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Chiral Pool Synthesis of *N*-Cbz-*cis*-(3*R*,4*R*)-3-methylamino-4-methylpiperidine from L-Malic acid

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A new synthetic route to *N*-Cbz-*cis*-(3*R*,4*R*)-3-methylamino-4-methylpiperidine, key intermediate for CP-690,550, was disclosed with L-malic acid as the chiral pool starting material. The title compound was obtained in 16 steps with a total yield of 26% and more than 98% ee.

Key Words : *N*-Cbz-*cis*-(3*R*,4*R*)-3-methylamino-4-methylpiperidine, CP-690,550, L-Malic acid, Chiral pool

Introduction

CP-690,550 (structure was shown in Figure 1), is developed by Pfizer and its discovery has been recently reported.[1] It is a potent first-in-class Janas tyrosine kinase (JAK) inhibitor for treatment of autoimmune disease and organ transplant rejection, while its enantiomer is less powerful (as shown in Figure 1).[1] Recent researches on the medicinal mechanism have revealed the potentially wide applications of this structural unit.[2-11] Thus, convenient synthetic route to CP-690,550 is demanded. In the view of retrosynthesis analysis of CP-690,550, disconnection at the methylamino group resulted in two fragments: *cis*-3-methylamino-4-methylpiperidine derivative (fragment A) and 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (fragment B) (Scheme 1). The synthesis of fragment B was divulged in our previous publication,[12] and by others.[13-17] To complete the total synthesis, fragment A is needed. We have reported a reasonable precursor for the synthesis of fragment A, *N*-Boc protected *cis*-3-methylamino-4-methylpiperidine.[18] Recently, other synthetic routes to *N*-protected *cis*-3-methylamino-4-methylpiperidine have also been reported.[19-21] However, all these methods suffered from unusual materials,[19-21] expensive catalysts,[18] reagents[18-21] and low yields. Thus, a new route with more accessible materials, high yield and most importantly, high ee, is required. In this paper, we disclose a new synthetic route to *N*-Cbz protected *cis*-(3*R*,4*R*)-3-methylamino-4-methylpiperidine (title compound) starting from L-malic acid with a total yield of 26% and ee of > 98%.

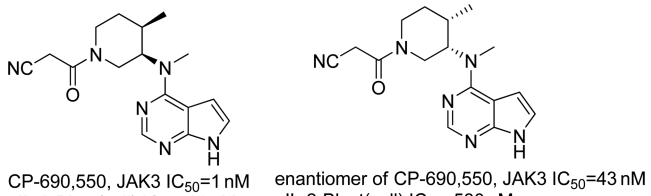
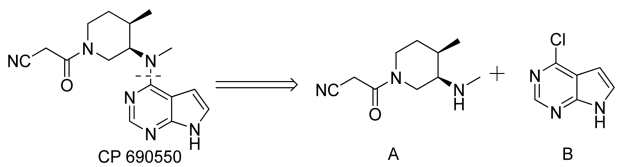


Figure 1. Structure of CP-690,550 and its enantiomer.

Experimental

General. All the reagents were chemical or analytical grade and were purified before use with standard procedure. Optical rotations were measured with a Perkin-Elmer 341 polarimeter in a 1 dm cell. ^{1}H and ^{13}C NMR spectra were recorded on a Varian AM-400 MHz spectrometer using $CDCl_3$ or DMSO-d_6 as the solvent and tetramethylsilane (TMS) as the internal standard. Chemical shifts (δ) were expressed in ppm downfield from internal TMS, and *J* values were given in Hz. LC-MS spectra were obtained using an Agilent Technologies 6120MSD mass spectrometer. HRMS were performed on a Waters Q-TOF spectrometer. Thin layer chromatography (TLC) analyses were accomplished on silica gel 60 F254 plates. Chromatographic purification was performed on silica gel (200-300 mesh).

(*S*)-Dimethyl 2-Hydroxysuccinate (2). Thionyl chloride (117 g, 0.98 mol) was added to the solution of L-malic acid (59.9 g, 0.45 mol) in methanol (400 mL) in ice-water bath. The resulting reaction mixture was stirred overnight at room temperature (rt, 25 °C) after the completion of the addition. The reaction was monitored with TLC (EtOAc:MeOH = 10:1). The solvent was removed *in vacuo*. Saturated $NaHCO_3$ solution (200 mL) was added, and the aqueous phase extracted with EtOAc (3 × 150 mL). The combined organic phases were washed successively with water (3 × 80 mL), brine (3 × 80 mL) and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The ester **2** was isolated as light yellow oil in 98% yield (71.5 g, 0.44 mol). $[\alpha]_D^{20}$ = +8.9 (EtOH, c 1.20, lit.[53] $[\alpha]_D^{20}$ = +8.6, EtOH, c



Scheme 1. Retrosynthesis of CP-690,550.

