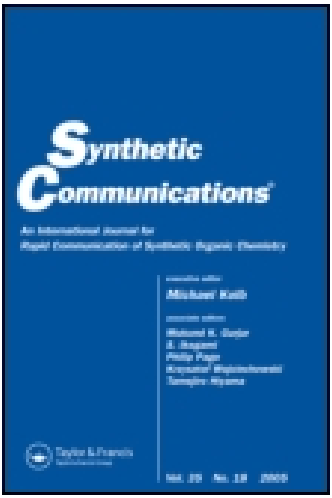

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A Novel and Facile Method to Synthesize (R)- and (S)-2-methylpiperazine

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A Novel and Facile Method to Synthesize (R)- and (S)-2-methylpiperazine

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ABSTRACT

A concise and efficient synthesis of (R)- and (S)-2-methylpiperazine in only five steps from (D)- and (L)-alanine is described. The key step is reaction of benzylamine with a bifunctional molecule to build a six-membered ring.

Key Words: (R)- and (S)-2-methylpiperazine; Synthesis.

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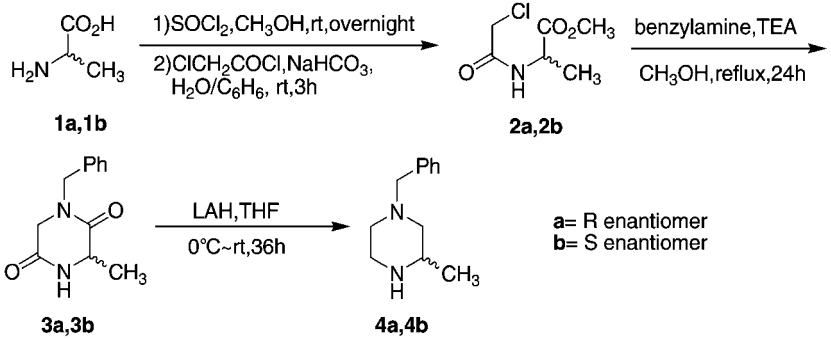
INTRODUCTION

Piperazine derivatives are particularly important to medicinal chemist. They were found to be used as base templates and substituents to impart the desired pharmacological and pharmacokinetic properties to several pharmaceutical agents, such as in quinolone antibiotics,[1] HIV-protease inhibitors,[2] 5HT-anxiolytics,[3] anti-hypertensives,[4] and δ-opioid receptor agonists.[5] Recently piperazine functioning as bifunctional linking agent to couple quinolone and oxazolidinone[6] through its six-membered heterocycle was reported. As part of our research involving the study of quinolone and oxazolidinone antibiotics we became interested in preparing enantiomerically pure 2-methylpiperazines and their analogue synthons.

There are some reports on the synthesis of the enantiomerically pure 2-methylpiperazines. The procedure of Armarego suffers from low yield (18%).[7] Enlightened by Armarego's idea, J.S. Kiely[8] and E.J. Jacobsen[9] made a modification and reported their methods in 1990 and 1995, respectively. However, due to the restricted availability of chemical reagents, it's still valuable for us to develop a simple and practical method to synthesize the enantiomerically pure 2-methylpiperazines, especially for preparation in large quantities.

RESULTS AND DISCUSSION

The intermediates of enantiomerically pure 2-methylpiperazines and their analogue synthons were prepared as shown in Scheme 1. Thus, the enantiomerically pure alanine was converted to its methyl ester with $SOCl_2$ in



Scheme 1.

methanol, and without purification, the resulting ester was treated with $ClCH_2COCl$ and $NaHCO_3$ in a mixture of water and benzene, which can give the product in high purity and yield than in homogeneous solution. The crude **2a** (or **2b**) reacted with benzylamine in methanol and the key intermediate diketopiperazine **3a** (or **3b**) was obtained in good yield (about 80%) through [5 + 1] cycling reaction.[10]

In general, the low concentration of reactant is beneficial for the intramolecular reaction. But to our surprise, the [5 + 1] cycling reaction didn't run well at low concentration, but gave better result when the concentration of **2a** (**2b**) was at about 0.5 mol/L. We considered that the chloro-group of **2a** (**2b**) reacted first with benzylamine through the intermolecular path which depended on the concentration of **2a** (or **2b**) and then the ester group in the molecule reacted with the secondary amine group in the same molecule going through the intramolecular path. The result of the cycling reaction run at different concentration is listed in Table 1.

