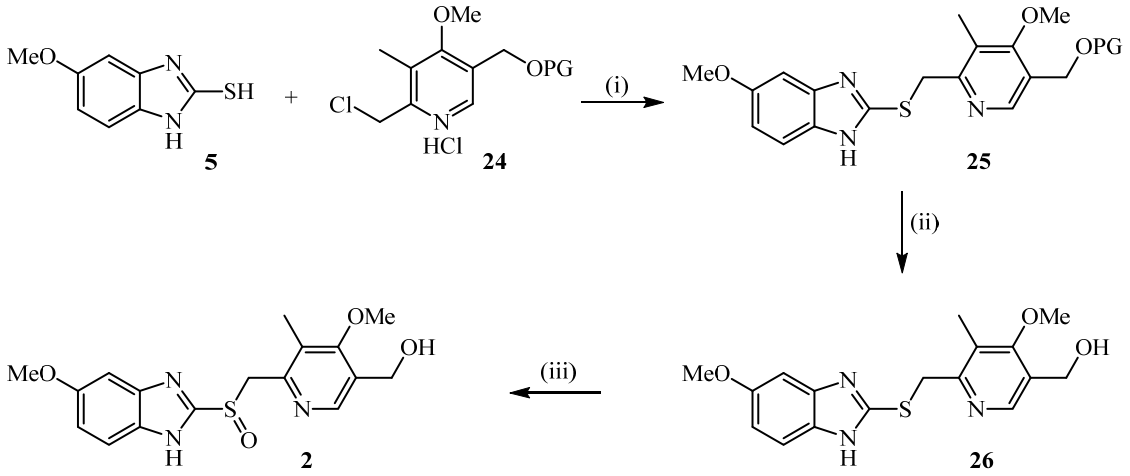
Scheme 5. (i): PCl_3, DCM, 40 °C. (ii): NBS, H_2SO_4, 60 °C. (iii): 1. LDA or LTMP, -78 °C; 2. DMF, -78 to 20 °C. (iv): 1. i-PrMgBr, 0 °C; 2. DMF. (v): CuCN, DMF, 153 °C.



Scheme 6. (i): 2-methylbenzoyl chloride, TEA, DCM, -5 – 20 °C. (ii): m-CPBA, $CHCl_3$, 5 – 25 °C. (iii): Ac_2O, 20 – 100 °C. (iv): NaOH, H_2O, THF, 20 °C. (v): $SOCl_2$, DCM, 0 to 2 °C.

Sulfide **25** has been synthesized under reaction conditions developed for synthesis of Omeprazole by Kuhler[9] using only one equivalent of NaOH instead of 2 equivalents. The alkylation of 5-methoxy-1H-benzimidazolethiol (**5**) with **24** in the presence of 2 equivalents of NaOH has proceeded with concomitant hydrolysis of 2-methylbenzoyl ester to furnish mixture of **25** and deprotected **26**. It was found that one equivalent of NaOH is sufficient to affect alkylation without the cleavage of protecting group. Subsequent hydrolysis of **25** with NaOH in aqueous

methanol overnight furnished **26** in excellent yield (90%). Since Omeprazole (**1**) and its analogues are sensitive to acidic conditions,[15] oxidation of sulfide **26** with m-CPBA was performed in DCM and aqueous $NaHCO_3$ solution under argon following the procedure reported by Kuhler.[9] The 5-hydroxyomeprazole (**2**) was isolated in 45% yield (Scheme 7).



Scheme 7. (i): NaOH, MeOH/H_2O, 20 °C. (ii): NaOH, MeOH/H_2O, 20 °C. (iii): m-CPBA, $NaHCO_3$, MeOH, DCM, H_2O, 2 – 3 °C.

