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Enantioconvergent Synthesis of (−)-(2*R*,5*S*)-1-Allyl-2,5-dimethylpiperazine, an Intermediate to δ-Opioid Receptor Ligands

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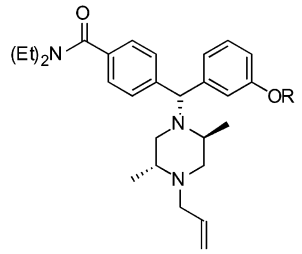
A convenient, high-yield enantioconvergent synthesis of (−)-1-allyl-(2*S*,5*R*)-dimethylpiperazine from *trans*-2,5-dimethylpiperazine has been developed. This compound is an important intermediate in the synthesis of δ-opioid receptor ligands. The process allows for the laboratory preparation of 100 g quantities of this enantiomerically pure diamine without chromatography. The key steps in the sequence were an efficient optical resolution using relatively inexpensive resolving agents, followed by interconversion of the unwanted (+)-enantiomer into the desired (−)-enantiomer.

Recent advances in the understanding of δ opioid receptor pharmacology have shown that peptidic δ agonists produce antinociception with fewer of the side effects commonly associated with the activation of μ and κ receptors.[1] Unlike analgesics such as morphine, which act mainly through the μ opioid receptor, it has been determined that δ agonists show little or no tendency to cause respiratory depression, constipation, or physical dependence,[2] although they may exhibit other side effects due to their interaction with the δ receptor. Recent animal studies have shown that δ antagonists can reverse μ receptor-mediated respiratory depression.[3] Selective δ receptor antagonists have been shown to elicit immunomodulatory effects[4] and to modulate the behavioral effects of drugs of abuse, such as cocaine.[3] Thus, compounds that selectively interact with the δ receptor may have broad clinical potential as analgesics, immunoregulatory agents, and treatment agents for drug addiction.[1]

A major advance in the area of nonpeptidic δ agonists came from reports on the preparation and pharmacological properties of benzhydrylpiperazines, such as BW373U86[5] [(±)-**1**), Chart 1] and SNC80[6−8] [(+)-**2**), Chart 1], that possess δ agonist activity. SNC80 exhibits a remarkable 2000-fold μ/δ selectivity in both receptor binding assays and bioassays.[7] Unlike the endogenous δ receptor agonist pentapeptide enkaphalins, SNC80 has excellent drug-like properties, possessing both good metabolic stability and CNS penetration.[9] It has also been shown to have antinociceptive activity[9] and to produce cocaine-like discriminative stimulus effects without cocaine-like reinforcing effects,[9] suggesting that this δ agonist, and possibly certain related derivatives, may have clinical utility.

CHART 1



1: R = H [(±)-BW373U86]
2: R = Me [(±)-SNC80]

To conduct comprehensive studies on the effects of SNC80 in nonhuman primates,[9,10] large amounts of the

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(1) Dondio, G.; Ronzoni, S.; Petrillo, P. *Expert Opin. Ther. Pat.* **1997**, *7*, 1075−1098.
(2) Rapaka, R. S.; Porreca, F. *Pharmaceut. Res.* **1991**, *8*, 1−8.
(3) Su, Y. F.; McNutt, R. W.; Chang, K. J. *J. Pharmacol. Exp. Ther.* **1998**, *287*, 815−823.
(4) House, R. V.; Thomas, P. T.; Kozak, J. T.; Bhargava, H. N. *Neurosci. Lett.* **1995**, *198*, 119−122.
(5) Chang, K. J.; Rigdon, G. C.; Howard, J. L.; McNutt, R. W. *J. Pharmacol. Exp. Ther.* **1993**, *267*, 852−857.
(6) Calderon, S. N.; Rothman, R. B.; Porreca, F.; Flippen-Anderson, J. L.; McNutt, R. W.; Xu, H.; Smith, L. E.; Bilsky, E. J.; Davis, P.; Rice, K. C. *J. Med. Chem.* **1994**, *37*, 2125−2128.
(7) Calderon, S. N.; Rice, K. C.; Rothman, R. B.; Porreca, F.; Flippen-Anderson, J. L.; Kayakiri, H.; Xu, H.; Becketts, K.; Smith, L. E.; Bilsky, E. J.; Davis, P.; Horvath, R. *J. Med. Chem.* **1997**, *40*, 695−704.
(8) Katsura, Y.; Zhang, X.; Homma, K.; Rice, K. C.; Calderon, S. N.; Rothman, R. B.; Yamamura, H. I.; Davis, P.; Flippen-Anderson, J. L.; Xu, H.; Becketts, K.; Foltz, E. J.; Porreca, F. *J. Med. Chem.* **1997**, *40*, 2936−2947.
(9) Negus, S. S.; Gatch, M. B.; Mello, N. K.; Zhang, X. Y.; Rice, K. *J. Pharmacol. Exp. Ther.* **1998**, *286*, 362−375.
(10) Brandt, M. R.; Furness, M. S.; Rice, K. C.; Fischer, B. D.; Negus, S. S. *J. Pharmacol. Exp. Ther.* **2001**, *299*, 629−637.

