2,3-Pyrrolidinedicarboxylates as Neurotransmitter Conformer Mimics: Enantioselective Synthesis via Chelation-Controlled Enolate Alkylation

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Conformationally restricted analogs of naturally-occurring amino acids can serve in a variety of ways as protein structure/function probes. A diastereo- and enantioselective synthesis of the four stereoisomers of 2,3-pyrrolidinedicarboxylic acid (an analog of aspartic acid) are described in this paper. The key step is a Rapoport-type aspartate alkylation that can be controlled to give good yields of either diastereomer as a function of enolate geometry. A novel type of chelation control is proposed to account for these results.

L-Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system. In this role glutamate binds to a number of different proteins, including several distinct receptors (categorized by their selective interaction with *N*-methyl-D-aspartate, kainate, or quisqualate), transport systems, and enzymes.[1] In addition, abnormal levels of glutamate have been linked to a wide spectrum of neurological disorders, including ischemia, anoxia, hypoglycemia, epilepsy, and Huntingtons, Parkinsons, and Alzheimers diseases.[2] To better understand the role of glutamate in these diseases, as well as in normal synaptic transmission, our laboratory and others have been investigating the interactions between synthetic acidic amino acids and the proteins to which glutamate binds. In particular, structure–activity studies with conformationally restricted glutamate analogs[3,4] have provided valuable new information about the structural requirements for binding to the various glutamate receptors and to the high-affinity glutamate uptake system responsible for removing glutamate from the synaptic cleft. For example, we have recently reported the synthesis and biological activity[5] of the four stereoisomers of 2,4-pyrrolidinedicarboxylate (PDC), the L-trans isomer of which is the most potent and selective inhibitor of glutamate uptake yet discovered. The success of this compound as a selective inhibitor of glutamate transport prompted us to investigate other geometrically defined pyrrolidinedicarboxylates (carboxyprolines). In this paper we report the diastereo- and enantioselective syntheses of

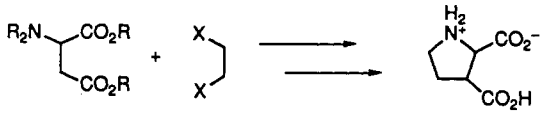

Figure 1.

the four stereoisomers of 2,3-pyrrolidinedicarboxylate (2,3-PDC)[6] from aspartic acid. The key step in these routes is a Rapoport-type aspartate alkylation[7] that can be controlled to give good yields of either diastereomer depending upon whether the (*Z*)-lithium or (*Z*)-potassium enolate is generated. A novel type of chelation control is proposed to account for these results.

The target PDCs **13a** and **13b** (Scheme 1) contain an embedded aspartate moiety, which immediately suggested the use of readily available, enantiomerically pure D- and L-aspartic acids as the starting point for a sequential double alkylation with a two-carbon electrophile (Figure 1). Because this strategy requires enolate formation exclusively at the β carbon of aspartate, we envisioned using chemistry developed by Rapoport et al.[7,8] that exploits the properties of the 9-phenylfluoren-9-yl nitrogen protecting group. This blocking group, a more stable counterpart to the triphenylmethyl (trityl) group,[9] suppresses α-deprotonation of α-amino acid derivatives and allows selective deprotonation at other sites in the molecule. For example, Rapoport has shown that the aspartate derivative **7** can be alkylated exclusively at the β-carbon to give **8**. Diastereomeric ratios for this alkylation can be as high as 25:1, but other examples are essentially nonselective.[7] The factors responsible for this selectivity—or lack of it—are complex and include variables such as ester identity (i.e., *tert*-butyl *vs* methyl) and electrophile reactivity.[7a] Since we wished to prepare both diastere-

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(4) For a review of structure–activity relationships of excitatory amino acid agonists and antagonists, see: Watkins, J. C.; Krogsgaard-Larson, P.; Honore, T. *Trends Pharmacol. Sci.* **1990**, *11*, 25.

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(6) For examples of racemic syntheses of 2,3-dicarboxypyrrolidine compounds, see: (a) Nobuyuki, I.; Nemoto, M.; Yoshiyasu, T.; Achiwa, K.; Minoru, S. *Chem. Pharm. Bull.* **1986**, *34*, 1080. (b) Gelas-Mialhe, par Y.; Hierle, R.; Vessiere, R. *Bull. Soc. Chim. Fr.* **1974**, 3–4, part 2, 709. (c) Roder, E.; Wiedenfeld, H.; Bourauel, T. *Liebigs Ann. Chem.* **1987**, *12*, 1117. (d) Imai, N.; Terao, Y.; Achiwa, K.; Sekiya, M. *Tetrahedron Lett.* **1984**, *25*, 1579. (e) Moss, W. O.; Bradbury, R. H.; Hales, N. J.; Gallagher, T. *Tetrahedron Lett.* **1990**, *39*, 5653. (f) Tsuge, O.; Kanemasa, S.; Ohe, M.; Yorozu, K.; Takenaka, S.; Ueno, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4067.