3a (or **3b**) was reduced to **4a** (or **4b**) by $LiAlH_4$ at rt for 36 hr to avoid possible racemization. Therefore, the target molecule 2-methylpiperazines **5a** (or **5b**) and the Boc-protected 2-methylpiperazines **7a** (or **7b**) were readily prepared as usual from **4a** (or **4b**) as shown in Scheme 2 and Scheme 3, respectively. **7a** and **7b** can be used as very useful synthon in the synthesis of the pharmaceutical agents containing 2-methylpiperazines.

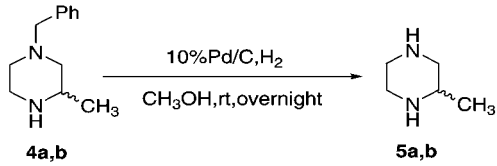
In summary, we report here a novel facile and practical method to synthesize enantiomerically pure 2-methylpiperazines and their analogue synthons starting from cheap reagents in fewer steps and high yield.

EXPERIMENTAL

The ^{1}HNMR spectra were recorded on a Varian Mercury-400 High Performance Digital FT-NMR with TMS as internal standard, and the mass spectra were determined by using Finnigan MAT 95, EI: 70 eV. Melting points were obtained at a Büchi 510 melting point apparatus and are uncorrected. Microanalyses were carried out on a Leco CHN-2000

Table 1. The experimental data of [5 + 1] cycling reaction.

2a(2b)	1 mol/L–higher concentration	0.2–0.8 mol/L	Lower concentration–0.1 mol/L
Side-product	Moderate	Low	High
3a(3b)	Moderate	High	Low



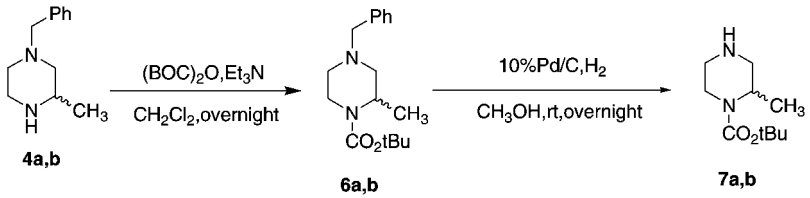
Scheme 2.

elemental analyzer. The optical rotation value $[\alpha]_D$ was determined with Perkin–Elmer-341 (589 nm).

(R)-1-benzyl-3-methylpiperazine-2,5-dione (3a)

To a suspension of D-alanine (26.70 g, 0.30 mol) in CH_3OH (200 mL) cooled in ice-salt bath, $SOCl_2$ (87.5 mL, 1.2 mol) was added dropwise while stirring. After the addition, the resulting mixture was stirred for an additional 6 hr at rt. The clear solution was concentrated to dryness, and without any purification, the solid was dissolved in water (120 mL) and cooled in ice-salt bath. To the solution, $NaHCO_3$ (60 g, 0.71 mol) was added in one portion, and then the solution of chloroacetyl chloride (23.8 mL, 0.3 mol) in benzene (100 mL) was added dropwise. After the addition, the reaction mixture was stirred for an additional 3 hr at rt. The aqueous layer was extracted twice with benzene (100 mL), and the combined organic phase was dried over anhydrous $MgSO_4$. Subsequent filtration and removal of organic solvent in vacuo gave a crude product (47.95 g, 89% based on **1a**), which was purified by chromatography on the silica gel (3 : 1, PE : EtOAC) to give 44.18 g (82% based on 1a) of **2a** as a colorless oil (solidified on standing). Mp 34–35°C; $[\alpha]_D^{25} = +50.5°$ (c = 2, MeOH); ^{1}HNMR($CDCl_3$): δ 7.12 (br s, 1 H), 4.60 (m, 1 H), 4.06 (s, 2 H), 3.77 (s, 3 H), 1.45 (d, $J = 7.13$ Hz, 3 H).

A solution of benzylamine (24.1 mL, 0.22 mol) in CH_3OH (180 mL) was added dropwise over 1.5 hr to a solution of **2a** (32.8 g, 0.183 mol) and TEA



Scheme 3.