1.21), ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.74 (d, J = 6.1 Hz, 1H), 4.36 (dt, J = 7.4 Hz, 5.5 Hz, 1H), 3.62 (s, 3H), 3.57 (s, 3H), 2.69 (dd, J = 15.7 Hz, 5.0 Hz, 1H), 2.60-2.52 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.6, 170.9, 67.3, 52.1, 51.8, 39.2. It was in agreement with literature.[53]

(2*S*,3*R*)-Dimethyl 2-Hydroxy-3-methylsuccinate (3). Ester **2** was added to a stirring solution of lithium hexamethyldisilazide (LiHMDS, 1 M in THF, 256 mL, 0.27 mol) in anhydrous THF (150 mL) at −78 °C under nitrogen atmosphere. The reaction mixture was stirred at −78 °C for 1.5 h, and then, MeI (19 mL, 0.31 mol) was added, after which, the resulting mixture was stirred at −78 °C for additional 4 h. The reaction was monitored by TLC (Petroleum Ether (PE): EtOAc = 3:2). After the completion of the reaction, to the content was added saturated aqueous NH_4Cl (80 mL) and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic phase was washed successively with water (3 × 100 mL), brine (3 × 100 mL) and dried over Na_2SO_4, and the solvent was removed under reduced pressure. Purification by flash chromatography (EtOAc:PE = 1:10-1:2) followed by evaporation of solvent yielded ester **3** (20.4 g, 0.116 mol, 97%) as light yellow oil. $[\alpha]_D^{20}$ = +3.3 (EtOH, c 1.44), dr > 20:1, *ee* = 98.4%, ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.72 (d, J = 5.8 Hz, 1H), 4.18 (t, J = 5.7 Hz, 1H), 3.62 (s, 3H), 3.55 (s, 3H), 2.78-2.85 (m, 1H), 1.03 (d, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.3, 173.1, 72.5, 51.99, 51.94, 43.6, 13.0. It was in agreement with literature.[54]

(2*R*,3*S*)-Methyl 3,4-Dihydroxy-2-methylbutanoate (4). The solution of borane methyl sulfide (BMS) in anhydrous THF (36.5 mL, 0.07 mol) was added to the solution of ester **3** (12.6 g, 0.07 mol) in anhydrous THF (150 mL) in ice-water bath under nitrogen atmosphere. The content was stirred 30 min at rt after the complete addition. Then, $NaBH_4$ (137 mg, 3.6 mmol) was added in ice-water bath, and after which, the reaction mixture was stirred for 30 min at rt. The reaction was monitored with TLC (PE:EtOAc = 3:2) and was quenched with methanol (40 mL) when completed. The solvent was removed under reduced pressure. Purification by flash chromatography (EtOAc:PE = 1:30-1:6) yielded diol **4** (9.06 g, 61.2 mmol 85%) as light yellow oil. $[\alpha]_D^{20}$ = +7.8 (EtOH, c 1.16), ESI *m/z* = 149.1 $[M+1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.73 (d, J = 5.4 Hz, 1H), 4.49 (t, J = 5.6 Hz, 1H), 3.55 (d, J = 1.1 Hz, 1H), 3.54 (s, 3H), 3.42-3.35 (m, 2H), 2.56-2.49 (m, 1H), 0.98 (d, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 73.6, 64.0, 51.9, 42.2, 13.8; HRMS: calcd for $C_6H_{12}O_4Na$ ($M+Na^+$) 171.0624, found 171.0633.

(2*R*,3*S*)-Methyl 3,4-Bis(*tert*-butyldimethylsilyloxy)-2-methylbutanoate (5). To a stirred solution of diol **4** (9.92 g, 66.9 mmol) in DMF (100 mL) were added TBSCl (30.26 g, 200.8 mmol) and imidazole (27.34 g, 401.6 mmol) in ice-water bath. The content was stirred overnight at rt after the completion of the addition. The reaction was monitored by TLC (EtOAc). Water (300 mL) was added after the completion of the reaction. The content was extracted with EtOAc (3 × 100 mL). The combined organic phase was washed with water (3 × 100 mL), brine (3 × 100 mL) and dried over Na_2SO_4, and the solvent was removed under reduced pressure. Crude product (35.0 g) was obtained as a brown oil. Purification by flash chromatography (EtOAc:PE = 1:20-1:6) followed by evaporation of solvent yielded di-TBS protected ester **5** (24.81 g, 0.66 mol, 99%) as light yellow oil. $[\alpha]_D^{20}$ = −9.2 (EtOH, c 0.84), ESI *m/z* = 377.1 $[M+1]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (q, J = 5.3 Hz, 1H), 3.64 (s, 3H), 3.57 (dd, J = 8.9 Hz, 5.2 Hz, 2H), 2.72 (dd, J = 7.1 Hz, 5.9 Hz, 1H), 1.12 (d, J = 7.1 Hz, 3H), 0.87 (s, 9H), 0.84 (s, 9H), 0.03 (d, J = 2.4 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.3, 80.3, 70.5, 56.8, 49.0, 31.4, 31.2, 23.9, 23.5, 17.9, 1.3, 0.4, 0.02; HRMS: calcd for $C_{18}H_{40}O_4NaSi_2$ ($M+Na^+$) 399.2370, found 399.2363.

