A Practical Preparation of Methyl 2-Methoxy-6-methylaminopyridine-3-carboxylate from 2,6-Dichloro-3-trifluoromethylpyridine

Tamaki HORIKAWA, Yoshimi HIROKAWA,* and Shiro KATO

Chemistry Research Laboratories, Dainippon Pharmaceutical Co., Ltd., Enoki 33–94, Suita, Osaka 564–0053, Japan.
Received August 20, 2001; accepted October 1, 2001

An effective and practical synthetic route to methyl 2-methoxy-6-methylaminopyridine-3-carboxylate (7), the key intermediate of 5-bromo-2-methoxy-6-methylaminopyridine-3-carboxylic acid (1), from 2,6-dichloro-3-trifluoromethylpyridine (12) was undertaken. Process improvements were highlighted by regioselectivity of 12 with a nitrogen nucleophile and conversion of the 3-trifluoromethyl group into the methoxycarbonyl group. The reaction of 12 with *N*-benzylmethylamine provided the 6-(*N*-benzyl-*N*-methyl)aminopyridine 26a and the regioisomer 26b in >98 : <2 ratio in a quantitative yield. Treatment of 2-methoxy-6-methylamino-3-trifluoropyridine (14a) with a large excess of sodium methoxide followed by acid hydrolysis gave the pyridine-3-carboxylic ester 7 in an excellent yield. The potential application of this reaction is also described.

Key words serotonin-3 receptor; dopamine D_2, D_3 receptor; antiemetic agent; 2-chloro-6-methylamino-3-trimethoxymethylpyridine; regioselective synthesis; 2,6-dichloro-3-trifluoropyridine

Potent and selective serotonin-3 (5-HT_3) receptor antagonists such as DAT-582[1] [(*R*)-*N*-[1-methyl-4-(3-methylbenzyl)hexahydro-1,4-diazepin-6-yl]-1*H*-indazole-3-carboxamide dihydrochloride], granisetron and ondansetron are known to be effective for the control of emesis induced by cancer chemotherapeutic agents.[2] In addition, the traditional antiemetic agent domperidone, a peripheral dopamine D_2 receptor antagonist, has been shown to be effective for the treatment of symptoms of chronic upper gastrointestinal distress and for the prevention of nausea and vomiting resulting from a variety of causes.[3] However, domperidone is only minimally effective against chemotherapy- or radiation-induced nausea and vomiting.[4] In the course of our studies on the structure–activity relationships of DAT-582,[5] novel benzamides with an alkyl group at the nitrogen atom in the hexahydro-1,4-diazepine ring such as, 1-ethyl-4-methylhexahydro-1,4-diazepine ring, were found to show dopamine D_2 receptor antagonistic activity along with a potent 5-HT_3 receptor antagonistic activity and to cause only weak central nervous system depression and extrapyramidal syndromes.[6] Thus, these compounds were expected to be broad antiemetic agents. These findings had led us to modify the benzoyl moiety and to prepare the optically active 6-aminohexahydro-1,4-diazepine ring, resulting in the discovery of (*R*)-5-bromo-*N*-(1-ethyl-4-methylhexahydro-1,4-diazepin-6-yl)-2-methoxy-6-methylaminopyridine-3-carboxamide difumarate (originally AS-8112), a potent dopamine D_2 and D_3,[7] and 5-HT_3 receptors antagonist. AS-8112 was finally selected as a promising candidate in our search for broad antiemetic agents.[1b] In order to obtain a large amount of AS-8112, an efficient synthesis of 5-bromo-2-methoxy-6-methylaminopyridine-3-carboxylic acid (**1**) and 6-amino-1-ethyl-4-methylhexahydro-1,4-diazepine was essential. This paper describes the efficient synthetic route to methyl 2-methoxy-6-methylaminopyridine-3-carboxylate (**7**), the key intermediate of **1**, from the commercially available 2,6-dichloro-3-trifluoromethylpyridine (**12**).

Results and Discussion

Large-Scale Synthesis of 5-Bromo-2-methoxy-6-methylaminopyridine-3-carboxylic Acid (1) from 2,6-Dichloro-3-trifluoromethylpyridine (12) We have previously reported a novel synthetic route to 5-bromo-2-methoxy-6-methylaminopyridine-3-carboxylic acid (**1**) from the commercially available 2,6-dichloropyridine-3-carboxylic acid with an overall yield of *ca.* 63% (Chart 1).[8] The key reaction of this method is the selective nucleophilic substitution reaction of methyl 2,6-dichloropyridine-3-carboxylate (**2**) with 4-methylbenzenethiolate anion produced from 4-methylbenzenethiol and potassium *tert*-butoxide in *N*,*N*-dimethylformamide (DMF) at −30 °C. The reaction gave a mixture of the desired 6-(4-methylbenzenethio)pyridine-3-carboxylic ester (**3**) and the regioisomer, 2-substituted pyridine derivative in a ratio of >97 : <3 in a quantitative yield. Treatment of the mixture containing **3** as a major product with sodium methoxide and purification by recrystallization afforded the 2-methoxy-6-(4-methylbenzenethio)pyridine-3-carboxylic ester **4** in 87% yield. Oxidation of **4** furnished 2-methoxy-6-(4-methylbenzenesulfinyl)pyridine-3-carboxylate (**5**) along with the corresponding sulfone **6** in a ratio of 11 : 1 in a good yield. After recrystallization of the mixture, the nucleophilic substitution reaction of **5** obtained with methylamine was carried out to produce methyl 2-methoxy-6-methylaminopyridine-3-carboxylate (**7**) in 80% yield from **4**. Treatment of **7** with *N*-bromosuccinimide (NBS) gave methyl 5-bromo-2-methoxy-6-methylaminopyridine-3-carboxylate (**8**) in 96%

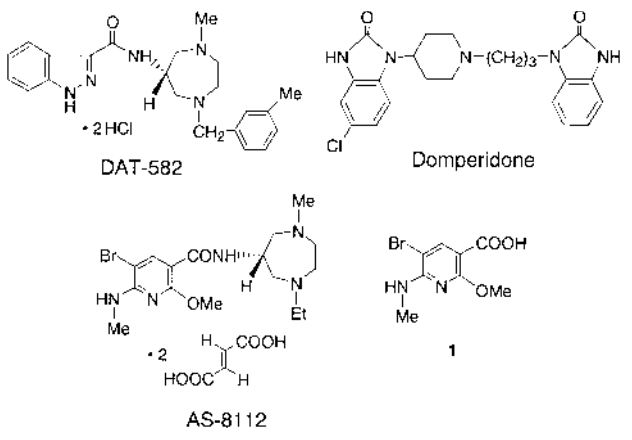


Fig. 1

* To whom correspondence should be addressed. e-mail: yoshimi-hirokawa@dainippon-pharm.co.jp