(73.2 mL, 0.55 mol) in CH_3OH (180 mL) and refluxed for 20 hr, the pale yellow solution was cooled to rt and concentrated, and the residue was dissolved in 150 mL CH_2Cl_2. The organic phase was washed by 100 mL 5% aqueous citric acid, 100 mL saturated aqueous $NaHCO_3$, and 100 mL brine, and dried over anhydrous Na_2SO_4. Subsequent filtration and removal of organic solvent in vacuo gave a pale yellow solid (38.9 g), which was recrystallized from toluene (175 mL) to give 31.1 g (78%) of **3a** as a white solid. Mp 137–139°C; $[\alpha]_D^{20} = +8.56^\circ$ (c=1, $CHCl_3$); ^{1}HNMR ($CDCl_3$): δ 7.39–7.23 (m, 5H), 4.59 (s, 2H), 4.14 (m, 1H), 3.84 (s, 2H), 1.53(d, $J = 6.86$ Hz, 3H); MS (EI): m/e(%) 218 (M+, 76), 91 (100), 57 (44); Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.46; N,12.84. Found: C, 66.09; H, 6.37; N, 12.68.

If crude **2a** was used directly for the next reaction, **3a** was obtained in 66% yield based on **1a**.

(S)-1-benzyl-3-methylpiperazine-2,5-dione (3b)

Starting from L-alanine (**1b**), this compound was prepared in 67.5% yield based on **1b** according to the procedure described above. Mp 138–139.5°C; $[\alpha]_D^{20} = -8.85^\circ$ (c = 2, $CHCl_3$); ^{1}HNMR ($CDCl_3$): δ 7.39–7.23 (m, 5H), 4.59 (s, 2H), 4.14 (m, 1H), 3.84 (s, 2H), 1.53 (d, $J = 7.04$ Hz, 3H); MS (EI): m/e(%) 218 (M+, 76), 91 (100), 57 (44); Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.46; N, 12.84. Found: C, 65.74; H, 6.40; N, 12.66.

(R)-1-benzyl-3-methylpiperazine (4a)

To dry THF (300 mL) cooled in ice-salt bath, lithium aluminum hydride (12.91 g, 0.331 mol) and **3a** (20 g, 0.092 mol) were added subsequently. Under N_2 atmosphere, the mixture was stirred for 36 hr at rt. The reaction mixture was cooled again by ice/water bath and 12.3 mL of H_2O was added cautiously, followed by addition of 14.6 mL aqueous 2N NaOH. After stirring for 1 hr, the pale solid was removed by filtration and washed with THF. The combined filtrate was concentrated, and the residue was distilled in vacuo to give 14.1 g (81%) of **4a** as a pale yellow liquid (0.1 mm Hg, Bp 92–95°C) which solidified on standing. Mp 30–32°C; $[\alpha]_D^{20} = +7.3^\circ$ (c = 0.68, $CHCl_3$) {lit.[9] $[\alpha]_D^{25} = +7^\circ$ (C = 0.65, $CHCl_3$)}; ^{1}HNMR ($CDCl_3$): δ 7.33–7.24 (m, 5H), 3.48 (s, 2H), 2.94–2.74 (m, 5H), 2.05–1.95 (m, 1H), 1.66 (apparent t, 1H), 1.00 (d, $J = 6.2$ Hz, 3H); MS (EI), m/e(%) 190 (M+, 10), 134 (70), 91 (100), 65 (17); Anal. Calcd. for $C_{12}H_{18}N_2$: C, 75.74; H, 9.35; N, 14.72. Found: C, 75.42; H, 9.46; N, 14.69.

(S)-1-benzyl-3-methylpiperazine (4b)

This compound was prepared in 79% yield from **3b** according to the procedure described above. Mp 31–33°C; $[\alpha]_D^{20} = -5.4^\circ$ (c = 0.51, $CHCl_3$) {lit.[9] $[\alpha]_D^{25} = -5^\circ$ (C = 0.51, $CHCl_3$)}; ^{1}HNMR ($CDCl_3$): δ 7.33–7.24 (m, 5H), 3.48 (s, 2H), 2.94–2.74 (m, 5H), 2.05–1.95 (m, 1H), 1.66 (apparent t, 1H), 1.00 (d, $J = 6.2$ Hz, 3H); MS (EI), m/e(%) 190 (M+, 10), 134 (70), 91 (100), 65 (17); Anal. Calcd. for $C_{12}H_{18}N_2$: C, 75.74; H, 9.35; N, 14.72. Found: C, 75.32; H, 9.61; N, 14.75.