(2*R*,3*S*)-3,4-Bis(*tert*-butyldimethylsilyloxy)-2-methylbutanaldehyde (6). Diisobutylaluminum hydride (DIBAL-H, 50.3 mL, 60.4 mmol) was added to the solution of di-TBS protected ester **5** (22.0 g, 58.4 mmol) in dichloromethane (DCM, 260 mL) at −78 °C under nitrogen atmosphere. The resulting mixture was stirred for additional 30 min. When the reaction completed, to the content was added saturated NH_4Cl (40 mL) and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic phase was washed with water (3 × 100 mL), brine (3 × 100 mL) and dried over Na_2SO_4, and the solvent was removed under reduced pressure, which gave crude product (28.4 g) as light yellow oil. Purification by flash chromatography (EtOAc:PE = 1:3-1:10) followed by evaporation of solvent yielded aldehyde **6** (18.84 g, 54.5 mmol, 93%) as colorless oil. $[\alpha]_D^{20}$ = −7.3 (EtOH, c 1.36), ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (d, J = 1.7 Hz, 1H), 3.99 (td, J = 6.2 Hz, 3.8 Hz, 1H), 3.54 (d, J = 6.1 Hz, 2H), 2.53 (ddd, J = 7.0 Hz, 3.7 Hz, 1.6 Hz, 1H), 1.07 (d, J = 7.0 Hz, 3H), 0.83 (s, 18H), 0.03 (s, 6H), –0.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.2, 79.6, 70.2, 55.4, 31.4, 23.8, 23.6, 15.0, 1.2, 0.6, 0.01. HRMS: calcd for $C_{17}H_{38}O_3NaSi_2$ ($M+Na^+$) 369.2276, found 369.2257.

(3*R*,4*S*)-4,5-Bis(*tert*-butyldimethylsilyloxy)-3-methyl-1-nitropentan-2-ol (7). Nitromethane (2.65 g, 43.4 mmol) was added to the solution of *t*-BuOK (0.41 g, 3.6 mmol) in the mixture of THF (40 mL) and *t*-BuOH (50 mL) in ice-water bath under nitrogen atmosphere. The resultant mixture was stirred for additional 20 min, and then aldehyde **6** was added dropwise. After the completion of the addition, the content was warmed to rt and stirred overnight. The reaction was monitored with TLC (PE:EtOAc = 10:1). When the reaction completed, to the content was added water (40 mL) and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic phase was washed with water (3 × 100 mL), brine (3 × 100 mL) and dried over Na_2SO_4, and the solvent was removed under reduced pressure. Crude product (16.7 g) was obtained as brown oil. Purification by flash chromatography (EtOAc:PE = 1:30-1:10) followed by evaporation of solvent yielded nitro alcohol **7** (13.76 g, 33.8 mmol, 94%) as light yellow oil. ESI *m/z* = 408.0 $[M+1]^+$; HRMS: calcd for $C_{18}H_{41}NO_5Si_2Na$ ($M+Na^+$) 430.2424, found 430.2421.

(3*R*,4*S*)-4,5-Bis(*tert*-butyldimethylsilyloxy)-3-methyl-1-nitropentane (8). MsCl (3.71 g, 32.4 mmol) was added to

the solution of nitro alcohol 7 (11.0 g, 27.0 mmol) and Et_3N (7.5 mL, 54.0 mmol) in DCM (150 mL) in ice-water bath under nitrogen atmosphere. The resultant mixture was stirred overnight at rt. The reaction was monitored with TLC (PE:EtOAc = 8:1). When the reaction completed, to the content was added water (40 mL) and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic phase was successively washed with water (3 × 100 mL), brine (3 × 100 mL) and dried over Na_2SO_4, and the solvent was removed under reduced pressure. Crude product (14.3 g) was obtained as light yellow oil and the oil was dissolved in anhydrous ethanol (100 mL). To the resulting mixture was added $NaBH_4$ (1.64 g, 43.2 mmol) under nitrogen atmosphere. The resulting mixture was stirred for additional 30 min. The reaction was monitored with TLC (PE:EtOAc = 10:1). When the reaction completed, to the content was added saturated NH_4Cl (60 mL) and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic phase was washed with water (3 × 100 mL), brine (3 × 100 mL) and dried over Na_2SO_4, and the solvent was removed under reduced pressure. Crude product (15.6 g) was obtained as yellow oil. Purification by flash chromatography (EtOAc: PE= 1:50-1:20) followed by evaporation of solvent yielded nitro compound **8** (8.91 g, 22.8 mmol, 85%) as light yellow oil. $[\alpha]_D^{20}$ = –6.5 (EtOH, c 0.72), ESI *m/z* = 392.0 $[M+1]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.51-4.35 (m, 3H), 3.60-3.46 (m, 3H), 2.25-2.17 (m, 1H), 1.89-1.86 (m, 1H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 18H), 0.05 (d, *J* = 2.2 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 81.8, 79.9, 70.2, 38.1, 33.9, 31.4, 28.5, 23.6, 21.9, 1.3, 0.6, 0.01. HRMS: calcd for $C_{18}H_{41}NO_4NaSi_2$ 414.2489, found 414.2472.