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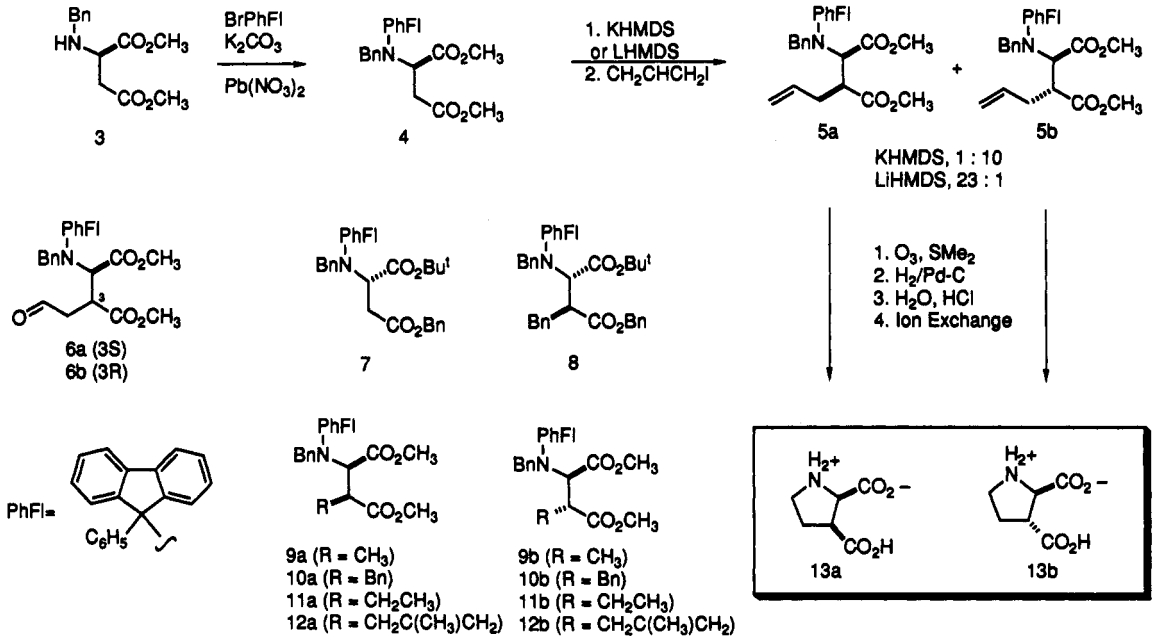
0022-3263/94/1959-2467$04.50/0

Scheme 1



omers of D- and L-2,3-PDC by this route, a more detailed study of the alkylation was carried out in hopes of obtaining either diastereomer with good control.

Initially, the addition of potassium hexamethyldisilazide (KHMDS, 0.5 M in toluene) to a solution of **4** in THF at −23 °C followed by quenching with allyl iodide produced **5b** as the major component of a 10:1 mixture of diastereomers (96% combined yield after chromatography). Interestingly, switching from KHMDS to the corresponding lithium amide (LHMDS, 1.0 M in THF) resulted in a reversal in the diastereoselectivity, giving the derivative **5a** in a 23:1 excess over **5b**. Trapping studies (TMSCl) clearly showed that the potassium and lithium enolates were different, giving the two distinct silyl ketene acetals **1a** and **1b**, respectively (Figure 2), neither of which was

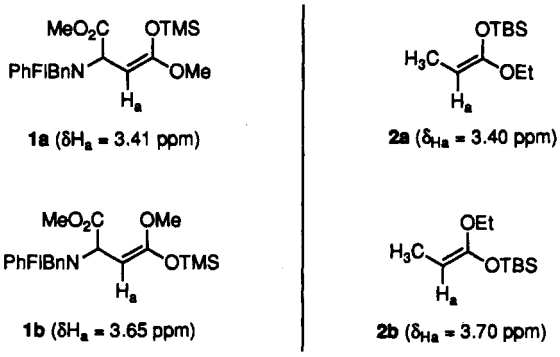


Figure 2.

contaminated with the other within the detection limits of NMR. Enolate geometries were assigned by comparison of the silyl ketene acetal chemical shift data for compounds **1a** and **1b** to literature values reported by Ireland et al. for compounds **2a** and **2b** (Figure 2). Interestingly, while Ireland et al.[10] report that LHMDS/THF systems produce (*E*)-lithium ester enolates, the opposite is true in our system. Although the reasons for this difference are not obvious, the assigned geometries are consistent with reports that (*Z*)-lithium ester enolates are significantly more reactive than the corresponding (*E*)-lithium ester enolates.[10] This correlation of enolate geometry with reactivity provides additional support for our stereochemical assignments: the proposed (*Z*)-lithium enolate is methylated within 2 h at −78 °C, while under identical conditions the (*E*)-potassium enolate requires several days of reaction time to reach completion.

Although it was not immediately evident how the enolate geometry could influence the facial selectivity of electrophilic attack, we now believe that the alkylation selectivity arises from a novel type of enolate–ester chelation that is controlled by enolate geometry.[11] Thus, for the (*Z*)-potassium enolate (Figure 3) the alkylation selectivity is

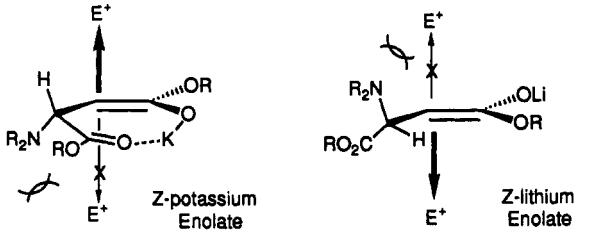


Figure 3.

determined by a preference for α-ester chelation by the counterion of the enolate oxygen atom, giving a cyclic chelate that the electrophile attacks preferentially opposite the bulky phenylfluorenyl nitrogen to form **5b**. The (*Z*)-lithium enolate, in which the OM^+ group cannot form a

(10) Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1981**, *46*, 479–485.

