Asymmetric Synthesis of 2,6-Methylated Piperazines

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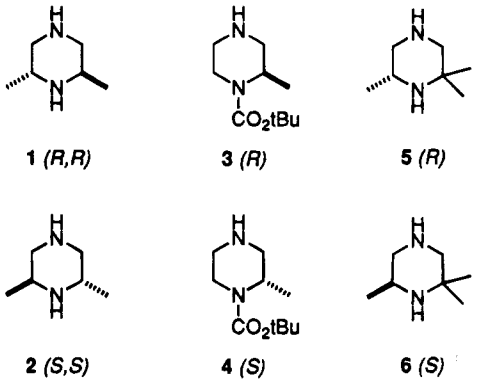
The complete series of enantiopure 2,6-methylated piperazines was synthesized utilizing two alternative reactions in the key bond-forming step. The dimethyl enantiomers, (2*R*,6*R*)- and (2*S*,6*S*)-2,6-dimethylpiperazine (**1**, **2**), were prepared using either a diastereoselective triflate alkylation or a novel intramolecular Mitsunobu reaction to set the required stereochemistry. The monomethyl derivatives, (*R*)- and (*S*)-*tert*-butyl 2-methyl-1-piperazinecarboxylate (**3**, **4**) were also synthesized employing the Mitsunobu cyclization strategy while the trimethyl compounds, (*R*)- and (*S*)-2,2,6-trimethylpiperazine (**5**, **6**) were prepared using an enantiospecific triflate alkylation as the principal reaction. These methods represent efficient, general strategies for preparing a variety of 2,6-methylated piperazines for which the absolute stereochemistry can be readily controlled.

Introduction

Many pharmaceutical agents contain piperazine derivatives as part of their core structures. In addition to serving as base templates and substituents to impart the desired pharmacological and pharmacokinetic properties to a compound, piperazines can also function as bifunctional linking agents to couple two components of an analog through a six-membered heterocycle. 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 synthesis of a variety of substituted piperazines is of particular importance to the medicinal chemist.[6] As part of our research involving the study of $GABA_A$-based anxiolytic agents we became interested in preparing analogs incorporating chiral, 2,6-polymethylated piperazines. Despite the prevalence of substituted piperazines in medicinal chemistry, there was a lack of general synthetic routes for preparing the chiral 2,6-methylated piperazines we required for our structure–activity relationship (SAR) study. The few syntheses for individual members of this class of piperazines that have been reported, utilize strategies that either lacked generality or selectivity and thus, were not adequate for our purposes. For example, the literature synthesis of racemic *trans*-2,6-dimethylpiperazine was not suitable for preparing the individual enantiomers due to overall inefficiency resulting from poor regioselectivity and stereoselectivity for the key bond-forming steps within the sequence (vide infra).[7] Likewise, although the enantiomers of 2-methylpiperazine have been synthesized[6,8] or obtained by resolution of the racemate,[1] the methodology utilized in these routes was not readily applicable to the preparation of other homologs within this series. Finally, we needed the enantiomers of 2,2,6-trimethylpiperazine which were unknown in either enantiopure or racemic form. Therefore, we sought to develop general, asymmetric syntheses for the enantiomers of *trans*-2,6-dimethylpiperazine[9] (**1**, **2**), *tert*-butyl 2-methyl-1-piperazinecarboxylate (**3**, **4**), and 2,2,6-trimethylpiperazine (**5**, **6**) (Figure 1).



1 *(R,R)* **3** *(R)* **5** *(R)*

2 *(S,S)* **4** *(S)* **6** *(S)*

Figure 1.

Two general strategies were utilized to control the absolute stereochemistry of the methyl groups within the piperazine framework. The first method relied on a highly efficient α-triflate alkylation to create the desired stereocenter. These types of alkylations are ideally suited for our purposes as they have been shown to proceed with a very high degree of inversion for amine alkylations.[10] The second method centered on a novel intramolecular Mitsunobu reaction[11] to generate the desired asymmetric center. To our knowledge this is the first report of a Mitsunobu reaction being used to prepare a piperazine ring. These routes are particularly attractive as they represent two general, alternative methods

[⊗] Abstract published in *Advance ACS Abstracts,* June 1, 1995.

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(2) Perregaard, J.; Sánchez, C.; Arnt, J. *Curr. Opin. Ther. Pat.* **1993**, 101.

(3) Askin, D.; Eng, K. K.; Rossen, K.; Purick, R. M.; Wells, K. M.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1994**, *35*, 673.

(4) Giardinà, D.; Gulini, U.; Massi, M.; Piloni, M. G.; Pompei, P.; Rafaiani, G.; Melchiorre, C. *J. Med. Chem.* **1993**, *36*, 690.

(5) Naylor, A.; Judd, D. B.; Lloyd, J. E.; Scopes, D. I. C.; Hayes, A. G.; Birch, P. J. *J. Med. Chem.* **1993**, *36*, 2075.

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(7) Cignarella, G.; Gallo, G. G. *J. Heterocycl. Chem.* **1974**, *11*, 985.

(8) (a) Armarego, W. L. F.; Schou, H.; Waring, P. *J. Chem. Res. (M)* **1980**, 1951. (b) Kiely, J. S.; Priebe, S. R. *Org. Prep. Proc. Int.* **1990**, *22*, 761.

(9) For a preliminary communication on the synthesis of both enantiomers of *trans*-2,6-dimethylpiperazine see: Mickelson, J. W.; Jacobsen, E. J. *Tetrahedron: Asymmetry* **1995**, *6*, 19.

(10) For work utilizing highly stereospecific triflate alkylations see: (a) Hoffman, R. V.; Kim, H. *Tetrahedron Lett.* **1990**, *31*, 2953. (b) Effenberger, F.; Burkhard, U.; Willfahrt, J. *Liebigs Ann. Chem.* **1986**, 314.

(11) (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) For a recent review of the Mitsunobu reaction see: Hughes, D. L. *Org. React.* **1992**, *42*, 335.

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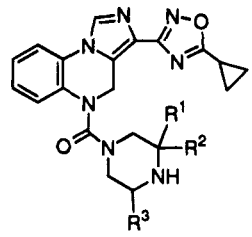
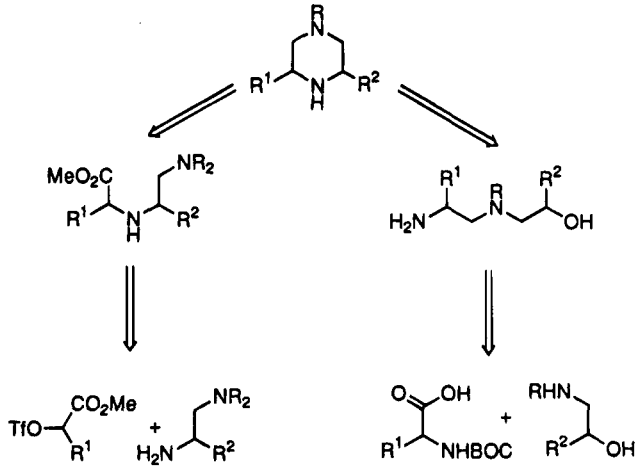


U-104030 *(R,R)*: R^1, R^3 = Me; R^2 = H
U-104499 *(S,S)*: R^1, R^3 = Me; R^2 = H
U-104143 *(R)*: R^1 = Me; R^2, R^3 = H
U-104142 *(S)*: R^1 = Me; R^2, R^3 = H
U-104110 *(R)*: R^1, R^2, R^3 = Me
U-104032 *(S)*: R^1, R^2, R^3 = Me

Figure 2.

