JOC*Note*

Scalable Synthesis and Isolation of the Four Stereoisomers of Methyl 1-Amino-3-(4-bromophenyl)cyclopentanecarboxylate, Useful Intermediates for the Synthesis of S1P1 Receptor Agonists

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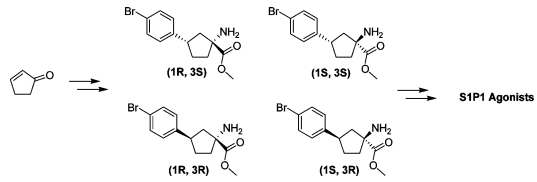


The individual isomers of methyl 1-amino-3-(4-bromophenyl)cyclopentanecarboxylate are useful intermediates for the synthesis of S1P1 receptor agonists. Herein we describe a scalable synthesis and isolation of each of the four stereoisomers of this compound in gram quantities with >98% ee and de. The utility of this approach is demonstrated by the synthesis of ((1*R*,3*R*)-1-amino-3-(4-octylphenyl)cyclopentyl)methanol in 7 steps, 11% overall yield, and >98% ee and de.

The sphingosine-1-phosphate (S1P) receptor family has emerged as an attractive target for immunomodulation.[1] In 2003 Novartis released positive results from phase II clinical trials of FTY720 (fingolimod) (Figure 1) in patients with relapsing remitting multiple sclerosis (RRMS).[2] FTY720 is phosphorylated in vivo providing FTY720-P, which is a potent agonist of the S1P-1, -3, -4, and -5 receptors. More recently, Lynch and Macdonald disclosed the discovery of VPC01091 (**1**), a conformationally constrained analogue of FTY720 containing two stereocenters and a unique receptor selectivity profile.[3] VPC01091 is a mixture of four stereoismoers that when dosed orally cause a lowering of circulating lymphocytes (lymphopenia). Following the separation of the stereoisomers of VPC01091, it was demonstrated that the cis-cyclic arylamine (1*R*,3*S*)-**1** and the trans-cyclic arylamine (1*R*,3*R*)-**1** could independently cause lymphopenia in mice. To more fully understand and expand on this discovery we set out to develop a scalable stereocontrolled synthesis of both the cis- and trans-isomers (1*R*,3*S*)-**1** and (1*R*,3*R*)-**1** that would allow for rapid structure activity relationship (SAR) studies of these interesting molecules. Lynch and Macdonald have published a stereoselective synthesis[4] that can be applied to the cis-isomers of **1**, delivering (*1R*,*3S*)-**1** in 12 steps and 11% overall yield with >95% ee and de. However, this approach has limited scope in that the trans-diasteromer (1*R*,3*R*)-**1** is delivered with 70% de. This Note describes the development of a synthetic route that allows for the multigram synthesis of all the stereoisomers of **1** with >98% ee and de as well as allowing for rapid structure activity relationship (SAR) studies of this class of molecules.

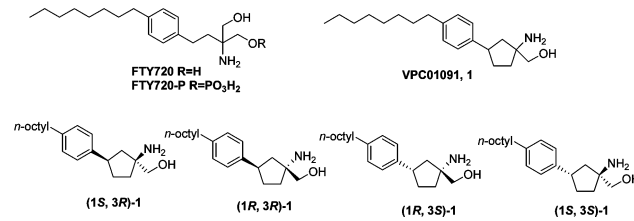
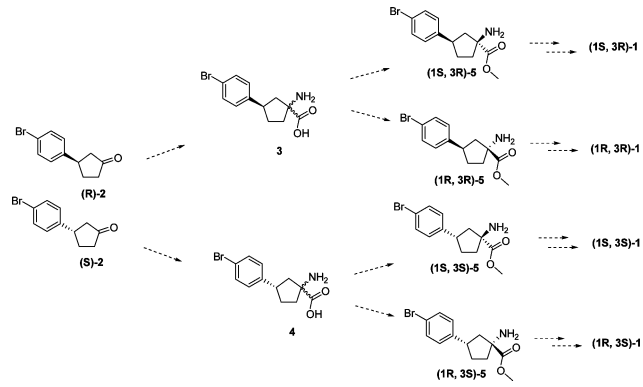


FIGURE 1. FTY-720 and the stereoisomers of VPC01091 (**1**).