(11) (a) Rapoport has reported a different system that involves formation of a cyclic chelate between the phenylfluorenyl nitrogen of an α-amino ketone and the potassium counterion of its (*Z*)-enolate. Alkylation occurs at the α′ position with diastereofacial selectivities of up to 5:1. Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1988**, *22*, 7451. (b) Yamamoto has published related examples of diastereoselective alkylations of β-amino ester enolates in which chelation is also controlled by enolate geometry. The Yamamoto intermediate is an enolate-ion–nitrogen chelate rather than an enolate-ion–ester chelate such as **1a**: Asas, N.;Uyehara, T.; Yamamoto, Y. *Tetrahedron Lett.* **1990**, *46*, 4563. (c) McGarvey has reported a chelation-controlled alkylation of aspartate in which chelation is disrupted through the addition of a polar solvent such as HMPA rather than by changing the geometry of the enolate. McGarvey, G. J.; Williams, J. M.; Hiner, R. N.; Matsubara, Y.; Oh, T. *J. Am. Chem. Soc.* **1986**, *108*, 4943.

Table 1: Alkylation Selectivity[a]

	KHMDS, −23 °C		LHMDS, −23 °C		LHMDS, −78 °C	
	a:b	% yield	a:b	% yield	a:b	% yield
allyl iodide	1:10	94	23:1	96		
MeI	2:1	99	>50:1	98	>50:1	98
BnBr	>1:50	73	>50:1	75	>50:1	75
iodoethane		0	6:1	98	>50:1[b]	97
## Ia ##	1:15	95			10:1	99

[a] The products designated "a" and "b" correspond with diastereomers a and b in Scheme 1. [b] This entry required 15 days of reaction time maintained at a constant temperature of −78 °C.

cyclic chelate because of its (*E*)-geometry, assumes a hydrogen-in-plane conformation (Figure 3) that is attacked opposite the bulky nitrogen group giving rise in this case to the other diastereomer, **5a**.

This interesting reversal in diastereofacialselectivity prompted us to investigate the selectivities of alkylation available with other electrophiles (Table 1). In general, alkylation of the (*Z*)-lithium enolate proceeds in good to excellent yields, with stereoselectivities ranging from 10:1 (for 2-methyl-3-iodopropene) to highs of greater than 50:1 (the diastereomers in each case are easily separated by silica gel chromatography). The (*Z*)-potassium enolate, although significantly less reactive, selectively provides the other diastereomer (with the exception of iodomethane, see Table 1), albeit with lower selectivities. The poorer ratios arising from the (*Z*)-potassium enolate may be explained in part by epimerization that is catalyzed by the excess base used in these alkylations.[12] Treating **9b** with 1 equiv of KHMDS at −20 °C resulted in the immediate appearance of detectable amounts of the diastereomer **9a** and a ratio of 1.5:1 (**9b**:**9a**) after 48 h. Likewise, when diastereomer **9a** was treated with KHMDS, the same equilibrium ratio was measured by NMR. In an identical experiment, **5a** equilibrated to a ratio of 6:1 (**5b**:**5a**). However, when the above experiments were repeated using LHMDS in place of KHMDS, no equilibration was evident over the same time frame. This result is likely due to the lower basicity of LHMDS relative to the potassium base. In addition, with the potassium enolates competing β-elimination can be a serious side reaction with electrophiles such as ethyl iodide. In contrast, the lithium enolate is ethylated smoothly in near-quantitative yield (Table 1).

The relative stereochemistry of the alkylated products was determined by single-crystal X-ray analysis of compounds **5a** and **9a**. Aside from confirming the stereochemistry of the allylated product, the crystal structure of **5a** (Figure 4) may shed some light on the remarkable efficiency of the 9-phenylfluorenyl group at preventing α-deprotonation.[13] While steric shielding of the α-proton by this bulky group may play a role in lowering the α-acidity of these esters, the structure of **5a** suggests that other, more subtle steric and/or stereoelectronic factors may also be important. The most favorable conformation for deprotonation is one in which the α-hydrogen–carbon bond lies in a plane orthogonal to the plane of the carbonyl system, allowing for maximum orbital overlap as the α-carbon rehybridizes from sp^3 to sp^2. The α-proton and the carbonyl group in **5a** are, however, nearly coplanar. The rate of α-deprotonation would thus be stereoelectronically retarded in any starting ester for which such a conformation is highly favored. As the space-filling structure in Figure 4 shows, there is close contact between the α-ester group and the fluorenyl ring. In addition, the proton NMR of **5a** shows a methyl ester resonance at unusually high field, 2.92 ppm, suggesting the proximity of the aromatic ring to the ester group in solution as well (in fact, the proton NMR spectra of most of the phenylfluorenyl derviatives show unusual upfield chemical shifts in the aspartate moiety; see Experimental Section for specific examples). To the extent that such an interaction is present in the starting ester, achieving a stereoelectronically favorable conformation during deprotonation would require the ester group to rotate into the region of space occupied by the phenylfluorenyl group, resulting in allylic strain in the enolate-like transition state.

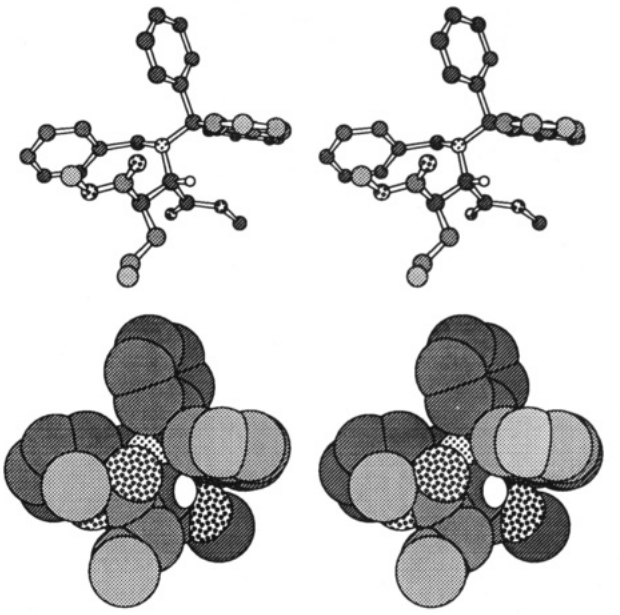


Figure 4. Stereoviews of **5a**.