(2*S*,3*R*)-2-(*tert*-Butyldimethylsilyloxy)-3-methyl-5-nitropentan-1-ol (9). HF-pyridine (4.0 mL, 46.0 mmol) was added to the solution of nitro compound **8** (4.5 g, 11.5 mmol) in pyridine (5 mL) and anhydrous THF (30 mL) in ice-water bath under nitrogen atmosphere. The resulting mixture was stirred overnight at rt. The reaction was monitored with TLC (PE:EtOAc = 8:1). When the reaction completed, to the content was added saturated $NaHCO_3$ (150 mL) and stirred for additional 30 min. To the content was added saturated $CuSO_4$ (300 mL) and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic phase was washed with water (3 × 100 mL), brine (3 × 100 mL) and dried over Na_2SO_4, and the solvent was removed under reduced pressure. Crude product (7.8 g) was obtained as yellow oil. Purification by flash chromatography (EtOAc: PE = 1:16-1:4) followed by evaporation of solvent yielded alcohol **9** (2.56 g, 9.2 mmol, 81%) as light yellow oil. $[\alpha]_D^{20}$ = +9.1 (EtOH, c 0.76), ESI *m/z* = 279.0 $[M+1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.54 (dd, *J* = 12.1 Hz, 6.7 Hz, 3H), 3.51-3.44 (m, 1H), 3.37-3.29 (m, 2H), 2.16-2.00 (m, 1H), 1.77-1.55 (m, 2H), 0.86 (d, *J* = 6.6 Hz, 3H), 0.83 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 81.7, 79.3, 68.0, 37.5, 33.2, 30.9, 22.9, 21.0, 0.9, 0.04. HRMS: calcd for $C_{12}H_{27}NO_4SiNa$ ($M+Na^+$) 300.1591, found 300.1607.

(2*S*,3*R*)-2-(*tert*-Butyldimethylsilyloxy)-3-methyl-5-nitropentyl methanesulfonate (10). MsCl (0.49 g, 4.3 mmol) was added to the solution of alcohol **9** (1.10 g, 2.70 mmol) and Et_3N (0.73 g, 7.2 mmol) in DCM (20 mL) in ice-water bath under nitrogen atmosphere. The resulting mixture was stirred for additional 1 h at rt. The reaction was monitored with TLC (PE:EtOAc = 3:1). When the reaction completed, the solvent was removed under reduced pressure. Purification by flash chromatography (EtOAc:PE = 1:8-1:4) followed by evaporation of solvent yielded compound **10** (1.23 g, 2.60 mmol, 96%) as light yellow oil. $[\alpha]_D^{20}$ = –4.1 (EtOH, c 0.76), ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.43-4.28 (m, 2H), 4.10-3.97 (m, 2H), 3.73 (td, *J* = 5.6 Hz, 3.4 Hz, 1H), 2.94 (s, 3H), 2.17 (dt, *J* = 10.6 Hz, 8.0 Hz, 1H), 1.79-1.65 (m, 2H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.81 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 78.6, 74.8, 42.3, 38.3, 33.5, 30.6, 22.9, 20.6, 0.5, 0.00.

(3*S*,4*R*)-Benzyl 3-(*tert*-Butyldimethylsilyloxy)-4-methylpiperidine-1-carboxylate (11). Compound **10** (0.60 g, 1.7 mmol) and Raney Ni (catalytic amount) were added to anhydrous ethanol (10 mL) and the atmosphere was exchanged with hydrogen for three times. The content was stirred for 1 h at rt. The reaction was monitored with TLC (PE:EtOAc = 2:1). Raney Ni was filtered off after the competition of the reaction. The solvent of the filtrate was removed under reduced pressure and light yellow oil (0.45 g) was obtained. The oil thus obtained together with Et_3N (0.428 g, 4.2 mmol) was dissolved in DCM (10 mL). The atmosphere was exchanged with hydrogen for three times. To the resulting mixture was added benzyl chloroformate (0.347 g, 2.0 mmol). The resulting mixture was stirred overnight at rt. The reaction was monitored with TLC (PE:EtOAc = 6:1). When the reaction completed, the reaction mixture was extracted with EtOAc (3 × 100 mL). The combined organic phase was washed with water (3 × 100 mL), brine (3 × 100 mL) and dried over Na_2SO_4, and the solvent was removed under reduced pressure. Crude product (0.815 g) was obtained as yellow oil. Purification by flash chromatography (EtOAc:PE = 1:18-1:5) followed by evaporation of solvent yielded piperidine **11** (0.554 g, 1.5 mmol, 91%) as light yellow oil. $[\alpha]_D^{20}$ = +11.8 (EtOH, c 0.64), ESI *m/z* = 364.0 $[M+1]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.30 (m, 5H), 4.97-5.29 (m, 2H), 4.18-3.90 (m, 2H), 3.68 (d, *J* = 25.9 Hz, 1H), 3.10-2.78 (m, 2H), 1.65 (d, *J* = 20.5, 2H), 1.37 (d, *J* = 10.2, 1H), 0.97-0.87 (m, 12H), 0.16-0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 142.1, 133.4, 132.8, 74.0, 71.9, 54.9, 48.5, 44.0, 40.5, 34.7, 32.7, 30.8, 23.1, 0.6, 0.0; HRMS: calcd for $C_{20}H_{33}NO_3SiNa$ ($M+Na^+$) 386.2128, found 386.2127.