SCHEME 1. Divergent Strategy to the Isomers of VPC01091 (1)



Since our goal targeted all of the individual stereoisomers of **1** a stereodivergent approach was designed (Scheme 1).[5] Beginning with the known 4-bromophenyl cyclopentanone **2**[6]

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‡ Abbott Laboratories.

(1) (a) *Drug News & Perspect.* **2008**, *21* (2), 89−96. (b) *Biochem. Pharmacol.* **2008**, *75* (10), 1893−1900. (c) Pyne, S.; Pyne, J. N. *Biochemistry* **2000**, *349*, 385–402. (d) Cyster, J. G. *Annu. Rev. Immunol.* **2005**, *23*, 127–159. (e) Pettus, B. J.; Chalfant, C. E.; Hannun, Y. A. *Curr. Mol. Med.* **2004**, *4*, 405–418. (f) Chun, J.; Rosen, H. *Curr. Pharm. Des.* **2006**, *12*, 161–171.

(2) Rosen, H.; Sanna, G.; Alfonso, C. *Immunol. Rev.* **2003**, *195*, 160.

(3) Zhu, R.; Snyder, A. H.; Kharel, Y.; Schaffter, L.; Sun, Q.; Kennedy, P. C.; Lynch, K. R.; Macdonald, T. L. *J. Med. Chem.* **2007**, *50*, 6428–6435.

(4) Of particular note in Lynch and Macdonald's synthesis is use of a stereospecific Dubois-type Rh(II)-stabilized nitrenoid intramolecular cyclization to deliver the quaternary stereocenter.[3]

(5) For an alternative approach that sets the quaternary stereocenter first see: Fix-Stenzel, S. R.; Hayes, M. E.; Zhang, X.; Wallace, G. A.; Grongsaard, P.; Schaffter, L. M.; Hannick, S. M.; Franczyk, T. S.; Stoffel, R. H.; Cusack, K. P. *Tetrahedron Lett.* DOI: 10.1016/j.tetlet.2009.04.099. Published Online: May 4, 2009.

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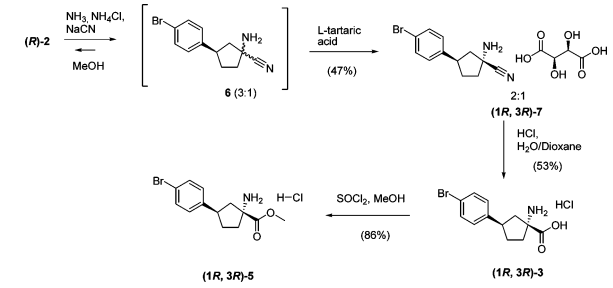
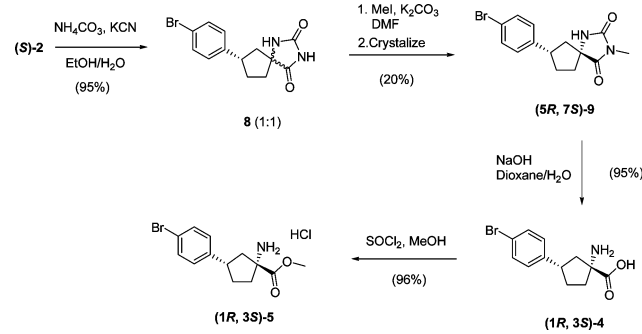
SCHEME 2



(available in either enantiomer) installation of the quaternary stereocenter utilizing methodology for the synthesis of α-amino acids would lead to diastereomeric mixtures of amino acids **3** or **4**.[7] Separation of these mixtures would provide the individual stereoisomers of amino-methylesters **5**, which would represent our point of divergence to the individual stereoisomers of **1**.[8,9] Installation of the *n*-octyl tail would then complete the syntheses of the individual isomers. This strategy would have the advantage of allowing rapid SAR studies of the *n*-alkyl portion of these molecules through the late stage amino-methylester intermediates **5**. Therefore gram-quantities of the individual stereoisomers of amino methyl ester **5** became our initial goal.