The synthesis of the diastereomers **13**, illustrated for the D-isomer (Scheme 1), begins with the hydrochloride salt of aspartic acid dimethyl ester, obtained in quantitative yield from D-aspartic acid.[14] Initial efforts to prepare the benzyl derivative **3** by reductive amination of aspartic acid dimethyl ester resulted in moderate-to-extensive racemization and significant dibenzylation. Optimum results are obtained by the rapid addition of 1 molar equiv of benzaldehyde to a vigorously stirred solution of aspartic acid dimethyl ester hydrochloride and sodium cyanoborohydride in methanol at a pH of 5.0. Under these conditions, pure dimethyl *N*-benzylaspartate (**3**) was obtained in 82% yield, with no detectable dialkylation or racemization.

The *N*-phenylfluorenyl derivative **4** was then prepared by a minor modification of the literature procedure.[7a,c] Although the simple *N*-phenylfluorenyl diester can also be alkylated, we found that the reaction is much cleaner with the *N*-benzyl derivative, and in addition, large-scale purification is considerably simpler: dimethyl *N*-(9-phenylfluoren-9-yl)aspartate is a slowly solidifying viscous

(12) Excess base is generally necessary for complete alkylation. This finding is consistent with the literature: see ref 7a.

(13) The author has deposited atomic coordinates for **5a** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(14) Gmeiner, P.; Feldman, P. L., Chu-Moyer, M. Y.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 3068.

oil while 4 is a crystalline solid obtainable in 79% yield from ether/isooctane (chromatography of the mother liquor raises the yield to 95%). Following the selective alkylations with allyl iodide as described above, ozonolysis/reduction gave the respective aldehyde derivatives **6a** and **6b** in 95% yield. Following ozonolysis, the simultaneous removal of both N-protecting groups and intramolecular reductive amination was induced by hydrogenation over 10% palladium on carbon at 53 psi to give the cyclized pyrrolidine diester derivatives. Acid hydrolysis and anion-exchange chromatography afforded **13a** and **13b** (35 and 43% overall yield, respectively, from the corresponding aldehyde precursors, and ca. 25% over seven steps from L-aspartic acid). An appealing aspect of these routes is that all of the products may be purified by crystallization, and at no point is silica gel chromatography necessary. Radioligand binding assays indicate that each of the four PDC isomers described in this paper interact with one or more of the excitatory amino acid receptors, and the detailed kinetic and pharmacological characterization of these compounds will be described elsewhere.

Experimental Section

General. Proton and carbon-13 nuclear magnetic resonance (NMR) spectra were obtained on either an Omega 500 (500 MHz) or a General Electric GN-500 (500 MHz) spectrometer. For spectra measured in organic solvents, data are reported in ppm from internal tetramethylsilane for ^{1}H NMR and in ppm from the solvent in ^{13}C NMR. For ^{1}H spectra taken in D_2O, data are reported in ppm relative to HDO (3.80 ppm). Data are reported as follows: chemical shift, multiplicity (app = apparent, par obsc = partially obscured, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant, and integration. Infrared (IR) spectra were taken with a Perkin-Elmer Model 1600 series FTIR spectrophotometer. Optical rotations were obtained on a JASCO DIP-360 digital polarimeter. Melting points (mp) were taken on a Laboratory Devices Mel-Temp melting-point apparatus and are reported uncorrected. Elemental analyses were performed by Desert Analytics, Tucson, AZ.

Dry tetrahydrofuran (THF) was distilled first from calcium hydride and then from potassium. Acetonitrile, as well as the bases KHMDS and LHMDS (0.5 M in toluene and 1.0 M in THF, respectively) were used from fresh bottles purchased from Aldrich Chemical Co. Tribasic potassium phosphate was ground into a powder and flame-dried under vacuum to constant mass. Lead nitrate $(PbNO_3)_2$ was ground into a powder and dried via azeotropic water removal using toluene. Trimethylsilyl chloride was freshly distilled from calcium hydride, and the electrophiles used in the alkylations as well as the benzaldehyde were passed through a short column of basic alumina immediately prior to use. All inert atmosphere operations were conducted under nitrogen passed through a Drierite drying tube in oven- or flame-dried glassware. Thin-layer chromatography (TLC) was performed on 0.25-mm Merck precoated silica gel plates (60 F-254). Flash chromatography was performed using ICN 200–400-mesh silica gel. Rotary chromatography was conducted on EM Science PF_{254} silica gel 60 using a Harrison Research Model 8924 Chromatotron.

(*Z*)-Silyl Ketene Acetal 1a. To 250 mg (0.51 mmol) of 4 in 2.5 mL of THF at −23 °C was added KHMDS (1.0 mmol, 0.5 M in toluene) dropwise over 5 min. After the mixture was stirred for 10 min, TMSCl (61 mg, 0.56 mmol) was added dropwise, neat. The solution was stirred for 20 min and was then allowed to warm to rt at which point the solvent was removed in vacuo. Crude NMR indicated ca. 54% conversion (relative to unreacted starting material) to a single silyl ketene acetal product: ^{1}H NMR (500 MHz, C_6D_6) δ 0.15 (s, 9H), 2.61 (s, 3H), 3.08 (s, 3H), 3.41 (d, J = 10.2 Hz, 1H), 4.35 (par obsc d, J = 15.3 Hz, 1H), 4.50 (d, J = 10.2 Hz, 1H), 4.71 (d, J = 15.3 Hz, 1H), 7.0–7.8 (m obsc by starting material, 18H).

