Preparation of (2*S*,4*R*)-4-Hydroxypipecolic Acid and Derivatives

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Introduction

(2*S*,4*R*)-4-Hydroxypipecolic acid (**1**), a naturally occurring amino acid isolated from leaves of *Calliandra pittieri* and *Strophantus scandeus*,[1] is a constituent of certain cyclodepsipeptide antibiotics such as virginiamycin S_2.[2] Compound **1** has served as a building block for the preparation of NMDA receptor antagonists, in which the six-membered pipecolic acid ring was used as a rigid scaffold for the construction of conformationally restricted analogs.[3] We have been involved in the synthesis of inhibitors of the human immunodeficiency virus (HIV) protease as a possible avenue for therapeutic intervention against AIDS. Recently, we introduced a new class of highly potent inhibitors of this enzyme. As represented by palinavir (**2**), these compounds contain a (*R*)-hydroxyethylamine transition state mimic[4] and a novel *cis*-4-substituted pipecolic amide entity.[5] X-ray crystal structures of some of these inhibitors bound to HIV-2 protease have revealed interactions between the pipecolic amide and $S_{1'}$-$S_{2'}$ binding sites of the enzyme.[6] As progress was made toward the development of this series of inhibitors, large amounts of isomerically pure (2*S*,4*R*)-4-hydroxypipecolic derivatives were required.

Published enantiospecific syntheses of **1** and derivatives have mostly relied on the elaboration of members of the chiral pool.[7] These procedures were judged unsuitable for the preparation of large quantities of material due to the hazardous, costly, or toxic nature of the reaction conditions or reagents. Furthermore, in several cases, isomeric mixtures of products were generated, which required chromatographic separations. Recently, starting from L-aspartic acid, our laboratory developed a synthetic approach to *N*-Boc-(2*S*,4*R*)-4-hydroxypipecolic *tert*-butylamide, based on an intramolecular Dieckmann condensation.[8] While this route was successfully applied to the synthesis of 1−2 kg quantities of material, we desired a more economical process for the preparation of larger batches of this fragment.

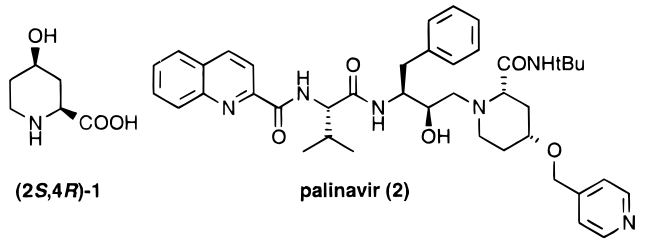

Figure 1.

Syntheses of racemic *cis*-4-hydroxypipecolic derivatives have appeared in the literature.[3ab,9] In particular, Hays has reported the iminium ion cyclization of homoallylic amine **3a** in presence of glyoxylic acid, leading to racemic lactone **4a** in 69% yield (Scheme 1).[3b] This approach to the construction of the pipecolic ring attracted us in terms of the simplicity, accessibility of reagents, and scale-up potential. We have investigated the chemical resolution of **4a** as an expeditious route to the (2*S*,4*R*)-isomer.[10] In addition, we have developed an asymmetric version of this iminium ion cyclization using chiral, nonracemic amine **3b**. The processes described herein are expeditious, economical, do not require chromatographic purifications, and are amenable to the preparation of large quantities of **1** and derivatives in high isomeric purity.

Results and Discussion

Our initial efforts were directed at the resolution of racemic lactone **4a** prepared in 41% yield overall from 3-buten-1-ol (**5**) by modification of literature procedures (Scheme 2).[3b,11] A variety of chiral acids were screened for their propensity to form crystalline addition salts with either **4a** antipodes. Best results were obtained using "selective" salt formation with 0.55 equiv of [(1*R*)-(*endo*,-*anti*)]-(+)-3-bromocamphor-8-sulfonic acid, (*R*)-**6**,[13] in methanol−ethanol−ethyl acetate. As depicted in Scheme 2, crystalline addition salt (2*S*,4*R*)-**7a** was obtained. Neutralization with dilute ammonium hydroxide gave (2*S*,4*R*)-**4a** in 30% overall yield from racemic **4a**, with a 95.4% enantiomeric excess. Enantiomeric purities and absolute configurations were determined by HPLC analysis on chiral supports (see Experimental Section for

(1) (a) Romeo, J. T.; Swain, L. A.; Bleecker, A. B. *Phytochemistry* **1983**, *22*, 1615. (b) Schenk, V. W.; Schutte, H. R. *Flora* **1963**, *153*, 426.

(2) Vanderhaeghe, H.; Janssen, G.; Compernolle, F. *Tetrahedron Lett.* **1971**, *28*, 2687.

(3) (a) Ornstein, P. L.; Schoepp, D. D.; Arnold, M. B.; Leander, J. D.; Lodge, D.; Paschal, J. W.; Elzey, T. *J. Med. Chem.* **1991**, *34*, 90. (b) Hays, S. J.; Malone, T. C.; Johnson, G. *J. Org. Chem.* **1991**, *56*, 4084.

(4) Beaulieu, P. L.; Wernic, D.; Duceppe, J.-S.; Guindon, Y. *Tetrahedron Lett.* **1995**, *36*, 3317.

(5) Anderson, P. C.; Soucy, F.; Yoakim, C.; Lavallée, P.; Beaulieu, P. L. *Eur. Patent Appl.* no. 560268, publ. September 15, 1993. SAR studies leading to palinavir will be published elsewhere.

(6) Tong, L.; Pav, S.; Mui, S.; Lamarre, D.; Yoakim, C.; Beaulieu, P. L.; Anderson, P. C. *Structure* **1995**, *3*, 33.

(7) (a) Golubev, A.; Sewald, N.; Burger, K. *Tetrahedron Lett.* **1995**, *36*, 2037. (b) Pellicciari, R.; Natalini, B.; Luneia, R.; Marinozzi, M.; Roberti, M.; Rosato, G. C.; Sadeghpour, B. M.; Snyder, J. P.; Monahan, J. B.; Moroni, F. *Med. Chem. Res.* **1992**, *2*, 491. (c) Callens, R. E. A.; Anteunis, M. J. O.; Reyniers, F. *Bull. Soc. Chim. Belg.* **1982**, *91*, 713. (d) Fujita, Y.; Kollonitsch, J.; Witkop, B. *J. Am. Chem. Soc.* **1965**, *87*, 2030. (e) Clark-Lewis, J. W.; Mortimer, P. I. *J. Chem. Soc.* **1961**, 189.

(8) Bousquet, Y.; Anderson, P. C.; Bogri, T.; Duceppe, J. -S.; Guse, I; Lavallée, P. Unpublished results. The sequence proceeds through a 4-oxo-(2*S*)-pipecolic acid intermediate which is reduced selectively to the desired (2*S*,4*R*)-4-hydroxypipecolic derivative using K-selectride. For other approaches to 4-oxopipecolic acid derivatives, see reference 7a and Jackson, R. F. W.; Graham, L. J.; Rettie, A. B. *Tetrahedron Lett.* **1994**, *35*, 4417.