Installation of the benzylic stereocenter was accomplished through modifications[6d] to the methodology originally described by Hayashi and Miyaura,[10] providing the desired 4-bromophenylcyclopentanones in 89% yield and >95% ee. Strecker reaction of ketone (*R*)-**2** provided a 3:1 mixture of diastereomers, favoring the trans-cyclic arylamine (Scheme 2).[11] Through diastereomeric salt formation it was possible to isolate the trans-isomer (1*R*,3*R*)-**7** in 47% yield and >95% de. Hydrolysis of the aminonitrile provided the corresponding amino acid that was converted to the methyl ester (1*R*,3*R*)-**5** by treatment with thionyl chloride in methanol. The relative and absolute stereochemistry of (1*R*,3*R*)-**5** was unambiguously assigned through single-crystal X-ray analysis of the corresponding L-tartrate salt.[12] This route proved scalable, providing hundreds of grams of key intermediate (1*R*,3*R*)-**5** in 18% overall yield (>98% de and >98% ee) from cyclopent-2-enone. However, the 3:1 trans-diastereoselectivity of the Strecker reaction made it impractical for synthesis of the cis-diastereomers. To address this shortcoming, alternative methods for installing the quaternary stereocenter were explored.

SCHEME 3



Initial attempts to utilize chiral auxiliaries or chiral Lewis acids to influence the diastereoselectivity of this Strecker reaction proved impractical for our purposes.[13] The additional steps required to install and remove these chiral auxiliaries or synthesize the chiral Lewis acids made these approaches untenable. Ultimately it was discovered that the Bucherer–Bergs reaction provides a 1:1 mixture of diastereomeric hydantoins in high yield (Scheme 3).[14] Attempts to separate these diastereomers through crystallization, trituration, or chromatography were unsuccessful, presumably due to their low solubility in most solvents. The strong hydrogen bond donor–acceptor network expected to be present in the solid state of these molecules may be responsible for these failed efforts. To overcome this limitation *N*-alkylated hydantoins were explored in hopes of providing a more separable mixture.

N-Alkylation of **8** with methyl iodide was uneventful leading to a 1:1 mixture of the *N*-methyl derivatives. This mixture had improved solubility in organic solvents and it was discovered that the cis-diastereomer could be selectively crystallized from acetonitrile to provide hydantoin (5*R*,7*S*)-**9** with >95% de in 20% yield. Hydrolysis of the *N*-methylhydantoin provided the corresponding amino acid (1*R*,3*S*)-**4**, which was converted to the methyl ester (1*R*,3*S*)-**5** by treatment with thionyl chloride in methanol. The stereochemical assignment of (1*R*,3*S*)-**5** was based on comparison of its analytical data with (1*R*,3*R*)-**5** in the trans-series (vide supra). This route also proved scalable, providing multigram quantities of key intermediate (1*R*,3*S*)-**5** in 15% overall yield (98% de and 98% ee) from cyclopent-2-enone.

Completion of the synthesis of (1*R*,3*R*)-**1** is shown in Scheme 4.[15] Sonogashira coupling installed the remaining carbons in the target molecule providing alkyne **10**. Hydrogenation of the alkyne, providing methyl ester **11**, followed by lithium aluminum hydride reduction of the methyl ester completed the synthesis of (1*R*,3*R*)-**1** in 7 steps and 11% overall yield (>98% ee and de).

In conclusion, synthetic routes have been developed that allow for the multigram isolation of each of the four stereoisomers of methyl 1-amino-3-(4-bromophenyl)cyclopentane carboxylate (**5**) with >98% ee and de. These key intermediates can be converted to each of the individual isomers of VPC01091 (**1**) through a straightforward three-step sequence. In addition, the routes we

(6) (a) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052–5058. (b) PCT Int. Appl., 2006047195, May 4, 2006. (c) Li, Z.; Chen, W.; Hale, J. J.; Lynch, C. L.; Mills, S. G.; Hajdu, R.; Keohane, C. A.; Rosenbach, M. J.; Milligan, J. A.; Shei, G.; Chrebet, G.; Parent, S. A.; Bergstrom, J.; Card, D.; Forrest, M.; Quankenbush, E. J.; Wickham, L. A.; Vargas, H.; Evans, R. M.; Rosen, H.; Mandala, S. *J. Med. Chem.* **2005**, *48*, 6169–6173. (d) Lukin, K.; Zhang, Q.; Leanna, R. *J. Org. Chem.* **2009**, *74*, 929–931.