(*E*)-Silyl Ketene Acetal 1b. To 250 mg (0.51 mmol) of 4 in 2.5 mL of THF at −23 °C was added LHMDS (1.0 mmol, 1.0 M in THF) dropwise over 5 min. After the mixture was stirred 10 min, TMSCl (61 mg, 0.56 mmol) was added dropwise, neat. The solution was stirred for 20 min and was then allowed to warm to rt at which point the solvent was removed in vacuo. Crude NMR revealed clean, complete conversion to a single silyl ketene acetal: ^{1}H NMR (500 MHz, C_6D_6) δ 0.36 (s, 9H), 2.91 (s, 3H), 3.05 (s, 3H), 3.65 (d, J = 10.0 Hz, 1H), 4.31 (d, J = 15.0 Hz, 1H), 4.46 (d, J = 10.0 Hz, 1H), 4.60 (d, J = 15.0 Hz, 1H), 6.9–8.0 (m, 18H).

Dimethyl D-*N*-Benzylaspartate (3). Small-Scale Preparation. To a vigorously stirred solution of 500 mg (2.54 mmol) of D-dimethyl aspartate hydrochloride and 160 mg (2.54 mmol) of sodium cyanoborohydride in 12 mL of methanol at rt was added 265 mg (2.54 mmol) of benzaldehyde in one portion. After being stirred for 4 h, the mixture was cooled in an ice bath, and the pH was lowered to ca. 1 with concd HCl. The mixture was then allowed to warm rt for 2 h, and the methanol was removed under reduced pressure at rt. The white residue was dissolved into a minimum volume of water, and the pH was raised to ca. 10 with saturated aqueous Na_2CO_3. After three ethyl acetate extractions, combined organic portions were washed with brine, dried over K_2CO_3, and evaporated to give a pale yellow oil. Purification by radial chromatography (25% EtOAc in hexanes) provided 531 mg (83%) of a colorless oil: $[\alpha]^{26}_D$ +34.7° (*c* 1.40, $CHCl_3$); IR (neat) 3250, 2952, 1736, 1436, 1202; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.68 (dd, J = 7.1, 15.9 Hz, 1H), 2.75 (dd, J = 6.0, 15.9 Hz, 1H), 3.65 (par obsc dd, J = 6.0, 7.1 Hz, 1H), 3.67 (s, 3H), 3.72 (d, J = 13.1 Hz, 1H), 3.74 (s, 3H), 3.88 (d, J = 13.1 Hz, 1H), 7.24–7.31 (m, 5H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 33.7, 49.9, 52.2, 53.2, 53.5, 128.8, 129.3, 129.5, 130.5; HRMS *m/e* calcd for $C_{14}H_{17}NO_4^+$ 252.1235, found 252.1240.

Dimethyl D-*N*-Benzylaspartate (3). Large-Scale Adaptation. To a vigorously stirred solution of 78.2 g (397 mmol) of D-dimethyl aspartate hydrochloride and 24.6 g (397 mmol) of sodium cyanoborohydride in 790 mL methanol at rt was added 42.1 g (397 mmol) of benzaldehyde in one portion (this was accompanied by copious gas evolution and warming to ca. 60 °C), followed by stirring for 4 h. The mixture was then cooled in an ice bath, and 50 mL of concd HCl was added to bring the pH to below 1.0 (caution! this step is accompanied by copious noxious gas evolution). The solution was warmed to rt for 1 h, and the methanol was removed under reduced pressure at rt. The white residue was then dissolved into a minimum volume of water, and the solution was extracted with five 250-mL portions of $CHCl_3$. Combined organic layers were dried over Na_2SO_4 and evaporated to give 101 g of an off-white solid. Crystallization from ethyl acetate provided 71.1 g (63%) of the hydrochloride salt of **3** (the mother liquor may be chromatographed to raise the yield to ca. 80%). The free amine was obtained as follows: to 71.1 g (248 mmol) of the hydrochloride salt of **3** in 200 mL of water was added 200 mL of saturated aqueous Na_2CO_3 and 200 mL of EtOAc. After the mixture was stirred vigorously for 5 min, the layers were separated and the aqueous portion was extracted with two additional 200-mL portions of EtOAc. Combined organic layers were washed with brine, dried over K_2CO_3, filtered through Celite, and evaporated to provide 58.0 g (93%) of **3** (see spectral information above).

Dimethyl D-*N*-(9-Phenylfluoren-9-yl)-*N*-benzylaspartate (4). To a 500-mL Morton flask charged with 18.0 g (72 mmol) of **3** (free amine) in 140 mL of dry CH_3CN was added 25.4 g (79.2 mmol) of 9-bromo-9-phenylfluorene, 17.0 g (79.2 mmol) of anhydrous, powdered K_3PO_4, and 20.3 g (61.2 mmol) of dry powdered $Pb(NO_3)_2$. After being stirred mechanically for 24 h, the mixture was filtered through Celite and concentrated. The oily orange residue was partitioned between 100 mL of 5% aqueous citric acid and 100 mL of ether. After extracting the aqueous layer with an additional 100 mL of ether, the combined organic extracts were washed with 100 mL of brine, dried over K_2CO_3, and evaporated to give a viscous orange oil. Crystallization from ether–isooctane yielded 27.8 g (79%) of **4** as an off-white solid. The mother liquor was chromatographed (15% ethyl acetate in hexanes) to provide an additional 5.9 g (95% total yield): mp 144–146 °C; $[\alpha]^{26}_D$ −54° (*c* 1.20, $CHCl_3$); IR (thin film) 3061, 2949, 2857, 1732 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.80 (dd, J = 2.9, 15.9 Hz, 1H), 2.53 (dd, J = 10.8, 15.9 Hz, 1H),

3.21 (s, 3H), 3.39 (s, 3H), 3.92 (par obsc dd, J = 2.9, 10.8 Hz, 1H), 3.95 (d, J = 13.7 Hz, 1H), 4.26 (d, J = 13.7 Hz, 1H), 7.23–7.81 (m, 18H). Anal. Calcd for $C_{32}H_{29}NO_4$: C, 78.19; H, 5.95; N, 2.85. Found: C, 78.27; H, 5.70; N, 2.54.

