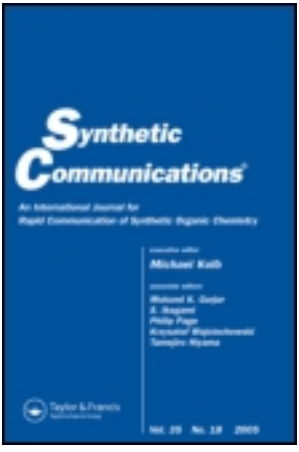

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PRACTICAL SYNTHESIS OF ETHYL CIS-4-AMINO-3-METHOXY-1-PIPERIDINE CARBOXYLATE, A KEY INTERMEDIATE OF CISAPRIDE

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PRACTICAL SYNTHESIS OF ETHYL *CIS*-4-AMINO-3-METHOXY-1-PIPERIDINE CARBOXYLATE, A KEY INTERMEDIATE OF CISAPRIDE

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ABSTRACT

A practical synthesis of ethyl *cis*-4-amino-3-methoxy-1-piperidinecarboxylate **1**, a key intermediate of cisapride as a potent gastrointestinal stimulant, has been accomplished from 1-methyl-1,2,3,6-tetrahydropyridine **2** *via* an efficient formation of *cis*-fused oxazolidinopiperidine **7**.

Ethyl *cis*-4-amino-3-methoxy-1-piperidinecarboxylate **1** has been used as a key intermediate for the synthesis of cisapride as a potent gastrointestinal stimulant. The intermediate **1** was synthesized from N-benzyl-4-piperidone by Van Daele *et al.*[1,7] Their synthetic strategy involved O-alkylation and reductive amination steps, which were dangerous and explosive in large-scale process.

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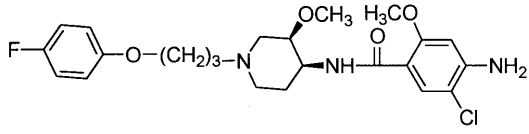
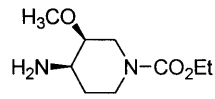
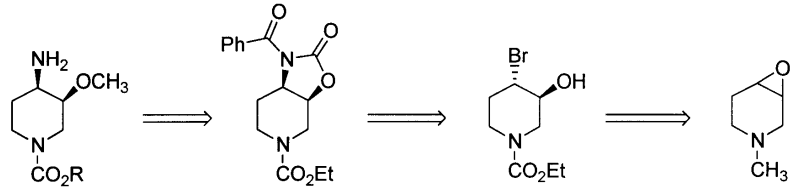


cisapride



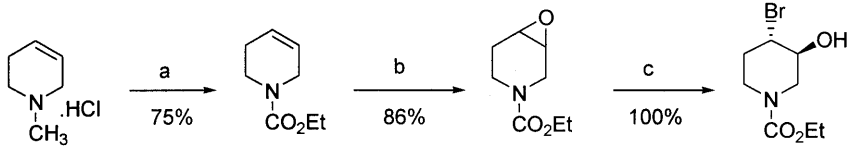
1

Reported herein is our highly efficient and stereoselective synthesis of ethyl *cis*-4-amino-3-methoxy-1-piperidinecarboxylate **1** from 1-methyl-1,2,3,6-tetrahydropyridine **2** in 10 steps. We envisioned that compound **1** could be synthesized through the selective ring opening of *cis*-fused N-benzoyloxazolidinopiperidine **7**, followed by O-methylation as shown in the following retrosynthetic plan. The requisite oxazolidinone **7** could be obtained from the bromohydrin **5**, which in turn could be regioselectively prepared from epoxide **4**.