Scheme 1



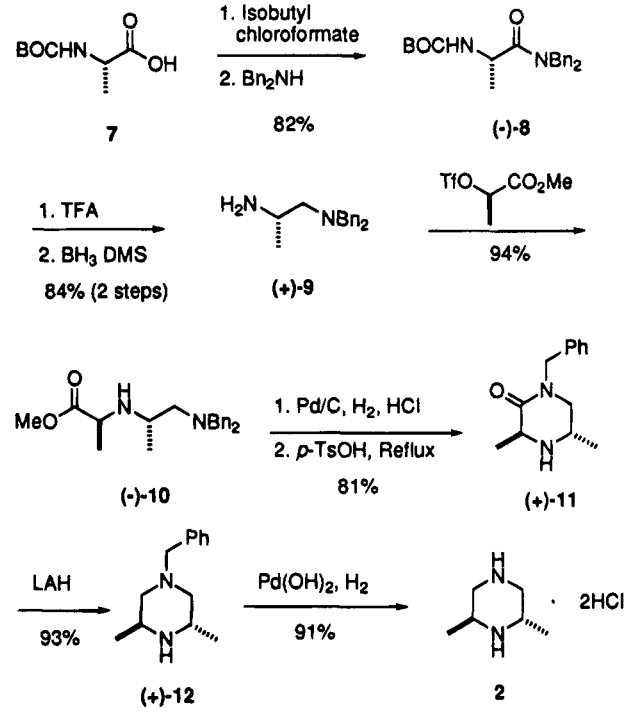
to prepare the complete series of chiral 2,6-methylated piperazines in which both the number and stereochemistry of the methyl groups is varied. This synthetic endeavor culminated in a series of unique piperazinyl imidazo[1,5-*a*]quinoxalines in which the absolute stereochemistry of the methyl groups on the piperazine moiety of the molecule had a profound effect on *in vitro* and *in vivo* efficacy, metabolism, and the side-effect profile (Figure 2).[12]

Results and Discussion

Retrosynthetic analysis of the 2,6-methylated piperazine template suggests a disconnection which would lead to carbon–nitrogen bond formation in the forward direction (Scheme 1). One possible synthetic route following this disconnection would utilize a triflate displacement of a chiral α-hydroxy ester by an appropriately substituted diamine to provide the desired stereochemistry. Ring closure followed by the appropriate transformations would complete the synthesis. Another option involved the coupling of an amino acid derivative with a chiral amino alcohol fragment followed by a stereoselective intramolecular Mitsunobu reaction. These routes are particularly attractive because of the efficiency and selectivity of the reactions involved in establishing the stereochemistry. Another notable advantage of these approaches is their generality. The utilization of an

(12) The biological aspects of the methylated piperazinyl imidazo[1,5-*a*]quinoxalines will be reported in due course.

Scheme 2



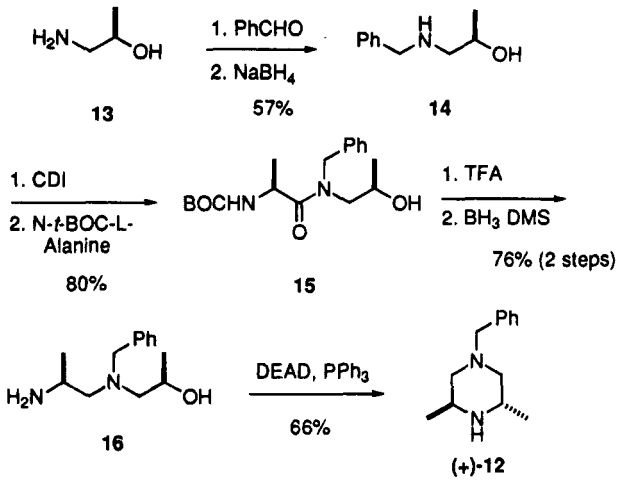
assortment of starting materials, readily available from the chiral pool, should facilitate the incorporation of a wide variety of R^1 and R^2 substituents within the piperazine template (including *cis*-2,6-disubstituted analogs).

The synthesis of the enantiomers of *trans*-2,6-dimethylpiperazine was explored initially. In contrast to the commercially available *cis*-2,6-dimethylpiperazine, the trans isomer is much more difficult to obtain. As was previously stated, the literature route provided by Cignarella and Gallo[7] for the trans compound is not a practical synthesis from which to obtain either optical antipode. Although one could theoretically arrive at either enantiomer via diastereoisomeric salt formation and resolution, poor regioselectivity and stereoselectivity prevented the scaleup of the racemic route to the levels required for our study. To address these limitations we developed two alternative synthetic routes (based on the disconnections described above) that led to the enantiomers of *trans*-2,6-dimethylpiperazine **1** and **2** in good to excellent overall yields. The first route utilized a highly efficient α-triflate alkylation in the key bond-forming step (Scheme 2). The synthesis began with the conversion of N-*t*-BOC-L-alanine to the dibenzylamide (−)-**8** through the mixed anhydride (i. *i*-BuOCOCl, ii. Bn_2NH). Removal of the protecting group with TFA followed by borane–methyl sulfide reduction gave diamine (+)-**9** in >98% ee.[13] Complete decomplexation of the amine from borane required heating at reflux in the presence of aqueous KOH. Alkylation of (+)-**9** with methyl (*R*)-2-[(trifluoromethanesulfonyl)oxy]propionate (generated by the sequential treatment of methyl (*R*)-lactate with trifluoromethanesulfonic anhydride and 2,6-lutidine)[14] proceeded smoothly with inversion of stereochemistry[15] to give the ester (−)-**10** in 94% yield. Initial

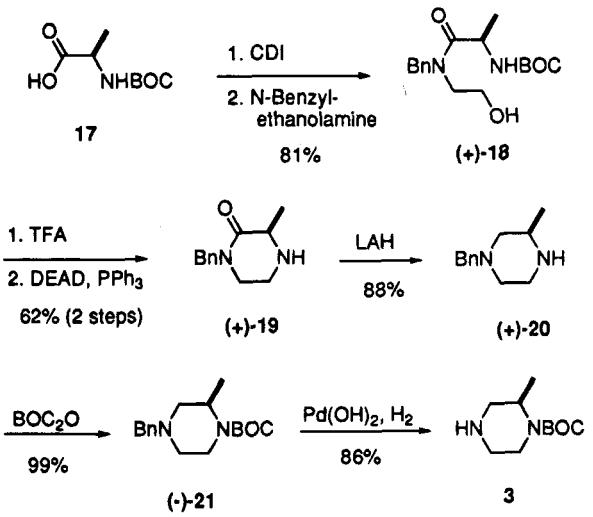
(13) Mosher amides prepared from (+)-**9** and (−)-**9** and an excess of (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride were >98% ee (HPLC analysis).

(14) Feenstra, R. W.; Stokkingreef, E. H. M.; Nivard, R. J. F.; Ottenheijm, H. C. J. *Tetrahedron Lett.* **1987**, *28*, 1215.

Scheme 3



Scheme 4



attempts at hydrogenolysis (Pd/C 5%) of (−)-**10** proceeded poorly; however, the inclusion of aqueous HCl (1.3 equiv) in the reaction mixture resulted in facile monodebenzylation and partial cyclization to provide piperazin-2-one (+)-**11**. Complete cyclization could be realized upon heating the filtered reaction mixture at reflux in the presence of catalytic *p*-toluenesulfonic acid. Lithium aluminum hydride (LAH) reduction of (+)-**11** followed by hydrogenolysis of the remaining benzyl group with Pearlman's catalyst gave the desired piperazine which was conveniently isolated as the dihydrochloride salt. Following this seven-step protocol (2*S*,6*S*)-2,6-dimethylpiperazine (**2**) was isolated in >98% ee[16] in an overall yield of 44%. None of the cis diastereomer was detected by ^{1}H NMR. This can be compared to the racemic route which required six steps and resulted in a 5% overall yield. The (*R*,*R*) enantiomer **1** was obtained in an analogous fashion (>98% ee) from N-*t*-BOC-D-alanine and methyl (*S*)-lactate.