(3*S*,4*R*)-Benzyl 3-Hydroxy-4-methylpiperidine-1-carboxylate (12). Piperidine **11** (0.248 g, 0.68 mmol) was added to 1 M TBAF in THF (3 mL). The resulting mixture was stirred overnight at rt. The reaction was monitored with TLC (PE: EtOAc = 2:1). When the reaction completed, to the content was added water (10 mL). The resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic phase was washed with water (3 × 10 mL), brine (3 × 10 mL) and dried over Na_2SO_4, and the solvent was removed under reduced pressure. Purification of crude product by flash chromatography (EtOAc:PE = 1:15-1:3) followed by

evaporation of solvent yielded hydroxy pyperidine **12** (0.159 g, 0.64 mmol, 94%) as light yellow oil. $[\alpha]_D^{20}$ = +4.7 (EtOH, c 0.68), ESI *m/z* = 250.0 $[M+1]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 13.3 Hz, 2.9 Hz, 5H), 5.13 (s, 2H), 4.13 (d, *J* = 12.9 Hz, 2H), 3.72 (s, 1H), 2.89 (dd, *J* = 63.6 Hz, 12.5 Hz, 2H), 1.68-1.53 (m, 2H), 1.40 (d, *J* = 20.2 Hz, 1H), 1.27 (d, *J* = 9.9 Hz, 2H), 1.01 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 128.5, 127.9, 68.7, 67.2, 50.4, 34.7, 31.4, 30.2, 17.3; HRMS: calcd for $C_{14}H_{19}NO_3Na$ ($M+Na^+$) 272.1270, found 272.1263.

(3*S*,4*R*)-Benzyl 4-Methyl-3-(methylsulfonyloxy)piperidine-1-carboxylate (13). MsCl (0.129 g, 1.12 mmol) was added to the solution of hydroxy pyperidine **12** (0.233 g, 0.93 mmol) and Et_3N (0.189 g, 1.86 mmol) in DCM (4 mL) in ice-water bath under nitrogen atmosphere. The resulting mixture was stirred for additional 1 h at rt. The reaction was monitored with TLC (PE:EtOAc = 3:2). When the reaction completed, the solvent was removed under reduced pressure. Purification by flash chromatography (EtOAc:PE = 1:10-1:4) followed by evaporation of solvent yielded piperidine **13** (0.30 g, 1.12 mmol, 99%) as colorless oil. $[\alpha]_D^{20}$ = −2.3 (EtOH, c 1.30), ESI *m/z* = 328.0 $[M+1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.39-7.26 (m, 6H), 5.08 (s, 2H), 4.66 (s, 1H), 4.31 (ddd, *J* = 14.5 Hz, 3.1 Hz, 2.0 Hz, 1H), 4.01 (dd, *J* = 13.7 Hz, 6.6 Hz, 1H), 3.10 (d, *J* = 22.5 Hz, 4H), 2.50 (dt, *J* = 3.7 Hz, 1.8 Hz, 1H), 1.90 (dddd, *J* = 11.8 Hz, 9.3 Hz, 4.4 Hz, 2.2 Hz, 1H), 1.51-1.41 (m, 1H), 1.37-1.22 (m, 2H), 0.95 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4, 128.5, 128.2, 127.0, 67.3, 47.7, 43.8, 39.1, 35.7, 34.2, 29.7, 17.4; HRMS: calcd for $C_{15}H_{21}NO_5SNa$ ($M+Na^+$) 350.1030, found 350.1038.

(3*R*,4*R*)-Benzyl 3-Amino-4-methylpiperidine-1-carboxylate (14). Piperidine **13** (0.784 g, 2.39 mmol) and NaN_3 (240 mg, 3.59 mmol) were added to DMF (15 mL) under nitrogen atmosphere. And the resulting mixture was stirred overnight at 80 °C. The reaction was monitored with TLC (PE:EtOAc = 2:1). When the reaction completed, to the content was added water (50 mL) and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed ten times with water (10 × 60 mL), brine (3 × 100 mL) and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was dissolved in THF (15 mL). The atmosphere was exchanged three times with nitrogen and the reaction temperature was set at −10 °C. Then, 28% ammonia (0.5 mL, 8.2 mmol) and PPh_3 (1.08 g, 4.1 mmol) were added. The reaction was slowly warmed to rt and stirred overnight. The solvent was removed under reduced pressure after the completion of the reaction. The residue was purified with flash chromatography (EtOAc:MeOH = 80:1-3:1). Amino piperidine **14** (0.494 g, 2.0 mmol, 84%) was isolated as light yellow oil. $[\alpha]_D^{20}$ = −6.3 (EtOH, c 0.70), ESI *m/z* = 249.0 $[M+1]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.18 (m, 5H), 5.12 (s, 2H), 4.24-4.01 (m, 2H), 2.77 (s, 1H), 2.51-2.28 (m, 2H), 1.65 (d, *J* = 10.2 Hz, 1H), 1.44 (s, 3H), 1.29-1.20 (m, 3H), 1.03 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 136.8, 128.4, 127.9, 67.0, 54.0, 51.3, 44.1, 38.9, 32.9, 18.3; HRMS: calcd for $C_{14}H_{20}N_2O_2Na$ ($M+Na^+$) 271.1402, found 271.1422.