(9) (a) Lawson, J. A.; Pandey, A.; Yasuda, D.; Tanabe, M. US Patent 5,260,286 Nov 9, 1993. (b) Nin, A. P.; Varela, O.; deLederkremer, R. M. *Tetrahedron* **1993**, *42*, 9459. (c) Herdeis, C.; Engel, W. *Arch. Pharm. (Weinheim)* **1992**, *325*, 419. (d) Esch, P. M.; de Boer, R. F.; Hiemstra, H.; Boska, I. M.; Speckamp, W. N. *Tetrahedron* **1991**, *47*, 4063 and references cited therein. (e) Hayes, N. F.; Scopes, D. I. C.; McElroy, A. B.; Hayes, A. G.; Meerholz, C. A. *Australian Patent* AU 8930295, August 24, 1989. (f) Esch, P. M.; Boska, I. M.; Hiemstra, H.; Speckamp, W. N. *Synlett* **1989**, 38. (g) Jollès, G.; Poiget, G.; Robert, J.; Terlain, B.; Thomas, J.-P. *Bull. Soc. Chim. Fr.* **1965**, 2252.

(10) Chiral 4-hydroxypipecolic derivatives have been prepared by enzymatic resolution or chemical resolutions necessitating multiple recrystallizations.[9g]

(11) Teng, T.-F.; Lin, J.-H.; Yang, T.-K. *Heterocycles* **1990**, *31*, 1201 (the tosylate was prepared instead of the mesylate, and 1.2 equiv of benzylamine was used instead of 2 equiv). *N*-(3-Butenyl)benzylamine can also be prepared from the more expensive 4-bromo-1-butene: Brands, K. M. J.; Meekel, A. A. P.; Pandit, U. K. *Tetrahedron* **1991**, *47*, 2005.

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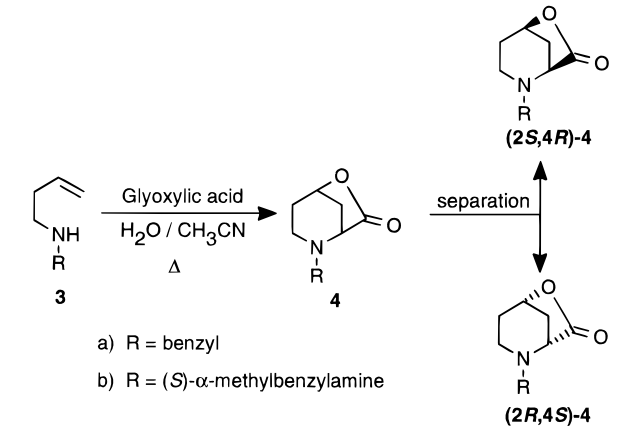
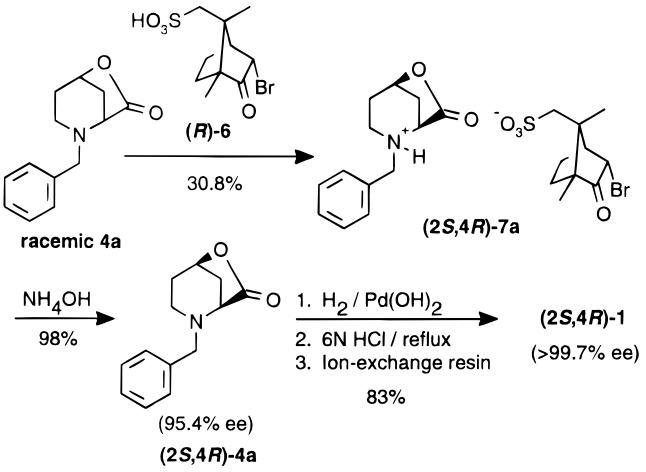
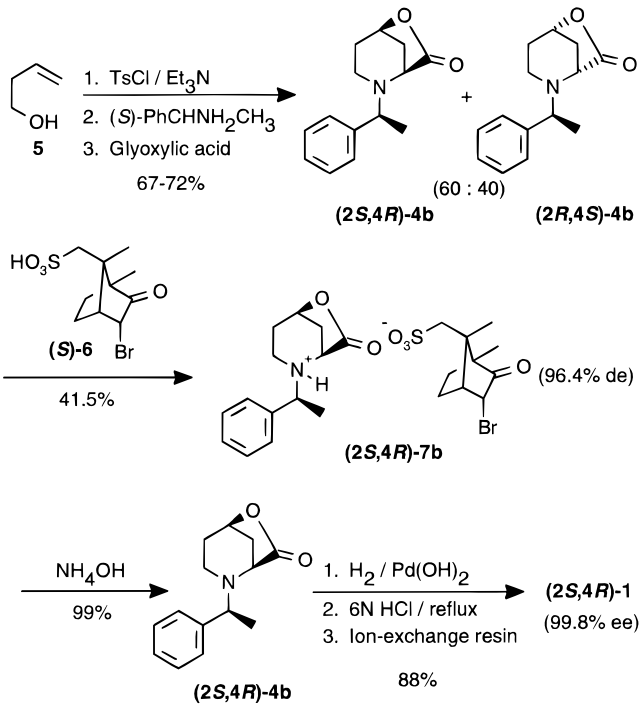
Scheme 1



Scheme 2



Scheme 3



details) and correlation with known (2*S*,4*R*)-**1**.[12] While this procedure did provide access to (2*S*,4*R*)-**4a** in good isomeric purity, substantial dialkylation and the difficult separation of unreacted benzylamine during the preparation of racemic **4a** resulted in low overall yields of lactone (2*S*,4*R*)-**4a** (12% overall from 3-buten-1-ol).

We sought to improve the overall efficiency of the process through asymmetric induction using an inexpensive, readily available chiral auxiliary in the iminium ion cyclization. To this end, homoallylic amine **3b** was prepared from **5** and (*S*)-α-methylbenzylamine and subjected to iminium ion cyclization with glyoxylic acid (Scheme 3). Because of increased steric bulk of the amine, very little *N,N*-dialkylation was observed (<5% as judged by ^{1}H NMR), and crude **3b** could be used directly without purification. Using this integrated three-step procedure, crude lactones (2*S*,4*R*)-**4b** and (2*R*,4*S*)-**4b** (>95% homogeneity by ^{1}H NMR) were obtained as a 60:40 mixture of diastereomers (as determined by ^{1}H NMR) in 67−72% overall yield from **5**.[14] Several alternative chiral auxiliaries (2-(α-naphthyl)-ethylamine, phenylglycinol, phenylglycine *tert*-butyl ester) were examined in an attempt to improve on the diastereoselectivity of the iminium ion cyclization. None proved superior to α-methylbenzylamine in terms of magnitude of asymmetric induction, cost and ease of removal from the end-product. Changing solvents or lowering reaction temperatures (25 °C) had no significant effect on diastereomeric ratios. Longer reaction times resulted in extensive hydrolysis of the lactone ring to the corresponding hydroxy acids.