1 **7** **5** **4**

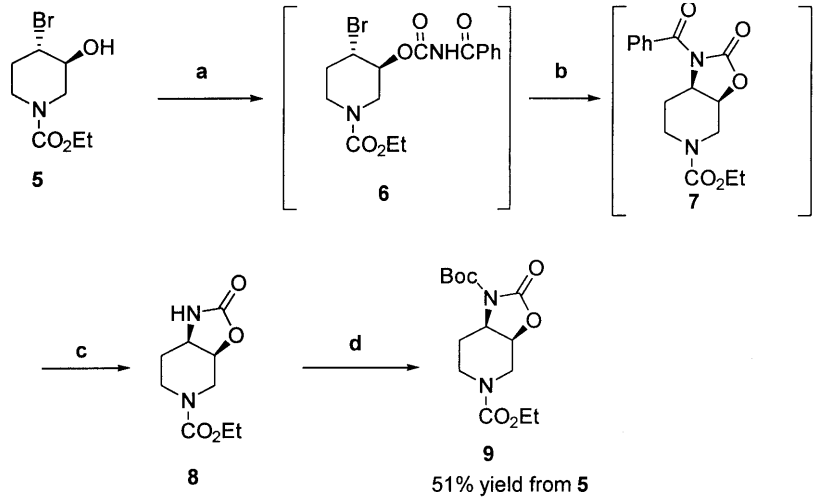
Known and inexpensive starting material **2** was converted into ethyl 1,2,3,6-tetrahydropiperidine-1-carboxylate **3** by reaction with ethyl chloroformate in refluxing toluene.[2,3] Epoxide **4** was readily prepared by the reaction of **3** with N-bomosuccinimide and aqueous DMSO, followed by treatment of the resulting mixture of bromohydrin with potassium carbonate in high overall yield. Exposure of epoxide **4** to 48% hydrobromic acid exclusively afforded the desired bromohydrin **5** in quantitative yield[4] (Scheme 1).



2 **3** **4** **5**

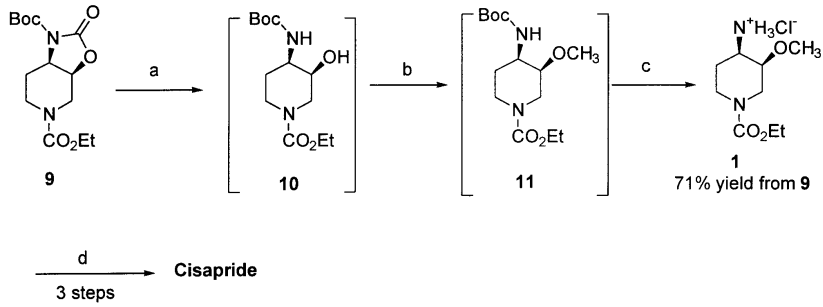
Scheme 1. Preparation of *trans*-4-bromo-3-hydroxypiperidine **5**: (a) (i) K_2CO_3/toluene, rt, (ii) EtOCOCl, toluene, reflux; (b) (i) NBS, DMSO, H_2O, rt, (ii) K_2CO_3, MeOH, rt; (c) 48% HBr/$CHCl_3$, $-40^{\circ}C$.

With multigrams of **5** in hand, we developed a one-pot synthesis of *cis*-fused bicyclic oxazolinopiperidine **8**, as summarized in Scheme 1. Thus, bromohydrin **5** was reacted with benzoyl isocyanate in THF to give the corresponding benzolyated compound **6**. Further treatment of **6** with potassium *tert*-butoxide, followed by the selective deprotection of the benzoyl group of compound **7** with lithium hydroxide in an aqueous solution afforded *cis*-fused bicyclic oxazolidinopiperidine **8**.[5] To open the oxazolidinone ring in a regioselective fashion, crude **8** was converted into N-Boc-protected oxazolidinone **9** to provide *cis*-N-Boc-oxazolidinopiperidine **9** in 51% yield from **5** (Scheme 2).



Scheme 2. Preparation of *cis*-N-Boc-oxazolidinopiperidine **9**: (a) benzoyl isocyanate, THF, rt; (b) t-BuOK, THF, reflux; (c) LiOH, THF, H_2O, rt; (d) Boc_2O, Et_3N, DMAP(cat.), CH_2Cl_2, 30°–35°C.