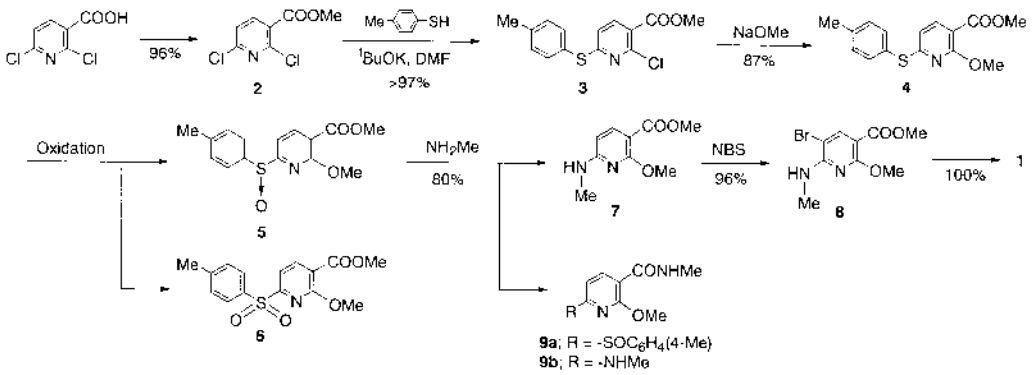


Chart 1. Previous Route[8] to the Preparation of **1**

yield. Finally, **8** was hydrolyzed under alkaline conditions to afford the desired carboxylic acid **1** in a quantitative yield (Chart 1). This route to **1** is quite adequate for the preparation of a wide variety of 2-alkoxy-6-alkylaminopyridine-3-carboxylic acids. However, when carried out on a large-scale (few hundreds gram), the yield of **5** from **3** decreased remarkably (*ca.* 25% yield) compared with that in a small-scale reaction. In addition, in the reaction of **5** with methylamine the unexpected 2-methoxy-*N*-methyl-6-(4-methylbenzenesulfinyl)pyridine-3-carboxamide (**9a**) and/or the corresponding 6-methylaminopyridine **9b** were isolated in *ca.* 20% yield, and the yield of **7** decreased (*ca.* 50% yield). In order to improve the overall yield of **1** in large-scale preparations, a novel and facile synthetic route to the key intermediate **7** with short steps was examined.

Previously, we reported that the nucleophilic substitution reaction of methyl 2,6-dichloro-3-carboxylate (**2**) with methylamine did not show good regioselectivity and gave the undesired 6-chloro-2-methylaminopyridine-3-carboxylic ester as a major product.[8] On the other hand, Dainter *et al.*[9] reported that treatment of 2,6-dichloro-3-trichloromethylpyridine (**10**) having strong electron-withdrawing trichloromethyl group at the 3 position of pyridine ring with 10 mol eq of piperidine as a nucleophile gave only the 2-chloro-6-piperidino-3-[tri(1-piperidinyl)methyl]pyridine **11**, which underwent displacement of all three chlorine atoms from the trichloromethyl group as well as the ring chlorine atom in a good yield. We, therefore, expected that commercially available 2,6-dichloro-3-trifluoromethylpyridine (**12**), which is the starting material for the preparation of 2,6-dichloropyridine-3-carboxylic acid,[10] undergoes the nucleophilic substitution reaction of the ring chlorine atom at the 6 position only (Chart 2). 3-Trifluoromethylpyridines show much less activation of the trifluoromethyl group on the nucleophilic substitution than do their trichloromethyl analogues, since the fluorine atom is a poorer leaving group than the chlorine atom. Thus, nucleophilic substitution reaction of **12** with methylamine was initially examined.

Treatment of **12** with 1.1 mol eq of methylamine generated from methylamine hydrochloride and triethylamine at room temperature gave a mixture of the 2-chloro-6-methylamino-3-trifluoropyridine (**13a**) as a solid and the regioisomer **13b** as a viscous oil in a ratio of *ca.* 4 : 1 in >90% yield. The ratio was determined by ^{1}H-NMR spectroscopy. As expected, the corresponding 3-tri(methylamino)-methylpyridine was not detected by ^{1}H-NMR spectrum. The reaction at *ca.* 60 °C

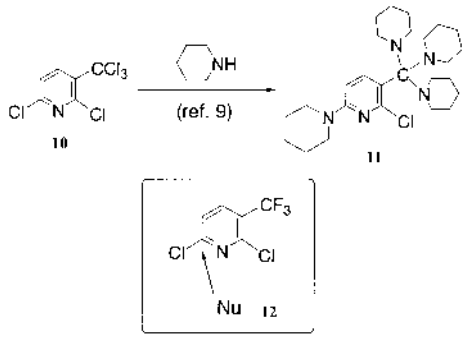
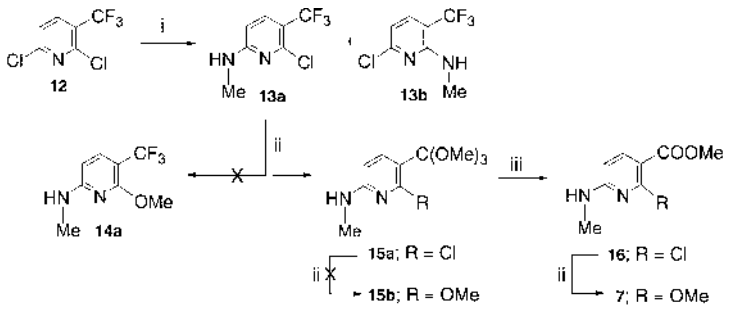


Chart 2

afforded a similar result. The desired 6-methylaminopyridine **13a** was found to be readily separable by washing with hexane. After washing of the mixture of **13a** and **b** with hexane, the crystals obtained (60% yield) consisted only of the isomer **13a** by ^{1}H-NMR spectrum and HPLC. The position of methylamino group of **13a** was determined by differential nuclear Overhauser effect (NOE) experiment; irradiation at δ 2.97 (*N*-Me) enhanced signal intensity of the adjacent pyridine 5-proton (δ 6.28). Conversion of **13a** into 2-methoxy-6-methylamino-3-trifluoromethylpyridine (**14a**) was then attempted. Reaction of **13a** with a large excess of sodium methoxide in MeOH at reflux temperature gave a mixture of unexpected two products instead of **14a** in a good yield. ^{1}H-NMR and mass spectra (MS) revealed these two products to be 2-chloro-6-methylamino-3-(trimethoxymethyl)-pyridine (**15a**) and the 2-methoxy counterpart **15b**. The ratio of **15a** and **b** (*ca.* 0.9 : 1) was determined by ^{1}H-NMR spectroscopy. Nucleophilic substitution reaction at the 2 position of **15a** with methoxide anion did not proceed to recover the starting material **15a**. The mixture of **15a** and **b** was then hydrolyzed with a catalytic amount of aqueous hydrochloric acid or sulfuric acid solution to afford a mixture of the corresponding pyridine-3-carboxylic esters **16** and **7** in an excellent yield in a ratio of *ca.* 0.7 : 1. The structure of **16** was confirmed by ^{1}H-NMR and MS, and **7** was identified with the sample obtained in a previously reported method,[8] on the basis of TLC, ^{1}H-NMR, mass and IR spectra and HPLC comparison. Once again, the mixture of **16** and **7** thus obtained was treated with sodium methoxide in MeOH. The 2-methoxylation of **16** with methoxide anion smoothly proceeded, and the key intermediate **7** was obtained ultimately in an excellent yield (Chart 3). A large amount of methyl 2-



Reagents and conditions: i, $MeNH_2 \cdot HCl$, Et_3N, DMF, *ca.* 5 °C, 14 h; ii, 28% NaOMe in MeOH, THF, reflux; iii, 5% aq. H_2SO_4 solution, MeOH, room temperature, 0.5 h.