Despite low levels of diastereoselective induction, readily available lactones **4b** were diastereomeric in nature and, in principle, separable by physical methods. Indeed, flash chromatography could be used on a small scale but was of limited value for the isolation of large quantities of material. Separation was also accomplished by fractional crystallization, but recovery was poor and the unwanted (2*R*,4*S*)-**4b** isomer crystallized preferentially. Attempts to prepare crystalline addition salts with nonchiral organic or mineral acids failed. Again, several readily available amine "resolving" agents[15] were screened and ultimately, a crystalline adduct was obtained with (*S*)-**6**, (Scheme 3).[13] This salt was shown by ^{1}H NMR to consist of the desired (2*S*,4*R*)-**7b** diastereomer,[16] contaminated with 5−10% of the (2*R*,4*S*)-**7b** isomer. Further optimization of this procedure led to a selective crystallization process in which only 0.65 equiv of the "resolving agent" was used (i.e., only a slight excess with respect to the proportion of the desired (2*S*,4*R*)-isomer present in **4b**), and crystallization was allowed to proceed for a minimum of 12 h. Following neutralization of the salt with dilute ammonium hydroxide, (2*S*,4*R*)-**4b** was

(12) Conversion of (2*S*,4*R*)-**4a** and (2*S*,4*R*)-**4b** to authentic (2*S*,4*R*)-**1** was carried out in two steps: hydrogenolysis in methanol gave (2*S*,4*R*)-4-hydroxypipecolic acid methyl ester.[3b] Subsequent hydrolysis followed by desalting gave (2*S*,4*R*)-**1**, identical to material reported in the literature[7e] (see Experimental Section for details).

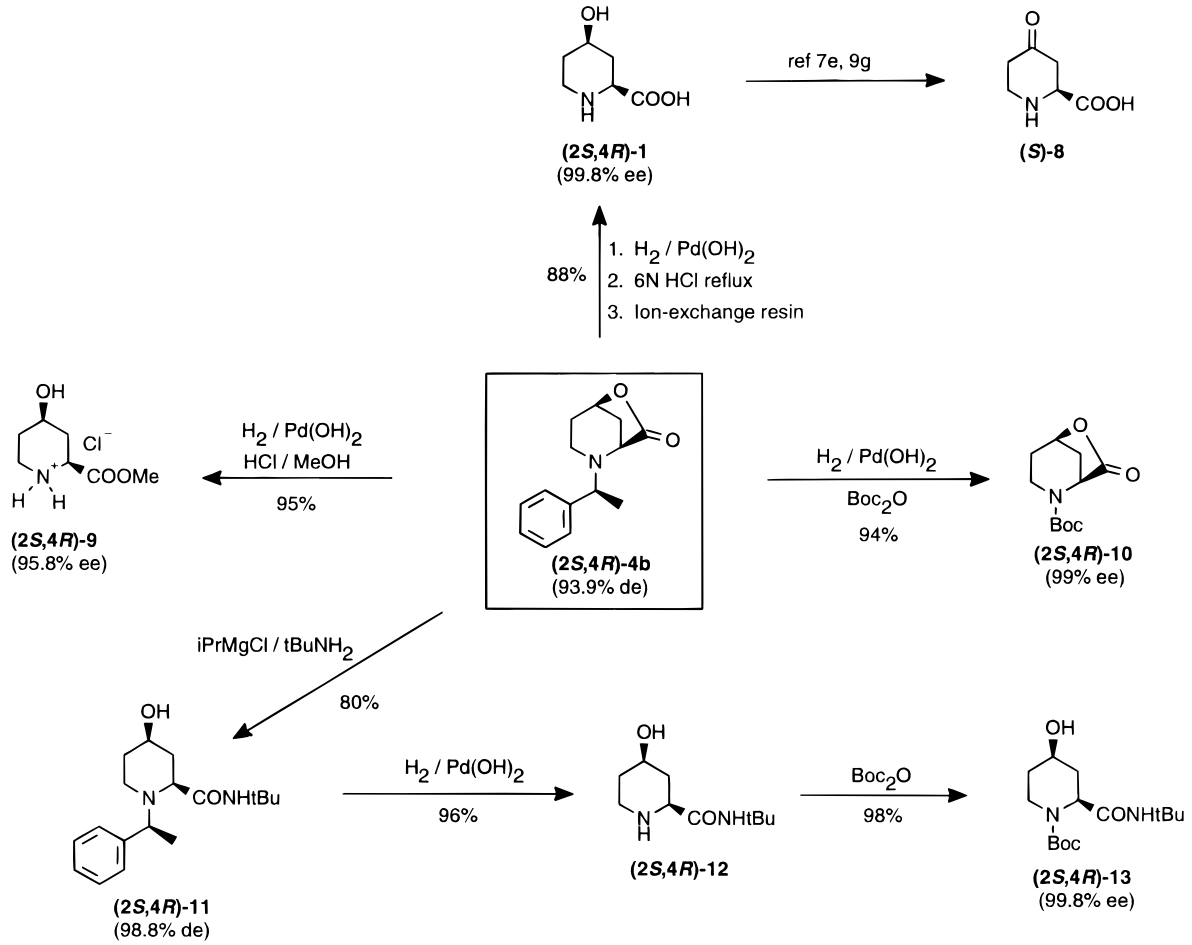
(13) Both (+) and (-) acids are readily available as their ammonium salts from Aldrich Chemical Co. or through the Interchem Corp. (Paramus, NJ). The free acids are generated by desalting on ion-exchange resin (see Experimental Section for details). The acids are easily recovered after neutralization and recycled.

(14) The same sequence starting from (*R*)-α-methylbenzylamine gave lactones **4b** (R = (*R*)-α-methylbenzyl) as a 60:40 mixture in favor of the undesired (2*R*,4*S*)-diastereomer. Stereochemical assignments are based on conversion to **1**.

(15) This is not a true resolution process *per se*, since lactones **4b** are diastereomeric in nature.

(16) Isomeric purities were assessed by HPLC on chiral supports. In all cases, isomers with opposite configuration of the pipecolic ring were used as controls in spiking experiments. Absolute configurations were determined by correlation with **1**.[12]

Scheme 4



obtained in 27−30% overall yield from **5** and 93.9% diastereomeric excess (a slight erosion of diastereomeric purity was detected during this neutralization).[16] The increased efficiency of this process more then offsets the added cost associated with the use of (*S*)-α-methylbenzylamine versus benzylamine. Neutralization of the mother liquors from the crystallization, followed by salt formation with (*R*)-**6** and conversion of the salt to the free base (dilute ammonium hydroxide) gave the minor (2*R*,4*S*)-**4b** isomer in 17−19% yield overall from **5** and 99.1% diastereomeric excess.[16]

Lactone **4b** is a versatile synthetic intermediate that can be used to access a variety of 4-substituted pipecolic derivatives (Scheme 4). The parent amino acid (2*S*,4*R*)-**1** was obtained in 88% yield (99.8% ee) by hydrogenolysis in MeOH,[3b] followed by hydrolysis and desalting on an ion-exchange resin.[12] Oxidation with CrO_3 was shown previously to give (*S*)-4-oxopipecolic acid (**8**),[7e,9g] also a naturally occurring amino acid and a versatile building block for the preparation of NMDA receptor antagonists.[9a] Hydrogenolysis in methanolic HCl gave (2*S*,4*R*)-4-hydroxypipecolic methyl ester hydrochloride (2*S*,4*R*)-**9** in 95% yield and 95.8% ee. Hydrogenolysis in the presence of di-*tert*-butyl dicarbonate and EtOAc as solvent gave *N*-Boc protected lactone (2*S*,4*R*)-**10** in 94% yield and 99% ee. For the synthesis of palinavir (**2**) and analogs, (2*S*,4*R*)-**4b** was allowed to react with *tert*-butylchloromagnesium amide (generated *in situ* from *tert*-butylamine and isopropylmagnesium chloride),[17] to give hydroxy amide (2*S*,4*R*)-**11** in 80% yield and 98.8% de. Hydrogenolysis gave amine (2*S*,4*R*)-**12**, and subsequent treatment with di-*tert*-butyl dicarbonate gave *N*-Boc-4-hydroxypipecolic *tert*-butylamide (2*S*,4*R*)-**13** in 94% yield and 99.7% ee. The material was identical in all respects to that derived from L-aspartic acid.[8]