Experimental Section

General. Melting points were determined in open capillaries and are uncorrected. NMR spectra were recorded on Varian Unity Inova (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) using residual solvent peaks as internal standards. Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved, broad s = broad singlet, integration, coupling constant in Hz). Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). Silica gel 60 F254 aluminum plates (Merck) were used for TLC analysis. Column chromatography was performed on silica gel 60 (0.04 – 0.063 mm) (Roth). 2,3-Dimethyl-4-methoxypyridine *N*-oxide (**15**) was synthesized following procedure reported by Kuhler.[9]

Ethyl 3-amino-2-methylbut-2-enoate (6). Ethyl 2-methyl-3-oxobutanoate (30 g, 0.21 mol) was dissolved in NH_4OH (50 mL) and stirred at 20 °C for 72 h. Precipitate was filtered and washed several times with ice cold water and recrystallized from hexane to yield 12.5 g (42%) of **6** as colorless crystals. Mp 47 – 48 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, 3H, *J* 7.1 Hz), 1.78 (s, 3H), 1.97 (s, 3H), 4.16 (q, 2H, *J* 7.1 Hz), 6.32 (broad s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.7, 14.9, 21.5, 59.2, 89.2, 156.5, 171.1, in agreement with the literature data.[12]

Ethyl 2-hydroxy-5,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxylate (7). Na (32.8 g, 1.43 mol) was dissolved in a mixture of 2-propanol (460 mL) and toluene (100 mL) under argon. 1,3-Diethyl propanedioate (222 g, 212 mL, 1.39 mol) was added during 30 min at 50 °C. Then, ethyl 3-amino-2-methylbut-2-enoate (**6**) (199 g, 1.39 mol) solution in toluene (300 mL) was added to reaction mixture during 20 min and heated to reflux for 6 h. 2-Propanol was removed under reduced pressure and residue was washed with water (3 × 200 mL). Combined aqueous phases was extracted with Et_2O (3 × 100 mL) and acidified to pH = 7. The resulting precipitate was filtered and washed several times with ice cold water and dried in air at 80 °C to yield 105 g (36%) of **7** as colorless crystals. Mp 220 – 221 °C (dec). ^{1}H NMR (300 MHz, DMSO-D6) δ 1.21 (t, 3H, *J* 7.1 Hz), 1.85 (s, 3H), 2.19 (s, 3H), 4.16 (q, 2H, *J* 7.1 Hz), 11.29 (broad s, 1H), 13.66 (broad s, 1H). ^{13}C NMR (75 MHz, DMSO-D6) δ 9.5, 17.5, 52.5, 96.0, 103.6, 150.6, 159.9, 173.1, 173.9, in agreement with the literature data.[12]

Methyl 2,4-dichloro-5,6-dimethylpyridine-3-carboxylate (8). Ethyl 2-hydroxy-5,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxylate (**7**) (67.5 g, 0.32 mol) was suspended in $POCl_3$ (150 mL) and the reaction mixture was heated to reflux for 3 h. Excess of $POCl_3$ was removed under reduced pressure and the residue was cooled to 0 °C. Methanol (350 mL) was added cautiously and the mixture was stirred for 1 h at 20 °C. Solvent was removed under reduced pressure and water (200 mL) was added to residue. Aqueous phase was basified with solid K_2CO_3 to pH = 8 and extracted with DCM (3 × 100 ml). Organic phases were combined, dried over Na_2SO_4 and DCM was removed under reduced pressure. Residue was recrystallized from 2-propanol to yield 60 g (80%) of **8** as light yellow crystals. Mp 89 – 90 °C. Anal. calcd. for $C_9H_9Cl_2NO_2$ (233.0): C (46.18%), H (3.88%), N (5.98%). Found: C (46.37%), H (3.65%), N (6.08%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.32 (s, 3H), 2.54 (s, 3H), 3.96 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.8, 25.6, 53.5, 127.8, 129.6, 142.7, 148.9, 159.7, 164.6.