Chart 3

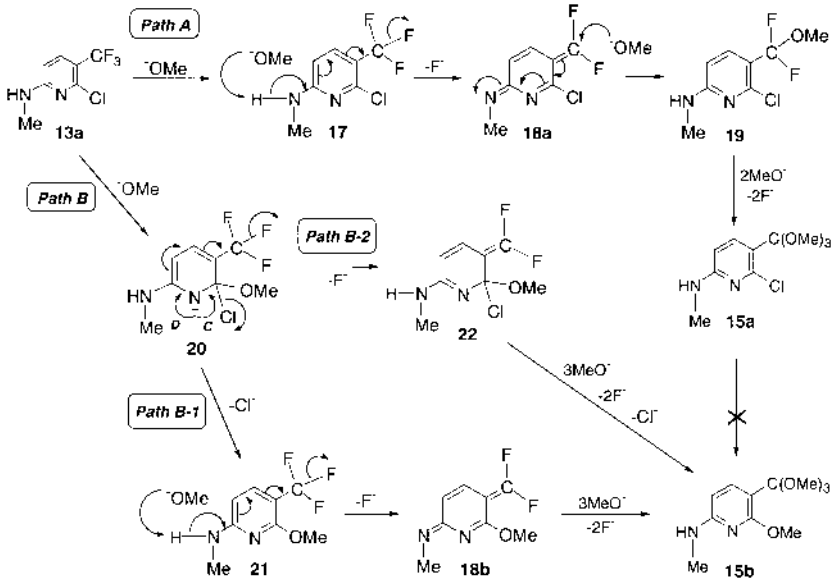


Chart 4. Proposed Mechanism for the Conversion of **13a** into **15a** and **b** with Methoxide Anion

methoxy-6-methylaminopyridine-3-carboxylate (**7**) was converted into the target **1** *via* methyl 5-bromo-2-methoxy-6-methylaminopyridine-3-carboxylate (**8**) in an excellent yield without serious problems according to a method reported previously.[8)]

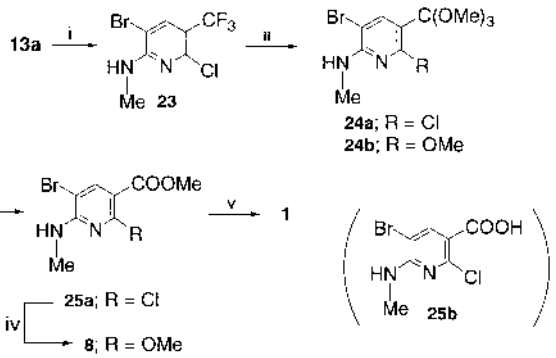
The speculated mechanism for transformation of the 3-trifluoromethylpyridine **13a** into the corresponding 3-trimethoxymethylpyridines **15a** and **b** is shown in Chart 4; initial deprotonation of the ionizable methylamino group with methoxide anion followed by elimination of the fluoro anion as shown by the arrows (see **17**) produce the highly reactive key intermediate **18** (path A). Subsequent attack on the CF_2 residue of intermediate **18** with second equivalent of methoxide anion leads to the rearomatization of **18**, and the formation of **19** which is capable of eliminating the second and ultimately the third fluoro anions to afford the 3-trimethoxymethylpyridine **15a**. On the other hand, the formation of **15b** might be explained as follows; initial methoxide anion attack at the 2 position of the pyridine ring of **13a** gives the Meisenheimer-type adduct **20** (path B). In path B-1, normal elimination of the chlorine atom at 2 position occurs (giving **21**), but the trifluoromethyl group in the product **21** is activated by methoxide anion to form the intermediate **18b**. Conversion of the reactive intermediate **18b** into **15b** would be due to a mechanism similar to that for the formation of the 3-trimethoxymethylpyridine **15a** from **18a**. In path B-2, **20** eliminates a fluoride ion from the trifluoromethyl group rather than a chloride ion from the ring to produce the reactive intermediate **22**, which can give the 3-trimethoxymethylpyridine **15b** *via* attack on the methox-ide anion at the side-chain carbon and analogous repeated sequences. Transformation of **15a** into **15b** did not occur, probably because of the steric hindrance of the bulky 3-trimethoxymethyl group. The high reactivity of the trifluoromethyl group conjugated with an *ortho*- or *para*-hydroxy or amino function has been accounted for by activation as in paths A and B-1.[11—13)] In addition, mechanisms analogous to path B-2 have been proposed to account for the abnormal reactivity of 3-trifluoromethyl-quinoline and -imidazole.[14,15)]

The development of a shorter route to **1** was desired. One strategy shown in Chart 5 was particularly attractive. Initially, bromination of **13a** with NBS was carried out to give the 5-bromo-2-chloro-6-methylamino-3-trifluoropyridine (**23**) in a quantitative yield. Reaction of **23** with a large amount of sodium methoxide produced a mixture of 2-chloro-3-trimethoxymethylpyridine **24a** and the corresponding 2-methoxypyridine **24b** in *ca.* 0.7 : 1 ratio, which was used in the next acid-hydrolysis step without further purification.

The mixture of **24a** and **b** was treated with 2 N HCl solution to provide a mixture of the pyridine-3-carboxylic esters **25a** and **8** as a crude solid. Once again, the mixture (**25a**, **8**) was treated with sodium methoxide to give **8** exclusively, which was hydrolyzed with an alkaline solution without isolation to produce the desired product **1** in 39% overall yield. The crude pyridine-3-carboxylic acid **1** was purified twice with EtOH at reflux temperature for 1 h. Unfortunately, the pyridine-3-carboxylic acid **1** obtained was unacceptably impure due to the presence of 5-bromo-2-chloro-6-methylaminopyridine-3-carboxylic acid (**25b**), a nonmethoxylation product of **25a** (0.8—0.7% by HPLC). The structure of **25b** was speculated by ^{1}H-NMR and MS.