An alternative method used to prepare (2*S*,6*S*)-2,6-dimethylpiperazine (**2**) relied on an intramolecular Mitsunobu reaction to set the required trans stereochemistry and is presented in Scheme 3. Generally, Mitsunobu reactions involving nitrogen nucleophiles require an acidic hydrogen (pK_a < 13)[17] to allow for the intermediacy of a nitrogen anion. However, several examples of intramolecular cyclizations of amino alcohols lacking such an acidic hydrogen have been disclosed. Heterocycles prepared following this protocol include aziridines,[18] pyrrolidines,[19] and piperidines.[19] We now report what we believe to be the first preparation of a piperazine ring utilizing this methodology. The first step in this sequence involved the reductive alkylation of (*R*)-1-amino-2-propanol with benzaldehyde to give **14** via an oxazolidine intermediate. The amino alcohol **14** was then coupled to N-*t*-BOC-L-alanine with 1,1′-carbonyldiimidazole (CDI) to provide **15** which was deprotected with TFA and reduced with borane−methyl sulfide to afford **16**. Cyclization of **16** using Mitsunobu conditions resulted in ring closure to the benzylated piperazine (+)-**12** in 66% yield. Conversion to the final dimethylpiperazine **2** (*S*,*S*-enantiomer) was accomplished by hydrogenolysis as depicted in the first route (Scheme 1). Although the overall yield to **2** (*S*,*S*-enantiomer) was lower in this route (Scheme 3) than in the previous alkylation route (19% versus 44%), it required one less step. As in the previous sequence, **2** was isolated in >98% ee without detectable amounts of the cis diastereomer.[16]

To expand our SAR study we needed to prepare analogs incorporating a chiral monomethyl piperazine moiety. Knowing that poor regioselectivity can occur when racemic 2-methylpiperazine is acylated,[20] we desired an enantioselective synthesis that would result in the ring nitrogens being differentially protected (Scheme 4). Such a strategy would allow for the piperazine to be acylated in a regioselective manner after appropriate deprotection. Although two recent papers have dealt with the enantioselective synthesis of 2-methylpiperazine,[6,8] neither route could be readily modified to prepare the other homologs within this series. As we were interested in expanding the generality of our approaches to the compounds within this series, as well as extending the utility of the Mitsunobu cyclization strategy, we chose to develop a synthesis for piperazine (−)-**21** based on this transformation. The first step in this synthesis involved the coupling of N-*t*-BOC-D-alanine to *N*-benzylethanolamine with CDI to provide amide (+)-**18**. Subsequent removal of the BOC group followed by cyclization using the Mitsunobu protocol gave piperazin-2-one (+)-**19** in 62% yield. Reduction of (+)-**19** with lithium aluminum hydride (LAH) provided (+)-**20** which was converted to

(15) Complete inversion of stereochemistry (>95%) was inferred in the alkylation step as (−)-**10** was the only diastereomer observed by ^{1}H NMR.

(16) Mosher amides prepared from **2** and **3** and a slight excess of (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (1.05 equiv) were >98% ee (GLC analysis). Since we had previously observed that *trans*-2,6-dimethylpiperazine can be diacylated in the presence of excess electrophile and prolonged reaction time, we were concerned about both the selective diacylation of one of the enantiomers or incomplete reaction since only a slight excess of the acid chloride was used. For this reason we prepared Mosher amides from (+)-**12** and (−)-**12** in which case a large excess of (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride was used to insure complete reaction without diacylation. Analysis of these amides indicated that the material was >98% ee. Although only trace amounts of the cis diastereomer could be observed by GLC, none could be detected by ^{1}H NMR.

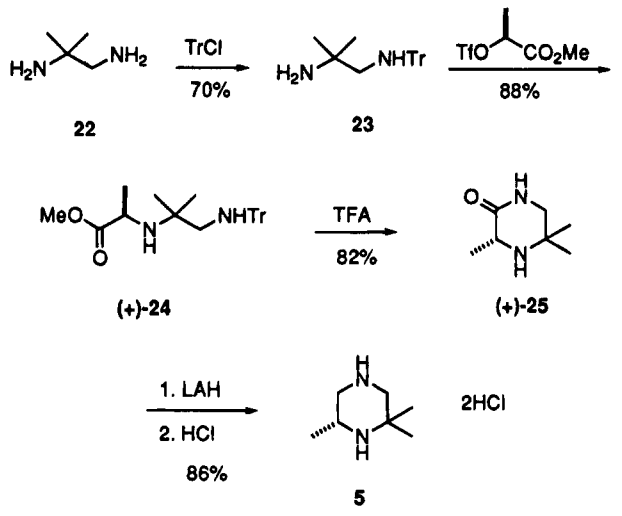
(17) Tsunoda, T.; Yamamiya, Y.; Itô, S. *Tetrahedron Lett.* **1993**, *34*, 1639.

(18) (a) Carlock, J. T.; Mack, M. P. *Tetrahedron Lett.* **1978**, *19*, 5153. (b) Pfister, J. R. *Heterocycles*, **1986**, *24*, 2099. (c) Pfister, J. R. *J. Chem. Soc. Chem. Commun.* **1984**, 969.

(19) Bernotas, R. C.; Cube, R. V. *Tetrahedron Lett.* **1991**, *32*, 161.

(20) When we prepared the racemic analog of **U-104142(3)** from 2-methylpiperazine and the imidazo[1,5-*a*]quinoxaline carbamoyl chloride, substantial amounts of diacylated material was formed unless 2-methylpiperazine was used in a very large excess.

Scheme 5



the carbamate (−)-**21**. Since we desired to couple the imidazo[1,5-*a*]quinoxaline template to the piperazine at the 4-position, the benzyl group of (−)-**21** was removed to obtain the desired 1-protected piperazine **3** in >98% ee.[21] In contrast, one could selectively acylate/alkylate the other nitrogen by using (+)-**20**. The (*S*)-enantiomer **4** was prepared (>98% ee) following the same procedure by using N-*t*-BOC-L-alanine as the starting material.

To complete the series of chiral 2,6-methylated piperazines, an enantioselective synthesis of (*R*)- and (*S*)-2,2,6-trimethylpiperazine (**5**, **6**) based upon the triflate alkylation chemistry was also developed (Scheme 5). The requisite protected diamine **23** was prepared by tritylation of 1,2-diamino-2-methylpropane with triphenylmethyl chloride (TrCl). Diamine **23** was then allowed to react with methyl (*S*)-2-[(trifluoromethanesulfonyl)oxy]propionate to provide ester (+)-**24** in 88% yield, which after deprotection with TFA underwent spontaneous cyclization to give piperazinone (+)-**25**. Reduction of (+)-**25** (LAH) gave the desired piperazine which was isolated as the dihydrochloride salt **5** in >98% ee,[21] strongly reinforcing the enantiospecific nature of the triflate alkylation. In contrast, deprotection and concomitant cyclization of (+)-**24** with an acetic acid/H_2O mixture ultimately led to **5** of lower enantiomeric purity (90−95% ee). (*S*)-2,2,6-Trimethylpiperazine (**6**) was prepared in a similar fashion (>98% ee) beginning from methyl (*R*)-lactate.

In conclusion, we have presented two efficient, concise, asymmetric sequences useful for the synthesis of the complete series of 2,6-methylated piperazines. These routes utilized either a novel Mitsunobu cyclization or a highly stereoselective triflate alkylation for the key transformation and resulted in the final piperazines being obtained in enantiopure form (ee > 98%) in good to excellent overall yield. Studies (SAR) utilizing these moieties are underway and will be reported in due course.

Experimental Section

General. Flash column and thin-layer chromatography utilized E. Merck silica gel (230−400 mesh). All reactions were run under either dry N_2 or Ar unless otherwise noted. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under N_2. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride under N_2. Mass spectra, infrared spectra, combustion analysis, and optical rotations were obtained by the Physical and Analytical Chemistry Department of The Upjohn Co. All melting points were obtained on a hot stage melting point apparatus and are uncorrected. D- and L-N-*t*-BOC-alanine were purchased from Sigma Chemical Co. Methyl (*R*)- and (*S*)-lactate, (*R*)-1-amino-2-propanol, and trifluoromethanesulfonic anhydride were all purchased from the Aldrich Chemical Co.

General Procedure for Preparation and Analysis of Mosher Amides. To a solution of the methylated piperazine or dibenzyldiamine (1 equiv) and diisopropylethylamine (1.25−1.50 equiv) in CH_2Cl_2 at 0 °C was added (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (1.2−1.4 equiv).[22] After stirring for 1 h at 0 °C the solution was allowed to warm to room temperature and stir for an additional 3−8 h. The solution was partitioned between CH_2Cl_2 and $NaHCO_3$, separated, and dried ($MgSO_4$). Filtration and concentration of the mixture provided the desired Mosher amide which was analyzed by either capillary gas chromatography using a J and W Scientific Inc. DB-5 5% phenylmethyl silicone column (15-m × 0.53-mm × 1.5-μm film thickness) or by HPLC equipped with a Chiralcell OJ column eluting with hexane:isopropyl alcohol (9:1).