Conclusion

We have developed a short and low-cost process for the preparation of 4-hydroxypipecolic acid derivatives in high isomeric purity. From 3-buten-1-ol, key lactone (2*S*,4*R*)-**4b** is produced in 27−30% overall yield. The sequence proceeds with crude intermediates throughout, does not require chromatographic purifications, and is amenable to the preparation of large quantities of material. Lactone (2*S*,4*R*)-**4b** is a versatile synthetic intermediate allowing rapid access to a variety of *cis*-4-substituted pipecolic acid derivatives, useful building blocks for HIV protease inhibitors[5] and NMDA receptor antagonists.[3b]

Experimental Section

General. All reagents and solvents were anhydrous, reagent grade, and were used as received. [(1*S*)-(*endo,anti*)]-(−)- and [(1*R*)-(*endo,anti*)]-(+)-3-bromocamphor-8-sulfonic acid, ammonium salts and 3-buten-1-ol were purchased from Aldrich Chemical Co. ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100 or 50 MHz, respectively. All mass spectral data was obtained in FAB mode. When necessary, elemental analyses were corrected for water content as determined by Karl Fisher analysis. Chiral columns for HPLC isomeric purity determinations were purchased from Daicel Industries (Chiralpak AS), Waters (Milford, MA; Symmetry C8), Supelco (Bellefonte, PA; Supelcosil LC-ABZ) and Phenomenex

(17) Bassett, H. L.; Thomas, C. R. *J. Chem. Soc.* **1954**, 1188.

(Torrance, CA; CHIREX *S*-Val and DNAn). Experimental procedures and full characterization of compounds (2*R*,4*S*)-**1**, (2*R*,4*S*)-**9**, (2*R*,4*S*)-**10**, (2*R*,4*S*)-**11**, (2*R*,4*S*)-**12**, and (2*R*,4*S*)-**13** are included in the supporting information.

(1*S*,5*R*)-2-(Phenylmethyl)-6-oxa-2-azabicyclo[3.2.1]octan-7-one, (2*S*,4*R*)-4a. (a) (*R*)-**6**: A column was charged with washed Dowex 50 × 8 (H^+) 200−400 mesh ion-exchange resin (250 g). (*R*)-**6**, ammonium salt (100.9 g, 0.307 mol) in H_2O (600 mL) was loaded on the column which was eluted and washed with additional H_2O (750 mL). The eluted solution of the free acid (1.4 L) was concentrated under reduced pressure at 70 °C to give an oil which was coevaporated with EtOH (2 × 100 mL). EtOAc (500 mL) was added to the residue, and some insoluble starting ammonium salt (5.64 g) was removed by filtration. The filtrate was evaporated to give the free acid as a yellow oil. EtOAc was added to the oil to a total mass of 226.4 g, giving a 40% w/w solution of the free acid.

(b) Resolution of **4a:** Racemic **4a**[11,3b] (45.50 g, 0.209 mol) was dissolved in a 1:1 mixture of MeOH and absolute EtOH (270 mL). The free acid solution from above (89.6 g, 0.55 equiv) was added and the mixture stirred for two days at room temperature. The precipitated (2*S*,4*R*)-**7a** was collected by filtration, washed with EtOH (100 mL), and dried under vacuum (34.08 g, 30.8% yield). An analytical sample of this material was obtained by drying in vacuo at 60 °C over P_2O_5 for 20 h: mp 208−212 °C dec. $[\alpha]^{25}_D$ +46.0° (*c* 1.005, $CHCl_3$). IR (KBr) ν 1780, 1755 cm^{-1}. ^1H NMR (DMSO-d_6) δ 7.55−7.42 (m, 5H), 5.10 (broad m, 1H), 4.98 (broad d, J = 4.5 Hz, 1H), 4.3−4.1 (broad m, 2H), 3.92 (broad s, 1H), 3.40 (broad m, 1H), 3.00 (t, J = 4.3 Hz, 1H), 2.86 (d, J = 14.1 Hz, 1H, AB system), 2.58−2.49 (m, 1H), 2.42 (d, J = 14.1 Hz, 1H, AB system), 2.35−1.95 (m, 3H), 1.83 (ddd, J = 13.0, 9.6, 3.6 Hz, 1H), 1.74 (m, 1H), 1.18 (ddd, J = 14.2, 9.0, 5.4 Hz, 1H), 1.10 (s, 3H), 0.82 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 212.0, 169.7, 131.3, 130.1, 129.6, 128.9, 76.3, 59.0, 58.5, 54.6, 53.9, 47.8, 47.2, 46.3, 33.8, 29.6, 26.7, 21.9, 17.3, 9.6. MS m/z 218 (MH^+). Anal. Calcd for $C_{23}H_{30}BrNO_6S$: C, 52.27; H, 5.72; N, 2.65. Found: C, 52.08; H, 5.75; N, 2.61. HPLC (neutralization with $NaHCO_3$, ether extraction, Chiralpak AS, 5% EtOH/hexane, 1 mL/min): t_R 12.1 min (2*R*,4*S*)-**4a** (2.7%); 13.9 min (2*S*,4*R*)-**4a** (97.3%; 94.6% ee).

(c) (2*S*,4*R*)-**4a: (2*S*,4*R*)-7a** from above (27.59 g, 52.2 mmol) was added to TBME (300 mL) and H_2O/concd NH_4OH (10:1, 100 mL), and the mixture was stirred until all solids were dissolved (3 min). The layers were separated, and the aqueous phase was extracted with TBME (100 mL). The combined extracts were washed with dilute NH_4OH (10:1, 100 mL), H_2O (2 × 50 mL) and brine (50 mL). After drying ($MgSO_4$) and removal of volatiles under vacuo, (2*S*,4*R*)-**4a** was obtained as a light yellow oil (11.08 g, 98% yield). An analytical sample was obtained after drying overnight under vacuum at 60 °C, over P_2O_5. R_f 0.60 (1:1 hexane/EtOAc). $[\alpha]^{25}_D$ −54.1° (*c* 1.04, $CHCl_3$). IR (neat) ν 1770 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.4−7.23 (m, 5H), 4.80 (t, J = 5.1 Hz, 1H), 3.71 (d, J = 13.0 Hz, 1H, AB system), 3.60 (d, J = 13.4 Hz, 1H, AB system), 3.28 (d, J = 5.1 Hz, 1H), 3.01 (dd, J = 12.1, 6.7 Hz, 1H), 2.45 (dt, J = 11.9, 5.1 Hz, 1H), 2.21 (ddt, J = 11.8, 5.4, 2.6 Hz, 1H), 2.03−1.95 (m, 1H), 1.90 (d, 11.8 Hz, 1H), 1.92−1.81 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 173.4, 137.4, 129.1, 128.3, 127.3, 76.7, 59.8, 58.3, 47.1, 37.2, 28.9. MS m/z 218 (MH^+). Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.75; H, 7.01; N, 6.53. HPLC (Chiralpak AS, 5% EtOH/hexane, 1 mL/min): t_R 11.1 min (2*R*,4*S*)-**4a** (2.3%); 12.5 min (2*S*,4*R*)-**4a** (97.7%; 95.4% ee).