(3*R*,4*R*)-Benzyl 3-(4-Methoxybenzylamino)-4-methylpiperidine-1-carboxylate (15). $NaBH(OAc)_3$ (249 mg, 1.18 mmol) was added to the solution of amino piperidine **14** (0.116 g, 0.47 mmol) and *p*-methoxybenzaldehyde (73 mg, 0.54 mmol) in DCM (5 mL) in ice-water bath under nitrogen atmosphere. The resulting reaction mixture was stirred overnight at rt. The reaction was monitored with TLC (PE:EtOAc = 1:3). When the reaction completed, the solvent was removed under reduced pressure. Purification by flash chromatography (EtOAc:PE = 1:10-1:4) followed by evaporation of solvent yielded compound **15** (158 mg, 0.43 mmol, 92%) as light yellow oil. $[\alpha]_D^{20}$ = +165.0 (EtOH, c 0.4). ESI *m/z* = 369.0 $[M+1]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.09 (m, 7H), 6.92-6.74 (m, 2H), 5.13 (s, 2H), 4.44-4.22 (m, 1H), 4.09-3.96 (m, 1H), 3.93-3.82 (m, 1H), 3.79 (s, 3H), 3.66 (d, *J* = 12.2 Hz, 1H), 2.81 (t, *J* = 18.2 Hz, 1H), 2.65-2.46 (m, 1H), 2.31-2.09 (m, 1H), 1.96 (s, 1H), 1.67 (d, *J* = 12.1 Hz, 1H), 1.43 (dd, *J* = 17.4 Hz, 8.0 Hz, 1H), 1.20 (dd, *J* = 17.8 Hz, 10.2 Hz, 1H), 0.98 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 136.9, 129.3, 128.5, 127.9, 113.8, 67.0, 59.4, 55.2, 50.7, 48.2, 43.8, 36.1, 18.3. HRMS: calcd for $C_{22}H_{29}N_2O_3$ ($M+H^+$) 369.2178, found 369.2178.

(3*R*,4*R*)-Benzyl 3-(4-Methoxybenzylmethylamino)-4-methylpiperidine-1-carboxylate (16). $NaBH(OAc)_3$ (186 mg, 0.88 mmol) was added to the solution of compound **15** (0.126 g, 0.35 mmol) and aqueous HCHO (142 mg, 1.75 mmol) in DCM (5 mL) in ice-water bath under nitrogen atmosphere. The resulting mixture was stirred overnight at rt. The reaction was monitored with TLC (PE:EtOAc = 1:3). When the reaction completed, the solvent was removed under reduced pressure. Purification by flash chromatography (EtOAc:PE = 1:8-1:4) followed by evaporation of solvent yielded compound **16** (133 mg, 0.35 mmol, 99%) as light yellow oil. $[\alpha]_D^{20}$ = +290.0 (EtOH, c 0.4). ESI *m/z* = 383.0 $[M+1]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.28 (m, 5H), 7.21 (s, 2H), 6.82 (d, *J* = 7.1 Hz, 2H), 5.13 (s, 2H), 4.39-4.24 (m, 1H), 4.17-4.03 (m, 1H), 3.79 (s, 3H), 3.71 (d, *J* = 13.1 Hz, 1H), 3.59-3.46 (m, 1H), 2.68 (t, *J* = 11.7 Hz, 2H), 2.22 (s, 3H), 1.70 (d, *J* = 11.1 Hz, 2H), 1.27-1.23 (m, 1H), 1.22-1.15 (m, 1H), 1.04 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 155.3, 137.0, 129.5, 128.5, 127.9, 113.6, 67.0, 57.5, 55.2, 44.3, 42.4, 36.4, 33.9, 18.8. HRMS: calcd for $C_{23}H_{31}N_2O_3$ ($M+H^+$) 383.2335, found 383.2330.

(3*R*,4*R*)-Benzyl 4-Methyl-3-(methylamino)piperidine-1-carboxylate (17). CAN (0.473 mg, 0.86 mmol) was added to the solution of compound **16** (0.110 g, 0.29 mmol) in acetonitrile (3 mL) and water (2 mL) in ice-water bath. The resulting mixture was stirred for additional 4 h at rt. The reaction was monitored with TLC (PE:EtOAc = 1:2). When the reaction completed, saturated $NaHCO_3$ (10 mL) was added. The aqueous phase was extracted with EtOAc (3 × 30 mL). Combined organic phase was washed with water (3 × 10 mL), saturated brine (3 × 10 mL) for three times and dried over Na_2SO_4. Purification by flash chromatography (EtOAc:MeOH = 60:1-4:1) followed by evaporation of solvent yielded compound **17** (70 mg, 0.27 mmol, 93%) as light yellow

oil. $[\alpha]_D^{20}$ = +137.5 (EtOH, c 0.32). ESI *m/z* = 263.0 $[M+1]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.28 (m, 5H), 5.14 (s, 2H), 4.35-4.19 (m, 1H), 3.98 (dt, *J* = 25.5 Hz, 10.3 Hz, 1H), 3.72-3.57 (m, 1H), 2.99-2.76 (m, 2H), 2.57 (s, 3H), 2.37-2.22 (m, 1H), 1.79-1.64 (m, 2H), 1.27 (d, *J* = 8.0 Hz, 1H), 1.11 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 135.6, 127.5, 126.9, 66.3, 60.4, 44.6, 42.3, 33.7, 32.0, 31.1, 17.3. HRMS: calcd for $C_{15}H_{23}N_2O_2$ ($M+H^+$) 263.1760, found 263.1762.