(*S*)-[2-[Bis(phenylmethyl)amino]-1-methyl-2-oxoethyl]-carbamic Acid 1,1-Dimethylethyl Ester (−)-8. A solution of N-*t*-BOC-L-alanine (15.0 g, 79.3 mmol) and triethylamine (12.5 mL, 89.8 mmol) in THF (250 mL) was cooled to −30 °C. Isobutyl chloroformate (10.8 mL, 83.2 mmol) in THF (50 mL) was added dropwise, and the reaction was stirred at −30 °C for 0.5 h followed by warming to room temperature and stirring for an additional 5 h. The reaction was then recooled to 0 °C, and a solution of dibenzylamine (16.5 mL, 85.8 mmol) and triethylamine (14.0 mL, 100 mmol) in THF (50 mL) was added dropwise. The mixture was allowed to warm to room temperature and stir for 48 h at which time the mixture was partitioned between EtOAc and $NaHCO_3$. The aqueous layer was extracted further with EtOAc, and the combined organic fractions were washed with H_2O, brine, and dried ($MgSO_4$). Filtration and concentration of the mixture gave a semisolid which was triturated with hexane to provide (−)-**8** as a white solid which was filtered and washed with hexane (17.7 g). The combined filtrates were concentrated and purified by flash chromatography (EtOAc) to provide an additional 6.32 g (24.0 g total, 82%) of (−)-**8** (mp 102−104 °C): $[\alpha]^{25}_D$ −19° (*c* 0.96, CH_2Cl_2); IR (mineral oil) 3346, 1679, 1649, 1529, 1454 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30−7.40 (m, 6 H), 7.15−7.20 (m, 4 H), 5.48 (d, J = 7.7 Hz, 1 H), 4.45−4.80 (m, 5 H), 1.45 (s, 9 H), 1.32 (d, J = 6.8 Hz, 3 H); MS (EI) *m/z* 368, 312, 295, 221, 196, 144, 106, 91. Anal. Calcd for $C_{22}H_{28}N_2O_3$: C, 71.71; H, 7.66; N, 7.60. Found: C, 71.73; H, 7.74; N, 7.70.

(*R*)-[2-[Bis(phenylmethyl)amino]-1-methyl-2-oxoethyl]-carbamic Acid 1,1-Dimethylethyl Ester (+)-8. The (+)-enantiomer was prepared from N-*t*-BOC-D-alanine in a similar fashion (78%) with identical spectral data (mp 102−104 °C): $[\alpha]^{25}_D$ +18° (*c* 0.90, CH_2Cl_2). Anal. Calcd for $C_{22}H_{28}N_2O_3$: C, 71.71; H, 7.66; N, 7.60. Found: C, 71.77; H, 7.71; N, 7.55.

(*S*)-2-Amino-1-[bis(phenylmethyl)amino]propane (+)-9. A solution of (−)-**8** (15.0 g, 40.7 mmol) in CH_2Cl_2 (50 mL) was cooled to 0 °C, and TFA (50 mL) was added dropwise. The reaction was stirred for 1 h at 0 °C and 18 h at room temperature at which time the mixture was concentrated under reduced pressure and partitioned between CH_2Cl_2 and $NaHCO_3$. The aqueous layer was extracted further with CH_2Cl_2, and the combined organic fractions were washed with H_2O and brine and dried ($MgSO_4$). The mixture was filtered and concentrated under reduced pressure to provide 10.5 g (96%) of the desired amine as a clear, viscous oil that was used without further purification: $[\alpha]^{25}_D$ −18° (*c* 0.79, CH_2Cl_2); IR (neat) 3030, 2974, 1646, 1495, 1453 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25−7.40 (m, 6 H), 7.15−7.20 (m, 4 H), 4.61 (ABq, J_{AB} = 14.7 Hz, Δγ = 216 Hz, 2 H), 4.46 (ABq, J_{AB} = 17.0 Hz,

(21) Mosher amides prepared from **3**−**6** and an excess of (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride were >98% ee (GLC analysis).

(22) Ward, D. E.; Rhee, C. K. *Tetrahedron Lett.* **1991**, *32*, 7165.

$\Delta\gamma$ = 50.9 Hz, 2 H), 3.84 (q, J = 6.8, 1 H), 1.81 (s, 2 H) 1.32 (d, J = 6.8 Hz, 3 H); HRMS (EI) calcd for $C_{17}H_{20}N_2O$ (M^+) 268.1576, found 268.1562.

Borane–methyl sulfide (40.0 mL, 400 mmol, 10.0 M) was added dropwise to a solution of the above amine (10.0 g, 37.3 mmol) in THF (250 mL) and allowed to stir for 48 h at room temperature. After cooling to 0 °C the reaction mixture was quenched by the slow addition of 10% HCl (40 mL). The mixture was turned basic with 50% NaOH, KOH (75 g) was added, and the mixture was heated at reflux for 24 h. After cooling to room temperature the mixture was partitioned between EtOAc and H_2O. The aqueous layer was further extracted with EtOAc, and the combined organic layers were washed with brine and dried ($MgSO_4$). The mixture was filtered and concentrated to give a residue that was purified by chromatography (9:1, CH_2Cl_2:MeOH) to provide 8.3 g (88%) of (+)-**9** as a white, semisolid in >98% ee by HPLC analysis of the (*S*)-Mosher amide: $[\alpha]^{25}_D$ +59° (*c* 0.39, CH_2Cl_2); IR (neat) 2959, 2928, 1494, 1453, 1064 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.35 (m, 10 H), 3.57 (ABq, J_{AB} = 13.6 Hz, $\Delta\gamma$ = 91.3 Hz, 4 H), 3.00–3.10 (m, 1 H), 2.20–2.35 (m, 2 H), 1.76 (s, 2 H), 0.97 (d, J = 6.3 Hz, 3 H); HRMS (EI) calcd for $C_{17}H_{22}N_2$ (M^+) 254.1783, found 254.1769.

(*R*)-2-Amino-1-[bis(phenylmethyl)amino]propane (−)-9. The (−)-enantiomer was prepared from (+)-**8** in a similar fashion (95%, two steps) with identical spectral data, >98% ee by HPLC analysis of the (*S*)-Mosher amide: $[\alpha]^{25}_D$ −48° (*c* 0.36, CH_2Cl_2); HRMS (FAB) calcd for $C_{17}H_{23}N_2$ (MH^+) 255.1861, found 255.1863.

(*S*)-*N*-[2-[Bis(phenylmethyl)amino]-1-methylethyl]-L-alanine Methyl Ester (−)-10. A solution of methyl (*R*)-(+)-lactate (1.80 mL, 18.8 mmol) in CH_2Cl_2 (100 mL) was cooled to 0 °C. Triflic anhydride (3.30 mL, 19.4 mmol) was added, and the reaction was stirred for 10 min at which time a solution of 2,6-lutidine (2.52 mL, 21.7 mmol) in CH_2Cl_2 (10 mL) was added. After an additional 10 min of stirring at 0 °C, a solution of (+)-**9** (4.00 g, 15.7 mmol) and triethylamine (3.5 mL, 25.1 mmol) in CH_2Cl_2 (20 mL) was added. The mixture was allowed to stir for 2 h at 0 °C and 2 h at room temperature at which time the mixture was partitioned between CH_2Cl_2 and $NaHCO_3$. The aqueous layer was extracted further with CH_2Cl_2, and the combined organic fractions were washed with H_2O, brine, and dried ($MgSO_4$). The mixture was filtered and concentrated under reduced pressure to give a residue which was purified by flash chromatography (EtOAc) to provide 5.01 g (94%) of (−)-**10** as a light yellow oil: $[\alpha]^{25}_D$ −13° (*c* 0.75, CH_2Cl_2); IR (neat) 2970, 2952, 2799, 1739, 1495, 1452, 1171 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.35 (m, 10 H), 3.70 (s, 3 H), 3.54 (ABq, J_{AB} = 13.5 Hz, $\Delta\gamma$ = 22.3 Hz, 4 H), 3.45 (q, J = 6.9 Hz, 1 H), 2.70–2.80 (m, 1 H), 2.49 (dd, J = 12.6, 7.7 Hz, 1 H), 2.30 (dd, J = 12.6, 5.5 Hz, 1 H), 1.91 (br s, 1 H), 1.22 (d, J = 6.9 Hz, 3 H), 0.94 (d, J = 6.2 Hz, 3 H); HRMS (EI) calcd for $C_{21}H_{28}N_2O_2$ (M^+) 340.2151, found 340.2166. Anal. Calcd for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23. Found: C, 73.68; H, 8.20; N, 7.99.