By the reaction with a catalytic amount of cesium carbonate, the oxazolidinone ring of **9** was cleaved to N-Boc-amino alcohol **10** in a regioselective manner,[5] which was further converted into the corresponding O-methylated piperidine **11**[7] by treatment with dimethylsulfate in aqueous NaOH. Exposure of the crude 11 to 13% hydrogen chloride in ethyl acetate gave the desired ethyl *cis*-4-amino-3-methoxy-1-piperidinecarboxylate hydrochloride **1** in 71% yield from the *cis*-N-Boc-oxazolidinopiperidine **9** as a white solid[8] (Scheme 3). The spectroscopic and physical properties of **1** such as ^1H and ^{13}C NMR, IR, MS, and m.p. were in excellent agreement with authentic material.[1]



Scheme 3. Preparation of *cis*-4-amino-3-methoxy-1-piperidine carboxylate hydrochloride 1: (a) cesium carbonate, MeOH, rt; (b) dimethylsulfate, aq. 50% NaOH, rt; (c) 13% HCl in EtOAc, rt; (d) (i) ArCOOH, EtOCOCl, Et_3N, $CHCl_3$, 0°C; (ii) KOH, i-PrOH, reflux; (iii) RX, Et_3N, DMF.

The key intermediate **1** could be converted into cisapride in three steps by known methods.[1,6] In summary, we have accomplished the synthesis of ethyl *cis*-4-amino-3-methoxy-1-piperidine carboxylate **1** on a large scale from inexpensive 1-methyl-1,2,3,6-tetrahydropyridine **2** by featuring an efficient, stereoselective, one-pot preparation of *cis*-oxazolidinopiperidine **8** from *trans*-bromohydrin **5** and a regioselective oxazolidinone ring opening of N-Boc protected oxazolidinone **9** as key steps.

EXPERIMENTAL

General

^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 (200 MHz ^1H, 50 MHz ^{13}C). Chemical shifts are reported in ppm (δ) units relative to tetramethylsilane. Infrared (IR) spectra were recorded on a Unicam mattson Genesis II FT-IR spectrometer. Mass spectral data were taken on a HP 1000 LC-MSD mass spectrometer an electrospray (ES) mode. Melting points were determined on a Thomas Hoover capillary melting point apparatus and were uncorrected. Column chromatography was performed using silica gel (0.05–0.2 mm, Merck).

Ethyl 1,2,3,6-Tetrahydropiperidine-1-carboxylate (**3**)

1-Methyl-1,2,3,6-tetrahydropiridine hydrochloride **2** (200 g, 1.5 mol) was dissolved in 500 mL of water and to this mixture was added

potassium carbonate (207 g, 1.5 mol). After being stirred for 10 min, the mixture was extracted with three times of toluene and the combined organic layers were dried over $MgSO_4$. After filtration, to the filtrate was added potassium carbonate (20 g) and the mixture was heated to refluxing temperature. To this was slowly added ethyl chloroformate (280 mL, 3 mol) during **1** h and the mixture was refluxed for 2 h. The resulting solution was cooled to room temperature, washed with water and brine, and dried over $MgSO_4$. Filtration and concentration in vacuo provided the oily residue, which was distilled under water pump vacuum to give **3** in 75% (174 g) yield as a colorless oil: b.p. 105°–110°C/15 mm; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.24 (t, J = 7.1 Hz, 3H), 1.90–2.20 (m, 2H), 3.16–3.28 (m, 4H), 3.45 (br, 1H), 3.68–3.76 (m, 1H), 3.86 (m, 1H), 4.09 (q, J = 7.2 Hz, 2H); IR (film, cm^{-1}) 1430, 1472, 1699, 2873, 2923, 3515; MS (70 eV) *m/z* 171 (M^+), 154, 142, 128, 115.