(2*S*,4*R*)-4-Hydroxypipecolic Acid, (2*S*,4*R*)-1. Resolved (2*S*,4*R*)-**4a** (6.49 g, 29.87 mmol) was hydrogenated (1 atm H_2) in MeOH (75 mL) over 20% $Pd(OH)_2$/C (650 mg) for 16 h. The catalyst was removed by filtration, and volatiles were removed under reduced pressure. The residue was dissolved in 6 N aqueous HCl (100 mL) and the solution refluxed overnight. After concentration under vacuum, the product was desalted by ion-exchange chromatography as follows: A column was packed with washed Dowex (H^+) 50 × 8 (200−400 mesh, 100 g) and loaded with a solution of the material from above in water (20 mL). The column was first washed with water (500 mL), and then the amino acid was eluted with 5% NH_4OH (500 mL). The solution was evaporated under vacuum and lyophilized to give a white solid. The amino acid was crystallized from hot 25% water in EtOH (20 mL) and washed with EtOH (2 × 10 mL). Concentration of mother liquors gave a second crop. Drying at 100 °C under vacuum over P_2O_5 gave pure (2*S*,4*R*)-**1** as a white solid (3.715 g, 83% yield). An analytical sample was obtained after drying as above for an additional 24 h: mp 273−275 °C dec. lit.[7e] mp 265 °C dec. $[\alpha]^{25}_D$ −21.0° (*c* 1.025, H_2O), lit.[7e] $[\alpha]^{23}_D$ −17° (1.1% in H_2O). IR (KBr) ν 3150, 2660, 2500, 1600 cm^{-1}. ^1H NMR and ^{13}C NMR data were identical to literature.[18] MS m/z 146 (MH^+). Anal. Calcd for $C_6H_{11}NO_3$ (0.98% w/w water): C, 49.16; H, 7.69; N, 9.56. Found: C, 49.27; H, 7.69; N, 9.56. The enantiomeric purity of the amino acid was determined by RP-HPLC analysis after conversion to the (+)-1-(9-fluorenyl)-ethyl carbamate:[19] RP-HPLC (CHIREX-(*S*)-Val and DNAn; 10 mM NH_4OAc/MeOH isocratic; 1 mL/min): t_R 15.3 min (2*S*,4*R*)-**1** (>99.7%, >99.7% ee).

(1*S*,5*R*)- and (1*R*,5*S*)-2-[(*S*)-2-Phenylethyl]-6-oxa-2-azabicyclo[3.2.1]octan-7-one, (2*S*,4*R*)-4b and (2*R*,4*S*)-4b. To a mixture of 3-buten-1-ol (216.33 g, 3.00 mol) and *p*-toluenesulfonyl chloride (600.50 g, 3.15 mol) in THF (670 mL) was added dropwise triethylamine (502 mL, 3.60 mol) over a period of 1.5 h. The internal temperature was maintained below 45 °C with the help of a cold water bath. After complete conversion to the tosylate (ca. 24 h) as shown by TLC analysis (R_f 0.46; 4:1 hexane/EtOAc), precipitated triethylamine hydrochloride was removed by filtration using THF (2 L) for washings. Filtrate and washings were combined and concentrated under reduced pressure to a volume of ca. 2 L. Triethylamine (500 mL, 3.60 mol) was added to the solution followed by (*S*)-α-methylbenzylamine (465 mL, 3.60 mol, dropwise addition over 1 h). The reaction mixture was stirred 42 h at 70 °C after which point TLC analysis indicated complete disappearance of the tosylate. After cooling to room temperature, NaOH (150 g, 3.75 mol) in H_2O (1.5 L) was added, the organic layer separated, and the aqueous phase extracted with ether (2 × 1 L). The combined organic phases were concentrated under reduced pressure to a volume of ca. 1 L. The above solution was diluted with THF (500 mL) and warmed to 35 °C. Glyoxylic acid (50% w/w aqueous solution, 500 g, 4.5 mol) was added dropwise, allowing the internal temperature to reach 60 °C at which point the heating source was removed. After completion of addition (1.5 h), the reaction was heated to 60−65 °C for 7 h and stirred an additional 9 h at room temperature. TLC analysis indicated complete conversion to a mixture of (2*R*,4*S*)-**4b** (R_f 0.87; EtOAc, minor diastereomer) and (2*S*,4*R*)-**4b** (R_f 0.80; EtOAc, major diastereomer). Water (500 mL) and brine (500 mL) were added, and the mixture was basified to pH 8−9 with 5 N NaOH (200 mL). EtOAc (1 L) was added, the organic layer separated, and the aqueous phase extracted with EtOAc (2 × 1 L). The combined organic phases were washed with saturated $NaHCO_3$ (750 mL), water (750 mL), and brine (750 mL). After drying ($MgSO_4$), volatiles were removed under vacuum to give the diastereomeric lactones as a brown solid (466.6 g, 67% yield). ^1H NMR analysis showed a 60:40 ratio of (2*S*,4*R*)-**4b** and (2*R*,4*S*)-**4b**, and approximately 4% of *N*,*N*-dialkylated-(*S*)-α-methylbenzylamine. Analytical samples of each components were obtained by flash chromatography on silica gel using 25% EtOAc/hexane as eluant:

***N*,*N*-Di(3-butenyl)-(*S*)-2-phenylethylamine:** R_f 0.73 (9:1 hexane/EtOAc). $[\alpha]^{25}_D$ −14.6° (*c* 1.025, MeOH). IR (neat) ν 1645 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.38−7.33 (m, 2H), 7.32−7.26 (m, 2H), 7.23−7.17 (m, 1H), 5.8−5.7 (m, 2H), 5.03-5.00 (m, 1H), 4.99−4.95 (m, 2H), 4.94−4.92 (m, 1H), 3.84 (q, J = 6.7 Hz, 1H), 2.60−2.44 (m, 4H), 2.17 (broad q, J = 7.3 Hz, 4H), 1.33 (d, J = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 144.6, 137.2, 127.9, 127.6, 126.5, 115.2, 59.1, 49.6, 32.4, 16.8. HR-MS m/z calcd for $C_{16}H_{23}N$: 230.1909 (MH^+). Found: m/z 230.1915. Anal. Calcd for: $C_{16}H_{23}N$: C, 83.79; H, 10.11; N, 6.11. Found: C, 83.34; H, 10.29; N, 5.57.

(2*R*,4*S*)-4b (minor diastereomer): R_f 0.73 (1:1 hexane/EtOAc). Mp 48−49 °C. $[\alpha]^{25}_D$ −16.2° (*c* 1.05, $CHCl_3$). IR (KBr) ν 1770 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.35−7.2 (m, 5H), 4.79 (t, J = 5.2 Hz, 1H), 3.80 (d, J = 10.3 Hz, 1H), 3.58 (q, J = 6.7 Hz, 1H), 2.73 (dd, J = 12.4, 6.7 Hz, 1H), 2.35−2.25 (m, 2H), 1.95 (d, J = 11.8 Hz, 1H), 1.91−1.84 (m, 1H), 1.79−1.69 (m, 1H), 1.44 (d, J = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 174.0, 144.5, 128.3, 126.9, 76.6, 62.8, 55.2, 46.0, 37.5, 29.1, 21.0. MS m/z 232 (MH^+). Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C,

(18) Esch, P. M.; Boska, I. M.; Hiemstra, H.; de Boer, R. F.; Speckamp, W. N. *Tetrahedron* **1991**, *47*, 4039.

(19) Einarsson, S.; Josefsson, B.; Möller, P.; Sanchez, D. *Anal. Chem.* **1987**, *59*, 1191.