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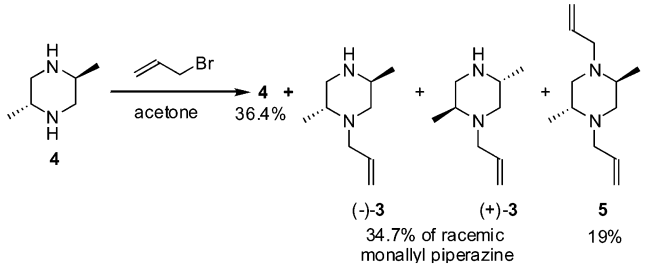
SCHEME 1

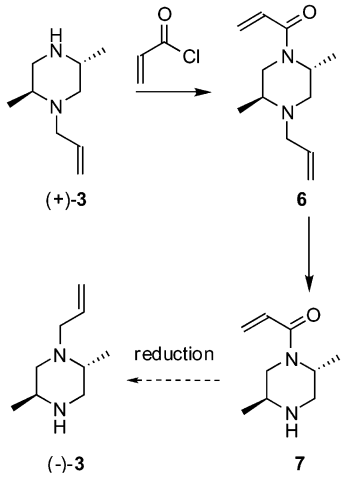


δ agonist were required. An additional quantity was also needed as starting material for a systematic structure−activity study of related nonpeptidic δ agonists. Several strategies currently exist for the preparation of benzhydrylpiperazine opioids in optically pure form.[6,11,12] Syntheses of those containing the (−)-(2*R*,5*S*)-1-allyl-2,5-dimethylpiperazine moiety, e.g., (+)-**1** and (+)-**2**, utilize the enantiopure dimethylpiperazine derivative, [(−)-**3**]. Accordingly, an efficient, large-scale preparation of this important intermediate was needed. Herein we report an efficient, nonchromatographic preparation of enantiopure (−)-**3** through the use of an optical resolution and enantiomer interconversion, enabling 100+ g laboratory synthesis.

Results and Discussion

Resolution. We previously reported that allylation of *trans*-2,5-dimethylpiperazine (**4**) gives a mixture of unchanged **4**, (±)-**3**, and 1,4-diallyl-*trans*-2,5-dimethylpiperazine (**5**) by a modification of the procedure of Ikeda et al.[13] Upon removal of diallylamine **5**, the enantiomeric pair of amines **3** could be resolved as their camphoric acid salts (Scheme 1).[6] Unfortunately, this resolution required the use of the unnatural and expensive (−)-camphoric acid to obtain the desired enantiomer (−)-**3**.[6,7] This led us to examine an enantiospecific route[14] for the preparation of (−)-**3**. In this study, briefly described earlier,[7] BOC-*N*-allyl-D-alanyl-L-alanine methyl ester was converted to a dimethyl diketopiperazine, which upon reduction provided (−)-**3**. Despite the good yields and the absence of racemization, this procedure proved less practical for large-scale production of the target. We therefore decided to reinvestigate the resolution procedure to determine if a more easily available and cost-effective chiral acid could be employed. It was found that resolution with (+)-tartaric acid of a mixture of (−)-**3** and (+)-**3**, enriched in (−)-**3** through removal of (+)-**3** as its salt with readily available (+)-camphoric acid in a manner described earlier,[7] provided (−)-**3** in approximately 42%, out of the theoretical 50%, yield. To our satisfaction, the material proved to be >99% optically pure when analyzed as its 1-naphthylurea by chiral HPLC.[7] We repeated this resolution numerous times using the simple procedure described below on amounts of up to 300 g of (±)-**3** and have found it to be reproducible in all respects. Resolution of (±)-**3** with tartaric acid enantiomers was not reproducible since in some experiments both enantiomeric salts crystallized.

SCHEME 2



Interconversion of Enantiomers. A resolution-based approach leads to a maximum 50% yield of each enantiomer. To increase the efficiency of the resolution process, we sought a method of converting the undesired antipode (+)-**3** to (−)-(2*R*,5*S*)-1-allyl-2,5-dimethylpiperazine [(−)-**3**]. One strategy entailed the recycling of amine (+)-**3** through the achiral diamine **4**. The reaction of **4** with allyl bromide would then provide (±)-**3**, which upon resolution would lead to an additional amount of the desired compound (−)-**3**. This approach was not ideal for our purposes.

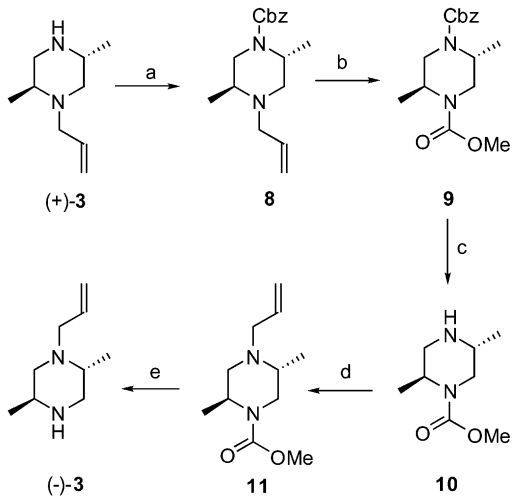
A different, more practical approach was sought. We recognized that moving the allyl group from N-1 to N-4 in (+)-**3** would lead to its enantiomer, (−)-**3**, and that this provided a means for interconversion. The success of such an interconversion requires a strategy for protection of the piperazine nitrogen atoms while maintaining constant differentiation between them.