(R)-2-methylpiperazine (5a)

A mixture of **4a** (9.51 g, 0.05 mol), 10% palladium on carbon (1.2 g) and CH_3COOH (0.5 mL) in CH_3OH (100 mL) was stirred under 1 atm of H_2 at rt for 24 hr.The catalyst was removed by filtration and washed with CH_3OH. The combined filtrate was concentrated to give a solid, which was recrystallized from ether (100 mL) to give **5a** as colorless needles (3.8 g, 76% yield). Mp 91–93°C. $[\alpha]_D^{20} = -16.6^\circ$ (c = 4.6, C_6H_6) {lit.[11] $[\alpha]_D^{20} = -16.5^\circ$ (C = 5, C_6H_6)}; ^{1}HNMR ($CDCl_3$): δ 3.00–2.64 (m, 6H), 2.35 (dd, $J = 9.89$, 11.81 Hz, 1H), 1.95 (s, 2H), 0.99 (d, $J = 6.26$ Hz, 3H); MS(EI): m/e(%) 100 (M+, 27), 85 (100), 56 (54); Anal. Calcd. for $C_5H_{12}N_2 \cdot 0.26H_2O$: C, 57.28; H, 12.04; N, 26.72. Found: C, 57.28; H, 11.95; N, 26.69.

(S)-2-methylpiperazine (5b)

This compound was prepared in 74% yield from **4b** according to the procedure described above. Mp 91–93°C; $[\alpha]_D^{20} = +6.7^\circ$ (c = 0.97, EtOH) {lit.[11] $[\alpha]_D^{20} = +6.8^\circ$ (C = 1, EtOH)}; ^{1}HNMR ($CDCl_3$): δ 3.00–2.64 (m, 6H), 2.35 (dd, $J = 9.89$, 11.81 Hz, 1H), 1.95 (s, 2H), 0.99 (d, $J = 6.26$ Hz, 3H); MS (EI): m/e(%) 100 (M+, 27), 85 (100), 56 (54); Anal. Calcd. for $C_5H_{12}N_2 \cdot 0.23H_2O$: C, 57.57; H, 12.04; N, 26.86. Found: C, 57.57; H, 12.12; N, 26.78.

(R)-tert-butyl 4-benzyl-2-methylpiperazine-1-carboxylate (6a)

A solution of di-tert-butyl bicarbonate (5.81 g, 26.6 mmol) in CH_2Cl_2 (30 mL) was added dropwise over 15 min to a solution of **4a** (4.6 g, 24.2 mmol) and TEA (3.96 mL, 26.6 mmol) in CH_2Cl_2 (30 mL) cooled in ice-water bath. After stirring for 20 hr at rt, the reaction mixture was

washed with brine and dried over $NaSO_4$. Subsequent filtration and removal of organic solvent in vacuo gave a residue that was purified by chromatography on silica gel (PE : EtOAC = 20 : 1) to give 7.0 g (99%) of **6a** as an oil. $[\alpha]_D^{20} = -62.6^\circ$ (c = 0.87, EtOH) {lit.[9] $[\alpha]_D^{25} = -62^\circ$ (C = 0.84, EtOH)}; ^{1}HNMR ($CDCl_3$): δ 7.39–7.21 (m, 5H), 4.21–4.12 (m, 1H), 3.80 (d, $J = 13.04$ Hz, 1H), 3.46 (ABq, $J_{AB} = 13.32$ Hz, $\Delta_\gamma = 41.23$ Hz, 2H), 3.18–3.02 (m, 1H), 2.75 (d, $J = 11.12$ Hz, 1H), 2.58 (d, $J = 11.13$ Hz, 1H), 2.12 (dd, $J = 11.13$, 3.85 Hz, 1H), 2.02–1.95 (m, 1H), 1.45 (s, 9H), 1.24 (d, $J = 6.73$ Hz, 3H); MS(EI) m/e(%) 290 (M+, 18), 233 (64), 160 (22), 146 (29), 134 (59), 91 (100); Anal. Calcd. for $C_{17}H_{26}N_2O_2$: C, 70.31; H, 9.02; N, 9.65. Found: C, 70.19; H, 9.21; N, 9.59.