72.65; H, 7.46; N, 5.98. RP-HPLC (Symmetry C8; 10−80% CH_3CN in 20 mM Na_2HPO_4 (pH 7.4) in 25 min; 0.8 mL/min): t_R 20.7 min (>99.5% de).

(2*S*,4*R*)-4b (major diastereomer): R_f 0.62 (1:1 hexane/EtOAc). Mp 83−84 °C. $[\alpha]^{25}_D$ −94.7° (*c* 1.01, $CHCl_3$). IR (KBr) ν 1765 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.42−7.37 (m, 2H), 7.35−7.29 (m, 2H), 7.28−7.22 (m, 1H), 4.77 (t, J = 5.1 Hz, 1H), 3.70 (q, J = 6.7 Hz, 1H), 3.33 (dd, J = 11.8, 6.7 Hz, 1H), 3.18 (d, J = 5.1 Hz. 1H), 2.48 (dt, J = 11.8, 5.1 Hz, 1H), 2.12−2.02 (m, 2H), 1.95−1.86 (m, 1H), 1.82 (d, J = 11.8 Hz, 1H), 1.33 (d, J = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 174.0, 144.5, 128.5, 127.4, 127.1, 76.4, 62.3, 57.1, 44.0, 37.2, 29.2, 21.3. MS *m*/*z* 232 (MH^+). Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.85; H, 7.50; N, 6.00. RP-HPLC (Symmetry C8; 10−80% CH_3CN in 20 mM Na_2HPO_4 (pH 7.4) in 25 min; 0.8 mL/min): t_R 19.6 min (>99.5% de).

(2*S*,4*R*)-7b. Crude diastereomeric lactones **4b** (50.01 g, 216.5 mmol) were dissolved in MeOH (150 mL). A solution of (*S*)-**6** in EtOAc (44% w/w, prepared from the ammonium salt as described previously for the resolution of **4a**, 99.5 g, 140.7 mmol, 0.65 equiv) was added dropwise with stirring. Absolute EtOH (150 mL) was added and the slurry stirred 16 h at room temperature. The salt was collected by filtration, washed with EtOH (2 × 100 mL), and dried (48.74 g, 41.5% yield). Mother liquor and washings were combined and concentrated to a viscous oil which was saved for isolation of (2*R*,4*S*)-**4b**. Mp 233−236 °C dec. $[\alpha]^{25}_D$ −63.9° (*c* 1, $CHCl_3$). IR (KBr) ν 3450, 2500, 1775, 1755 cm^{-1}. ^1H NMR ($CDCl_3$) δ 11.95 (broad s, 1H), 7.70 (m, 2H), 7.50 (m, 3H), 5.10 (broad t, J = 4.9 Hz, 1H), 4.66 (broad d, J = 4.8 Hz, 1H), 4.42 (broad m, 1H), 4.28 (broad m, J = 7.2 Hz. 1H), 3.75 (broad d, J = 4.8 Hz, 1H), 3.31 (d, J = 14.3 Hz, 1H, AB system), 3.25 (t, J = 4.1 Hz, 1H), 3.15−3.04 (m, 1H), 3.06 (d, J = 14.0 Hz, 1H), 2.99−2.9 (m, 1H), 2.91 (d, J = 14.0 Hz, 1H, AB system), 2.4−2.17 (m, 4H), 1.86 (d, J = 7.0 Hz, 3H), 1.74 (m, 1H), 1.51 (ddd, J = 14.3, 8.6, 6.0 Hz, 1H), 1.32 (s, 3H), 1.02 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 211.8, 169.5 (broad), 137 (broad), 129.3, 128.3, 76.0, 65.2 (broad), 59.0, 57.0, 54.5, 53.9, 47.2, 46.3, 33.7 (broad), 29.6, 26.9 (broad), 21.8, 18.0 (broad), 17.2, 9.5. MS *m*/*z* 232 (MH^+ of free base lactone). Anal. Calcd for $C_{24}H_{32}BrNO_6S$: C, 53.14; H, 5.95; N, 2.58. Found: C, 52.83; H, 5.94; N, 2.53. RP-HPLC (Symmetry C8; 10−80% CH_3CN in 20 mM Na_2HPO_4 (pH 7.4) in 25 min; 0.8 mL/min): t_R 19.6 min, (2*S*,4*R*)-**4b** (98.2%, 96.4% de); t_R 20.6 min, (2*R*,4*S*)-**4b** (1.8%).

(2*R*,4*S*)-7b. The mother liquors from the crystallization of (2*S*,4*R*)-**7b** (see above) were stirred with a mixture of TBME (300 mL), H_2O (80 mL), and concd NH_4OH (20 mL). The organic layer was separated and the aqueous phase again extracted with TBME (100 mL). The combined extracts were washed with 10% NH_4OH (100 mL), H_2O (2 × 100 mL), and brine (100 mL). After drying ($MgSO_4$) and evaporation of the solvent, a dark brown oil was obtained. The oil was dissolved in EtOAc (30 mL), and a solution of (*R*)-**6** in EtOAc (33% w/w, 118 g, 1 equiv based on estimated lactone content) was added. The mixture was stirred overnight at room temperature. The precipitated solids were collected by filtration, washed with EtOAc (3 × 75 mL), and dried (31.35 g, 26.7% yield, 98.8% de by RP-HPLC). The material was stirred overnight in EtOAc (300 mL), collected, washed with EtOAc (2 × 50 mL), and dried to give (2*R*,4*S*)-**7b** as an off-white solid (30.37 g, 25.8% yield): mp 229−230 °C dec. $[\alpha]^{25}_D$ +53.9° (*c* 1, $CHCl_3$). IR (KBr) ν 3460, 2590, 2500, 1785, 1750 cm^{-1}. ^1H NMR ($CDCl_3$) δ 11.95 (broad s, 1H), 7.60 (m, 2H), 7.47 (m, 3H), 5.10 (broad t, J = 4.9 Hz, 1H), 4.66 (broad d, J = 4.8 Hz, 1H), 4.4 (m, 2H), 3.41 (broad d, J = 14.0 Hz, 1H), 3.30 (d, J = 14.3 Hz, 1H), 3.24 (t, J = 4.1 Hz, 1H), 3.21 (m, 1H), 2.89 (d, J = 14.0 Hz, 1H), 2.85−2.72 (m, 1H), 2.68−2.52 (m, 2H), 2.3−2.08 (m, 3H), 1.94 (d, J = 7.0 Hz, 3H), 1.72 (m, 1H), 1.51 (ddd, J = 14.5, 8.7, 6.0 Hz, 1H), 1.31 (s, 3H), 1.01 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 212.7, 170.6, 136.8, 129.8, 129.5, 128.7, 76.6, 65.0, 59.5, 57.3, 54.8, 54.2, 47.5, 47.2, 46.7, 34.2, 30.0, 27.2, 22.2, 18.8, 17.7, 9.9. MS *m*/*z* 232 (MH^+ of free base lactone). Anal. Calcd for $C_{24}H_{32}BrNO_6S$: C, 53.14; H, 5.95; N, 2.58. Found: C, 52.85; H, 5.97; N, 2.51. RP-HPLC (symmetry C8; 10−80% CH_3CN in 20 mM Na_2HPO_4 (pH 7.4) in 25 min; 0.8 mL/min): t_R 19.6 min, (2*S*,4*R*)-**4b** (0.4%); t_R 20.6 min, (2*R*,4*S*)-**4b** (99.6%, 99.1% de).