Methyl 2-chloro-4-methoxy-5,6-dimethylpyridine-3-carboxylate (9). Na (3.9 g, 0.171 mol) was dissolved in dry MeOH (200 mL) and the reaction mixture was cooled to 20 °C. Methyl 2,4-dichloro-5,6-dimethylpyridine-3-carboxylate (**8**) (20 g, 0.085 mol) was added in portions at 20 – 30 °C and the mixture was stirred at 20 °C for 14 h. Reaction mixture was concentrated under reduced pressure and the residue was dissolved in water (300 mL) and extracted with DCM (3 × 100 mL). Organic phases were combined and dried over Na_2SO_4. Solvent was removed under reduced pressure and residue was recrystallized from 2-propanol to yield 17 g (87%) of **9** as colorless crystals. Mp 52 – 53 °C. Anal. calcd. for $C_{10}H_{12}ClNO_3$ (229.0): C (52.30%), H (5.27%), N (6.10%). Found: C (52.59%), H (5.09%), N (5.92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.14 (s, 3H), 2.45 (s, 3H), 3.83 (s, 3H), 3.93 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.0, 25.3, 53.7, 62.0, 127.8, 129.6, 143.0, 149.2, 161.0, 164.0.

Recycling procedure. Mixture of compounds **9**, **10a** and **10b** (50 g) was dissolved in conc. HBr (200 mL) and heated to reflux for 12h, then cooled to 20 °C and kept overnight. Precipitate was filtered off, washed with ice cold water (3 × 100 mL) and air dried to yield 40 g of colorless solid that was suspended in $POCl_3$ (150 ml) and heated to reflux for 3 h. Excess of $POCl_3$ was removed under reduced pressure and the residue was cooled to 0 °C. Methanol (350 mL) was

added cautiously and the mixture was stirred for 1 h at 20 °C. Solvent was removed under reduced pressure and water (200 mL) was added to residue. Aqueous phase was basified with solid K_2CO_3 to pH = 8 and extracted with DCM (3 × 100 ml). Organic phases were combined, dried over Na_2SO_4 and DCM was removed under reduced pressure. Residue was recrystallized from 2-propanol to yield 30 g (60% of total weight of the mixture of compounds **9**, **10a** and **10b**) of light yellow crystals that were identified as compound **8**.

Methyl 4-methoxy-5,6-dimethylpyridine-3-carboxylate (12)

Method A: Methyl 2-chloro-4-methoxy-5,6-dimethylpyridine-3-carboxylate (**9)** (15 g, 0.065 mol) was dissolved in MeOH (150 mL) under argon atmosphere. Reaction vessel was degassed and 10% Pd/C (0.42 g) was added. The hydrogen gas was attached and reaction mixture was stirred for 12 h at 20 °C (1.5 L of H_2 was consumed). Reaction mixture was filtered, MeOH was evaporated and residue was dissolved in DCM (300 mL) and washed with 2M NaOH (3 × 100 mL). Organic phases were combined, dried over Na_2SO_4 and filtered. Solvent was removed under reduced pressure and residue was purified by silica gel column chromatography (EtOAc-hexane from 1:2 to 1:1) to yield 3.5 g (27%) of **12** as colorless oil.

Method B. Na (2.8 g, 0.12 mol) was dissolved in MeOH (150 mL) and obtained solution was cooled to 20 °C. Methyl 4-chloro-5,6-dimethylpyridine-3-carboxylate (**14**) (21.5 g, 0.11 mol) was added in portion of 5 g during 30 min and reaction mixture heated to reflux for 5 h. Solvents were removed under reduced pressure and residue was dissolved in water (100 mL) and extracted with DCM (5 × 50 mL). Organic phases were combined and dried over Na_2SO_4. Solvent was removed under reduced pressure and residue was purified by vacuum distillation (1 Torr) to yield 15.4 g (75%) of **12** as colorless oil. B. p. 112 °C (1 Torr). Anal. calcd. for $C_{10}H_{13}NO_3$ (195.1): C (61.53%), H (6.71%), N (7.18%). Found: C (61.74%), H (6.48%), N (7.56%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.18 (s, 3H), 2.50 (s, 3H), 3.83 (s, 3H), 3.89 (s, 3H), 8.68 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.7, 23.6, 52.6, 61.9, 117.9, 125.9, 157.3, 163.3, 165.1, 165.8.