(*R*)-*N*-[2-[Bis(phenylmethyl)amino]-1-methylethyl]-D-alanine Methyl Ester (+)-10. The enantiomer was prepared from (−)-**9** in a similar fashion (95%) with identical spectral data: $[\alpha]^{25}_D$ +14° (*c* 0.91, CH_2Cl_2). Anal. Calcd for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23. Found: C, 73.89; H, 8.33; N, 8.14.

(3*S*,5*S*)-3,5-Dimethyl-1-(phenylmethyl)piperazin-2-one (+)-11. A mixture of (−)-**10** (3.75 g, 11.0 mmol), concentrated hydrochloric acid 37% (1.4 mL), 5% palladium on carbon (1.5 g), and EtOH (70 mL) was hydrogenated at 4 psi for 2 h. The mixture was filtered through Celite, and the solids were washed with MeOH and CH_2Cl_2. The filtrates were combined and concentrated under reduced pressure. The residue was redissolved in EtOH (100 mL), *p*-toluenesulfonic acid (0.60 g) was added, and the mixture was heated at reflux for 16 h. The mixture was concentrated under reduced pressure and partitioned between CH_2Cl_2 and $NaHCO_3$. The aqueous layer was extracted further with CH_2Cl_2, and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (9:1, CH_2Cl_2:MeOH) to provide 1.95 g (81%) of (+)-**11** as light yellow oil: $[\alpha]^{25}_D$ +35° (*c* 0.19, CH_2Cl_2); IR (neat) 3292, 2970, 2929, 1638, 1495, 1453 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.35 (m, 5 H), 4.58 (ABq, J_{AB} = 14.6 Hz, $\Delta\gamma$ = 54.5 Hz, 2 H), 3.76 (q, J = 7.1 Hz, 1 H), 3.25–3.35 (m, 1 H), 3.15 (dd, J = 11.8, 3.9 Hz, 1 H), 2.94 (dd, J = 11.6, 9.6 Hz, 1 H), 1.56 (s, 1 H), 1.48 (d, J = 7.1 Hz, 3 H), 1.09 (d, J = 6.3 Hz, 3 H); HRMS (EI) calcd for $C_{13}H_{18}N_2O$ (M^+) 218.1419, found 218.1429.

(3*R*,5*R*)-3,5-Dimethyl-1-(phenylmethyl)piperazin-2-one (−)-11. The (−)-enantiomer was prepared from (+)-**10** in a similar fashion (80%) with identical spectral data: $[\alpha]^{25}_D$ −39° (*c* 0.70, CH_2Cl_2); HRMS (FAB) calcd for $C_{13}H_{19}N_2O$ (MH^+) 219.1497, found 219.1502.

(3*S*,5*S*)-3,5-Dimethyl-1-(phenylmethyl)piperazine (+)-12. Piperazinone (+)-**11** (1.50 g, 6.87 mmol) was added portionwise to a solution of LAH (0.750 g, 19.8 mmol) in THF (40 mL). The reaction was allowed to stir at room temperature for 0.5 h and at reflux for an additional 6 h. After cooling to room temperature the reaction was quenched by the sequential addition of H_2O (0.75 mL), 15% NaOH (0.75 mL), and H_2O (2.25 mL). The mixture was stirred for 0.5 h, and the solids were filtered off and washed with excess THF. The combined filtrates were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide 1.3 g (93%) of (+)-**12** as a yellow oil, >98% ee by GLC analysis of the (*S*)-Mosher amide: $[\alpha]^{25}_D$ +9° (*c* 0.60, CH_2Cl_2); IR (neat) 2958, 2930, 2800, 1453 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.35 (m, 5 H), 3.43 (ABq, J_{AB} = 13.4 Hz, $\Delta\gamma$ = 28.7 Hz, 2 H), 3.15–3.25 (m, 2 H), 2.44 (dd, J = 10.7, 2.9 Hz, 2 H), 2.05–2.15 (m, 2 H), 1.5–1.9 (br s, 1 H), 1.15 (d, J = 6.6 Hz, 6 H); HRMS (EI) calcd for $C_{13}H_{20}N_2$ (M^+) 204.1626, found 204.1631.

(3*R*,5*R*)-3,5-Dimethyl-1-(phenylmethyl)piperazine (−)-12. The (−)-enantiomer was prepared from (−)-**11** in a similar fashion (94%) with identical spectral data, >98% ee by GLC analysis of the (*S*)-Mosher amide: $[\alpha]^{25}_D$ −9° (*c* 0.89, CH_2Cl_2); HRMS (FAB) calcd for $C_{13}H_{21}N_2$ (MH^+) 205.1705, found 205.1696.

(2*S*,6*S*)-2,6-Dimethylpiperazine Dihydrochloride (2). A mixture of (+)-**12** (1.14 g, 5.58 mmol), palladium hydroxide (0.5 g) and MeOH (50 mL) was hydrogenated at 35 psi for 24 h. The reaction mixture was filtered through Celite, and the solids were washed with MeOH and CH_2Cl_2. The filtrates were combined, and methanolic HCl (10 mL, 4.1 N) was added. The mixture was stirred for 1 h and concentrated under reduced pressure. Trituration of the residue with diethyl ether gave 0.95 g (91%) of **2** as an off-white solid (mp >260 °C), >98% ee by GLC analysis of the (*S*)-Mosher amide: $[\alpha]^{25}_D$ +5° (*c* 0.98, MeOH); IR (mineral oil) 1587, 1577, 1460 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95–4.0 (m, 2 H), 3.56 (dd, J = 13.8, 3.8 Hz, 2 H), 3.30–3.40 (m, 4 H), 1.51 (d, J = 6.9 Hz, 6 H); MS (EI) m/z 114, 99, 86. Anal. Calcd for $C_6H_{14}N_2$·$(HCl)_2$: C, 38.51; H, 8.62; N, 14.97. Found: C, 38.11; H, 8.46; N, 14.62.

(2*R*,6*R*)-2,6-Dimethylpiperazine Dihydrochloride (1). The (−)-enantiomer was prepared from (−)-**12** in a similar fashion (83%) with identical spectral data (mp >260 °C), >98% ee by GLC analysis of the (*S*)-Mosher amide: $[\alpha]^{25}_D$ −4° (*c* 0.85, MeOH). Anal. Calcd for $C_6H_{14}N_2$·$(HCl)_2$: C, 38.51; H, 8.62; N, 14.97. Found: C, 38.38; H, 8.37; N, 14.93.

(*R*)-1-[(Phenylmethyl)amino]-2-propanol (14). A mixture of (*R*)-(−)-1-amino-2-propanol (3.61 g, 48.1 mmol), benzaldehyde (6.0 mL, 59 mmol), THF (120 mL), and $MgSO_4$ (3.00 g) was stirred at room temperature for 3 h. The mixture was filtered and the solution concentrated. The residue was combined with 120 mL of ethanol, and sodium borohydride (600 mg, 15.9 mmol) was added. Additional sodium borohydride (600 mg, 15.9 mmol) was added after 1 and 3 h. The mixture was stirred for 72 h at room temperature, concentrated, and partitioned between EtOAc and 10% HCl. The aqueous layer was neutralized, extracted with CH_2Cl_2, and the combined organic fractions were dried ($MgSO_4$). The mixture was then filtered and concentrated to provide 4.53 g (57%) of **14** as an oil which was carried on without further purification: $[\alpha]^{25}_D$ −45° (*c* 1.02, $CHCl_3$); IR (neat) 3309, 2968, 1453, 748, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.40 (m, 5 H), 3.70–3.90 (m, 3 H), 2.75 (dd, J = 12.0, 3.0 Hz, 1 H), 2.43 (dd, J = 12.0, 9.5 Hz, 1 H), 2.10–2.50 (m, 2 H), 1.15 (d, J =