Initially, we considered that formation of the acrylamide **6** in Scheme 2 followed by N-deallylation would give amide **7**. The reduction of **7** should then provide the desired piperazine (−)-**3**. Unfortunately, attempts at deallylation by three procedures[15−17] led to mixtures of polymeric compounds, probably the result of Michael attack by the generated secondary amine on the α,β-unsaturated amide.

Our attention then turned toward differential protection of the piperazine's nitrogen atoms as carbamates. It was found that protecting the free secondary amine of (+)-**3** as a benzyl carbamate (**8**), followed by N-deallylation and carbamoylation with methyl chloroformate, gave the differentially protected dicarbamate **9** in quantitative yield. Removal of the benzyloxycarbonyl group of **9** by catalytic hydrogenation gave secondary amine **10**, which upon reaction with allyl bromide provided amine **11**.

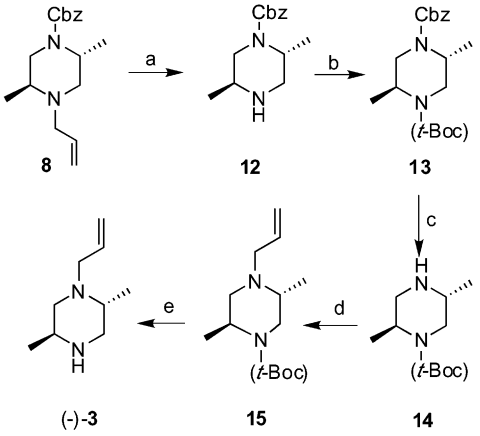
(11) Bishop, M. J.; McNutt, R. W. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1311−1314.
(12) Delorme, D.; Berthelette, C.; Lavoie, R.; Roberts, E. *Tetrahedron*: *Asymmetry* **1998**, *9*, 3963−3966.
(13) Ikeda, Y.; Nitta, Y.; Yamada, K. *Yakugaku Zasshi* **1969**, *89*, 669−676; *Chem. Abstr.* **1969**, *71*, 61337.
(14) Chang, K. J.; Boswell, G. E.; Bubacz, D. G.; Collins, M. A.; Davis, A. O.; McNutt, R. W. Int. Patent WO 9315062, Aug 5, 1993; *Chem. Abstr.* **1994**, *121*, 83367.
(15) Magnus, P.; Thurston, L. S. *J. Org. Chem.* **1991**, *56*, 1166−1170.
(16) Garro-Helion, F.; Merzouk, A.; Guibe, F. *J. Org. Chem.* **1993**, *58*, 6109−6113.
(17) Tomori, H.; Shibutani, K.; Ogura, K. *Heterocycles* **1997**, *44*, 213−225.

SCHEME 3[a]



[a] Reagents: (a) $ClCO_2Bn$, $NaHCO_3$ (aq), $CHCl_3$ (98%); (b) $ClCO_2Me$, K_2CO_3, 1,2-DCE (100%); (c) H_2, Pd/C, EtOH (98%); (d) allyl bromide, K_2CO_3, THF (95%); (e) L-Selectride, THF (82%).

SCHEME 4[a]



[a] Reagents: (a) Pd/C, H_2O, AcOH (100%); (b) (t-Boc_2O, CH_2Cl_2 (98%); (c) Pd/C, $HCOONH_4$, MeOH (97%); (d) allyl bromide, K_2CO_3, acetone (95%); (e) TFA, Et_3SiH, CH_2Cl_2 (89%).

Finally, the methoxycarbonyl group was removed in high yield by the use of our recently developed L-Selectride method[18,19] for opioid O-demethylation to give (−)-**3** in 75% overall yield from (+)-**3** (Scheme 3).

Alternatively (Scheme 4), catalytic N-deallylation[17] of allylamine **8** by a one-pot palladium-mediated isomerization and hydrolysis of resultant enamine provided secondary amine **12**. Carbamoylation of **12** with dibutyl dicarbonate produced dicarbamate **13**, which upon catalytic transfer hydrogenation gave secondary amine **14**. Treatment of **14** with allyl bromide to give **15** was followed by removal of the *tert*-butoxycarbonyl group with trifluoroacetic acid to give (−)-**3** in 79% overall yield from (+)-**3**.

Interestingly, simply replacing allyl bromide with other alkyl halides in the alkylation portion of this reaction (**10** → **11** in Scheme 3, or **14** → **15** in Scheme 4) should allow practical preparation of dimethylpiperazine N-substituted analogues of (+)-**1** and (+)-**2**. Moreover, modification of the procedure shown in Scheme 3, starting with (−)-**3** in place of (+)-**3**, would lead to enantiomeric forms of these analogues.

