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Asymmetric Synthesis of (2*R*,6*R*) and (2*S*,6*S*)-2,6-Dimethylpiperazine

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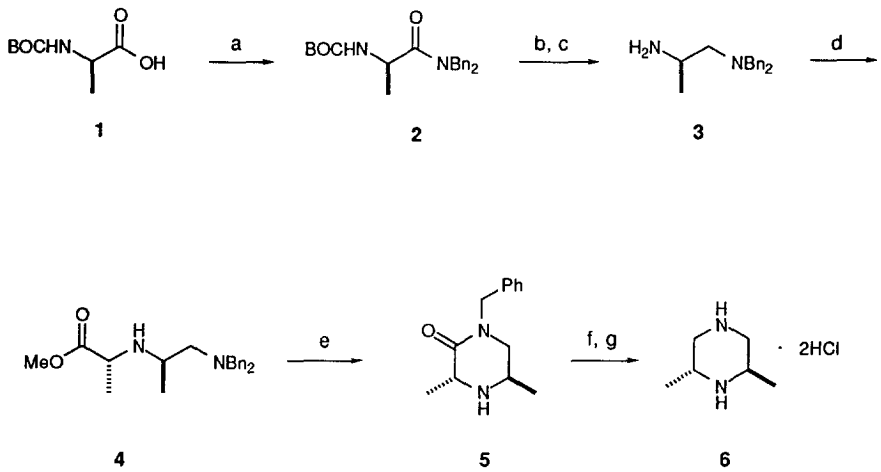
Abstract: The title compounds were prepared via two efficient routes. The first sequence utilized a diastereospecific triflate alkylation in the key bond forming step while the second method relied on a novel intramolecular Mitsunobu reaction to set the required stereochemistry.

Many pharmaceutical agents contain piperazine derivatives as part of their core structures. Examples can be found in the quinolone antibiotics,[1] 5HT-anxiolytics,[2] HIV protease inhibitors,[3] antihypertensives,[4] and κ-receptor agonists.[5] Thus, the asymmetric synthesis of substituted piperazines continues to be of interest.[6] As part of our ongoing research towards the development of anxiolytic agents containing substituted piperazines, we had the need to prepare both enantiomers of *trans*-2,6-dimethylpiperazine. Although a synthesis of racemic *trans*-2,6-dimethylpiperazine was reported by Cignarella and Gallo, it suffered from poor regioselectivity and stereoselectivity.[7] These problems, in combination with a low overall yield, precluded an efficient asymmetric synthesis of the respective enantiomers. To address these limitations, we developed two alternative synthetic routes that led to the title compounds in >98% enantiomeric excess with good to excellent overall yields.

The first method utilized a highly efficient triflate alkylation as the key step (Scheme I). These alkylations typically proceed in high yields with inversion of stereochemistry[8] and thus were well suited to control the chirality within the piperazine framework. The synthesis began with the conversion of N-t-BOC-D-alanine to the dibenzylamide **2** via the mixed anhydride. Removal of the BOC protecting group with trifluoroacetic acid (TFA) followed by borane-methyl sulfide reduction[9] gave diamine **3.** Alkylation of diamine **3** with methyl (*S*)-2-[(trifluoromethylsulfonyl)oxy]propionate (generated by the sequential treatment of methyl (*S*)-lactate with trifluoromethanesulfonic anhydride and 2,6-lutidine)[10] proceeded smoothly with inversion of stereochemistry to give the amine **4.** Hydrogenolysis of **4** (palladium on charcoal) resulted in mono-debenzylation and partial cyclization to provide piperazin-2-one **5.** Complete cyclization could be effected by refluxing the mixture in the presence of *p*-toluenesulfonic acid. Reduction of **5** with lithium aluminum hydride (LAH) and hydrogenolysis of the remaining benzyl group with Pearlman's catalyst gave the desired piperazine **6** which was conveniently isolated as the dihydrochloride salt. Following this seven

step sequence, (2*R*,6*R*)-2,6-dimethylpiperazine[11] **6** was isolated in >98% ee[12] in an overall yield of 44%. This can be compared to the racemic literature route which required six steps and resulted in a 5% overall yield. The (*S*,*S*)-enantiomer was prepared in an analogous manner from N-t-BOC-L-alanine and methyl (*R*)-lactate.