Methyl 5,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxylate (13). Methyl 2-chloro-4-methoxy-5,6-dimethylpyridine-3-carboxylate (**9**) (45.9 g, 0.2 mol) was dissolved in MeOH (300 mL) under argon atmosphere and placed in steel autoclave. Reaction vessel was degassed and 10% Pd/C (0.5 g) was added. The hydrogen gas was attached and pressure was increased to 80 atm. Reaction mixture was stirred at 20 °C for 12 h. Catalyst was filtered and washed with MeOH (2 × 50 mL). Methanol was evaporated, the residue was dissolved in H_2O (300 mL) and neutralized with 2M NaOH (pH = 7). Precipitate were filtered of, washed with ice cold water and dried in air yielding 25.3 g (70%) of **13** as colorless crystals. Mp 231 °C (dec). Anal. calcd. for $C_9H_{11}NO_3$ (181.1): C (59.66%), H (6.12%), N (7.73%). Found: C (59.91%), H (5.91%), N (7.45%). ^{1}H NMR (300 MHz, CDCl3) δ 2.58 (s, 3H), 2.70 (s, 3H), 3.83 (s, 3H), 7.94 (s, 1H), 12.15 (broad s, 1H). ^{13}C NMR (75 MHz, CDCl3) δ 11.7, 18.8, 52.6, 109.4, 117.9, 125.9, 148.6, 165.1, 179.0.

Methyl 4-chloro-5,6-dimethylpyridine-3-carboxylate (14). Methyl 5,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxylate (**13**) (24.5 g, 0.135 mol) was suspended in $POCl_3$ (50 mL) and reaction mixture was stirred at 50 °C for 4 h, then the excess of $POCl_3$ was removed under reduced pressure. MeOH (50 mL) was added slowly to residue that was cooled to 0 °C. Reaction mixture was stirred at 20 °C for 4 h. Excess of MeOH was removed under reduced pressure and residue was dissolved in H_2O (100 mL) and NaOH was added to pH = 8 – 9. Aqueous solution was extracted with DCM (3 × 50 mL). Organic phases were combined and dried over Na_2SO_4. Solvent was removed under reduced pressure to yield 21.5 g (80%) of **14** as light yellow crystals. Mp 40 – 41 °C. Anal. calcd. for $C_9H_{10}ClNO_2$ (199.0): C (54.15%), H (5.05%), N (7.02%). Found: C (54.38%), H (4.86%), N (6.82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36 (s, 3H), 2.56 (s, 3H), 3.90 (s, 3H), 8.65 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1, 24.4, 52.8, 124.4, 131.4, 143.4, 148.2, 161.8, 165.4.

2,3-Dimethyl-4-methoxypyridine (16). 2,3-Dimethyl-4-methoxypyridine N-oxide (**15**) (36.7 g, 0.24 mol) was dissolved in DCM (200 mL) and reaction mixture was cooled to 0 °C. Phosphorus trichloride (25.1 mL, 0.29 mol) was added drop-wise and the reaction mixture heated to reflux for 3 h. Solvent was evaporated under reduced pressure and residue was dissolved in water (100 mL), then K_2CO_3 was added to pH = 10. Aqueous phase was extracted with DCM (5 × 50 mL), organic phases were combined and dried over Na_2SO_4. Solvent was evaporated over reduced pressure and residue was distilled under vacuum to yield 31.2 g (95%) of **16** as colorless oil. Bp 75-76 °C (2 Torr). ^{1}H NMR (300 MHz, CDCl3) δ 2.08 (s, 3H), 2.43 (s, 3H), 3.79 (s, 3H), 6.58 (d, 1H, *J* 5.7 Hz), 8.18 (d, 1H, *J* 5.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.9, 24.5, 55.7, 112.7, 121.9, 152.7, 157.4, 160.1, in agreement with the literature data.[16]