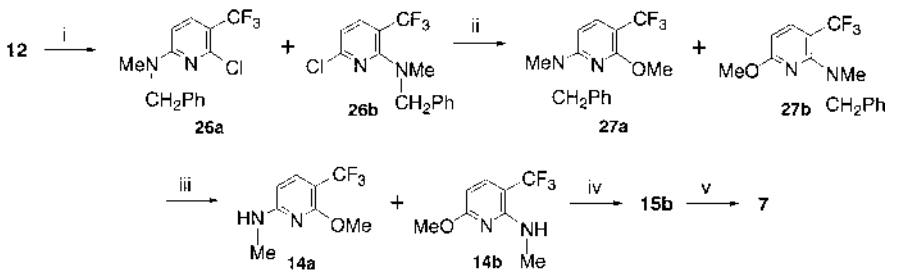
In order to improve the regioselectivity at position-6 of the pyridine ring, reaction of **12** with the more bulky *N*-benzylmethylamine was examined. Treatment of **12** with *ca.* 1.1 mol eq of *N*-benzylmethylamine in DMF at 60 °C afforded a mixture of the 6-benzylmethylamino derivative **26a** and the regioisomer **26b** as an oil in a ratio of >98 : <2 in a quantitative yield. The structure of the major product **26a** was confirmed by ^{1}H-NMR and MS, and the position of the benzylmethylamino group of **26a** was determined by differential NOE experiment; irradiation at δ 3.11 (*N*-Me) enhanced signal intensity of the adjacent pyridine 5-proton (δ 6.36). Without further purification of the oil, the mixture of **26a** and **b** was treated with sodium methoxide in MeOH to give a mixture of 6-benzylmethylamino-2-methoxy-3-trifluoropyridine (**27a**) and the regioisomer **27b** as an oil in a ratio of <98 : <2 in 91% yield. In the mixture thus obtained, the 3-trimethoxymethylpyridines were not detected by ^{1}H-NMR spectrum and the trifluoromethyl group of **27a** and **b** was left intact. Due to the absence of an acidic proton at the amino group, the normal nucleophilic substitution reaction was proceeded at the 2 and 6 positions of the pyridine ring to produce the corresponding 2- and 6-methoxy derivatives. This experimental result reveal that path B→B-1 would be exclusive in our proposed two mechanisms for the formation of **15b** as shown in Chart 4. After hydrogenolysis of the mixture of **27a** and **b**, the resulting mixture of **14a** and **b** was reacted with a large excess of sodium methoxide in MeOH at reflux temperature to afford only the 3-trimethoxymethylpyridine **15b** as a solid in a good yield. From ^{1}H-NMR spectrum and HPLC, the regioisomer of **15b** was not detected in the solid. Acid hydrolysis of **15b** and recrystallization from ethyl acetate gave the key intermediate **7** in 55% overall yield from the starting material **12** (Chart 6). Preparation of multikirogram amounts of **1** *via* **7** using this process was carried out without any significant problems or yield loss.

Synthesis of Methyl 6-Amino-2-methoxypyridine-3-carboxylate (32) from 2,6-Dichloro-3-trifluoromethylpyridine (12) Coldwell *et al.*[16] reported that methyl 6-amino-2-methoxypyridine-3-carboxylate (**32**) was prepared from 2,6-difluoropyridine *via* 2-fluoro-6-pivaloylaminopyridine and ethyl 2-fluoro-6-pivaloylamino-3-pyridinecarboxylate in *ca.* 20% overall yield. The disadvantage of this method is the moderate yield (44%) of the ethoxycarboxylation at the 3 position of 2-fluoro-6-pivaloylaminopyridine at −78 °C and the use of silica gel column chromatography for purification. In order to improve this method, we applied the novel synthetic route to **7** from 2,6-dichloro-3-trifluoromethylpyridine (**12**). Treatment of **12** with more bulky and diprotected amine of ammonia, dibenzylamine instead of *N*-benzylmethylamine in 1-methyl-2-pyrrolidone as a solvent at 120 °C gave only 6-dibenzylamino-2-chloro-3-trifluoromethylpyridine (**28**) in 89% yield. The formation of the regioisomer was not detected by ^{1}H-NMR spectrum. The position of the dibenzylamino group of **28** was determined by NOE experiment; irradiation at δ 4.80 ($C\underline{H}_2Ph$) enhanced signal intensity of the adjacent pyridine 5-proton (δ 6.32). When **28** was treated with sodium methoxide in MeOH, only the 2-methoxy-3-trifluoromethylpyridine **29** was obtained and the non-corresponding 3-trimethoxymethylpyridine was formed owing to the absence of acidic proton at the 6-amino group. Hydrogenolysis of **29** over palladium hydroxide afforded 6-amino-2-methoxy-3-trifluoromethylpyridine (**30**) in 98% yield. In a similar reaction to that described for the pathway



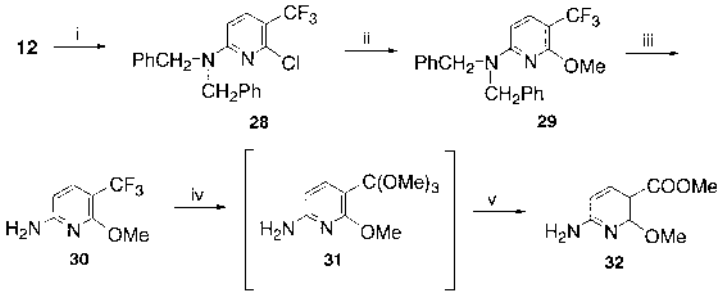
Reagents and conditions: i, NBS, DMF, room temperature, 2 h; ii, 28% NaOMe in MeOH, THF, reflux, 2 h; iii, 2 N HCl solution, MeOH, *ca.* 5 °C, 20 min; iv, 28% NaOMe in MeOH, THF, reflux, 10 h; v, H_2O, NaOH, room temperature, 30 min.

Chart 5



Reagents and conditions: i, *N*-benzylmethylamine, Et_3N, DMF, 60 °C, 2 h; ii, 28% NaOMe in MeOH, THF, reflux, 12 h; iii, Pd/C, H_2, aq. EtOH, *ca.* 50 °C; iv, 28% NaOMe in MeOH, reflux, 0.5 h; v, 2 N HCl solution, MeOH, room temperature, 30 min.

Chart 6



Reagents and conditions: i, dibenzylamine, Et_3N, 1-methyl-2-pyrrolidone, 120 °C, 8.5 h; ii, 28% NaOMe in MeOH, THF, reflux, 10 h; iii, Pd $(OH)_2$/C, H_2, aq. MeOH, AcOH, 3.2 kg/cm^2, room temperature; iv, 28% NaOMe in MeOH, reflux, 0.5 h; v, 5% aq. H_2SO_4 solution, MeOH, room temperature, overnight.

Chart 7

to **7** from **15a**, the trifluoromethyl group of **30** was converted into the corresponding methoxycarbonyl group (giving **32**) *via* the 3-trimethoxymethylpyridine **31** in an excellent yield. The ^{1}H-NMR spectrum of **32** thus obtained was identical to that of the sample reported by Coldwell *et al.* The total yield of **32** from **12** was 59% (Chart 7).

Conclusion

We have established an efficient route for the synthesis of **1**, the carboxylic acid moiety of a novel promising broad antiemetic agent AS-8112, from 2,6-dichloro-3-trifluoropyridine (**12**). Synthesis of methyl 2-methoxy-6-methylaminopyridine-3-carboxylate (**7**), the key intermediate of **1**, by a sequence containing regioselective nucleophilic substitution reaction of **12** with *N*-benzylmethylamine, methoxylation of 3-trifluoromethyl group conjugated with a *para*-methylamino function, and acid hydrolysis of the orthoester group was accomplished. The novel route with seven steps, which was applied to a large-scale synthesis of **1** improved significantly the overall yield (>50%).