Ethyl 3-Oxo-1-piperidinecarboxylate (**4**)

To a solution of ethyl 1,2,3,6-tetrahydropiridine-1-carboxylate **3** (155 g, 1 mol) in dimethyl sulfoxide (2 L) was gradually added N-bromosuccinimide (356 g, 2 mol) over 10 min. The reaction mixture was maintained to 40°–50°C for an additional 10 min. The mixture was poured into ice water and extracted three times with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was treated with potassium carbonate (138 g, 2 mol) in 95% aqueous methanol (2.5 L) for 30 min. Insoluble materials were filtered off, and the filtrate was diluted with H_2O. The resulting mixture was extracted twice with ethyl acetate and dried over $MgSO_4$. Filtration and concentration in vacuo provided oily residue, which was distilled under water pump vacuum to give **4** in 86% (148 g) yield as a colorless oil: b.p. 80°–85°C/15 mm; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.16 (t, J = 7.2 Hz, 3H), 2.13 (bs, 2H), 3.53 (t, J = 5.7 Hz, 2H), 3.92 (t, J = 2.5 Hz, 3H), 4.13 (q, J = 5.6 Hz, 2H), 5.67 (m, 1H), 5.81 (m, 1H); IR (film, cm^{-1}) 1432, 1703, 2843, 2916, 2987, 3038; MS (70 eV) *m/z* 155 (M^+), 126, 110, 96.

Ethyl *trans*-4-Bromo-3-hydroxy-1-piperidinecarboxylate (**5**)

To a solution of ethyl 3-oxo-1-piperidinecarboxylate **4** (147 g, 0.86 mol) in chloroform (3 L) was added dropwise 48% hydrobromic acid (289 mL) at −40°C. After being stirred for 30 min at the same temperature, the mixture was treated with 5% aqueous sodium bicarbonate (1 L) and

extracted twice with ethyl acetate. The combined extracts were washed with dilute HCl, H_2O, and brine. The organic phase was dried over $MgSO_4$, evaporated in vacuo to obtain **5** in quantitative yield as a yellowish oil, which was pure enough to be used for the next step without further purification: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.26 (t, J = 7.1 Hz, 3H), 1.92–2.06 (m, 1H), 2.26–2.38 (m, 1H), 2.67 (bs, 1H), 3.71–3.75 (m, 1H), 3.92–3.99 (m, 2H), 4.08 (q, J = 7.2 Hz, 2H), 4.25 and 4.28 (dd, J = 1.8, 3.6 Hz, 1H); IR (film, cm^{-1}) 1246, 1430, 1699, 2870, 2931; MS (70 eV) m/z 252 (M^+), 236, 222, 172.

cis-1-*tert*-Butyloxycarbonyl-5-ethoxycarbonyl-2-oxo-hexahydro-oxazolo[5,4-c]pyridine (**9**)

Benzoyl isocyanate (14.4 mL, 0.14 mol) was added to a solution of ethyl *trans*-4-bromo-3-hydroxy-1-piperidinecarboxylate **5** (28 g, 0.12 mol) in THF (30 mL) and stirred for 1 h. The reaction mixture was diluted with THF (300 mL) and added potassium *tert*-butoxide (13.4 g, 0.12 mol). After refluxing for 1 h, the mixture was cooled and insoluble materials were filtered off. The resulting ethyl *cis*-1-benzoyl-2-oxo-hexahydro-oxazolo[5,4-c]-pyridine-5-carboxylate **7** solution was diluted with H_2O (300 mL) and treated with lithium hydroxide monohydrate (4.78 g, 0.12 mol) for 1 h. The mixture was extracted twice with ethyl acetate and dried over $MgSO_4$. Filtration and concentration in vacuo provided ethyl *cis*-2-oxo-hexahydro-oxazolo[5,4-c]pyridine-5-carboxylate **8**, which was dissolved in methylene chloride (300 mL). To the resulting solution of **8** was added di-*tert*-butyldicarboxylate (24.6 g, 0.11 mol), triethylamine (15.7 mL, 0.112 mol), and 4-dimethylaminopyridine (2 g, 1.6 mmol). After being stirred for 2 h at 30°–35°C, the mixture was evaporated in vacuo. The residue was chromatographed on silica gel (n-hexane:ethyl acetate = 2:1) to afford **9** in 51% (18.2 g) as a syrup.