5-Bromo-2,3-dimethyl-4-methoxypyridine (17). 2,3-Dimethyl-4-methoxypyridine (**16**) (21 g, 0.15 mol) was added drop-wise to H_2SO_4 (80 mL) cooled to 0 °C, then the reaction mixture was heated to 60 °C. NBS (30 g, 0.17 mol) was added in portions (5 g each) and reaction kept at 60 °C for 2h. After complete reaction, mixture was poured on ice (200 g), basified with K_2CO_3 and extracted with DCM (5 × 50 mL). Organic phases were combined and dried over Na_2SO_4. Solvent was evaporated over reduced pressure to yield 26 g (80%) of **17** as light yellow oil. Anal. calcd. for $C_8H_{10}BrNO$ (216.1): C (44.47%), H (4.66%), N (6.48%). Found: C (44.72%), H (4.24%), N (6.71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.24 (s, 3H), 2.47 (s, 3H), 3.85 (s, 3H), 8.39 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.9, 24.1, 61.7, 111.7, 147.9, 155.7, 157.4, 159.1.

(4-Methoxy-5,6-dimethylpyridin-3-yl)methanol (4). Methyl 4-methoxy-5,6-dimethylpyridine-3-carboxylate (**12**) (15 g, 0.077 mol) and $NaBH_4$ (20.5 g, 0.54 mol) was added to THF (1.5 L), then the reaction mixture was heated to reflux for 15 – 20 min. MeOH (60 mL, 0.27 mol) was added drop-wise during 30 min and the reaction mixture was heated to reflux for 3 h. Reaction mixture was cooled to 10 °C and saturated aqueous solution of NH_4Cl (100 mL) was added keeping reaction temperature below 30 °C. Then, reaction mixture was stirred at 20 °C for 4 h. The resulting precipitate was filtered and washed with DCM (100 mL). Aqueous filtrates were extracted with DCM (5 × 50 mL). Organic phases were combined and dried over Na_2SO_4. Solvent was removed under reduced pressure and residue was mixed with water (50 mL) and

acidified with aqueous HCl (35%) to pH = 5. Aqueous solution was extracted with DCM (3 × 25 mL), organic phases were combined and dried over Na_2SO_4. Solvent was removed under reduced pressure and residue was recrystallized from toluene to yield 7 g (55%) of **4** as colorless crystals. Mp 87 – 89 °C. Anal. calcd. for $C_9H_{13}NO_2$ (167.1): C (64.65%), H (7.84%), N (8.38%). Found:C (64.91%), H (7.52%), N (8.21%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.16 (s, 3H), 2.44 (s, 3H), 3.41 (broad s, 1H), 3.80 (s, 3H), 4.65 (s, 2H), 8.18 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9, 23.7, 58.7, 62.7, 124.9, 127.7, 147.4, 159.1, 163.9.

(4-Methoxy-5,6-dimethylpyridin-3-yl)methyl 2-methylbenzoate (20). (4-Methoxy-5,6-dimethylpyridin-3-yl)methanol (**4**) (65 g, 0.39 mol) was dissolved in a mixture of DCM (750 mL) and TEA (65.5 ml, 0.47 mol). Reaction mixture was cooled to -5 °C and 2-methylbenzoyl chloride (61 ml, 0.47 mol) was added drop-wise keeping reaction temperature below -2 °C. After addition of 2-methylbenzoyl chloride the reaction mixture was stirred at 20 °C for 10 h. Reaction mixture was concentrated under reduced pressure to 150 mL and Et_2O (500 mL) was added. Precipitate was filtered of and washed with Et_2O (2 × 150 ml). Organic phases were combined and solvent removed under reduced pressure. Residue was purified by silica gel column chromatography (DCM-MeOH 40:1) to yield 100 g (80%) of **20** as colorless glass. Anal. calcd. for $C_{17}H_{19}NO_3$ (285.1): C (71.56%), H (6.71%), N (4.91%). Found: C (71.32%), H (6.46%), N (4.73%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.21 (s, 3H), 2.51 (s, 3H), 2.58 (s, 3H), 3.82 (s, 3H), 5.33 (s, 2H), 7.15 – 7.24 (m, 2H), 7.37 (td, 1H, *J* 7.7 Hz, *J* 1.5 Hz), 7.88 (dd, 1H, *J* 7.7 Hz, *J* 1.5 Hz), 8.41 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.1, 22.1, 23.1, 60.2, 61.7, 122.9, 125.2, 125.9, 129.4, 130.9, 132.0, 132.4, 140.7, 148.7, 160.4, 164.5, 167.4.