(1*S*,5*R*)-2-[(*S*)-2-Phenylethyl]-6-oxa-2-azabicyclo[3.2.1]-octan-7-one, (2*S*,4*R*)-4b. To a mixture of TBME (300 mL), H_2O (90 mL) and concd NH_4OH (10 mL) was added (2*S*,4*R*)-**7b** (43.49 g, 80.2 mmol). After stirring 5 min, additional H_2O (40 mL) was added to dissolve all solids. The organic layer was separated and the aqueous phase extracted with TBME (100 mL). The combined extracts were washed with 10% NH_4OH (100 mL), H_2O (2 × 100 mL), and brine (100 mL). After drying ($MgSO_4$) and concentration, a colorless oil was obtained which solidified on standing (18.40 g, 99% yield). The material was identical to (2*S*,4*R*)-**4b** isolated previously by flash chromatography: mp 81−84 °C. $[\alpha]^{25}_D$ −99.4° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.84; H, 7.52; N, 6.00. RP-HPLC (symmetry C8; 10−80% CH_3CN in 20 mM Na_2HPO_4 (pH 7.4) in 25 min; 0.8 mL/min): t_R 19.65 min (2*S*,4*R*)-**4b** (96.9%, 93.9% de); t_R 20.7 min, (2*R*,4*S*)-**4b** (3.1%).

(1*R*,5*S*)-2-[(*S*)-2-Phenylethyl]-6-oxa-2-azabicyclo[3.2.1]-octan-7-one, (2*R*,4*S*)-4b. Following the procedure described above for (2*S*,4*R*)-**4b**, (2*R*,4*S*)-**7b** (25.13 g, 46.32 mmol) was neutralized to the free base which was obtained as a white solid (10.57 g, 99% yield) identical to (2*R*,4*S*)-**4b** isolated previously by flash chromatography: mp 46−47 °C. $[\alpha]^{25}_D$ −15.9° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.80; H, 7.51; N, 6.00. RP-HPLC (symmetry C8; 10−80% CH_3CN in 20 mM Na_2HPO_4 (pH 7.4) in 25 min; 0.8 mL/min): t_R 19.6 min (2*S*,4*R*)-**4b** (0.5%); t_R 20.65 min, (2*R*,4*S*)-**4b** (99.5%, 99% de).

(2*S*,4*R*)-4-Hydroxypipecolic acid, (2*S*,4*R*)-1 from (2*S*,4*R*)-4b. The procedure described previously for the conversion of (2*S*,4*R*)-**4a** into (2*S*,4*R*)-**1** was used. *cis*-4-Hydroxypipecolic acid was obtained in 88% yield and was identical in all respect to the material described in the literature:[7e,18] mp 270.5−271.5 °C dec, lit.[7e] mp 265 °C dec. $[\alpha]^{25}_D$ −23.5° (*c* 1, H_2O), $[\alpha]^{25}_{365}$ −56.3° (*c* 1, H_2O), lit.[7e] $[\alpha]^{23}_D$ −17° (1.1% in H_2O). Anal. Calcd for $C_6H_{11}NO_3$ (1.14% w/w water): C, 49.08; H, 7.69; N, 9.54. Found: C, 49.30; H, 7.81; N, 9.47. The enantiomeric purity of the amino acid was determined by RP-HPLC analysis after conversion to the (+)-1-(9-fluorenyl)ethyl carbamate:[19] RP-HPLC (CHIREX-(*S*)-Val and DNAn; 10 mM NH_4OAc/MeOH isocratic; 1 mL/min): t_R 13.2 min (2*R*,4*S*)-**1** (0.1%); t_R 15.2 min (2*S*,4*R*)-**1** (99.9%, 99.8% ee).

(2*S*,4*R*)-4-Hydroxypipecolic Acid Methyl Ester Hydrochloride, (2*S*,4*R*)-9. Lactone (2*S*,4*R*)-**4b** (0.750 g, 3.24 mmol) was dissolved in a mixture of 4 N HCl in dioxane (890 μL; 3.57 mmol) and MeOH (20 mL). 20% $Pd(OH)_2/C$ (75 mg) was added and the suspension stirred under 1 atm of H_2 gas for 18 h. The catalyst was removed by filtration and the solvent removed under reduced pressure to give a beige solid. The material was triturated with 10% MeOH in ether (10 mL), filtered, washed with a small amount of the same solvent, and dried overnight at 60 °C under vacuum over P_2O_5 (0.604 g, 95% yield): mp 172.5−174.5 °C dec. $[\alpha]^{25}_D$ +9.9° (*c* 1.01, MeOH). IR (KBr) ν 3200, 1740 cm^{-1}. ^1H NMR (DMSO-d_6) δ 9.66 (broad s, 2H), 5.28 (broad s, 1H), 4.14 (dd, J = 11.4, 3.3 Hz, 1H), 3.8−3.73 (m, 1H), 3.72 (s, 3H), 3.25 (dt, J = 12.9, 4.0 Hz, 1H), 2.90 (dt, J = 12.4, 3.0 Hz, 1H), 2.19 (m, 1H), 1.87 (m, 1H), 1.67−1.55 (m, 2H). ^{13}C NMR (DMSO-d_6) δ 168.9, 63.5, 54.0, 52.8, 40.9, 34.1, 30.1. MS *m*/*z* 160 (MH^+). Anal. Calcd for $C_7H_{14}ClNO_3$ (0.6% w/w water): C, 42.17; H, 7.25; N, 7.12. Found: C, 42.32; H, 7.29; N, 7.06. The enantiomeric purity of (2*S*,4*R*)-**9** was determined by RP-HPLC analysis after conversion to the (+)-1-(9-fluorenyl)-ethyl carbamate:[19] RP-HPLC (Chiralpak AS; 5% EtOH/hexane isocratic; 0.5 mL/min): t_R 26.4 min (2*R*,4*S*)-**9** (2.1%); t_R 28.5 min (2*S*,4*R*)-**9** (97.9%, 95.8% ee).

(1*S*,5*R*)-2-(*tert*-butoxycarbonyl)-6-oxa-2-azabicyclo[3.2.1]-octan-7-one, (2*S*,4*R*)-10. Lactone (2*S*,4*R*)-**4b** (0.750 g, 3.24 mmol) and di-*tert*-butyl dicarbonate (0.780 g, 3.57 mmol) were dissolved in EtOAc (20 mL). 20% $Pd(OH)_2/C$ (75 mg) was added and the mixture stirred under 1 atm of H_2 gas for 18 h. The catalyst was removed by filtration, and volatiles were removed under reduced pressure to give a white solid. Pure (2*S*,4*R*)-**10** was obtained after trituration with 10% ether in hexanes (10 mL) and drying overnight at 60 °C under vacuum over P_2O_5 (0.695 g, 94% yield): R_f 0.77 (1:3 hexane/EtOAc). Mp 144−145.5 °C. $[\alpha]^{25}_D$ −136.9° (*c* 1.075, $CHCl_3$). IR (KBr) ν 1775, 1685 cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.98 (t, J = 5.1 Hz, 1H), 4.74 (broad m, 1H), 4.07 (broad m, 1H), 3.19 (broad m, 1H), 2.31 (m, 1H), 2.05 (m, 1H), 1.96 (d, J = 12.1 Hz, 1H), 1.95−1.85 (m, 1H), 1.48 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 173.2, 153.6, 80.9, 76.9, 53.7 (broad), 38.0 (broad), 36.5, 28.5, 28.1. MS *m*/*z* 228 (MH^+). Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 57.94; H, 7.61;

N, 6.08. HPLC (Chiralpak AS, 5% EtOH/hexane isocratic, 1 mL/min): t_R 13.2 min (2*R*,4*S*)-**10** (0.5%); t_R 15.1 min (2*S*,4*R*)-**10** (99.5%, 99% ee).