6.2 Hz, 3 H); MS (EI) m/z 165, 120, 91; HRMS (EI) calcd for $C_{10}H_{15}NO$ (M^+) 165.1154, found 165.1154.

(*S*)-[2-[(2(*R*)-Hydroxypropyl)(phenylmethyl)amino]-1-methyl-2-oxoethyl]carbamic Acid 1,1-Dimethylethyl Ester (15). 1,1'-Carbonyldiimidazole (CDI) (4.59 g, 28.3 mmol) was added to a solution of N-*t*-BOC-L-alanine (5.30 g, 28.0 mmol) in CH_2Cl_2 (85 mL) and stirred for 1 h at room temperature. A solution of **14** (4.68 g, 28.3 mmol) in CH_2Cl_2 (10.0 mL) was then added. The solution was stirred for 16 h at room temperature and was concentrated. Purification by flash chromatography (1:1, EtOAc:hexane) gave 7.54 g (80%) of **15** as a clear oil: $[\alpha]^{25}_D$ −14° (*c* 0.68, $CHCl_3$); IR (mineral oil) 1707, 1636, 1497, 1478, 1452, 1367, 1251, 1169 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.10−7.45 (m, 5 H), 5.30−5.45 (m, 0.8 H, rotamer), 4.50−5.00 (m, 2.8 H, rotamer), 3.90−4.20 (m, 1 H, rotamer), 3.35−3.70 (m, 1.5 H, rotamer), 3.10−3.30 (m, 0.9 H, rotamer), 1.45 (s, 4 H), 1.43 (s, 5 H), 1.37 (d, J = 6.8 Hz, 1.25 H, rotamer), 1.26 (d, J = 6.8 Hz, 1.75 H, rotamer), 1.20 (d, J = 6.3 Hz, 1.25 H, rotamer), 1.13 (d, J = 6.3 Hz, 1.75 H, rotamer); MS (EI) m/z 336, 292, 236, 192, 164, 144, 120; HRMS (FAB) calcd for $C_{18}H_{29}N_2O_4$ (MH^+) 337.2127, found 337.2133.

(*R*)-1-[(2(*S*)-Aminopropane)(phenylmethyl)amino]-2-propanol (16). A solution of **15** (5.24 g, 15.6 mmol), CH_2Cl_2 (100 mL), and TFA (53 mL) was stirred at 0 °C for 1 h. The mixture was concentrated and partitioned between CH_2Cl_2 and $NaHCO_3$. The aqueous layer was extracted further with CH_2Cl_2, and the combined organic fractions were dried ($MgSO_4$). After filtration, the solvent was removed under reduced pressure to provide 3.69 g of the deprotected amine as an oil which was carried on crude: $[\alpha]^{25}_D$ −39° (*c* 0.36, $CHCl_3$); IR (neat) 3355, 1689, 1634, 1608, 1453, 1203, 1134 cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{21}N_2O_2$ (MH^+) 237.1603, found 237.1606.

Borane−methyl sulfide complex (4.40 mL, 44.0 mmol, 10.0 M) was added to a solution of the above amine (15.6 mmol) in THF (100 mL). The solution was stirred for 16 h at room temperature and was quenched slowly with 10% HCl. Water (40 mL) and KOH (20 g) were added, and the mixture was heated at reflux for 24 h. Methanol (10 mL) was added, and the mixture heated at reflux for an additional 3 days. After cooling to room temperature, the organics were removed under reduced pressure. The aqueous layer was saturated with sodium chloride and was extracted several times with CH_2Cl_2. The organic layers were dried ($MgSO_4$), filtered, and concentrated to give 2.63 g (76% overall) of **16** as an oil, sufficiently pure to be carried on crude: $[\alpha]^{25}_D$ −45° (*c* 0.59, $CHCl_3$); IR (neat) 3348, 2965, 2930, 2875, 2811, 1453, 1374, 1073, 1058, 743, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20−7.40 (m, 5 H), 3.70−3.90 (m, 1 H), 3.66 (ABq, J_{AB} = 13.6 Hz, $\Delta\gamma$ = 40.7 Hz, 2 H), 2.90−3.05 (m, 1 H), 2.25−2.60 (m, 7 H), 1.07 (d, J = 6.2 Hz, 3 H), 0.99 (d, J = 6.3 Hz, 3 H); MS (EI) m/z 204, 178, 134, 91; HRMS (FAB) calcd for $C_{13}H_{23}N_2O$ (MH^+) 223.1810, found 223.1810.

(3*S*,5*S*)-3,5-Dimethyl-1-(phenylmethyl)piperazine (+)-12. DEAD (1.60 mL, 10.2 mmol) was added to a solution of crude **16** (1.79 g, 8.05 mmol), triphenylphosphine (2.84 g, 10.8 mmol), and THF (72 mL). The solution was stirred at room temperature for 2.5 h and was concentrated. Purification by flash chromatography (4:1:0.01, CH_2Cl_2:MeOH:NH_4OH) gave 1.08 g (66%) of (+)-**12** as an oil, with identical spectral data to that reported for (+)-**12** above, >98% ee by GLC analysis of the (*S*)-Mosher amide: $[\alpha]^{25}_D$ +12° (*c* 0.73, CH_2Cl_2).

(*R*)-[2-[(2-Hydroxyethyl)(phenylmethyl)amino]-1-methyl-2-oxoethyl]carbamic Acid 1,1-Dimethylethyl Ester (+)-18. CDI (6.88 g, 42.4 mmol) was added to a solution of N-*t*-BOC-D-alanine (8.00 g, 42.3 mmol) in THF (128 mL). After the solution was stirred for 1 h at room temperature a solution of *N*-benzylethanolamine (6.66 g, 44.0 mmol) in THF (20 mL) was added. The solution was stirred for 16 h at room temperature and was concentrated. Purification by flash chromatography (1.5:1, EtOAc:hexane) gave 11.1 g (81%) of (+)-**18** as an oil: $[\alpha]^{25}_D$ +33° (*c* 0.63, EtOH); IR (neat) 1705, 1638, 1452, 1367, 1168 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.15−7.45 (m, 5 H), 5.35−5.50 (m, 1 H), 4.95 (apparent d, J = 15.1 Hz, 0.5 H, rotamer), 4.60−4.90 (m, 2 H), 4.37 (apparent d, J = 15.1 Hz, 0.5 H), 3.30−3.85 (m, 5 H), 1.44 (s, 6 H, rotamer), 1.42 (s, 3 H, rotamer), 1.35 (d, J = 6.9 Hz, 1.5 H, rotamer), 1.26 (d, J = 6.8 Hz, 1.5 H, rotamer); MS (EI) m/z 322, 292, 266, 249, 178, 150, 120; HRMS (FAB) calcd for $C_{17}H_{27}N_2O_4$ (MH^+) 323.1971, found 323.1968.

(*S*)-[2-[(2-Hydroxyethyl)(phenylmethyl)amino]-1-methyl-2-oxoethyl]carbamic Acid 1,1-Dimethylethyl Ester (−)-18. The (−)-enantiomer was prepared from N-*t*-BOC-L-alanine in a similar fashion (76%) with identical spectral data: $[\alpha]^{25}_D$ −31° (*c* 0.52, EtOH); HRMS (EI) calcd for $C_{17}H_{26}N_2O_4$ (M^+) 322.1892, found 322.1876.

(*R*)-3-Methyl-1-(phenylmethyl)piperazin-2-one (+)-19. Trifluoroacetic acid (50 mL) was added to a solution of (+)-**18** (11.1 g, 34.4 mmol) and CH_2Cl_2 (100 mL) at 0 °C. The solution was stirred at 0 °C for 1.75 h, concentrated, and partitioned between CH_2Cl_2 and 25% NaOH. The aqueous layer was further extracted with CH_2Cl_2, and the combined organic fractions were dried ($MgSO_4$). After filtration the solvent was removed under reduced pressure to provided 8.30 g of the intermediate amino alcohol as a thick syrup which was carried on as the crude product: $[\alpha]^{25}_D$ +36° (*c* 0.78, $CHCl_3$); IR (mineral oil) 1685, 1608, 1204, 1183, 1134 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.15−7.4 (m, 5 H), 4.68 (ABq, J_{AB} = 15.3 Hz, $\Delta\gamma$ = 299.5 Hz, 1 H, rotamer), 4.65 (ABq, J_{AB} = 17.6 Hz, $\Delta\gamma$ = 29.2 Hz, 1 H, rotamer), 3.95−4.10 (m, 0.5 H, rotamer), 3.45−3.90 (m, 3.5 H, rotamer), 3.15−3.30 (m, 0.5 H, rotamer), 2.80−2.90 (m, 0.5 H, rotamer), 2.35 (br s, 3 H), 1.37 (d, J = 6.5 Hz, 1.5 H, rotamer), 1.28 (d, J = 6.7 Hz, 1.5 H, rotamer); MS (EI) m/z 222, 205, 179, 120.