4-Methoxy-2,3-dimethyl-5-[(2-methylbenzoyloxy)methyl]pyridin-1-ium-1-olate (21). (4-Methoxy-5,6-dimethylpyridin-3-yl)methyl 2-methylbenzoate (**20**) (85 g, 0.298 mol) was dissolved in DCM (550 ml). Reaction mixture was cooled to 5 °C and *m*-CPBA (74 g, 0.3 mol, 70 – 75% suspension in water) was added in portions of 10 – 12 g during 40 min. After addition of *m*-CPBA the reaction mixture was stirred at 25 °C for 24 h. Reaction mixture was washed with saturated solution of Na_2CO_3 (3 × 500 mL). Aqueous phase was extracted with DCM (2 × 100 mL), organic phases were combined and dried over Na_2SO_4. DCM was removed under reduced pressure to yield 83 g (92%) of **21** as colorless crystals. Mp 95 – 96 °C. Anal. calcd. for $C_{17}H_{19}NO_4$ (301.1): C (67.76%), H (6.36%), N (4.65%). Found: C (67.42%), H (6.16%), N (4.27%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.25 (s, 3H), 2.50 (s, 3H), 2.58 (s, 3H), 3.80 (s, 3H), 5.29 (s, 2H), 7.18 – 7.28 (m, 2H), 7.40 (td, 1H, *J* 7.7 Hz, *J* 1.5 Hz), 7.90 (dd, 1H, *J* 7.7 Hz, *J* 1.5 Hz), 8.30 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9, 14.8, 22.1, 58.9, 62.0, 125.9, 126.1, 128.6, 128.7, 130.9, 131.0, 132.1, 132.8, 141.1, 150.1, 155.0, 166.8.

[6-(Hydroxymethyl)-4-methoxy-5-methylpyridin-3-yl]methyl-2-methylbenzoate (23). Compound (**21**) (83 g, 0.276 mol) was dissolved in Ac_2O (170 mL) at 20 ºC. Reaction mixture was slowly heated to 100 ºC and stirred for 2 h. Ac_2O was removed under reduced pressure and Et_2O (300 mL) was added to the residue. Organic phase was washed with saturated solution of Na_2CO_3 (2 × 300 mL). Aqueous phases extracted with Et_2O (2 × 300 mL). Organic phases were combined, dried over Na_2SO_4 and solvent was removed under reduced pressure to yield (90 g,

0,262 mol) of **22** as a syrup that was dissolved in THF (500 ml) and aqueous solution of NaOH (11 g 500 ml) was added at room temperature. Reaction mixture was stirred at 20 ºC for 3 h, then THF was removed under reduced pressure and the residue was extracted with DCM (3 × 200 mL). Organic phases were combined and dried over Na_2SO_4. Solvent was removed under reduced pressure and residue was recrystallized from toluene to yield 70 g of **23** as white crystals (84% from compound **21**). M. p. 98 – 100 °C. Anal. calcd. for $C_{17}H_{19}NO_4$ (301.1): C (67.76%), H (6.36%), N (4.65%). Found: C (67.89%), H (6.13%), N (4.24%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.14 (s, 3H), 2.59 (s, 3H), 3,86 (s, 3H), 4.67 (s, 2H), 5.38 (s, 2H), 7.17 – 7.26 (m, 2H), 7.39 (td, 1H, *J* 7.7 Hz, *J* 1.5 Hz), 7.88 (dd, 1H, *J* 7.7 Hz, *J* 1.5 Hz), 8.50 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.7, 22.1, 60.0, 61.8, 61.9, 123.1, 124.3, 126.1, 129.2, 130.9, 132.1, 132.5, 140.9, 147.6, 159.3, 164.8, 167.3.