Recycling of Diallylated Piperazine. Whereas the interconversion of the enantiomers of **3** significantly improved the yield in the resolution portion of the synthesis of (−)-(2*R*,5*S*)-1-allyl-2,5,-dimethylpiperazine-[(−)-**3**], the formation of ∼20% of 1,4-diallyl-2,5-dimethylpiperazine (**5**) in the initial alkylation reaction represented a substantial loss in material and overall efficiency. It was clearly desirable to develop a means of directing **5** back into the overall reaction. To this end, we adopted the catalytic deallylation procedure[17] described above (Scheme 4, **8** → **12**) for conversion of **5** to *trans*-2,5-dimethylpiperazine, **4**, in 85% yield.

Experimental Section

^1H NMR (300 MHz) spectra were recorded in $CDCl_3$ with tetramethylsilane (TMS) as the internal standard. Optical rotations were obtained at 23 °C. Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA, and the results were within ±0.4% of the theoretical values. High-resolution mass spectral data are provided for samples that failed to give satisfactory elemental analytical results.

(±)-1-Allyl-*trans*-2,5-dimethylpiperazine [(±)-3]. To a refluxing solution of *trans*-2,5-dimethylpiperazine (**4**) (228.4 g, 2.0 mol) in acetone (1.68 L, dried for 18 h[20] over 3 Å molecular sieves)[19] was added allyl bromide (193.6 g, 1.6 mol) in dried acetone (256 mL) over a period of about 1 h. Dried acetone was utilized to prevent crystallization of hydrated **4**·HBr as the reaction proceeded. External heating was discontinued at the start of the addition, and the rate of addition was controlled so that a gentle reflux was maintained. After addition, the reaction mixture was stirred under reflux for 30 min and was then cooled to rt. Crystallization of the hydrated hydrobromide salt of **4** was induced by the addition of H_2O (8.3 mL). To ensure rapid and complete crystallization of **4** as the hydrated HBr salt, additional water (16.5 mL) was added to the stirred solution. The resulting solids were filtered, washed with acetone, and dried to give 147.0 g (35.2%) of the **4**·HBr·0.75H_2O salt: mp 100−101 °C dec. Anal. Calcd for $C_6H_{15}N_2Br$·0.75 H_2O: C, 34.54; H, 7.97; N, 13.42. Found: C, 34.43; H, 7.81; N, 13.03. The filtrate and wash were evaporated, free based with concd NH_4OH (125 mL) and H_2O (345 mL), and extracted with $CHCl_3$. The aqueous layer was saturated with NaCl, and the resulting suspension was extracted with $CHCl_3$. The combined organic extracts were evaporated to give 221.0 g of mixed bases. NaOH (20.0 g) was added to the salt-saturated aqueous residue. Extraction with $CHCl_3$ provided 2.73 g of **4** as the free base, bringing the total of unreacted starting material to 36.4%. The 221.0 g of mixed bases were dissolved with succinic acid (270.0 g, 2.29 mol) in hot acetone (1.7 L). The salt crystallized rapidly. After crystallization was complete at rt, the solids were collected, washed with acetone, and dried in vacuo to give 273.6 g (35%) of the disuccinate salt of (±)-**3**. The analytical sample showed mp 104−105 °C. Anal. Calcd for $C_{17}H_{30}N_2O_8$: C, 52.30; H, 7.75; N, 7.18. Found: C, 52.29; H, 7.75; N, 7.17.

This disuccinate salt was partitioned between a mixture of concd NH_4OH (200 mL), H_2O (160 mL), and $CHCl_3$ (150 mL). After separation of the layers, the aqueous layer was saturated with NaCl and extracted with $CHCl_3$ (4×). The combined organic extracts were evaporated to afford 107 g (99% recovery from succinate salt, 34.7% from **4**) of (±)-**3** as a clear oil. The

(18) Coop, A.; Janetka, J. W.; Lewis, J. W.; Rice, K. C. *J. Org. Chem.* **1998**, *63*, 4392−4396.
(19) Coop, A.; Rice, K. C. *Tetrahedron Lett.* **1998**, *39*, 8933−8934.
(20) Burfield, D. R.; Smithers, R. H. *J. Org. Chem.* **1978**, *43*, 3966−3968.

distillation of this base and its enantiomers (see below) is complicated by considerable foaming under the conditions described below.

The procedure described above on a 2 mol scale has been repeated numerous times and also using as much as 4 mol of *trans*-2,5-dimethylpiperazine, with similar success.