Diethyl azodicarboxylate (7.00 mL, 44.5 mmol) was added to a solution of the above crude amino alcohol (34.4 mmol), triphenylphosphine (12.1 g, 46.1 mmol), and THF (200 mL). The solution was stirred at room temperature for 16 h and was concentrated. Purification by flash chromatography (4:1 EtOAc:MeOH) gave 4.37 g (62% overall) of (+)-**19** as an oil: $[\alpha]^{25}_D$ +61° (*c* 0.67, $CHCl_3$); IR (neat) 1637, 1496, 1453, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20−7.40 (m, 5 H), 4.60 (ABq, J_{AB} = 14.6 Hz, $\Delta\gamma$ = 75.0 Hz, 2 H), 3.62 (q, J = 7.7 Hz, 1 H), 3.25−3.40 (m, 1 H), 3.05−3.20 (m, 2 H), 2.95−3.05 (m, 1 H), 1.73 (s, 1 H), 1.45 (d, J = 6.9 Hz, 3 H); MS (EI) m/z 204, 161, 113, 91; HRMS (EI) calcd for $C_{12}H_{16}N_2O$ (M^+) 204.1263, found 204.1246.

(*S*)-3-Methyl-1-(phenylmethyl)piperazin-2-one (−)-19. The (−)-enantiomer was prepared from (−)-**18** in a similar fashion (59%) with identical spectral data: $[\alpha]^{25}_D$ −50° (*c* 0.80, $CHCl_3$); HRMS (EI) calcd for $C_{12}H_{16}N_2O$ (M^+) 204.1263, found 204.1264.

(*R*)-3-Methyl-1-(phenylmethyl)piperazine (+)-20. A mixture of (+)-**19** (4.36 g, 21.3 mmol), LAH (2.33 g, 61.4 mmol), and THF (125 mL) was heated at reflux for 16 h. After cooling to room temperature, the mixture was quenched slowly with water (2.3 mL), 10% NaOH (3.5 mL), and water (5.7 mL). The residue was diluted with 100 mL of ether and was stirred for 1 h. The solids were filtered and washed successively with ether, CH_2Cl_2, and ether. The combined filtrates were dried (K_2CO_3), filtered, and concentrated to give 3.56 g (88%) of (+)-**20** as an oil, sufficiently pure to be carried on crude: $[\alpha]^{25}_D$ +7° (*c* 0.68, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.20−7.40 (m, 5 H), 3.49 (s, 2 H), 2.70−3.00 (m, 5 H), 1.95−2.10 (m, 1 H), 1.70−1.90 (br s, 1 H), 1.68 (apparent t, J = 10.8 Hz, 1 H), 1.02 (d, J = 6.4 Hz, 3 H); HRMS (EI) calcd for $C_{12}H_{18}N_2$ (M^+) 190.1470, found 190.1468.

(*S*)-3-Methyl-1-(phenylmethyl)piperazine (−)-20. The (−)-enantiomer was prepared from (−)-**19** in a similar fashion (85%) with identical spectral data: $[\alpha]^{25}_D$ −5° (*c* 0.51, $CHCl_3$); HRMS (EI) calcd for $C_{12}H_{18}N_2$ (M^+) 190.1470, found 190.1468.

***tert*-Butyl (*R*)-2-Methyl-4-(phenylmethyl)-1-piperazinecarboxylate (−)-21.** A solution of di-*tert*-butyl dicarbonate (4.60 g, 21.1 mmol) in CH_2Cl_2 (16 mL) was added dropwise over 10 min to a solution of (+)-**20** (3.56 g, 18.7 mmol) in CH_2Cl_2 (55 mL). After stirring for 16 h at room temperature the reaction was partitioned between CH_2Cl_2 and $NaHCO_3$. The aqueous layer was extracted further with CH_2Cl_2, and the combined organic fractions were dried ($MgSO_4$). The mixture was filtered, and the solvent removed under reduced pressure to give a residue that was purified by chromatography (3:1, hexane:EtOAc) to give 5.40 g (99%) of (−)-**21** as an oil: $[\alpha]^{25}_D$

−62° (*c* 0.84, EtOH); IR (neat) 1695, 1411, 1365, 1177, 1161 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20−7.40 (m, 5 H), 4.10−4.25 (m, 1 H), 3.80 (d, *J* = 13.0 Hz, 1 H), 3.47 (ABq, J_{AB} = 13.3 Hz, Δγ = 37.5 Hz, 2 H), 3.05−3.20 (m, 1 H), 2.77 (d, *J* = 10.0 Hz, 1 H), 2.59 (d, *J* = 11.2 Hz, 1 H), 2.12 (dd, *J* = 10.0, 3.8 Hz, 1 H), 1.95−2.10 (m, 1 H), 1.45 (s, 9 H), 1.24 (d, *J* = 6.7 Hz, 3 H); MS (EI) *m/z* 290, 233, 160, 146, 134; HRMS (FAB) calcd for $C_{17}H_{26}N_2O_2$ (M^+) 290.1994, found 290.1997.

***tert*-Butyl (*S*)-2-Methyl-4-(phenylmethyl)-1-piperazinecarboxylate (+)-21.** The (+)-enantiomer was prepared from (−)-**20** in a similar fashion (94%) with identical spectral data: $[\alpha]^{25}_D$ +56° (*c* 0.44, EtOH); HRMS (FAB) calcd for $C_{17}H_{26}N_2O_2$ (M^+) 290.1994, found 290.2006.

***tert*-Butyl (*R*)-2-Methyl-1-piperazinecarboxylate (3).** A mixture of (−)-**21** (5.40 g, 18.6 mmol), ethanol (200 mL), and Pearlman's catalyst (1.36 g) was hydrogenated (36 psi) for 16 h at room temperature in a Parr flask. The mixture was filtered, and the solids were washed successively with ethanol, CH_2Cl_2, and MeOH. The combined filtrates were concentrated, diluted with CH_2Cl_2, filtered, and concentrated to give 3.19 g (86%) of **3** as a clear oil which solidified upon standing (mp 33−36 °C), >98% ee by GLC analysis of the (*S*)-Mosher amide: $[\alpha]^{25}_D$ −59° (*c* 0.92, $CHCl_3$); IR (mineral oil) 1695, 1408, 1363, 1301, 1226, 1173, 1095 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.10−4.30 (m, 1 H), 3.70−3.85 (m, 1 H), 2.60−3.05 (m, 5 H), 1.84 (s, 1 H), 1.46 (s, 9 H), 1.22 (d, *J* = 6.9 Hz, 3 H); MS (EI) *m/z* 200, 144, 127, 99, 70, 57. Anal. Calcd for $C_{10}H_{20}N_2O_2 \cdot {}^1/_8C_2H_6O$: C, 59.75; H, 10.15; N, 13.60. Found: C, 59.82; H, 9.79; N, 13.37.

***tert*-Butyl (*S*)-2-Methyl-1-piperazinecarboxylate (4).** The (*S*)-enantiomer was prepared from (+)-**21** in a similar fashion (97%) with identical spectral data in >98% ee by GLC analysis of the (*S*)-Mosher amide: $[\alpha]^{25}_D$ +67° (*c* 0.65, $CHCl_3$). Anal. Calcd for $C_{10}H_{20}N_2O_2$: C, 59.97; H, 10.07; N, 13.99. Found: C, 59.91; H, 9.77; N, 13.87.