[6-(Chloromethyl)-4-methoxy-5-methylpyridin-3-yl]methyl 2-methylbenzoate hydrochloride (24). Compound (**23**) (5 g, 0.017 mol) was dissolved in DCM (20 ml) and reaction mixture was cooled to 0 °C and $SOCl_2$ solution in DCM (2.14 g, 0.018 mol, 10 ml) was added drop-wise keeping reaction temperature below 2 °C. After addition of $SOCl_2$ reaction mixture was stirred at 20 °C for 30 min. DCM was removed under reduced pressure and excess of $SOCl_2$ was removed by evaporating several portions of DCM under reduced pressure to yield 5.88 g (97%) of **24** as light yellow crystals which were used for further reaction without purification. Mp 148-155 °C. ^{1}H NMR (300 MHz, CDCl3) δ 2.48 (s, 3H), 2.58 (s, 3H), 4.18 (s, 3H), 5.13 (s, 2H), 5.46 (s, 2H), 7.20 – 7.30 (m, 2H), 7.44 (td, 1H, *J* 7.5 Hz, *J* 1.2 Hz), 7.91 (dd, 1H, *J* 7.5 Hz, *J* 1.2 Hz), 8.62 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.9, 21.1, 41.1, 60.5, 66.0, 121.4, 122.9, 125.7, 130.1, 130.7, 131.7, 131.9, 140.0, 145.3, 157.9, 158.4, 167.7.

(4-Methoxy-6-{[(5-methoxy-1*H*-1,3-benzodiazol-2-yl)sulfanyl]methyl}-5-methylpyridin-3-yl)methyl 2-methylbenzoate (25). 5-Methoxy-1H-1,3-benzodiazole-2-thiol (**5**) (0.59 g, 0.00324 mol) was dissolved in methanol (2 mL) and aqueous solution of NaOH (0.13 g, 0.00324mol, 1.62 mL). After 15 min solution of compound **24** in MeOH (1.05 g, 0.003 mol, 2 mL) was added drop-wise during 15 min and reaction mixture was heated to reflux for 3 h, then MeOH was removed under reduced pressure and water (25 mL) was added to the residue. Aqueous phase was extracted with DCM (5 × 10 mL), organic phases were combined, dried over Na_2SO_4 and DCM was removed under reduced pressure to yield 1.3 g (93%) of **25** as light yellow glass. Anal. calcd. for $C_{25}H_{25}N_3O_4S$ (463.2): C (64.78%), H (5.44%), N (9.06%). Found: C (64.43%), H (5.69%), N (8.77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 3H), 2.59 (s, 3H), 3.82 (s, 3H) 3.88 (s, 3H), 5.28 (s, 2H), 5.38 (s, 2H), 6.81 (dd, 1H, *J* 8.7 Hz, *J* 2.7 Hz), 7.02 (d, 1H, *J* 2.7 Hz), 7.17 – 7.26 (m, 2H), 7.35 – 7.43 (m, 2H), 7.90 (dd, 1H, *J* 7.7 Hz, *J* 1.2 Hz), 8.56 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.8, 21.7, 25.2, 55.5, 60.5, 66.5, 98.6, 114.8, 115.6, 122.7, 125.7, 127.2, 130.1, 130.5, 131.7, 131.8, 134.1, 140.0, 140.2, 147.4, 149.3, 156.9, 157.2, 157.8, 167.7.