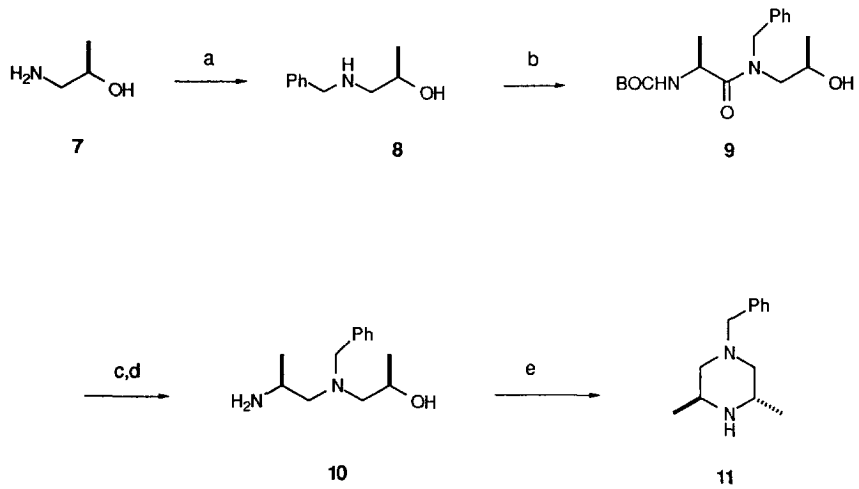
Scheme I



Reagents and conditions: (a) Isobutyl chloroformate, Et_3N, THF, -30 °C; dibenzylamine, rt; 78%. (b) TFA, CH_2Cl_2, 0 °C; 98%. (c) BH_3·DMS, rt; KOH, reflux; 97%. (d) (*S*)-$CH_3CH(OSO_2CF_3)CO_2CH_3$ (1.2 equiv.), Et_3N, CH_2Cl_2, 0 °C to rt; 95%. (e) Pd/C, H_2, HCl, MeOH, rt; TsOH, reflux; 80%. (f) LAH, THF, reflux; 94%. (g) $Pd(OH)_2$, H_2, MeOH, rt; methanolic HCl; 83%.

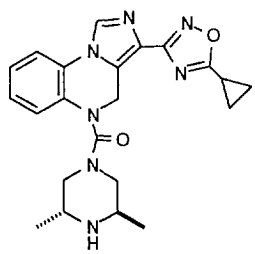
Concurrent with the development of the above sequence was research on a second route that led to the (*S*,*S*)-enantiomer of piperazine **6**. This route relied on an intramolecular Mitsunobu reaction to set the required stereochemistry (Scheme II). To our knowledge, this is the first report of the Mitsunobu reaction being used to prepare a piperazine derivative. The first step involved the reductive alkylation of (*R*)-1-amino-2-propanol with benzaldehyde to give **8** via an intermediate oxazolidine. The amino-alcohol **8** was then coupled to N-t-BOC-L-alanine with carbonyl diimidazole (CDI) to provide **9** which was deprotected with TFA and the amide reduced with borane-methyl sulfide.[9] Mitsunobu cyclization of **10** resulted in ring closure to the benzylated piperazine **11**. Conversion to the final dimethylpiperazine **6** (*S*,*S*-enantiomer) was accomplished as depicted in Scheme I. Although the overall yield of **6** (*S*,*S*-enantiomer) was lower in the cyclization route (Scheme II) than in the triflate alkylation approach (19% versus 44%), the former required one less step. As in the first sequence, the final *trans*-2,6-dimethylpiperazine was isolated in >98% ee.[12]

Scheme II



Reagents and Conditions: (a) Benzaldehyde, $MgSO_4$, THF, rt; $NaBH_4$, EtOH, rt; 57%. (b) CDI; N-t-BOC-L-alanine, CH_2Cl_2, rt; 80%. (c) TFA, CH_2Cl_2, 0 °C; 100%. (d) BH_3·DMS, THF, rt; KOH, THF/H_2O, reflux; 76%. (e) DEAD, PPh_3, THF, rt; 65%.

In summary, two asymmetric synthetic sequences for the preparation of the enantiomers of *trans*-2,6-dimethylpiperazine were developed. These routes make use of preparatively simple, good to high yielding reactions, and represent a significant improvement over the previous racemic synthesis. Another notable advantage is the generality of these routes. By judicious choice of the proper starting materials readily available from the chiral pool, it should be possible to incorporate a wide variety of substituents within the piperazine framework.[13] Studies are currently underway to determine what effect these chiral piperazines may have on the pharmacological and pharmacokinetic characteristics of various anti-anxiety agents including the imidazo[1,5-*a*]quinoxaline **U-104030**.



U-104030

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11. All new compounds were fully characterized by NMR, IR, and elemental analysis or mass spectrometry. The physical data for the title compounds are provided: **(2*R*,6*R*)-2,6-Dimethylpiperazine dihydrochloride (6).** Decomp. >260 °C; $[\alpha]^{25}_D$ -4 (c 0.85, MeOH); IR (mineral oil) 2951, 2924, 1587, 1577, 1460 cm^{-1}; ^1H NMR (300 MHz, MeOH) δ 3.9-4.0 (m, 2 H), 3.56 (dd, *J* = 13.8 Hz, *J* = 3.8 Hz, 2 H), 3.30-3.40 (m, 4 H), 1.51 (d, *J* = 6.9 Hz, CH_3). Anal. Calcd. for $C_6H_{14}N_2 \cdot (HCl)_2$: C, 38.51; H, 8.62; N. 14.97. Found: C, 38.38; H, 8.37; N, 14.93.

    (2*S*,6*S*)-2,6-Dimethylpiperazine dihydrochloride. $[\alpha]^{25}_D$ +5 (c 0.98, MeOH); Spectral data identical to **6.** Anal. Calcd. for $C_6H_{14}N_2 \cdot (HCl)_2$: C, 38.51; H, 8.62; N, 14.97. Found: C, 38.11; H, 8.46; N, 14.62.
12. Enantiomeric excesses were determined by GLC analysis of the mono (*S*)-Mosher amides derived from (2*R*,6*R*) and (2*S*,6*S*)-2,6-dimethylpiperazine dihydrochloride.
13. We have succeeded in synthesizing both monoalkyl and trimethylpiperazine derivatives by these routes, thus demonstrating their generality. Full experimental details of this investigation will be published in due course.

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