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus without correction. IR spectra were recorded on a Shimadzu FTIR-8200PC spectrometer with KBr disks. Atmospheric pressure chemical ionization (APCI) and fast atom bombardment (FAB) MS were obtained on a Hitachi M-1000 spectrometer and JEOL JMS-SX 102A QQ, respectively. ^{1}H-NMR spectra were recorded on a Varian Gemini-200 (200 MHz) or a JEOL JNM-LA300 (300 MHz) spectrometer using dilute solution in $CDCl_3$. Chemical shifts were expressed as δ (ppm) values from tetramethylsilane as an internal standard. Organic extracts were dried over anhydrous $MgSO_4$. The solvents were evaporated under reduced pressure. Flash chromatography was carried out on 60 μm mesh silica gel (Fuji Silysia FL60D). 2,6-Dichloro-3-trifluoromethylpyridine (**12**) was purchased from Ishihara Sangyo Kaisha, Ltd. (Japan); 97.76% purity. HPLC [column, CAPCELL PAK C18 (Shiseido Industries, Ltd., Japan); 4.6 mm ϕ×250 mm; eluent, CH_3CN (A)–0.05% aqueous CF_3CO_2H (B); flow rate, 0.8 ml/min; column temperature, 25 °C].

2-Chloro-6-methylamino-3-trifluoromethylpyridine (13a) and 6-Chloro-2-methylamino-3-trifluoromethylpyridine (13b) Triethylamine (151 g, 1.50 mol) was added dropwise to a solution of 2,6-dichloro-3-trifluoromethylpyridine (**12**, 108 g, 0.50 mol) and methylamine hydrochloride (37.1 g, 0.54 mol) in DMF (500 ml) at *ca.* 5 °C. The mixture was stirred at room temperature for 14 h and then poured into ice-water. The resulting clammy crystals were collected by filtration and dried to give a mixture of **13a** and **b**. ^{1}H-NMR δ: 2.96 (3H, d, J=5.1 Hz, NMe of **13a**), 3.04 (*ca.* 0.7H, d, J=5 Hz, NMe of **13b**), 5.10 (*ca.* 0.25H, br, NHMe of **13b**), 5.53 (1H, br, NHMe of **13a**), 6.30 (1H, d, J=8.6 Hz, Py-5 of **13a**), 6.60 (*ca.* 0.25H, d, J=8.6 Hz, Py-5 of **13b**), 7.56 (*ca.* 0.25H, d, J=8 Hz, Py-4 of **13b**), 7.65 (1H, d, J=8.6 Hz, Py-4 of **13a**). MS (APCI) *m/z*: 211 (MH^+). The pure **13a** (64.0 g, 60%) was obtained as a colorless crystal by washing of the mixture with hexane (500 ml), mp 92—94 °C. ^{1}H-NMR δ: 2.97 (3H, d, J=5.1 Hz, NMe), 5.15 (1H, br, NHMe), 6.28 (1H, d, J=8.6 Hz, Py-5), 7.67 (1H, d, J=8.6 Hz, Py-4). *Anal.* Calcd for $C_7H_6ClF_3N_2$: C, 39.93; H, 2.87; Cl, 16.84; F, 27.07; N, 13.30. Found: C, 39.85; H, 2.92; Cl, 16.75; F, 26.95; N, 13.05. IR cm^{-1} 3296, 1612, 1385, 1319. HPLC [(A : B=65 : 35), detection, 245 nm]; the retention times of **13a** and **b** were 5.5 and 6.4 min, respectively.

2-Chloro-6-methylamino-3-trimethoxymethylpyridine (15a) and 2-Methoxy-6-methylamino-3-trimethoxymethylpyridine (15b) A mixture of **13a** (70.0 g, 0.33 mol), 28% sodium methoxide in MeOH (321 g, 1.65 mol) and tetrahydrofuran (THF) (210 ml) was heated to reflux for 13 h and cooled to room temperature. After evaporation of the solvent, the residue was poured into ice-water (300 ml). The resulting precipitates were collected by filtration and dried to give a mixture of **15a** and **b** (87 g) as a white solid. ^{1}H-NMR δ: 2.92 (3H, d, J=5.4 Hz, NMe of **15b**), 2.94 (*ca.* 3H, d, J=5.9 Hz, NMe of **15a**), 3.11 (9H, s, $(OMe)_3$ of **15b**), 3.14 (*ca.* 9H, s, $(OMe)_3$ of **15a**), 3.90 (3H, OMe of **15b**), 4.52 (1H, br, NH of **15b**), 5.07 (*ca.* 0.9H, br, NH of **15a**), 5.92 (1H, d, J=8.3 Hz, Py-5 of **15b**), 6.28 (*ca.* 0.9H, d, J=8.6 Hz, Py-5 of **15a**), 7.72 (1H, d, J=8.3 Hz, Py-4 of **15b**), 7.87 (*ca.* 0.9H, d, J=8.6 Hz, Py-4 of **15a**). MS (APCI) *m/z*: 243 (MH^+ of **15b**), 247 (MH^+ of **15a**). IR cm^{-1} 3373, 2945, 1609, 1508, 1375, 1275.

Methyl 2-Chloro-6-methylaminopyridine-3-carboxylate (16) and Methyl 2-Methoxy-6-methylaminopyridine-3-carboxylate (7) Five percent aqueous H_2SO_4 solution (20 ml) was added dropwise to a solution of **15a** and **b** (87 g) in a mixture of MeOH (435 ml) and water (12 ml) at room temperature. The mixture was stirred at the same temperature for 0.5 h and concentrated to dryness to give 63 g of a mixture of **16** and **7** as a white solid. ^{1}H-NMR δ: 2.97 (*ca.* 2H, d, J=5.1 Hz, NMe of **7**), 2.98 (3H, d, J=5.1 Hz, NMe of **16**), 3.82 (3H, s, OMe of **7**), 3.87 (3H, s, CO_2Me of **16**), 3.97 (*ca.* 2H, CO_2Me of **7**), 4.87 (*ca.* 0.7H, br, NH of **7**), 5.35 (1H, br, NH of **16**), 5.94 (*ca.* 0.7H, d, J=8.4 Hz, Py-5 of **7**), 6.29 (1H, d, J=8.6 Hz, Py-5 of **16**), 8.01 (*ca.* 0.7H, d, J=8.4 Hz, Py-4 of **7**), 8.04 (1H, d, J=8.6 Hz, Py-4 of **16**). IR cm^{-1} 3356, 1693, 1601, 1269. MS (APCI) *m/z*: 197 (MH^+ of **7**), 201 (MH^+ of **16**).

5-Bromo-2-chloro-6-methylamino-3-trifluoromethylpyridine (23) A solution of NBS (59.5 g, 0.33 mol) in DMF (160 ml) was added dropwise to a solution of **13a** (64.0 g, 0.30 mol) in DMF (500 ml) at room temperature for about 20 min. The mixture was stirred at the same temperature for 2 h. After addition of water (2000 ml), the reaction mixture was extracted with ethyl acetate (1000 ml×2). The extract was washed successively with water (500 ml) and brine (500 ml). The solvent was evaporated to give 88 g (quantitative yield) of **23** as a pale yellow oil. ^{1}H-NMR δ: 3.08 (3H, d, J=5 Hz, NMe), 5.53 (1H, br, NHMe), 7.81 (1H, s, Py-4). MS (APCI) *m/z*: 290 (MH^+). HPLC [(A : B=65 : 35), detection, 245 nm]; the retention time of **23** was 12.1 min.