(4-Methoxy-6-(((5-methoxy-1*H*-benzo[d]imidazol-2-yl)thio)methyl)-5-methylpyridin-3-yl)methanol (26). Compound **25** (1.3 g, 0.00281 mol) was dissolved in MeOH (5 ml) and aqueous solution of NaOH (0.14 g, 0.00351 mol, 1 ml). Reaction mixture was stirred at 20 °C for 24 h and MeOH was removed under reduced pressure and water (20 mL) was added to residue.

Aqueous phase was extracted with DCM (5 × 10 ml DCM), organic phases were combined, dried over Na_2SO_4 and DCM was removed under reduced pressure to yield 0.87 g (90%) of **26** as colorless glass. Anal. calcd. for $C_{17}H_{19}N_3O_3S$ (345.1): C (59.11%), H (5.54%), N (12.17%). Found: C (58.86%), H (5.79%), N (11.92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.23 (s, 3H), 3.78 (s, 3H), 3.81 (s, 3H), 4.29 (s, 2H), 4.74 (s, 2H), 6.76 (dd, 1H, *J* 8.7 Hz, *J* 2.7 Hz), 6.94 (d, 1H, *J* 2.7 Hz), 7.33 (d, 1H, *J* 8.7 Hz), 8.40 (s, 1H).^{13}C NMR (75 MHz, $CDCl_3$) δ 11.6, 35.4, 56.1, 58.7, 61.6, 111.6, 125.8, 125.9, 129.5, 131.2, 147.4, 147.7, 150.4, 156.2, 157.8, 164.2, 165.0.

(4-Methoxy-6-(((5-methoxy-1*H*-benzo[d]imidazol-2-yl)sulfinyl)methyl)-5-methylpyridin-3-yl)methanol (5-Hydroxyomeprazole) (2). Compound **26** (3 g, 0.0087 mol) was dissolved in the mixture of DCM (65 mL) and MeOH (15 mL) under argon. Aqueous solution of $NaHCO_3$ (1.5 g / 25 mL) was added and the reaction mixture was cooled to 2 °C. Solution of *m*-CPBA in DCM (2 g, 30 mL) was added drop-wise keeping reaction temperature below 3 °C. Reaction mixture was stirred at 2 °C for 1 h, then an aqueous solution of NaOH (1.07 g / 70 mL) was added. After 15 min organic phase was separated. Ethyl formate (3.30 g) was added to the water phase and cooled to 5 °C. Aqueous phase was extracted with DCM (8 × 50 mL), organic phases were combined, dried over Na_2SO_4 and DCM was removed under reduced pressure to yield 2.3 g of **2** as violet glass that was tritured with acetonitrile (30 mL) and cooled to 5 °C. The crystals were filtered, washed with ice cold acetonitrile and air dried to yield 1.41 g (45%) of **2** as light violet crystals. Mp 136 – 138 °C. Anal. calcd. for $C_{17}H_{19}N_3O_4S$ (361.1): C (56.50%), H (5.30%), N (11.63%). Found: C (56.73%), H (5.12%), N (11.23%). ^{1}H NMR (300 MHz, DMSO-D6) δ 2.19 (s, 3H), 3.74 (s, 3H), 3.83 (s, 3H), 4.56 (s, 2H), 4.63 (ABq, 2H, $\Delta\delta_{AB}$ = 0.075, J_{AB} = 15 Hz), 5.29 (broad s, 1H), 6.95 (dd, 1H, *J* 9 Hz, *J* 3 Hz), 7.12 (d, 1H, *J* 3 Hz), 7.57 (d, 1H, *J* 9 Hz), 8.35 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.6, 35.4, 56.1, 58.7, 61.6, 111.6, 125.8, 125.9, 129.5, 131.2, 147.4, 147.7, 150.4, 156.2, 157.8, 163.2, 165.5.

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