(7) (a) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry.* **2007**, *18*, 569. (b) Vogt, H.; Brase, S. *Org. Biomol. Chem.* **2007**, *5*, 406. (c) Trigalo, F.; Buisson, D.; Azerad, R. *Tetrahedron Lett.* **1988**, *47*, 6109–6112.

(8) For a recent review on optical resolution, see: Faigl, F.; Fogassy, E.; Nogradi, M.; Palovics, E.; Schindler, J. *Tetrahedron: Asymmetry* **2008**, *19* (5), 519–536.

(9) A similar approach has been taken to synthesize the four stereoisomers of ACPD: Curry, K.; Peet, M. J.; Magnuson, D. S. K.; McLennan, H. *J. Med. Chem.* **1988**, *31*, 864–867.

(10) Hayashi, T.; Ogasawara, M.; Takaya, Y.; Miyaura, N.; Sakai, M. *J. Am. Chem. Soc.* **1998**, *120*, 5579–5580.

(11) Recent reviews of the Strecker reaction, see: (a) Groger, H. *Chem. Rev.* **2003**, *103*, 2795. (b) Vilaivan, T.; Bhanthumnavin, Y.; Sritana-Anant, Y. *Curr. Org. Chem.* **2005**, *9*, 1315.

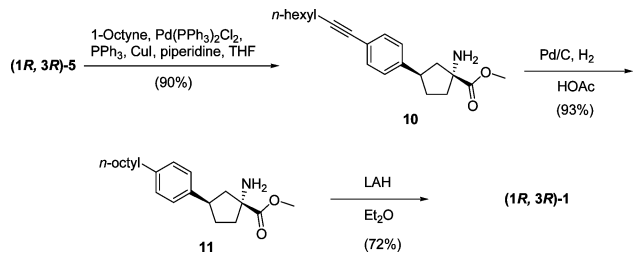
(12) Coordinates for the X-ray structure of **5**-(1*R*,3*S*) have been deposited with the Cambridge Crystallographic Data Centre and are available free of charge at http://www.ccdc.cam.ac.uk/, reference code CCDC 713456.

(13) For recent reviews on the catalytic asymmetric Strecker reaction, see: (a) Cannon, S. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1176–1178. (b) Groger, H. *Chem. Rev.* **2003**, *103*, 2795–2827.

(14) (a) Edward, J. T.; Jitrangsri, C. *Can. J. Chem.* **1975**, *53*, 3339–3350. (b) Alonso, F.; Mico, I.; Najera, C.; Sansano, J. M.; Yus, M.; Ezquerra, J.; Yruretagoyena, B.; Gracia, I. *Tetrahedron* **1995**, *51* (37), 10259–10280.

(15) Similar results were obtained for both the cis- and trans-diastereomers. For clarity only the cis-isomer is shown in Scheme 4.

SCHEME 4



have developed to these intermediates have provided ample material to conduct SAR studies on this class of molecule, the results of which will be reported elsewhere.