(S)-tert-butyl 4-benzyl-2-methylpiperazine-1-carboxylate (6b)

This compound was prepared in 99% yield from **4b** according to the procedure described above. $[\alpha]_D^{20} = +59.5^\circ$ (c = 1.29, EtOH) {lit.[9] $[\alpha]_D^{25} = +56^\circ$ (C = 0.44, EtOH)}; ^{1}HNMR ($CDCl_3$): δ 7.39–7.21 (m, 5H), 4.21–4.12 (m, 1H), 3.80 (d, $J = 12.78$ Hz, 1H), 3.46 (ABq, $J_{AB} = 13.32$ Hz, $\Delta_\gamma = 41.23$ Hz, 2H), 3.18–3.02 (m, 1H), 2.75 (d, $J = 11.12$ Hz, 1H), 2.58 (d, $J = 11.13$ Hz, 1H), 2.12 (dd, $J = 11.13$, 3.85 Hz, 1H), 2.02–1.95 (m, 1H), 1.45 (s, 9H), 1.24 (d, $J = 6.73$ Hz, 3H); MS(EI) m/e(%) 290 (M+, 18), 233 (64), 160 (22), 146 (29), 134 (59), 91 (100); Anal. Calcd. for $C_{17}H_{26}N_2O_2$: C, 70.31; H, 9.02; N, 9.65. Found: C, 70.25; H, 9.01; N, 9.51.

(R)-tert-butyl 2-methylpiperazine-1-carboxylate (7a)

A mixture of **6a** (5.81 g, 20 mmol), 10% palladium on carbon (1.2 g) and CH_3COOH (8 drops) in CH_3OH (50 mL) was stirred under 1 atm of hydrogen at rt for 24 hr, and the catalyst was removed by filtration and washed with CH_3OH. The combined filtrate was concentrated, the residue was diluted with CH_2Cl_2 (50 mL) and filtered. The filtrate was concentrated again to give 3.68 g (92%) of **7a** as a colorless oil that solidified on standing: m.p. 34–36°C; $[\alpha]_D^{20} = -60.4^\circ$ (C = 0.92, $CHCl_3$) {lit.[9] $[\alpha]_D^{25} = -59^\circ$ (C = 0.92, $CHCl_3$)}; ^{1}HNMR ($CDCl_3$): δ 4.10–4.30 (m, 1H), 3.75–3.80 (m, 1H), 2.60–3.00 (m, 5H), 1.84 (s, 1H), 1.46 (s, 9H), 1.22 (d, $J = 6.88$ Hz, 3H); MS(EI): m/e(%) 200 (M+, 20), 144 (42), 127 (30), 99 (32), 70 (31), 57 (100); Anal. Calcd. for $C_{10}H_{20}N_2O_2$: C, 59.97; H, 10.07; N, 13.99. Found: C, 59.86; H, 9.95; N, 13.92.

(S)-tert-butyl 2-methylpiperazine-1-carboxylate (7b)

This compound was prepared in 90% yield from **6b** according to the procedure described above. Yield. Mp 34–36°C; $[\alpha]_D^{20} = +68.5^\circ$ (C = 0.65, $CHCl_3$) {lit.[9] $[\alpha]_D^{25} = +67^\circ$ (C = 0.65, $CHCl_3$)}; ^{1}HNMR ($CDCl_3$): δ 4.10–4.30 (m, 1H), 3.75–3.80 (m, 1H), 2.60–3.00 (m, 5H), 1.84 (s, 1H), 1.46 (s, 9H), 1.22 (d, $J = 6.88$ Hz, 3H); MS(EI): m/e(%) 200 (M+, 29), 144 (54), 127 (40), 99 (33), 70 (36), 57 (100); Anal. Calcd. for $C_{10}H_{20}N_2O_2$: C, 59.97; H, 10.07; N, 13.99. Found: C, 59.92; H, 10.13; N, 13.78.

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