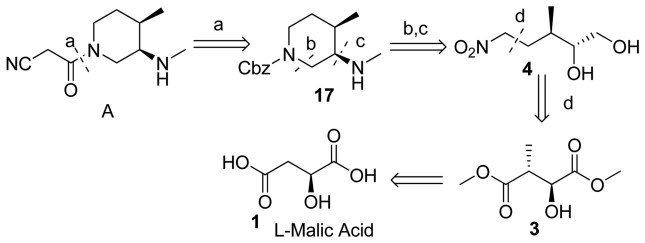
Results and Discussion

The retrosynthesic concept is depicted in Scheme 2. It was envisaged that the fragment **A** could be prepared from an *N*-Cbz *cis*-(3*R*,4*R*)-3-methylamino-4-methylpiperidine (**17**), whereas **17** can be obtained from nitro compound **4** by reduction and a successive sequence of reactions. Compound **4** in turn could be formed from ester **3** by reduction and Henry reaction. Ester **3** is accessible from L-malic acid by successive esterification and methylation. Enantiomerically pure L-malic acid is commercially available.

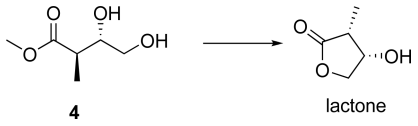
Our synthesis is shown in Schemes 3, 5 and 6, and started from the successive esterification and α-methylation of L-malic acid (Compound **1**) to afford ester **3**, by following the literature procedures with few modifications.[22-26] Ester **3** was obtained in high yield (95%), de (> 20:1) and ee (> 98%) according to ^{1}H NMR spectrum. More importantly, the two stereocenters in ester **3** (*trans*) could be readily converted to *cis* by S_N2 substitution with NaN_3 (see below). The base used in the α-methylation of methyl L-malic acid was lithium hexamethyldisilazide (LiHMDS), in lieu of lithium diisopropylamide (LDA) for shorter reaction time and easier operation. Attention must be paid to the work-up of the α-methylation of methyl L-malic acid. Water cannot be used to quench the reaction because LiOH, a strong base, could be formed, which led to the saponification of ester **3**. Thus, a lower yield was obtained. Our experiments demonstrated that saturated aqueous NH_4Cl was a good option and gave high yield.

The chemical environment differences between the two ester carbonyl groups make the selective reduction possible. Our experiments showed that with borane methyl sulfide (BMS)- $NaBH_4$, the chemoselective reduction of ester **3** could be achieved and gave the diol **4** in good yield, according to the literature precedents.[27-31] The reason for the chemoselectivity was discussed by Moriwake *et al*.[54] The best ratio for BMS: $NaBH_4$:ester **3** was 1:0.1:1. Excess BMS could lead to over-reduction and thus lower yield was obtained. To obtain the key nitro compound **8**, a Henry reaction is required, which means an aldehyde group has to be installed. As a result, the diol **4** had to be protected. Usually, reagents used for the protection of the adjacent diol are acetone and *p*-methyloxyphenyl aldehyde (PMP). However, the protection of diol **4** with either acetone or PMP was failed because the lactone was formed in acidic conditions (as seen in Scheme 4). While the diol **4** was stable at basic conditions, *tert*-butyldimethylsilyl (TBS) was chosen to be the proper protective group for further reactions. The protection was done under the standard conditions.

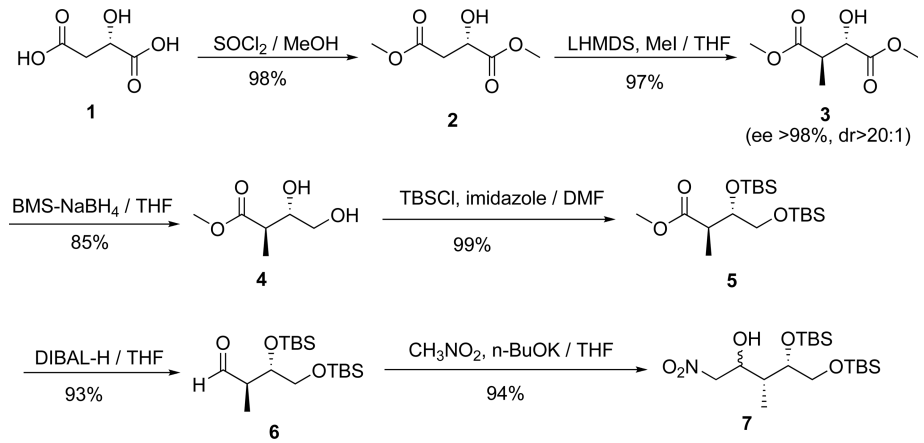
Aldehyde **6** was obtained from the reduction of ester **5** with DIBAL-H in excellent yield according to the literature procedure.[28,32,33] Over-reduction could be restrained by using 1.0-1.15 equivalent DIBAL-H employed and shorter reaction time (30 min). Moreover, the over-reduction product could be oxidized to aldehyde **6** with Dess-Martin reagent at rt in quantitative yield. Henry reaction of aldehyde **6** with