Dimethyl D-(3*S*)-*N*-(9-Phenylfluoren-9-yl)-*N*-benzyl-3-allylaspartate (5a). To a stirred solution of **4** (25.0 g, 50.9 mmol) in 254 mL of THF at −23 °C was added dropwise over 17 min 102 mmol of LHMDS (102 mL of a 1.0 M solution in THF). After the mixture was stirred for 20 min, allyl iodide (17.1 g, 102 mmol) was added dropwise over 4 min, and stirring was continued for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and warmed to rt. The mixture was then shaken with water, and the layers were separated. The aqueous layer was extracted once with Et_2O. Combined organic extracts were washed with brine, dried over K_2CO_3, and evaporated, providing **5a** and **5b** (in a 23:1 ratio of diastereomers, respectively) as 27.6 g of an off-white foam. Crystallization from hot hexanes afforded 24.2 g (90%) of **5a** and trace **5b** (first crop crystals consisted mainly of **5a**, 49:1 by NMR). Alternatively, the crude foam may be chromatographed on silica gel (10% EtoAc in hexanes) to give pure **5a** and pure **5b** in 96% combined yield. **5a**: mp 117–119 °C; IR (KBr) 2945, 1721, 1450, 1157 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.64 (m, 1H), 1.73 (m, 1H), 2.63 (m, 1H), 2.92 (s, 3H), 3.52 (s, 3H), 3.84 (d, J = 11.5 Hz, 1H), 4.35 (d, J = 13.9 Hz, 1H), 4.62 (d, J = 13.9 Hz, 1H), 4.71 (m, 2H), 5.24 (m, 1H), 7.18–7.90 (m, 18H). Anal. Calcd for $C_{35}H_{33}NO_4$: C, 79.07; H, 6.26; N, 2.63. Found: C, 79.37; H, 6.15; N, 2.29.

Dimethyl D-(3*R*)-*N*-(9-Phenylfluoren-9-yl)-*N*-benzyl-3-allylaspartate (5b). To a solution of **4** (4.00 g, 8.1 mmol) in 40 mL of THF at −23 °C was added 16 mmol of KHMDS (32 mL of a 0.5 M solution in toluene) dropwise over 5 min, followed by stirring for an additional 5 min. Allyl iodide (2.7 g, 16.2 mmol) was then added dropwise over 3 min, and the solution was stirred for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and warmed to rt. The mixture was then shaken with water, and the layers were separated. The aqueous layer was extracted once with Et_2O. Combined organic layers were washed with brine, dried over K_2CO_3, and evaporated, providing **5a** and **5b** (in a 1/10 ratio of diastereomers, respectively) as 2.0 g of an orange foam. Pure **5a** and pure **5b** were obtained in 94% combined yield after chromatography (10% EtOAc in hexanes). Alternatively, the crude foam may be crystallized from hexanes–EtOAc to give **5b** and trace **5a** (ca. 21:1) as colorless prisms. Repeated recrystallization afforded pure **5b**: mp 185–186 °C; IR (thin film) 3061, 2948, 1732, 1197, 1166 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.03 (m, 1H), 2.29 (app dt, J = 2.9, 11.3 Hz, 1H), 2.93 (s and obsc m, 4H), 3.30 (s, 3H), 3.57 (d, J = 11.5 Hz, 1H), 4.33 (d, J = 13.4 Hz, 1H), 4.42 (d, J = 13.4 Hz, 1H), 4.79–4.82 (m, 2H), 5.06 (m, 1H), 7.22–7.78 (m, 18H). Anal. Calcd for $C_{35}H_{33}NO_4$: C, 79.07; H, 6.29; N, 2.63. Found: C, 78.97; H, 6.13; N, 2.45.

(3*S*,4*R*)-*N*-(9-Phenylfluoren-9-yl)-*N*-benzyl-4-amino-3,4-dicarbomethoxybutanal (6a). Into a solution of **5a** (16.0 g, 30.1 mmol) in 70 mL of CH_2Cl_2 and 140 mL of methanol at −78 °C was bubbled ozone until a blue solution resulted. Fifty mL of dimethyl sulfide was added, and the solution was warmed to rt for 1 h. After concentration in vacuo, the residue was partitioned between CH_2Cl_2 and water. The aqueous layer was extracted with two additional portions of CH_2Cl_2. Combined organic layers were dried over K_2CO_3 and evaporated to give an orange foam. Silica gel chromatography (20% EtOAc in hexanes) provided 15.0 g (94%) of pure **6a**. Alternatively, pure **6a** may be obtained (albeit with difficulty) as crystals from hexanes–EtOAc: mp 157–159 °C; IR (thin film) 3031, 2949, 2840, 2730, 1726, 1450 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.93 (ddd, J = 1.4, 4.4, 17.5 Hz, 1H), 2.14 (ddd, J = 2.0, 9.1, 17.5 Hz, 1H), 2.99 (s, 3H), 3.06 (ddd, J = 4.4, 9.5, 9.5 Hz, 1H), 3.55 (s, 3H), 3.9 (d, J = 9.8 Hz, 1H), 4.34 (d, J = 14.4 Hz, 1H), 4.55 (d, J = 14.4 Hz, 1H), 7.20–7.89 (m, 18H), 9.19 (app s, 1H). Anal. Calcd for $C_{34}H_{31}NO_5$: C, 76.53; H, 5.86; N, 2.63. Found: C, 76.30; H, 5.58; N, 2.43.