Ethyl *trans*-4-Bromo-3-benzoylaminocarbonyloxy-1-piperidine-carboxylate (**6**)

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.29 (t, J = 7.1 Hz, 3H), 1.90–2.03 (m, 1H), 2.27–2.40 (m, 1H), 3.58 (m, 2H), 3.94 (m, 1H), 4.13 (q, J = 7.2 Hz, 2H), 4.27 (d, J = 15 Hz, 1H), 4.80 (bs, 2H), 7.34–7.84 (m, 5H); IR (film, cm^{-1}) 1425, 1690, 1785, 2980; MS (70 eV) m/z 400 (M^+), 355, 319, 268.

Ethyl *cis*-1-Benzoyl-2-oxo-hexahydro-oxazolo[5,4-c]pyridine-5-carboxylate (**7**)

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.29 (t, J = 7.1 Hz, 3H), 2.19–2.22 (m, 2H), 3.35 (m, 1H), 3.40–3.47 (m, 2H), 3.60–3.79 (m, 1H), 4.17 (q, J = 7.2 Hz, 2H), 4.00 (m, 1H), 5.0 (m, 1H), 7.34–7.84 (m, 5H), 8.25 (br, 1H); ^{13}C NMR ($CDCl_3$, 50.0 MHz) δ 14.4, 23.2, 38.2, 40.7, 51.5, 61.6, 71.7, 127.8, 128.8, 132.4, 132.7, 150.7, 152.5, 169.4; IR (film, cm^{-1}) 1442, 1684, 1784, 2934, 2984; MS (70 eV) *m*/*z* 318 (M^+).

Ethyl *cis*-2-Oxo-hexahydro-oxazolo[5,4-c]pyridine-5-carboxylate (**8**)

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.26 (t, J = 7.1 Hz, 3H), 1.76–1.94 (m, 2H), 3.42–3.51 (m, 3H), 4.13 (q, J = 7.1 Hz, 2H), 4.04–4.20 (m, 2H), 4.78 (bs, 1H), 5.70 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50.0 MHz) δ 14.12, 25.4, 37.1, 41.3, 47.9, 61.0, 73.2, 155.5, 159.0; IR (film, cm^{-1}) 1427, 1692, 1747, 2978, 3293; MS (70 ev) *m*/*z* 215 (M^+), 185, 169, 153, 141.

cis-1-*tert*-Butyloxycarbonyl-5-ethoxycarbonyl-2-oxo-hexahydro-oxazolo[5,4-c]pyridine (**9**)

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.27 (t, J = 7.1 Hz, 3H), 1.55 (s, 9H), 2.09 (m, 2H), 3.35 (m, 2H), 3.60 (m, 1H), 4.13 (q, J = 7.2 Hz, 2H), 4.15 (m, 1H), 4.24 (m, 1H), 4.40 (m, 1H); ^{13}C NMR ($CDCl_3$, 50.0 MHz) δ 13.8, 24.3, 27.2, 37.4, 40.3, 51.0, 60.9, 70.1, 83.3, 148.3, 150.7, 155.0; IR (film, cm^{-1}) 1382, 1698, 1812, 2980; MS (70 eV) *m*/*z* 315 (M^+), 299, 258, 213.