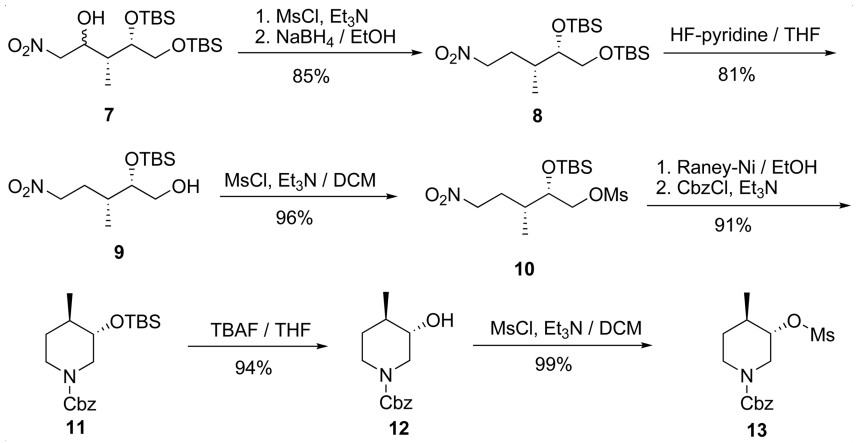
Scheme 2. Retrosynthesis of fragment A from L-malic acid.



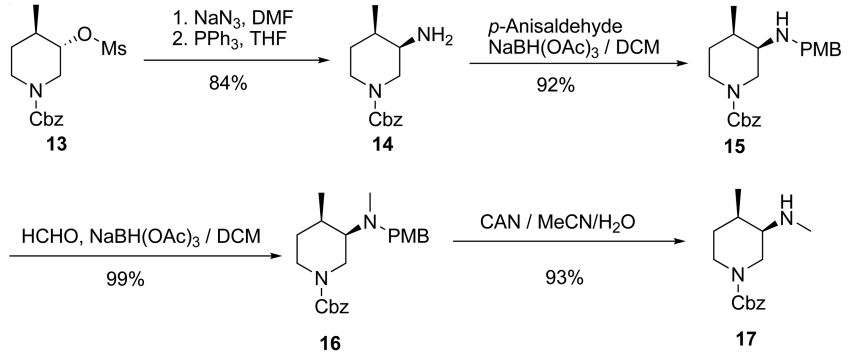
Scheme 4. Lactone formation.



Scheme 3. Synthesis of key intermediate nitro compound **7**.



Scheme 5. Synthesis of pyperidine **13**.



Scheme 6. Synthesis of title compound **17**.

nitromethane under basic condition could afford nitro alcohol **7**,[34-37] which was a mixture of two diastereomers. There was no need for further separation of the diasteromers because both of them could be transformed into nitro compound **8** through successive reaction with MsCl and $NaBH_4$.[38,39]

Chemoselective deprotection of nitro compound **8** with HF-pyridine at rt furnished alcohol **9** in high yield,[40,41] substitution of which with MsCl at rt provided compound **10**. Cbz protected piperidine **11** was obtained from the subsequent reduction of the nitro group with H_2/Raney Ni, intramolecular cyclization and substitution reaction with benzyl chloroformate. The one-pot operation made the route concise. These reactions are carried out under ordinary conditions and high to excellent yields were obtained.

The deprotection of piperidine **11** with TBAF at rt offered the hydroxy piperidine **12**,[42-44] substitution of which with MsCl at rt produced pyperidine **13**, which was initially to undergo a S_N2 reaction with aliphatic amine such as methylamine and benzylamine to form the final product. However, the conversion of piperidine **13** with the aliphatic amines was no more than 10% in solvents such as THF, DMF, dioxane, EtOH and MeOH, presumably due to the low nucleophilicity of the amine and severe steric hindrance.

To overcome this, the piperidine **13** was transformed to azide compound, which underwent Staudinger reduction to form amino piperidine compound **14**.[45-47] The direct methylation of amino piperidine compound **14** was not achievable for the reasons described before.[18] Reactions of amino piperidine **14** with *p*-anisaldehyde and formaldehyde under reductive conditions in DCM gave compound **16**.[48-50] Final product **17** was ultimately obtained upon removal of *p*-methoxybenzyl with CAN.[51,52] Thus, the installation of methyl was achieved.

Conclusion

In summary, we disclosed a new synthetic route to *N*-Cbz-*cis*-(3*R*,4*R*)-3-methyl-amino-4-methylpiperidine starting from L-malic acid in 16 steps. The final product was obtained in 26% total yield and > 98% ee. The route benefited from cheap raw materials, mild reaction conditions and easy operation. CP-690,550 should be readily accessible from title compound with reported procedure.[1]

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