(3*R*,4*R*)-*N*-(9-phenylfluoren-9-yl)-*N*-benzyl-4-amino-3,4-dicarbomethoxybutanal (6b). Into a solution of **5b** (15.9 g, 28.1 mmol) in 65 mL of CH_2Cl_2 and 100 mL of methanol at −78 °C was bubbled ozone until a blue solution resulted. Fifty mL of dimethyl sulfide was added, and the solution was warmed to rt for 1 h. After concentration, the residue was partitioned three times between CH_2Cl_2 and water. Combined organic layers were dried over K_2CO_3 and evaporated. Pure **6b** (12.8 g, 85%) was obtained as colorless prisms from hexanes–EtOAc. Alternatively, **6b** may be obtained in 95% purified yield after silica gel chromatography (20% EtOAc in hexanes): mp 164 °C; IR (thin film) 3061, 2949, 2831, 2732, 1731, 1451 cm^{-1}; ^1H NMR (500 MHz, CDCl3) δ 2.33 (m, 1H), 2.86 (m, 1H), 2.97 (s, 3H), 3.34 (s and obsc m, 4H), 3.52 (d, J = 11.8 Hz, 1H), 4.35 (d, J = 13.2 Hz, 1H), 4.43 (d, J = 13.2 Hz, 1H), 7.22–7.79 (m, 18H), 8.77 (br s, 1H). HRMS m/e calcd for $C_{34}H_{32}NO_5^+$ 534.2280, found 534.2290.

Dimethyl D-(3*S*)-*N*-(9-Phenylfluoren-9-yl)-*N*-benzyl-3-methylaspartate (9a). To 27.3 g (55.6 mmol) of **4** in 165 mL of THF at −23 °C was added dropwise 83.4 mmol of LHMDS (83 mL of a 1.0 M solution in THF). After being stirred for 5 min, the solution was cooled to −78 °C and methyl iodide (9.94 g, 69.6 mmol) was added rapidly dropwise. After being stored at −78 °C for 20 h, the reaction was quenched with 100 mL of saturated aqueous ammonium chloride. The layers were separated, and the aqueous portion was extracted with an additional 100 mL of ether. Combined organic extracts were washed with brine, dried (K_2CO_3), and evaporated to give an off-white foam that provided prisms from hexanes–EtOAc in two crops (27.6 g, 98%): mp 154–155 °C; IR (thin film) 3060, 2946, 1725, 1602, 1450 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.62 (d, J = 7.0 Hz, 3H), 2.56 (dq, J = 7.0, 11.3 Hz, 1H), 2.91 (s, 3H), 3.54 (s, 3H), 3.79 (d, J = 11.3 Hz, 1H), 4.35 (d, J = 14.2 Hz, 1H), 4.69 (d, J = 14.2 Hz, 1H), 7.2–8.0 (m, 18H). Anal. Calcd for $C_{33}H_{31}NO_4$: C, 78.39; H, 6.18; N, 2.77. Found: C, 78.44; H, 6.16; N, 2.66.

Dimethyl D-(3*R*)-*N*-(9-Phenylfluoren-9-yl)-*N*-benzyl-3-methylaspartate (9b). To 3.00 g (6.10 mmol) **4** in 30 mL of THF at −23 °C was added dropwise 12.2 mmol of KHMDS (0.5 M in toluene). After the mixture was stirred for 10 min, methyl iodide (6.93 g, 48.8 mmol) was added rapidly dropwise. The reaction was kept at −23 °C for 2 h and was then quenched with 30 mL of saturated aqueous ammonium chloride. The layers were separated, and the aqueous portion was extracted with an additional 30 mL of ether. Combined organic extracts were washed with brine, dried over $MgSO_4$, and evaporated. Crude NMR revealed a diastereomeric ratio of 1:2 (**9b**:**9a**). Silica gel chromatography (15% EtOAc in hexanes) provided 1.97 g of pure **9a** (spectral qualities identical to those listed above) and 987 mg of pure **9b** (99% combined yield). **9b** was crystallized from hexanes/EtOAc to give colorless prisms: mp 184–185 °C; IR (thin film) 2948, 1731, 1450 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.15 (d, J = 7.1 Hz, 3H), 2.27 (dq, J = 7.1, 11.4 Hz, 1H), 2.96 (s, 3H), 3.35 (s, 3H), 3.54 (d, J = 11.4 Hz, 1H), 4.16 (br d, J = 13.1 Hz, 1H), 4.40 (d, J = 13.1 Hz, 1H), 7.2–7.8 (m, 18H); HRMS m/e calcd for $C_{33}H_{32}NO_4^+$ 506.2331, found 506.2331. Anal. Calcd for $C_{33}H_{31}NO_4$: C, 78.39; H, 6.18; N, 2.77. Found: C, 78.38; H, 6.12; N, 2.66.