***trans*-1,4-Diallyl-2,5-dimethylpiperazine·2HBr (5·2HBr).** The filtrate and washing from the preparation of the disuccinate salt of (±)-**3** were evaporated to a syrup and partitioned between a mixture of NH_4OH (180 mL), H_2O (50 mL), and $CHCl_3$ (150 mL). The aqueous phase was extracted further with $CHCl_3$ (3×). The combined organic extracts were evaporated to give the crude free base, which was dissolved in warm acetone (600 mL). Upon addition of HBr (48%, 100 mL), the dihydrobromide salt of **5** crystallized almost immediately. After the mixture was cooled to rt and filtered, the crystalline material was washed with acetone and dried to afford 135.0 g (19%) of **5**·2HBr: mp 264−265 °C dec. Anal. Calcd for $C_{12}H_{24}N_2Br_2$: C, 40.47; H, 6.79; N, 7.87. Found: C, 40.56; H, 6.73; N, 7.80.

(+)-(2*S*,5*R*)-1-Allyl-2,5-dimethylpiperazine [(+)-3]. Isolation of (+)-**3** through resolution with (+)-camphoric acid was carried out in a manner similar to that outlined previously.[7] (+)-Camphoric acid (118.0 g, 0.59 mol) was dissolved in hot acetone (1 L), and (±)-**3** (181.7 g, 1.18 mol) in acetone (88 mL) was added. The camphorate salt began crystallization from the warm solution within 15 min. After being cooled to rt, the mixture was filtered and the salt washed with acetone (5×). This salt was recrystallized by dissolving it in hot MeOH (650 mL), adding acetone (1.3 L), and cooling to 15 °C. After being washed with acetone (3×), the salt was recrystallized once more from MeOH and acetone to yield 138.0 g (33% of the theoretically possible 50%) of the (+)-**3**·(+)-camphoric acid: $[\alpha]_D$ +47.7 (*c* 1.08, MeOH) (lit.[7] $[\alpha]_D$ +46.8 (*c* 1.0, MeOH)).

The salt (138.0 g, 0.39 mol) was partitioned between 15% NaOH (300 mL) and $CHCl_3$ (250 mL). The aqueous layer was extracted with $CHCl_3$ (4×), and the combined extracts were evaporated. Purification by distillation at aspirator vacuum (bp 85−95 °C/12−14 Torr) afforded 60 g (100%) of (+)-**3** from the camphorate salt (33% of the theoretically possible 50% from (±)-**3**): $[\alpha]_D$ +58.2 (*c* 3.18, EtOH) (lit.[7] $[\alpha]_D$ +55.5 (*c* 1.4, EtOH)).

(−)-(2*R*,5*S*)-1-Allyl-2,5-dimethylpiperazine [(−)-3]. All of the filtrates and washings from the initial crystallization and recrystallizations of (+)-**3**·(+)-camphoric acid were combined and evaporated. To remove residual acetone, toluene (200 mL) was added and removed under reduced pressure. A solution of NaOH (26.0 g) in H_2O (140 mL) was added, and the solution (pH ≥13) was extracted with $CHCl_3$. After separation of the phases, the aqueous layer was further extracted with $CHCl_3$ (3×). The combined organic extracts were evaporated to give 113.0 g (0.733 mol) of mixed bases enriched in (−)-**3**. These mixed bases were dissolved together with (+)-tartaric acid (220.5 g, 1.47 mol) in hot MeOH (670 mL). The tartrate salt crystallized rapidly in 10−15 min from the hot solution. After being cooled to rt, the solids were filtered and washed with MeOH (3×), MeOH/acetone (1:1, 2×), and petroleum ether (2×). After the solids were dried in vacuo, 270.0 g of the tartrate salt of (−)-**3** was obtained. This salt was dissolved by portionwise addition to warm DMF (up to 100 °C, 200 mL) and then diluted with MeOH (800 mL), whereupon crystallization occurred. After being cooled to rt, the crystalline material was collected by filtration and washed with MeOH (3×), MeOH/acetone (1:1, 3×), and petroleum ether (2×). After the material was dried in vacuo, 250.0 g (87%) of (−)-**3**·2(+)-tartaric acid salt containing 1 mol of MeOH was obtained: mp 119−121 °C (softens), 148−150 °C dec. Anal. Calcd for $C_{17}H_{30}N_2O_{12}\cdot CH_3OH$: C, 44.44; H, 7.05; N, 5.76. Found: C, 44.11; H, 6.96; N, 5.83. The salt was partitioned between 15% NaOH (600 mL) and $CHCl_3$ (300 mL). The aqueous portion was extracted with $CHCl_3$ (4×), and the combined organic extracts were evaporated. Distillation at aspirator vacuum (bp 85−90 °C/12−14 Torr) provided 76 g (96%) of pure (−)-**3** from the tartrate salt (41.8% from (±)-**3**): $[\alpha]_D$ −57.1 (*c* 4.02, EtOH) (lit.[7] $[\alpha]_D$ −52.3 (*c* 2.5, EtOH)). Optical purity was found to be >99% by HPLC of the urea formed with 1-naphthyl isocyanate, as noted:[7] ^{1}H NMR δ 5.84−5.93 (m, 1H), 5.14−5.20 (m, 2H) 5.15 (s, 1H), 3.47 (ddd, 1H, J = 3.3, 5.4, 13.8 Hz) 2.80−2.91 (m, 4H), 2.58 (dd, 1H, J = 10.2, 12.3), 2.16−2.19 (m, 1H), 1.77 (dd, 1H, J = 10.2, 12.3 Hz), 1.4 (br s, 1H), 1.05 (d, 3H, J = 6.0 Hz), 1.02 (d, 3H, J = 6.09 Hz); MS (CI) *m/z* 155 (M + 1).