Experimental Section

Preparation of (1*R*,3*R*)-1-Amino-3-(4-bromophenyl)cyclopentanecarbonitrile Bi-L-tartrate ((1*R*,3*R*)-7). A solution of (*R*)-3-(4-bromophenyl)cyclopentanone ((*R*)-**2**) (21.5 g, 90.0 mmol) in 7 M methanolic ammonia solution (220 mL) was treated with ammonium chloride (9.63 g, 180 mmol) and sodium cyanide (8.82 g, 180 mmol). The reaction was stoppered and stirred at room temperature for 3 days. The reaction was concentrated, treated with sat. $NaHCO_3$ solution (400 mL), and extracted with EtOAc (400 mL). The EtOAc layer was washed with sat. NaCl (300 mL) and treated with L-tartaric acid (13.5 g, 90.0 mmol) and the EtOAc was removed in vacuo. The resulting white solid was filtered and triturated with water (9 × 250 mL) until the more soluble isomer was very nearly gone as indicated by HPLC (ThermoQuest 50 × 4.6 mm, 5 u, Hypercarb column, part no. 35005-025). The remaining white solid was dried in vacuo to provide (1*R*,3*R*)-1-amino-3-(4-bromophenyl)cyclopentanecarbonitrile 2:1 salt with L-tartaric acid ((1*R*,3*R*)-**7**) (14.5 g, 47% yield). ^{1}H NMR (DMSO-d_6) δ 7.45 (d, 2H, J = 8.3 Hz), 7.23 (d, 2H, J = 8.4 Hz), 4.01 (s, 1H), 3.30−3.45 (m, 1H), 2.50 (m, 1H), 2.10−2.35 (m, 3H), 1.8−2.0 (m, 2H), 1.6−1.75 (m, 1H). Due to instability (significant amounts of retro-Strecker reaction were observed on standing in solution) full characterization of this intermediate was not practical.

Preparation of (1*R*,3*R*)-1-Amino-3-(4-bromophenyl)cyclopentanecarboxylic Acid Hydrochloride ((1*R*,3*R*)-3). A suspension of (1*R*,3*R*)-1-amino-3-(4-bromo-phenyl)cyclopentanecarbonitrile 2:1 salt with L-tartaric acid ((1*R*,3*R*)-**7**) (14.4 g, 42.4 mmol) in 6 N hydrochloric acid (72 mL) and *p*-dioxane (72 mL) was heated at 100 °C. After 24 h the reaction mixture was cooled to rt and the product was collected by filtration, washed with water (2 × 25 mL), and dried in vacuo to provide the crude amino acid. The crude product was further purified by trituration with EtOAc (3 × 25 mL) then redried to provide (1*R*,3*R*)-1-amino-3-(4-bromophenyl)-cyclopentanecarboxylic acid hydrochloride ((1*R*,3*R*)-**3**) as a colorless solid (6.29 g, 53% yield). ^{1}H NMR (DMSO-d_6) δ 13.9 (br s, 1H), 8.52 (br s, 3H), 7.51 (d, 2H, J = 8.5 Hz), 7.23 (d, 2H, J = 8.5 Hz), 3.50 (m, 1H), 2.30−2.42 (m, 2H), 2.10−2.26 (m, 2H), 1.90−2.05 (m, 1H), 1.75−1.88 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.6, 143.1, 132.3, 130.1, 120.3, 64.5, 44.02, 43.95, 37.3, 34.7. Mp 224−231 °C. HRMS *m*/*z* calcd for $C_{12}H_{15}NO_2{}^{79}Br$ is 284.0286, measured is 284.0278. HRMS *m*/*z* calcd for $C_{12}H_{15}NO_2{}^{81}Br$ is 286.0266, measured is 286.0269.

Preparation of (1*R*,3*R*)-Methyl 1-Amino-3-(4-bromophenyl)cyclopentanecarboxylate Hydrochloride ((1*R*,3*R*)-5). To a solution of (1*R*,3*R*)-1-amino-3-(4-methoxyphenyl)cyclopentanecarboxylic acid hydrochloride ((1*R*,3*R*)-**3**) (6.20 g, 19.4 mmol) in methanol (150 mL) at 0 °C was added thionyl chloride (8.20 mL, 160 mmol) at a dropwise rate. The ice bath was removed and the reaction was heated at 70 °C for 6 h and then was allowed to stir at rt for 15 h. The reaction was filtered and concentrated. The crude product was recrystallized from methanol and ether to obtain (1*R*,3*R*)-1-amino-3-(4-bromophenyl)cyclopentanecarboxylic acid methyl ester hydrochloride ((1*R*,3*R*)-**5**) (5.59 g, 86% yield) as a colorless solid in three crops. ^{1}H NMR (DMSO-d_6) δ 8.68 (br s, 3H), 7.52 (d, 2H, J = 8.5 Hz), 7.23 (d, 2H, J = 8.5 Hz), 3.81 (s, 3H), 3.50 (m, 1H), 3.32−3.48 (m, 2H), 2.18−2.26 (m, 2H), 1.93−2.02 (m, 1H), 1.74−1.85 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.8, 142.9, 132.4, 130.2, 120.5, 65.4, 55.1, 44.9, 44.8, 38.3, 35.6. Mp 191−192 °C. HRMS *m*/*z* calcd for $C_{13}H_{17}{}^{79}BrNO_2$ is 298.0442, measured is 298.0439. HRMS *m*/*z* calcd for $C_{13}H_{17}{}^{81}BrNO_2$ is 300.0422, measured is 300.0410.