5-Bromo-2-chloro-6-methylamino-3-trifluoromethylpyridine (24a) and 5-Bromo-2-methoxy-6-methylamino-3-trifluoromethylpyridine (24b) A mixture of **23** (88 g, 0.30 mol) and 28% sodium methoxide in MeOH (703 g, 3.6 mol) was heated to reflux for 2 h and cooled to room temperature. The solvent was concentrated to dryness and the residue was triturated with water to give 113 g of the mixture of **24a** and **b** as a white solid. ^{1}H-NMR δ: 3.07 (3H, d, J=5 Hz, NMe of **24b**), 3.04 (d, J=5 Hz, NMe of **24a**), 3.11 (9H, s, $(OMe)_3$ of **24b**), 3.15 (*ca.* 6H, s, $(OMe)_3$ of **24a**), 3.95 (3H, s, OMe of **24b**), 4.95 (1H, br, NHMe of **24b**), 5.19 (*ca.* 0.6H, br, NHMe of **24a**), 7.85 (1H, s, Py-4 of **24b**), 8.03 (0.7H, s, Py-4 of **24a**). MS (APCI) *m/z*: 322 (MH^+ of **24b**), 326 (MH^+ of **24a**). IR cm^{-1} 3385, 2936, 1597, 1379, 1263. HPLC [(A : B=65 : 35), detection, 245 nm]; the retention times of **24b** and **a** were 6.5 and 7.6 min, respectively.

Methyl 5-Bromo-2-chloro-6-methylaminopyridine-3-carboxylate (25a) and Methyl 5-Bromo-2-methoxy-6-methylaminopyridine-3-carboxylate (8) 2 N HCl solution (500 ml) was added dropwise to a suspension of a mixture of **24a** and **b** (113 g) in MeOH (400 ml) at *ca.* 5 °C. The mixture was stirred at the same temperature for 20 min. After neutralization with $NaHCO_3$ powder, the insoluble materials were collected by filtration to give 130 g of a mixture of methyl 5-bromo-2-chloro-6-methylaminopyridine-3-carboxylate (**25a**) and methyl 5-bromo-2-methoxy-6-methylaminopyridine-3-carboxylate (**8**) as a white solid. ^{1}H-NMR δ: 3.08 (3H, d, J=5 Hz, NMe of **8**), 3.10 (*ca.* 2H, d, J=5 Hz, NMe of **25a**), 3.82 (3H, s, CO_2Me of **8**), 3.88 (*ca.* 2H, s, CO_2Me of **25a**), 4.02 (3H, s, OMe of **8**), 5.38 (1H, br, NHMe of **8**), 5.52 (*ca.* 0.6H, br, NHMe of **25a**), 8.15 (1H, s, Py-4 of **8**), 8.20 (*ca.* 0.7H, s, Py-4 of **25a**). MS (APCI) *m/z*: 276 (MH^+ of **8**), 280 (MH^+ of **25a**). HPLC [(A : B=65 : 35), detection, 245 nm]; the retention times of **8** and **25a** were 6.5 and 7.0 min, respectively.

Methoxylation of 25a and 8 and Acid Hydrolysis A mixture of **25a** and **8** (130 g), 28% sodium methoxide in MeOH (289 g, 1.5 mol) and THF (1000 ml) was heated to reflux for 10 h and cooled to room temperature. After addition of water (1000 ml), the mixture containing only **8** was stirred at room temperature for 30 min and acidified with 30% HCl solution under ice-cooling. The resulting precipitates were collected by filtration to give 54 g of **1** as a solid [5-bromo-2-chloro-6-methylaminopyridine-3-carboxylic acid (**25b**) was detected in *ca.* 5% by HPLC]. After concentration of the filtrate, the precipitates were collected by filtration to afford 18 g of **1**. EtOH (250 ml) was added to the solid (72 g) and the suspension was heated to reflux for 1 h and cooled to room temperature. The insoluble **1** was collected by filtration. Once again, a suspension of **1** in EtOH (200 ml) was heated to reflux for 1 h and cooled to room temperature. The insoluble **1** was collected by filtration and dried to give 51 g (65% from **13a**) as a white solid (**25b** was detected in 0.7—0.8% by HPLC). Compound **1** was identified with the sample obtained in an alternative synthesis,[8] on the basis of HPLC and ^{1}H-NMR comparison. ^{1}H-NMR δ: 3.10 (3H, d, J=5 Hz, NMe of **1**), 3.82 (s, NMe of **25b**), 4.13 (3H, s, OMe of **1**), 5.58 (1H, br, NHMe of **1**), 8.15 (s, Py-4 of **25b**), 8.29 (1H, s, Py-4 of **1**). MS (APCI) *m/z*: 262 (MH^+ of **25b**), 266 (MH^+ of **1**). HPLC [(A : B=35 : 65), detection, 245 nm]; the retention times of **25b** and **1** were 10.3 and 11.0 min, respectively.

6-(*N*-Benzyl-*N*-methyl)amino-2-chloro-3-trifluoromethylpyridine (26a) and 2-(*N*-Benzyl-*N*-methyl)amino-6-chloro-3-trifluoromethylpyridine (26b) A mixture of **12** (100 g, 0.46 mol), *N*-benzylmethylamine (61.0 g, 0.50 mol), triethylamine (93.5 g, 0.93 mol) and DMF (500 ml) was heated to 60 °C for 2 h then cooled to room temperature. The resulting precipitates of triethylamine hydrochloride were filtered off, and water (500 ml) and ethyl acetate (300 ml) were added to the filtrate. The organic layer was separated, washed with water, and concentrated to dryness to give *ca.* 150 g (quantitative yield) of a mixture of **26a** and **b** as an orange oil. This oil was used in the next step without further purification. ^{1}H-NMR δ: 2.94 (<0.1H, s, NMe of **26b**), 3.11 (3H, s, NMe of **26a**), 4.68 (*ca.* 0.05H, s, CH$_2$Ph of **26b**), 4.80 (2H, s, CH$_2$Ph of **26a**), 6.36 (1H, d, J=8.8 Hz, Py-5 of **26a**), 6.80 (<0.05H, d, J=8.8 Hz, Py-5 of **26b**), 7.20—7.36 (*ca.* 5H, m, arom. H), 7.63 (1H, d, J=8.8 Hz, Py-4 of **26a**), 7.76 (<0.05H, d, J=8.8 Hz, Py-4 of **26b**). MS (APCI) *m/z*: 301 (MH^+). HPLC [(A : B=65 : 35), detection, 270 nm]; the retention times of **26a** and **b** were 18.8 and 24.8 min, respectively.