Ethyl *cis*-4-Amino-3-methoxy-1-piperidinecarboxylate hydrochloride (**1**)

To a solution of *cis*-1-*tert*-butyloxycarbonyl-5-ethoxycarbonyl-2-oxo-hexahydro-oxazolo[5,4-c]pyridine **9** (12.8 g, 40.7 mmol) in methanol (180 mL) was added cesium carbonate (2.65 g, 8.1 mmol) and stirred for 4 h. After evaporation of solvent in vacuo, the residue was dissolved in toluene (100 mL) and insoluble materials were filtered off. To this crude ethyl *cis*-4-*tert*-butyloxycarbonylamino-3-hydroxy-1-piperidinecarboxylate **10** solution was added aqueous 50% of sodium hydroxide (60 mL), dimethylsulfate (4.63 mL, 48.8 mmol), and benzyl triethylammonium chloride (100 mg, 0.3 mmol). After being stirred for 5 h, the mixture was diluted

with ice water (70 mL) and extracted twice with ethyl acetate. The combined organic phases were dried over $MgSO_4$. Filtration and concentration in vacuo provided crude ethyl *cis*-4-*tert*-butyloxycarbonylamino-3-methoxy-1-piperidinecarboxylate **11**, which was further treated with 13% hydrogen chloride solution in ethyl acetate (130 mL). The mixture was stirred for 6 h. The white solids formed were collected and washed with ethyl ether to give desired ethyl *cis*-4-amino-3-methoxy-1-piperidinecarboxylate hydrochloride **1** in 71% (6.88 g) yield as a whie solid.

Ethyl *cis*-4-*tert*-Butyloxycarbonylamino-3-hydroxy-1-piperidinecarboxylate (**10**)

M.p. 116°–117°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.18 (t, J = 7.1 Hz, 3H), 1.37 (s, 9H), 1.61 (m, 2H), 2.71–2.95 (m, 3H), 3.60 (m, 1H), 3.82 (bs, 1H), 4.03 (q, J = 7.2 Hz, 2H), 4.04–4.10 (m, 2H), 5.01 (d, J = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50.0 MHz) δ 14.1, 26.3, 28.3, 42.7, 48.9, 50.5, 61.5, 66.7, 79.4, 150.8, 155.3; IR (film, cm^{-1}) 1467, 1526, 1685; MS (70 eV) *m*/*z* 289 (M^+), 233, 213, 185, 141.

Ethyl *cis*-4-*tert*-Butyloxycarbonylamino-3-methoxy-1-piperidinecarboxylate (**11**)

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.23 (t, J = 7.2 Hz, 3H), 1.42 (s, 9H), 1.61–1.67 (m, 2H), 2.71–2.80 (m, 3H), 3.32 (m, 1H), 3.36 (s, 3H), 3.65 (m, 1H), 4.08 (m, 1H), 4.09 (q, J = 7.2 Hz, 2H), 4.04 (m, 1H), 5.01 (d, J = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50.0 MHz) δ 14.7, 26.9, 28.2, 42.5, 43.6, 50.1, 56.5, 61.1, 75.6, 79.2, 155.1, 155.7; IR (film, cm^{-1}) 1435, 1497, 1702, 2978, 3344, 3454; MS (70 eV) *m*/*z* 302 (M^+), 270, 246, 214, 185.

Ethyl *cis*-4-Amino-3-methoxy-1-piperidinecarboxylate hydrochloride (**1**)

M.p. 217°–218°C; ^{1}H NMR (CD_3OD, 200 MHz) δ 1.13 (t, J = 7.2 Hz, 3H), 1.57–1.67 (m, 2H), 2.68–2.83 (m, 2H), 3.16 (m, 1H), 3.30 (s, 3H), 3.42 (m, 1H), 3.96 (q, J = 7.2 Hz, 2H), 3.96–4.06 (m, 1H), 4.31–4.38 (m, 1H), 4.72 (bs, 3H); ^{13}C NMR ($CDCl_3$, 50.0 MHz) δ 15.8, 26.5, 43.8, 45.0, 58.2, 63.7, 75.3, 158.5; IR (film, cm^{-1}) 1237, 1442, 1523, 1698, 2902; MS (70 eV) *m*/*z* 238 (M^+).

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