Preparation of (1*S*,3*S*)-Methyl 1-Amino-3-(4-bromophenyl)cyclopentanecarboxylate Hydrochloride ((1*S*,3*S*)-5). See ref 16.

Preparation of (7*S*)-7-(4-bromophenyl)-1,3-diazaspiro[4.4]nonane-2,4-dione (8). To a round-bottomed flask charged with ammonium carbonate (268 g, 2.79 mol) and potassium cyanide (44.4 g, 0.681 mol) was added water (1.5 L). The mixture was heated at 80 °C and a solution of (*S*)-3-(4-bromophenyl)cyclopentanone **2**-(*S*) (148.09 g, 0.62 mol) in ethanol (1.5 L, 25 mol) was added. The reaction mixture was heated to reflux for 15 h. The reaction mixture was then cooled to room temperature. The crude reaction mixture was filtered and washed with water. The solid was triturated with ether (1.5 L), filtered, washed with ether, and dried in vacuo to yield (*S*)-7-(4-bromophenyl)-1,3-diazaspiro[4.4]nonane-2,4-dione (**8**) (181 g, 95% yield) as a 1:1 mixture of diastereomers. ^{1}H NMR (DMSO-d_6) δ 10.61 (s, 1H), 8.29 (s, 0.5H), 8.24 (s, 0.5H), 7.49 (d, 2H, J = 8.4 Hz), 7.27 (d, 1H, J = 8.5 Hz), 7.24 (d, 1H, J = 8.5 Hz), 3.14−3.35 (m, 1H), 2.47(dd, 0.5H, J = 8.3, 13.6 Hz), 1.68−2.27 (m, 5.5H). ^{13}C NMR (100 MHz, DMSO-d_6 δ 180.3, 179.9, 157.2, 157.1, 144.14, 144.08, 132.2, 132.1, 130.3, 130.2, 120.1, 68.9, 68.6, 45.9, 45.2, 45.0, 44.3, 37.8, 34.5, 34.0. Mp 192−198 °C. HRMS *m*/*z* calcd for $C_{13}H_{12}{}^{79}Br\,N_2O_2$ $(M - H)^-$ is 307.0082, measured is 307.0086. HRMS *m*/*z* calcd for $C_{13}H_{12}{}^{81}BrN_2O_2$ $(M - H)^-$ is 309.0062, measured is 309.0111.

Preparation of (5*R*,7*S*)-7-(4-Bromophenyl)-3-methyl-1,3-diazaspiro[4.4]nonane-2,4-dione ((5*R*,7*S*)-9). To a flask containing (*S*)-7-(4-bromophenyl)-1,3-diazaspiro[4.4]nonane-2,4-dione (**8**) (1:1 mixture of diastereomers, 180 g, 0.583 mol) was added potassium carbonate (121 g, 0.875 mol) followed by DMF (1 L). After the mixture was stirred for 15 min at room temperature, methyl iodide (39.9 mL, 0.642 mol) was added in one portion. The reaction was stirred at rt for 48 h. The reaction mixture was partially concentrated in vacuo at 25 °C, removing approximately 400 mL of DMF and excess methyl iodide. The crude mixture was cooled with an ice water bath and water (2 L) was added. After the reaction mixture was stirred for 1 h the resulting colorless precipitate was filtered and rinsed with water (1 L). The filter cake was dried in vacuo to provide 220 g of crude (*S*)-7-(4-bromophenyl)-3-methyl-1,3-diazaspiro[4.4]nonane-2,4-dione as a 1:1 mixture of diastereomers.