6-(*N*-Benzyl-*N*-methyl)amino-2-methoxy-3-trifluoromethylpyridine (27a) and 2-(*N*-Benzyl-*N*-methyl)amino-6-methoxy-3-trifluoromethylpyridine (27b) Twenty-eight percent sodium methoxide in MeOH (1307 g, 6.8 mol) was added dropwise to a solution of a mixture of **26a** and **b** (680 g, 2.3 mol) in THF (2040 ml) at room temperature. The mixture was heated to reflux for 12 h and cooled to room temperature. After evaporation of the solvent, water (1360 ml) and ethyl acetate (1360 ml) were added to the residue. The organic layer was separated and concentrated to dryness to give 630 g (91%) of a mixture of **27a** and **b** as an orange oil, which was used in the next step without further purification. ^{1}H-NMR δ: 3.07 (3H, s, NMe of **27a**), 3.11 (<0.1H, s, NMe of **27b**), 3.81 (<0.1H, s, OMe of **27b**), 3.91 (3H, s, OMe of **27a**), 4.68 (*ca.* 0.05H, s, CH$_2$Ph of **27b**), 4.82 (2H, s, CH$_2$Ph of **27a**), 6.02 (1H, d, J=8.4 Hz, Py-5 of **27a**), 6.37 (<0.05H, d, J=8.4 Hz, Py-5 of **27b**), 7.19—7.38 (*ca.* 5H, m, arom. H), 7.57 (1H, d, J=8.4 Hz, Py-4 of **27a**), 7.64 (<0.05H, d, J=8.4 Hz, Py-4 of **27b**). MS (APCI) *m/z*: 297 (MH^+). HPLC [(A : B=65 : 35), detection, 245 nm]; the retention times of **27a** and **b** were 18.3 and 25.1 min, respectively.

2-Methoxy-6-methylamino-3-trifluoromethylpyridine (14a) and 6-Methoxy-2-methylamino-3-trifluoromethylpyridine (14b) A solution of a mixture of **27a** and **b** (315 g, 1.5 mol) in a mixture of EtOH (990 ml), water (60 ml), and acetic acid (6.6 ml) was hydrogenated over 10% palladium on carbon (33 g) at *ca.* 50 °C at atmosphere pressure. After absorption of the theoretical hydrogen (*ca.* 5 h), the catalyst was filtered off. The filtrate was concentrated to leave a residue, which was dissolved in ethyl acetate (990 ml). The solution was washed with 5% aqueous Na_2CO_3 solution (300 and 150 ml) and concentrated to dryness to give *ca.* 220 g (quantitative yield) of a mixture of **14a** and **b** as a yellow oil, which was used in the next step without further purification. ^{1}H-NMR δ: 2.93 (3H, d, J=4.9 Hz, NMe of **14a**), 3.03 (<0.1H, d, J=4.9 Hz, NMe of **14b**), 3.93 (3H, s, OMe of **14a**), 4.02 (<0.1H, s, OMe of **14b**), 4.73 (1H, br, NHMe of **14a**), 5.89 (1H, d, J=8.3 Hz, Py-5 of **14a**), 5.99 (<0.05H, d, J=8.3 Hz, Py-5 of **14b**), 7.55 (1H, d, J=8.3 Hz, Py-4 of **14a**), 7.72 (<0.05H, d, J=8.3 Hz, Py-4 of **14b**). MS (APCI) *m/z*: 207 (MH^+). HPLC [(A : B=65 : 35), detection, 245 nm]; the retention times of **14a** and **b** were 7.1 and 8.6 min, respectively.

2-Methoxy-6-methylamino-3-trimethoxymethylpyridine (15b) A solution of a mixture of **14a** and **b** (388 g, 1.9 mol) in MeOH (388 ml) was added dropwise to 28% sodium methoxide in MeOH (2540 g, 12.1 mol) at *ca.* 60 °C for 1 h. The mixture was heated to reflux for 0.5 h, cooled to room temperature and poured into ice-water (9000 ml). The resulting solid was collected by filtration and dissolved in a mixture of $CHCl_3$ (2000 ml) and water (500 ml). The organic layer was separated, dried over anhydrous $MgSO_4$ and evaporated to leave 347 g (76%) of **15b** as a white solid, mp 148—150 °C. ^{1}H-NMR δ: 2.92 (3H, d, J=5.1 Hz, NMe), 3.11 (9H, s, $(OMe)_3$), 3.91 (3H, s, OMe), 4.46 (1H, br, NHMe), 5.92 (1H, d, J=8.2 Hz, Py-5), 7.72 (1H, d, J=8.2 Hz, Py-4). MS (APCI) *m/z*: 243 (MH^+). IR cm^{-1} 3381, 2947, 1609, 1510, 1373, 1281. HPLC [(A : B=55 : 45), detection, 319 nm]; the retention time of **15b** was 5.1 min.

Methyl 2-Methoxy-6-methylaminopyridine-3-carboxylate (7) 1) A solution of a mixture of **16** and **7** (60 g) and 28% sodium methoxide in MeOH (1731 g, 9.0 mol) in THF (180 ml) was heated to reflux for 24 h and cooled to room temperature. After evaporation of the solvent, the residue was poured into ice-water (500 ml). The resulting solid was collected by filtration and dried to give 74 g of crude **7** as a white solid, which was recrystallized from ethyl acetate/hexane to furnish 41.0 g (63% from **13a**) of **7** as colorless crystals, mp 126.5—127.5 °C. ^{1}H-NMR δ: 2.97 (3H, d, J=5.1 Hz, NMe), 3.81 (3H, s, OMe), 3.97 (3H, s, CO_2Me), 4.85 (1H, br. d, NHMe), 5.94 (1H, d, J=8.5 Hz, Py-5), 8.01 (1H, d, J=8.5 Hz, Py-4). IR cm^{-1} 3393, 2949, 1709, 1597, 1566, 1263, 1236. HPLC [(A : B=55 : 45), 319 nm]; the retention time of **7** was 4.9 min. The crystals obtained were identified with the sample obtained in an alternative synthesis,[8] on the basis of TLC, ^{1}H-NMR, and HPLC comparison.

2) Compound **15b** (350 g, 1.4 mol) was dissolved in hot MeOH (1750 ml) and cooled to room temperature. After addition of water (52 ml, 2.9 mol), 2 N HCl solution (72 ml, 0.14 mol) was added dropwise at room temperature. The mixture was stirred at the same temperature for 0.5 h and concentrated to *ca.* 1200 ml. The resulting precipitates were collected by filtration to give a powder (250 g), which was recrystallized from ethyl acetate to afford 224 g (79%) of **7**. The crystals obtained were identified with the sample described above, on the basis of TLC, ^{1}H-NMR, and HPLC comparison.

6-Dibenzylamino-2-chloro-3-trifluoromethylpyridine (28) A mixture of **12** (50.0 g, 0.23 mol), dibenzylamine (46.9 g, 0.24 mol), triethylamine (45.7 g, 0.45 mol) and 1-methyl-2-pyrrolidone (300 ml) was heated at 120 °C for 8.5 h and cooled to room temperature. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The extract was washed with brine and evaporated to give a brown oil, which was chromatographed on silica gel with hexane/ethyl acetate=5 : 1 to afford 77.7 g (89%) of **28** as a fawn oil. The oil solidified on standing at room temperature, mp 74—79 °C. ^{1}H-NMR δ: 4.80 (4H, s, CH$_2$Ph×2), 6.32 (1H, d, J=8.8 Hz, Py-5), 7.16—7.45 (10H, m, arom. H×2), 7.59 (1H, d, J=8.8 Hz, Py-4). FAB-high resolution (HR)-MS *m/z*: 377.1029 (MH^+) (Calcd for $C_{20}H_{16}ClF_3N_2$: 377.1032). MS (APCI) *m/z*: 377 (MH^+). IR cm^{-1} 1601, 1504, 1319.