(2*S*,5*R*)-1-Allyl-4-benzyloxycarbonyl-2,5-dimethylpiperazine (8). A biphasic mixture of (+)-**3** (32.7 g, 0.212 mol) in $CHCl_3$ (400 mL) and saturated $NaHCO_3$ (400 mL) was cooled to 0 °C, and benzyl chloroformate (33.3 mL, 0.233 mol) was added slowly over a period of 5−10 min with vigorous stirring. Stirring was continued for 4 h at rt. The layers were separated, and the aqueous layer was extracted with $CHCl_3$. The combined organic extracts were dried over Na_2SO_4 and concentrated. Distillation (bp 167 °C/0.7 Torr) provided pure **8** (60.2 g, 98%) as a colorless viscous oil: ^{1}H NMR δ 7.35 (s, 5H) 5.72−5.88 (m, 1H) 5.08−5.24 (m, 4H) 4.22−4.36 (m, 1H) 3.75 (d, 1H, J = 12.6 Hz) 3.35 (dd, 1H, J = 3.9, 13.8 Hz) 3.07 (dd, 1H, J = 5.7, 13.8 Hz) 2.92−3.01 (m, 1H) 2.94 (dd, 1H J = 6.9, 13.8 Hz) 2.64 (dd, 1H, J = 3.9, 11.7 Hz) 2.31 (dd, 1H, J = 1.8, 11.7 Hz) 1.26 (d, 3H, J = 6.9 Hz) 0.92 (d, 3H, J = 6.0 Hz); MS *m/z* (CI) 289 (M + 1); $[\alpha]_D$ −46.3 (*c* 2.9, EtOH). Anal. Calcd for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71. Found: C, 70.71; H, 8.31; N, 9.47.

(2*S*,5*R*)-1-Methoxycarbonyl-4-benzyloxycarbonyl-2,5-dimethylpiperazine (9). To a stirred solution of **8** (35.3 g, 0.122 mol) in 1,2-dichloroethane (350 mL) were added K_2CO_3 (17.0 g, 0.122 mol) and methyl chloroformate (20.0 mL, 0.26 mol). After the mixture had been refluxed for 15 h, additional methyl chloroformate (20 mL, 0.26 mol) was added and refluxing was continued for an additional 10 h. Upon cooling, the mixture was filtered and concentrated. The residue was dissolved in EtOAc, and the solution was washed with saturated $NaHCO_3$, 10% $KHSO_4$, and brine and dried over Na_2SO_4. Removal of the solvent gave **9** (37.4 g, 100%) as a clear light yellow oil. An analytical sample was prepared by passage through a short column of silica gel (acetone/hexane, 1:1): ^{1}H NMR δ 7.32−7.42 (m, 5H) 5.08−5.22 (m, 2H) 4.18−4.52 (m, 2H) 3.60−3.85 (m, 5H) 3.18−3.34 (m, 2H) 1.10−1.22 (m, 6H); MS *m/z* (CI) 307 (M + 1); $[\alpha]_D$ +1.53 (*c* 5.4, EtOH). Anal. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.72; H, 7.24; N, 9.14. Found: C, 62.86; H, 7.21; N, 9.02.

(2*S*,5*R*)-1-Methoxycarbonyl-2,5-dimethylpiperazine (10). A solution of **9** (37.1 g, 0.121 mol) in absolute EtOH (150 mL) was hydrogenated over 10% Pd/C (3.2 g) at 40 lb/in.^{2} for 14 h. The catalyst was removed by filtration through Celite, and the solvent was evaporated to give **10** as a clear and colorless oil (20.3 g, 98%). An analytical sample was prepared by distillation (66−68 °C/0.5 Torr): ^{1}H NMR δ 9.92 (br s, 1H) 4.52−4.64 (m, 1H) 3.86 (d, 1H, J = 14.6 Hz) 3.70−3.80 (m, 4H) 3.60 (dd, 1H, J = 2.9, 14.6 Hz) 3.30 (dd, 1H, J = 4.9, 12.7 Hz) 3.00 (d, 1H, J = 14.6 Hz) 1.48 (t, 6H, J = 6.8 Hz); $[\alpha]_D$ +90.6 (*c* 7.7, EtOH); HRMS (FAB) calcd for (M + H$^+$) $C_8H_{16}N_2O_2$ 173.1296, found 173.1290.