Hydantoin ((5*R*,7*S*)-**9**) can be separated by crystallization as follows: The material was separated into two batches of 110 g each. The crude material (110 g) was suspended in MeCN (2.5 L) then heated to 70 °C until near complete dissolution occurred. The material was filtered rapidly at 70 °C and rinsed with MeCN (2 × 500 mL). The combined filtrates were reheated to 65 °C with stirring. After a clear solution was obtained the mixture was allowed to cool slowly to 50 °C at which point material began to drop out of solution. The solution was allowed to slowly cool to 30 °C with stirring (100 rpm). After aging for 2 h the solution was filtered and the solid was dried at 65 °C under vacuum to provide (5*R*,7*S*)-7-(4-bromophenyl)-3-methyl-1,3-diazaspiro[4.4]nonane-2,4-dione ((5*R*,7*S*)-**9**) (22.2 g, 20% yield) as a colorless solid. ^{1}H NMR (DMSO-d_6) δ 8.56 (s, 1H), 7.50 (d, 2H, J = 8.42 Hz), 7.27 (d, 2H, J = 8.53 Hz), 3.16−3.31 (m, 1H), 2.84 (s, 3H), 2.46 (dd, 1H, J =

(16) The (1*S*,3*S*) stereoisomer ((1*S*,3*S*)-**5**) was prepared by using the above procedures substituting ketone (*S*)-**2** for ketone (*R*)-**2** and D-tartaric acid for L-tartaric acid. From ketone (*S*)-**2** (9.5 g, 39.7 mmol) was obtained (1*S*,3*S*)-methyl 1-amino-3-(4-bromophenyl)cyclopentanecarboxylate hydrochloride ((1*S*,3*S*)-**5**) (4.15 g, 31% overall yield). The ^{1}H, ^{13}C, mp, and HRMS matched that obtained for ((1*R*,3*R*)-**5**). See the Supporting Information for details of chiral purity analysis.

13.62, 8.40 Hz,), 2.02−2.18 (m, 2H), 1.72−1.95 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 178.6, 156.7, 144.0, 132.1, 130.2, 120.1, 67.5, 45.1, 45.0, 38.4, 34.5, 25.0. Mp 230−235 °C. HRMS exact mass calcd for $C_{14}H_{14}N_2O_2{}^{79}Br$ $(M - H)^-$ is 321.0239, measured is 321.0247. HRMS exact mass calculated for $C_{14}H_{14}N_2O_2{}^{81}Br$ $(M - H)^-$ is 323.0218, measured is 321.0244.

Preparation of (1*R*,3*S*)-Methyl 1-Amino-3-(4-bromophenyl)cyclopentanecarboxylate Hydrochloride ((1*R*,3S)-4). To a slurry of (5*R*,7*S*)-7-(4-bromophenyl)-3-methyl-1,3-diazaspiro[4.4]nonane-2,4-dione ((5*R*,7*S*)-**9**) (79 g, 0.24 mol) in water (1 L) was added 2 M aqueous NaOH (1 L, 2 mol) and dioxane (200 mL). The resulting mixture was heated to reflux. After 24 h the reaction mixture was cooled to rt, diluted with water (2 L), and acidified with concentrated HCl until a precipitate began to form (pH 7). Acetic acid (20 mL) was added, producing a thick precipitate. The colorless precipitate was collected and washed with water (2 × 1 L) and EtOAc (1 L). The filter cake was suspended in toluene (1 L) and concentrated in vacuo at 45 °C. This process was repeated once more. The white precipitate was dried to a constant weight under vacuum to provide (1*R*,3*S*)-1-amino-3-(4-bromophenyl)cyclopentanecarboxylic acid ((1*R*,3*S*)-**4**) (65 g, 95%) as a colorless solid. To obtain material with sufficient solubility for full characterization the zwitterion (1*R*,3*S*)-**4** was converted to the corresponding HCl salt by dissolving the material in 1 N aqueous HCl and concentrating the solution in vacuo. The resulting solid was suspended in DCM, filtered, and dried in vacuo to provide (1*R*,3*S*)-**4** as the HCl salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.2 (br s, 1H), 8.55−8.75 (m, 2H), 7.54 (d, 2H, J = 8.4 Hz), 7.35 (d, 2H, J = 8.4 Hz), 3.27−3.36 (m, 1H), 2.61 (dd, 1H, J = 7.5, 13.5 Hz), 2.27−2.35 (m, 1H), 2.05−2.2.19 (m, 3H),1.93 (dd, 1H, J = 12.3, 12.3 Hz). ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.6, 143.2, 132.1, 130.5, 120.3, 64.2, 46.2, 44.9, 36.7, 34.0. HRMS *m*/*z* calcd for $C_{12}H_{15}N\ O_2{}^{79}Br$ is 284.0286, measured is 284.0278. HRMS *m*/*z* calcd for $C_{12}H_{15}N\ O_2{}^{81}Br$ is 286.0266, measured is 286.0281.