6-Dibenzylamino-2-methoxy-3-trifluoromethylpyridine (29) Twenty-eight percent sodium methoxide in MeOH (473 g, 2.45 mol) was added dropwise to a solution of a mixture of **28** (307.8 g, 0.84 mol) in THF (4000 ml) at room temperature. The mixture was heated to reflux for 10 h and cooled to room temperature. After evaporation of the solvent, water (800 ml) and $CHCl_3$ (600 ml) were added to the residue. The organic layer was separated, washed with brine and concentrated to dryness to give a pale brown oil, which was recrystallized from iso-PrOH to afford 250.2 g (67.5%) of **29** as colorless crystals. After concentration of the mother liquid, the residue was chromatographed on silica gel with hexane/ethyl acetate=9 : 1 to 4 : 1 to give a pale yellow oil. The oil was crystallized from iso-PrOH to afford 22.2 g (7.3%) of **29** as colorless crystals, mp 88—89 °C. ^{1}H-NMR δ: 3.91 (3H, s, OMe), 4.81 (2H, s, CH$_2$Ph×2), 6.05 (1H, d, J=8.8 Hz, Py-5), 7.22—7.42 (10H, m, arom. H×2), 7.55 (1H, d, J=8.4 Hz, Py-4). *Anal.* Calcd for $C_{21}H_{19}F_3N_2O$: C, 67.73; H, 5.14; N, 7.52; F, 15.31. Found: C,

67.58; H, 5.08; N, 7.61; F, 15.57. MS (APCI) *m/z*: 373 (MH^+). IR cm^{-1} 1614, 1574, 1504, 1452, 1398, 1333.

6-Amino-2-methoxy-3-trifluoromethylpyridine (30) A solution of **29** (38.0 g, 0.10 mol) in a mixture of 10% aqueous MeOH (600 ml) and acetic acid (100 ml) was hydrogenated over 20% palladium hydroxide on carbon (wet, 3.8 g) at room temperature under a pressure of 3.2 kg/cm^2. After absorption of the theoretical hydrogen, the catalyst was filtered off. The filtrate was concentrated to leave an aqueous solution, which was neutralized with solid K_2CO_3 and extracted with $CHCl_3$. The extract was washed with brine and concentrated to give 19.3 g (98%) of **30** as a pale yellow oil, which solidified on standing at room temperature, mp 51—55 °C. ^{1}H-NMR δ: 3.92 (3H, s, OMe), 4.61 (2H, br s, NH_2), 5.88 (1H, d, J=8.2 Hz, Py-5), 7.56 (1H, d, J=8.2 Hz, Py-4). HRFAB-MS *m/z*: 192.0517 (Calcd for $C_7H_7F_3N_2O$: 192.0510). MS (APCI) *m/z*: 193 (MH^+). IR cm^{-1} 3508, 3369, 1643, 1605, 1585, 1406, 1323.

Methyl 6-Amino-2-methoxypyridine-3-carboxylate (32) A solution of a mixture of **30** (86.5 g, 0.45 mol) in MeOH (450 ml) was added dropwise to 28% sodium methoxide in MeOH (608 g, 3.15 mol) at *ca.* 65 °C for 2.5 h. The mixture was heated to reflux for 0.5 h and cooled to room temperature. The solvent was evaporated and the residue was dissolved in H_2O and $CHCl_3$. The organic layer was separated and washed with brine and the aqueous layer was extracted with ethyl acetate. The extract was again washed with brine. The solvent of $CHCl_3$ and ethyl acetate extracts was evaporated to give an yellow solid containing 6-amino-2-methoxy-3-trimethoxymethylpyridine (**31**). The solid was dissolved in a mixture of MeOH (500 ml) and water (250 ml). After addition of 5% aqueous H_2SO_4 solution (25 ml), the mixture was stirred overnight at room temperature. The mixture was concentrated and then the resulting precipitates were collected by filtration, washed with EtOH and dried to give 73.6 g (90%) of **32** as colorless crystals, mp 162—164 °C. ^{1}H-NMR δ: 3.83 (3H, s, OMe), 3.96 (3H, s, CO_2Me), 4.75 (2H, br s, NH_2), 6.05 (1H, d, J=8.3 Hz, Py-5), 8.01 (1H, d, J=8.3 Hz, Py-4). MS (APCI) *m/z*: 183 (MH^+). *Anal.* Calcd for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.64; H, 5.56: N, 15.21. IR cm^{-1} 3425, 3346, 3248, 1695, 1682, 1651, 1593, 1564.

References and Note

1) *a*) Kato S., Morie T., Ito T., Yoshida N., *Jpn. Kokai Tokkyo Koho* JP 05,230,057 [93,230,57] [*Chem. Abstr*., **120**, 164242*c* (1994)]; *b*) Kato S., Fujiwara I., Yoshida N., *Med. Res. Rev*., **19**, 25—73 (1999).
2) King F. D., Jones B. J., Sanger G. J. (eds.), "5-Hydroxytryptamine-3 Receptor Antagonists," CRC Press Inc., Boca Raton, 1994.
3) *a*) Brogden R. N., Carmine A. A., Heel R. C., Speight T. H., Avery G. S., *Drugs*, **24**, 360—400 (1982); *b*) Davis R. H., Clench M. H., Mathiae J. R., *Dig. Dis. Sci*., **33**, 1505—1511 (1988).
4) Triozzi P. L., Laszlo J., *Drugs*, **34**, 136—149 (1987).
5) Harada H., Morie T., Hirokawa Y., Yoshida N., Kato S., *Chem. Pharm. Bull*., **43**, 1364—1378 (1995).
6) Hirokawa Y., Yoshida N., Kato S., *Bioorg. Med. Chem. Lett*., **8**, 1551—1554 (1998).
7) The dopamine D_3 receptors in the area postrema play an important role in the regulation of emesis. See: Yoshikawa T., Yoshida N., Hosoki K., *Eur. J. Pharmacol*., **301**, 143—149 (1996).
8) Hirokawa Y., Horikawa T., Kato S., *Chem. Pharm. Bull*., **48**, 1847—1852 (2000).
9) Dainter R. S., Suschitzky H., Wakefield B. J., Hughes N., Neslon A. J., *J. Chem. Soc., Perkin Trans. 1*, **1988**, 227—233.
10) Haga T., Koyanagi T., Nakajima T., Ohshima T., *Eur. Pat. Appl.* EP 92117 (1983) [*Chem. Abstr*., **100**, 68179 (1983)].
11) Jones R. G., *J. Am. Chem. Soc*., **69**, 2346—2350 (1947).
12) Belcher R., Stacey M., Sykes A., *J. Chem. Soc*., **1954**, 3846—3851.
13) Kiselyov A. S., Strekoxski L., *Org. Prep. Proc. Int*., **28**, 291—318 (1996).
14) Kobayashi Y., Kumadaki I., *Acc. Chem. Res*., **11**, 197—204 (1978).
15) Kimoto H., Cohen L. A., *J. Org. Chem*., **44**, 2902—2906 (1979).
16) Coldwell M. C., Gadre A., Jerman J., King F. D., Nash D., *Bioorg. Med. Chem. Lett*., **5**, 39—42 (1995).