(2*S*,5*R*)-1-Methoxycarbonyl-4-allyl-2,5-dimethylpiperazine (11). To a mixture of **10** (20.3 g, 0.118 mol) and Na_2CO_3 (12.7 g, 0.120 mol) in THF (250 mL) was added freshly distilled allyl bromide (10.4 mL, 0.120 mol) dropwise at 0 °C over a period of 5−10 min. Stirring was continued for 8−10 h at rt. After the mixture was filtered, the solvent was removed in vacuo and the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated to give **11** (23.8 g, 95%) as a yellow oil. An analytical sample was prepared by distillation (69−70 °C/0.44 Torr): ^{1}H NMR δ 5.74−5.89 (m, 1H) 5.20 (dd, 1H, J = 2.0, 17.6 Hz) 5.12 (d, 1H, J = 9.8 Hz) 4.18−4.30 (m, 1H) 3.65−3.72 (m, 4H) 3.34 (dd, 1H, J = 3.9, 12.7 Hz) 3.08 (dd, 1H, J = 5.8 Hz, 13.6 Hz) 2.95 (dd, 2H, J = 6.8, 13.6 Hz)

2.64 (dd, 1H, J = 3.9, 11.7 Hz) 2.32 (dd, 1H, J = 2.0, 11.7 Hz) 1.25 (d, 3H, J = 6.8 Hz) 0.93 (d, 3H, J = 6.8 Hz); MS (CI) *m/z* 213 (M + 1); $[\alpha]_D$ +67.1 (*c* 10.3, EtOH). Anal. Calcd for $C_{11}H_{20}N_2O_2$: C, 62.23; H, 9.50; N, 13.19. Found: C, 62.06; H, 9.57; N, 13.10.

(−)-(2*R*,5*S*)-1-Allyl-2,5-dimethylpiperazine [(−)-3] from 11. Compound **11** (54.0 g, 0.254 mol) was added to a solution of lithium tri-*sec*-butyl borohydride (L-Selectride) (1 M in THF, 600 mL, 0.60 mol) over a period of 15 min with stirring at rt. Stirring was continued for 3 days, at which time the mixture was cooled to 0 °C and the reaction was quenched by cautious addition of H_2O. After an additional 30 min, the solvent was removed under vacuum and the residue was partitioned between H_2O and $CHCl_3$. The aqueous layer was saturated with NaCl and extracted with $CHCl_3$ (3×). The combined organic extracts were washed with saturated $NaHCO_3$ and extracted with 10% citric acid (5×). The aqueous extracts were combined and brought to pH 9−10 by the addition of 5 N NaOH. The solution was cooled in an ice bath and extracted with $CHCl_3$. The combined organic extracts were dried over Na_2SO_4 and concentrated to give a dark yellow oil (40.1 g). The crude oil was purified by distillation (bp 45−50 °C/1 Torr) to give 32.1 g (82%) of (−)-**3** as a clear colorless oil: $[\alpha]_D$ −54.2 (*c* 6.51, EtOH) (lit.[7] $[\alpha]_D$ −52.3 (*c* 2.5, EtOH)). The ^{1}H NMR and mass spectra were identical to those given above for (−)-**3**.

(2*R*,5*S*)-1-Benzyloxycarbonyl-2,5-dimethylpiperazine (12). A mixture of **8** (22.2 g, 0.077 mol), glacial acetic acid (10 mL, 0.176 mol), 10% Pd/C (2.0 g), and water (80 mL) was refluxed for 3 h. The catalyst was removed by filtration through Celite, and the solvents were evaporated to yield **12** (19.0 g, 100%) as a light yellow oil. An analytical sample was prepared by distillation (140 °C/0.5 Torr): ^{1}H NMR δ 7.26−7.39 (m, 5H), 5.11−5.18 (2d, 2H, J = 12.6 Hz), 4.16−4.20 (m, 1H), 3.64 (d, 1H, J = 2.1, 13.2 Hz), 3.09−3.32 (m, 3H), 3.51 (d, 1H, J = 2.7, 13.2 Hz), 1.24 (d, 3H, J = 6.9 Hz), 1.16 (d, 3H, J = 6.9 Hz); $[\alpha]_D$ = −63.7 (c 4.8, EtOH); HRMS (FAB) calcd for (M + H$^+$) $C_{14}H_{21}N_2O_2$ 249.1596, found 249.1603.

(2*R*,5*S*)-1-Benzyloxycarbonyl-4-*tert*-butoxycarbonyl-2,5-dimethylpiperazine (13). To a stirred solution of **12** (12.4 g, 0.05 mol) in CH_2Cl_2 (150 mL) at 0 °C was added a solution of di-*tert*-butyl dicarbonate (12.0 g, 0.055 mol) in CH_2Cl_2 (50 mL) over a period of 5−10 min. Stirring was continued overnight (rt). The reaction mixture was washed with cold 5% citric acid, saturated $NaHCO_3$, water, and brine and dried over Na_2SO_4. Removal of solvent and passage through a short column of silica gel (acetone/hexanes 1:4) yielded pure **13** (17.0 g, 98%): ^{1}H NMR δ 7.34−7.36 (m, 5H), 5.10−5.17 (2d, 2H, J = 12.0 Hz), 4.10−4.45 (m, 1H), 3.62−3.78 (m, 1H), 3.10−3.30 (m, 1H), 2.08−3.23 (m, 3H), 1.46 (s, 9H), 1.15 (m, 6H); MS-CI *m/z* 349 (M + 1); $[\alpha]_D$ = −1.08 (*c* 2.3, EtOH). Anal. Calcd for ($C_{19}H_{29}N_2O_4$): C, 65.49; H, 8.10; N, 8.04. Found: C, 65.48; H, 8.17; N, 7.99.