Preparation of (1*R*,3*S*)-Methyl 1-Amino-3-(4-bromophenyl)cyclopentanecarboxylate Hydrochloride ((1*R*,3*S*)-5). A slurry of (*1R*,3*S*)-1-amino-3-(4-bromophenyl)cyclopentanecarboxylic acid (79 g, 0.28 mol) suspended in MeOH (1.8 L) was cooled in an ice/water bath and thionyl chloride (178 mL, 2.44 mol) was added to the reaction mixture dropwise. Following the addition the reaction was heated to reflux, resulting in a nearly homogeneous solution. After 36 h the reaction mixture was cooled to rt, filtered, and rinsed with MeOH (2 × 200 mL). The filtrate was concentrated in vacuo to provide a colorless solid. The solid was triturated with EtOAc (1 L), collected by filtration, rinsed with EtOAc (2 × 500 mL), and dried under vacuum to give the (1*R*,3*S*)-1-amino-3-(4-bromophenyl)cyclopentanecarboxylic acid methyl ester hydrochloride ((1*R*,3*S*)-**5**) as a colorless solid (79 g, 96%). ^{1}H NMR (DMSO-d_6) δ 8.96 (br s, 1H), 7.55 (d, 2H, J = 8.4 Hz), 7.39 (d, 2H, J = 8.6 Hz), 3.84 (s, 3H), 3.20−3.35 (m, 1H), 2.62 (dd, 1H, J = 7.5, 13.6 Hz), 2.10−2.36 (m, 4H), 2.06 (dd, 1H, J = 13.0, 13.0 Hz), 2.05 (dd, 1H, J = 13.0, 13.0). ^{13}C NMR (DMSO-d_6) δ 173.3, 143.0, 132.2, 130.4, 120.4, 64.3, 54.2, 46.0, 44.8, 36.7, 33.8. Mp 131−135 °C. HRMS *m*/*z* calcd for $C_{13}H_{17}NO_2{}^{79}Br$ is 298.0442, measured is 298.0443. HRMS *m*/*z* calcd for $C_{13}H_{17}NO_2{}^{81}Br$ is 300.0422, measured is 300.0462.

Preparation of (1*S*,3*R*)-Methyl 1-Amino-3-(4-bromophenyl)cyclopentanecarboxylate Hydrochloride ((1*S*,3*R*)-5). See ref 17.

Supporting Information Available: Experimental details for the preparation of compounds (*R*)-**2**, (*S*)-**2**, **11**, **12**, and (1*R*,3*R*)-**1**; conditions for the chiral HPLC separation of the individual isomers of **5**; ^{1}H NMR and ^{13}C spectra of all new compounds; CIF and thermal ellipsoid plot of (1*R*,3*R*)-5-L-tartrate. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The (1*S*,3*R*) stereoisomer ((1*S*,3*R*)-**5**) was prepared by using the above procedures substituting ketone (*R*)-**2** for ketone (*S*)-**2**. From ketone (*R*)-**2** (9.5 g, 39.7 mmol) was obtained (1*S*,3*R*)-methyl 1-amino-3-(4-bromophenyl)cyclopentanecarboxylate hydrochloride ((1*S*,3*R*)-**5**) (4.15 g, 31% overall yield). The ^{1}H, ^{13}C, mp, and HRMS matched that obtained for ((1*R*,3*S*)-**5**). See the Supporting Information for details of chiral purity analysis.