2-Methyl-1-[(triphenylmethyl)amino]-2-aminopropane (23). A solution of 1,2-diamino-2-methylpropane (10.0 mL, 94.4 mmol) and triethylamine (20.0 mL, 144 mmol) in CH_2Cl_2 (400 mL) was cooled to −40 °C. Trityl chloride (26.0 g, 93.3 mmol) in CH_2Cl_2 (75 mL) was added dropwise, and the solution was allowed to warm to room temperature and stir for 40 h. The mixture was partitioned between CH_2Cl_2 and $NaHCO_3$. The aqueous layer was extracted further with CH_2Cl_2, and the combined organic fractions were dried ($MgSO_4$). The mixture was filtered and the solvent removed under reduced pressure to give a residue that was purified by flash chromatography (9:1, EtOAc:MeOH) to provide 22.0 g (70%) of **23** as a white powder (mp 97−98 °C): IR (mineral oil) 2869, 2855, 1487, 1462, 1449, 747, 708 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.4 Hz, 6 H), 7.15−7.30 (m, 9 H), 1.95−2.00 (m, 2 H), 1.70−1.85 (m, 1 H), 1.12 (s, 6 H); MS (EI) *m/z* 273, 258, 243, 165, 58. Anal. Calcd for $C_{23}H_{26}N_2$: C, 83.59; H, 7.93; N, 8.48. Found: C, 83.25; H, 7.93; N, 8.38.

***N*-[2-Methyl-1-[(triphenylmethyl)amino]-2-propyl]-D-alanine Methyl Ester (+)-24.** A solution of methyl (*S*)-(−)-lactate (2.53 mL, 26.5 mmol) in CH_2Cl_2 (130 mL) was cooled to 0 °C. Triflic anhydride (4.90 mL, 29.2 mmol) was added, and the reaction was stirred for 10 min at which time 2,6-lutidine (3.55 mL, 30.5 mmol) was added. After an additional 10 min of stirring at 0 °C, a solution of **23** (7.00 g, 21.2 mmol) and triethylamine (4.20 mL, 30.3 mmol) in CH_2Cl_2 (50 mL) was added. The reaction mixture was allowed to stir for 1 h at 0 °C and 4 h at room temperature and was then partitioned between CH_2Cl_2 and $NaHCO_3$. The aqueous layer was extracted further with CH_2Cl_2, and the combined organic fractions were washed with brine and dried ($MgSO_4$). Filtration of the mixture and removal of the solvent under reduced pressure gave a residue that was purified by flash chromatography (4:1, hexane:EtOAc) to provide 7.8 g (88%) of (+)-**24** as a cream colored solid (mp 78−80 °C): $[\alpha]^{25}_D$ +18° (*c* 0.99, $CHCl_3$); IR (mineral oil) 2853, 1734, 1457, 1451, 1197 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.4 Hz, 6 H), 7.15−7.30 (m, 9 H), 3.60 (s, 3 H), 2.93 (q, *J* = 7.0 Hz, 1 H), 1.90−2.05 (m, 3 H), 1.13 (s, 3 H), 1.08 (d, *J* = 7.0 Hz, 3 H), 1.00 (s, 3 H); MS (EI) *m/z* 243, 165, 144, 84; HRMS (FAB) calcd for $C_{27}H_{33}N_2O_2$ (MH^+) 417.2542, found 417.2531.

***N*-[2-Methyl-1-[(triphenylmethyl)amino]-2-propyl]-L-alanine Methyl Ester (−)-24.** The (−)-enantiomer was prepared from methyl (*R*)-lactate in a similar fashion (80%) with identical spectral data: $[\alpha]^{25}_D$ −18° (*c* 0.98, $CHCl_3$). Anal. Calcd for $C_{27}H_{32}N_2O_2$: C, 77.85; H, 7.74; N, 6.72. Found: C, 77.49; H, 7.70; N, 6.67.

(*R*)-3,5,5-Trimethylpiperazin-2-one (+)-25. A solution of (+)-**24** (3.00 g, 7.20 mmol) in CH_2Cl_2 (15 mL) was cooled to 0 °C, and TFA (10 mL) was added dropwise. After stirring for 2 h at room temperature the mixture was concentrated under reduced pressure while warming to room temperature. The mixture was partitioned between CH_2Cl_2 and 25% aqueous NaOH (20 mL). The aqueous layer was extracted with an additional aliquot of CH_2Cl_2, and the combined extracts were dried ($MgSO_4$). The mixture was filtered and concentrated under reduced pressure, and the residue was purified by chromatography (85:15, CH_2Cl_2:MeOH) to give 0.84 g (82%) of (+)-**25** as a white solid (mp 130−133 °C): $[\alpha]^{25}_D$ +30° (*c* 0.81, MeOH); IR (mineral oil) 1670, 1649, 1492, 1340, 1060, 864 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.51 (br s, 1 H), 3.60 (q, *J* = 6.9 Hz, 1 H), 3.26 (d, *J* = 11.7 Hz, 1 H), 3.08 (dd, *J* = 11.7, 4.3 Hz, 1 H), 1.38 (d, *J* = 6.9 Hz, 3 H), 1.30 (s, 3 H), 1.19 (s, 3 H); MS (EI) *m/z* 142, 127, 99, 84, 70, 58; HRMS (EI) calcd for $C_7H_{14}N_2O$ (M^+) 142.1106, found 142.1104.

(*S*)-3,5,5-Trimethylpiperazin-2-one (−)-25. The (−)-enantiomer was prepared from (−)-**24** in a similar fashion (85%) with identical spectral data: $[\alpha]^{25}_D$ −29° (*c* 0.61, MeOH); HRMS (EI) calcd for $C_7H_{14}N_2O$ (M^+) 142.1106, found 142.1107.

(*R*)-2,2,6-Trimethylpiperazine Dihydrochloride (5). Piperazinone (+)-**25** (0.500 g, 3.51 mmol) was added portionwise to a mixture of LAH (0.250 g, 6.59 mmol) in THF (30 mL). The mixture was allowed to stir at room temperature for 0.5 h and at reflux for an additional 2.5 h. After cooling to room temperature, the mixture was quenched by the successive addition of 0.25 mL of H_2O, 0.25 mL of 15% NaOH, and 0.75 mL of H_2O. After stirring for 0.5 h the solids were filtered off and washed with THF and diethyl ether, and the combined filtrates were dried ($MgSO_4$). The mixture was filtered, and excess methanolic HCl (5.0 mL, 22 mmol) was added. After stirring for 1 h the solvents were removed under reduced pressure and the remaining solid was triturated with diethyl ether to provide 0.61 g (86%) of **5** as a white solid (mp > 250 °C), >98% ee by GLC analysis of the (*S*)-Mosher amide: $[\alpha]^{25}_D$ −10° (*c* 0.71, MeOH); IR (mineral oil) 1580, 1390, 990 cm^{-1}; ^1H NMR (300 MHz, MeOD-d_4) δ 3.80−3.95 (m, 1 H), 3.50−3.65 (m, 2 H), 3.15−3.30 (m, 4 H), 1.59 (s, 3 H), 1.56 (s, 3 H), 1.45 (d, *J* = 6.5 Hz, 3 H); MS (EI) *m/z* 128, 113, 84. Anal. Calcd for $C_7H_{16}N_2 \cdot (HCl)_2$: C, 41.80; H, 9.02; N, 13.93. Found: C, 41.43; H, 8.94; N, 13.74.

(*S*)-2,2,6-Trimethylpiperazine Dihydrochloride (6). The (+)-enantiomer was prepared from (−)-**25** in a similar fashion (83%) with identical spectral data, >98% ee by GLC analysis of the (*S*)-Mosher amide: $[\alpha]^{25}_D$ +9° (*c* 0.82, MeOH). Anal. Calcd for $C_7H_{16}N_2 \cdot (HCl)_2$: C, 41.80; H, 9.02; N, 13.93. Found: C, 41.62; H, 8.99; N, 13.88.

Supplementary Material Available: ^1H NMR spectra of (+)-**9**, (−)-**9**, (+)-**11**, (−)-**11**, (+)-**12**, (−)-**12**, **14**, **15**, **16**, (+)-**18**, (−)-**18**, (+)-**19**, (−)-**19**, (+)-**20**, (−)-**20**, (+)-**21**, (−)-**21**, (+)-**24**, (+)-**25** and (−)-**25** (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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