(2*S*,5*R*)-1-*tert*-Butoxycarbonyl-2,5-dimethylpiperazine (14). To a mixture of **13** (8.7 g, 0.025 mol) and 10% Pd/C (1.0 g) in MeOH (100 mL) at reflux was added a solution of ammonium formate (8.3 g, 0.1 mol) in water (16 mL), and the mixture was refluxed for an additional 3 h. The catalyst was removed by filtration through Celite and the solvent evaporated. The residue was dissolved in $CHCl_3$, and this solution was washed with brine (2×). After drying over Na_2SO_4 and removal of solvent, the resulting solid was dissolved in water (25 mL) and made basic with concentrated NH_4OH. After extractiion with ether, the aqueous layer was saturated with NaCl and again extracted with ether (2×). The combined ether extracts were dried over Na_2SO_4 and evaporated to yield **14** (5.5 g, 97%) as a light yellow oil. An analytical sample was prepared by distillation (65 °C/0.6 Torr): ^{1}H NMR δ 4.08−4.13 (m, 1H) 3.54 (dd, 1H, J = 1.5, 13.5 Hz) 3.10−3.24 (m, 3H) 2.47 (dd, 1H, J = 1.5, 13.5 Hz) 1.46 (s, 9H) 1.2 (d, 3H, J = 6.9 Hz) 1.16 (d, 3H, J = 6.9 Hz); $[\alpha]_D$ = +71.2 (*c* 7.4, EtOH); HRMS (EI) calcd for (M + H$^+$) $C_{11}H_{22}N_2O_2$ 214.1684, found 214.1681.

(2*S*,5*R*)-1-*tert*-Butoxycarbonyl-4-allyl-2,5-dimethylpiperazine (15). A mixture of **14** (10.7 g, 0.05 mol), K_2CO_3 (7.05 g, 0.051 mol), and freshly distilled allyl bromide (8.8 mL, 0.051 mol) in acetone (200 mL) was refluxed for 2 h, at which time additional allyl bromide (8.8 mL, 0.051 mol) was added. After an additional 2 h of reflux, the mixture was cooled and filtered and the filtrate concentrated. Passage through a short column of silica gel (acetone/hexanes 1:4) gave **15** (12.1 g, 95%) as a clear colorless oil. An analytical sample was prepared by distillation (75 °C/0.6 Torr): ^{1}H NMR δ 5.74−5.87 (m, 1H) 5.09−5.22 (m, 2H) 4.14−4.28 (m, 1H) 3.54 (d, 1H, J = 13.0 Hz) 3.65 (d, 1H, J = 13.0 Hz) 2.91−3.10 (m, 3H) 2.62 (d, 1H, J = 11.7 Hz) 2.29 (d, 1H, J = 11.7 Hz) 1.46 (s, 9H) 1.23 (d, 3H, J = 6.6 HZ) 0.91 (d, 3H, J = 6.6 Hz); $[\alpha]_D$ = +54.6 (*c* 7.1, EtOH); HRMS (FAB) calcd for (M + H$^+$) $C_{14}H_{26}N_2O_2$ 254.1987, found 254.1994.

(−)-(2*R*,5*S*)-1-Allyl-2,5-dimethylpiperazine [(−)-3] from 15. To a mixture of **15** (7.63 g, 0.03 mol) and triethylsilane (12 mL, 0.075 mol) in CH_2Cl_2 (60 mL) was added trifluoroacetic acid (35 mL, 0.39 mol) with stirring under nitrogen. After 2 h, the reaction mixture was evaporated and the resultant oil was dissolved in ether and again evaporated. After repeated treatment with ether and evaporation, the material solidified. The white solid was dissolved in water (50 mL) and the solution basified with concentrated NH_4OH. After extraction with $CHCl_3$, the aqueous layer was saturated with NaCl and again extracted with $CHCl_3$ (4×). The combined extracts were dried (Na_2SO_4) and evaporated to yield (−)-**3** as a light yellow oil (4.12 g, 89%): $[\alpha]_D$ = −55.4 (*c* 3.4, EtOH).

Formation of 4 by Deallylation of 5. Glacial acetic acid (26.3 mL, 0.46 mol) and 10% palladium on charcoal (10.0 g) were added to a mixture of *trans*-1,4-diallyl-2,5-dimethylpiperazine·2HBr (**5**·2HBr) (35.6 g, 0.1 mol) and aqueous NaOH solution (2 M, 100 mL). The mixture was stirred under reflux for 24 h. After cooling and filtering through Celite, the solution was decolorized, again filtered through Celite, adjusted to pH >13 by addition of solid NaOH (24.0 g), and saturated with NaCl. Continuous extraction with $CHCl_3$ over a period of 18 h afforded 9.7 g (85%) of **4**.

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