***N*-[(*S*)-2-Phenylethyl]-(2*S*,4*R*)-4-hydroxypipecolic Acid *tert*-Butylamide, (2*S*,4*R*)-11.** Isopropylmagnesium chloride (2.0 M in THF, 34 mL, 67.9 mmol) was cooled to 5 °C in an ice−water bath. *tert*-Butylamine (7.5 mL, 71.0 mmol) was added slowly (caution: gas evolution!). The resulting grey slurry was stirred 1 h at ambient temperature and cooled again to 5 °C, and (2*S*,4*R*)-**4b** (7.136 g, 30.9 mmol) in THF (10 mL + 5 mL rinse) was added. The reaction mixture was allowed to warm up to room temperature and stirred overnight. H_2O (10 mL) was added dropwise (caution: exothermic!) and the pH adjusted to 8 by addition of 4 N HCl (ca. 20 mL). The product was extracted with EtOAc (400 mL), washed with H_2O (50 mL) and brine (50 mL), and dried over anhydrous $MgSO_4$. Removal of solvents under reduced pressure gave a white solid (8.93 g, 95% yield). The amide was recrystallized from hot TBME (25 mL)/hexanes (50 mL) to give (2*S*,4*R*)-**11** as fine white needles (7.56 g, 80% yield). An analytical sample was prepared by drying overnight under vacuum at 110 °C. R_f 0.36 (EtOAc). Mp 107.5−108.5 °C. $[\alpha]^{25}_D$ −79.4° (*c* 1, MeOH). IR (KBr) ν 3350, 1670, 1645 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.37−7.3 (m, 2H), 7.3−7.2 (m, 3H), 6.67 (s, 1H), 3.94 (q, J = 7.0 Hz, 1H), 3.61 (m, J = 3.8 Hz, 1H), 3.06 (dd, J = 7.5, 4.6 Hz, 1H), 3.01 (ddd, J = 12.5, 7.4, 3.5 Hz, 1H), 2.69 (d, J = 4.8 Hz, 1H), 2.08−1.98 (m, 2H), 1.88−1.79 (m, 1H), 1.74 (dt, J = 13.0, 7.6 Hz, 1H), 1.42 (d, J = 7.0 Hz, 3H), 1.40 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 173.8, 139.6, 128.4, 128.1, 127.3, 66.2, 61.9, 59.1, 50.6, 40.9, 36.1, 32.2, 28.6, 19.9. MS *m*/*z* 305 (MH^+). Anal. Calcd for $C_{18}H_{28}N_2O_2$: C, 71.02; H, 9.27; N, 9.20. Found: C, 70.86; H, 9.43; N, 9.18. RP-HPLC (Supelcosil LC-ABZ; 10−35% CH_3CN/TFA (0.1%) in 0.1% aqueous TFA in 25 min; 1 mL/min): t_R 11.2 min (2*S*,4*R*)-**11** (99.4%, 98.8% de); t_R 12.1 min (2*R*,4*S*)-**11** (0.6%).

(2*S*,4*R*)-4-Hydroxypipecolic Acid *tert*-Butylamide, (2*S*,4*R*)-12. Amide (2*S*,4*R*)-**11** (1.002 g, 3.3 mmol) was dissolved in MeOH (25 mL), and 20% $Pd(OH)_2$/C (100 mg) was added. The suspension was stirred under 1 atm of H_2 gas for 4 h, at which point the reaction was complete by TLC (R_f 0.33, 1:1 MeOH/EtOAc). The catalyst was removed by filtration, and volatiles were evaporated under reduced pressure. After drying at 60 °C under vacuum for 36 h, (2*S*,4*R*)-**12** was obtained as a white solid (0.632 g, 96% yield): R_f 0.33 (1:1 MeOH/EtOAc). Mp 165.5−168 °C. $[\alpha]^{25}_D$ −18.5° (*c* 1.015, MeOH). IR (KBr) ν 3300, 1665, 1550, 1450 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 7.06 (s, 1H), 4.60 (broad s, 1H), 3.41 (m, 1H), 2.98−2.87 (m, 2H), 2.40 (dt, J = 12.7, 2.4 Hz, 1H), 1.99−1.90 (m, 1H), 1.73−1.65 (m, 1H), 1.24 (s, 9H), 1.14−1.03 (m, 1H), 0.97 (q, J = 11.4 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 172.2, 67.5, 59.0, 49.6, 43.4, 39.8, 35.8, 28.4. MS *m*/*z* 201 (MH^+). Anal. Calcd for $C_{10}H_{20}N_2O_2$ (0.62% w/w water): C, 59.59; H, 10.09; N, 13.90. Found: C, 59.60; H, 10.16; N, 13.94.

***N*-Boc-(2*S*,4*R*)-4-Hydroxypipecolic Acid *tert*-Butylamide, (2*S*,4*R*)-13.** Amine (2*S*,4*R*)-**12** (0.218 g, 1.09 mmol) was dissolved in MeOH (2 mL) and di-*tert*-butyl dicarbonate (0.262 g, 1.20 mmol) was added. The solution was stirred overnight at room temperature and subsequently evaporated to dryness under reduced pressure. The residual solid was triturated with hexanes (10 mL), filtered, washed with small amounts of hexanes, and dried at 75 °C under vacuum for 6 h. Concentration of mother liquors gave a second crop. (2*S*,4*R*)-**13** was obtained as a white solid (0.319 g total, 98% yield). R_f 0.43 (1:1 hexane/EtOAc). Mp 131−133 °C. $[\alpha]^{25}_D$ −64.9° (*c* 1.01, MeOH). IR (KBr) ν 3350, 1675, 1650, 1545 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.79 (broad s, 1H), 5.90 (broad s, 1H), 4.70 (broad s, 1H), 4.03 (broad m, 1H), 3.83 (broad m, 1H), 3.14 (t, J = 12.9 Hz, 1H), 2.24 (broad d, J = 14.0 Hz, 1H), 1.89−1.78 (m, 1H), 1.78−1.69 (m, 1H), 1.67−1.49 (m, 1H), 1.50 (s, 9H), 1.33 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 172.7, 156.3, 80.8, 61.3, 53.4, 51.3, 35.9, 32.4, 30.4, 28.5, 28.3. MS *m*/*z* 301 (MH^+). Anal. Calcd for $C_{15}H_{28}N_2O_4$ (0.30% w/w water): C, 59.80; H, 9.42; N, 9.30. Found: C, 59.46; H, 9.49; N, 9.28. HPLC (Chiralpak AS, 0.5% EtOH/hexane isocratic, 1 mL/min): t_R 12.4 min (2*S*,4*R*)-**13** (99.9%, 99.8% ee); t_R 14.2 min (2*R*,4*S*)-**13** (0.1%).

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Supporting Information Available: Experimental procedures and full characterization of compounds (2*R*,4*S*)-**1**, (2*R*,4*S*)-**9**, (2*R*,4*S*)-**10**, (2*R*,4*S*)-**11**, (2*R*,4*S*)-**12**, and (2*R*,4*S*)-**13** (3 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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