Dimethyl D-(3*S*)-*N*-(9-Phenylfluoren-9-yl)-*N*,3-dibenzylaspartate (10a). To 250 mg (0.509 mmol) of **4** in 2.5 mL of THF at −23 °C was added dropwise 1.0 mmol of a 1.0 M solution of LHMDS in THF. After the mixture was stirred 5 min, 174 mg (1.0 mmol) benzyl bromide was added dropwise, and the mixture was warmed to 0 °C. After being stirred for 2.5 h, the mixture was quenched with 2.0 mL of saturated aqueous ammonium chloride. The layers were separated, and the aqueous portion was extracted with an equal volume of ether. Combined organic portions were washed with brine, dried over anhydrous sodium sulfate, and evaporated to give an oil. Radial chromatography (15% ethyl acetate in hexanes) provided pure **10a** in 75% yield: IR (thin film) 3029, 2945, 1727, 1448 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.14 (dd, J = 9.8, 13.5 Hz, 1H), 2.28 (dd, J = 4.7, 13.5 Hz, 1H), 2.89 (ddd, J = 4.7, 9.8, 11.3 Hz, 1H), 2.95 (s, 3H), 3.33 (s, 3H), 3.90 (d, J = 11.3 Hz, 1H), 4.35 (d, J = 13.7 Hz, 1H), 4.60 (d, J = 13.7 Hz, 1H), 6.69 (br s, 2H), 7.05 (br s, 3H), 7.07–7.80 (m, 20H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 36.0, 48.6, 50.8, 51.2, 61.8, 80.3, 119.4, 120.0, 126.2, 126.8, 126.9, 127.1, 127.3, 127.4, 127.5, 127.6, 127.7, 127.9, 128.1, 128.2, 128.48, 128.52, 129.9, 137.5, 139.3, 140.8, 142.3, 144.4, 147.1, 170.8, 172.5; HRMS m/e calcd for $C_{39}H_{36}NO_4^+$ 582.2644, found 582.2653.

Dimethyl D-(3*R*)-*N*-(9-Phenylfluoren-9-yl)-*N*,3-dibenzylaspartate (10b). To 250 mg (0.509 mmol) of **4** in 2.5 mL of THF at −23 °C was added dropwise 1.0 mmol of a 0.5 M solution of KHMDS in toluene. After the mixture was stirred for 15 min,

349 mg (2.0 mmol) of benzyl bromide was added dropwise, and the mixture was held at −20 °C for 48 h. The mixture was quenched with 4 mL of saturated aqueous ammonium chloride, the layers were separated, and the aqueous portion was extracted with an equal volume of ether. Combined organic portions were washed with brine, dried over anhydrous sodium sulfate, and evaporated to give **10b** as the only diastereomer by crude NMR. Radial chromatography (15% EtOAc in hexanes) provided pure **10b** in 73% yield: IR (thin film) 2948, 1732, 1451 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.41 (br m, 1H), 2.73 (ddd, J = 3.9, 11.5, 11.5 Hz, 1H), 2.95 (s, 3H), 3.04 (s, 3H), 3.58 (dd, J = 3.9, 13.2 Hz, 1H), 3.72 (d, J = 11.5 Hz, 1H), 4.37 (d, J = 13.3 Hz 1H), 4.45 (d, J = 13.3 Hz, 1H), 6.49 (br s, 2H), 7.08 (m, 3H), 7.21–7.81 (m, 18H); HRMS m/e calcd for $C_{39}H_{36}NO_4$ (MH^+) 582.2644, found 582.2534.

Dimethyl D-(3*S*)-*N*-(9-Phenylfluoren-9-yl)-*N*-benzyl-3-ethylaspartate (11a). To 556 mg (1.13 mmol) of **4** in 6.0 mL of THF at −78 °C was added dropwise 2.2 mL (2.2 mmol) of a 1.0 M solution of LHMDS in THF. After the mixture was stirred for 1 h, 1.06 g (6.79 mmol) of iodoethane was added dropwise, and the solution was maintained at −78 °C for 15 days. The mixture was then quenched with 5.0 mL of saturated aqueous ammonium chloride, the layers were separated, and the aqueous portion was extracted with two equal volumes of ether. Combined organic portions were washed with brine, dried over anhydrous magnesium sulfate, and evaporated to give **11a** as the only product detectable by crude NMR. Crystallization (hexanes–EtOAc) provided 572 mg (97%) of analytically pure **11a**: mp 161–163 °C; IR (thin film) 2946, 1725, 1450 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.47 (t, J = 7.4 Hz, 3H), 0.88 1.03 (m, 2H), 2.49 (ddd, J = 4.2, 5.0, 12.2 Hz, 1H), 2.91 (s, 3H), 3.55 (s, 3H), 3.82 (d, J = 11.4 Hz, 1H), 4.32 (d, J = 14.0 Hz, 1H), 4.62 (d, J = 14.0 Hz, 1H), 7.13–7.91 (m, 18H), HRMS m/e calcd for $C_{34}H_{34}NO_4^+$ 520.2487, found 520.2471.

Dimethyl D-(3*S*)-*N*-(9-Phenylfluoren-9-yl)-*N*-benzyl-3-ethylaspartate (11b). To 500 mg (1.02 mmol) of **4** in 5.0 mL of THF at −23 °C was added dropwise 2.04 mmol of a 1.0 M solution of LHMDS in THF. After the mixture was stirred for 15 min, 954 mg (6.12 mmol) of iodoethane was added dropwise. After being stirred for 24 h at −20 °C, the mixture was quenched with 5.0 mL of saturated aqueous ammonium chloride, the layers were separated, and the aqueous portion was extracted with an equal volume of ether. Combined organic portions were washed with brine, dried over anhydrous sodium sulfate, and evaporated to give a diastereomeric mixture of 6:1 (**11a**:**11b**) by crude NMR. Radial chromatography (12% ethyl acetate in hexanes) provided 440 mg of pure **11a** (spectral qualities given above) and 79 mg of pure **11b** (98% combined yield). **11b**: mp 131–132 °C; IR (thin film) 2950, 1731, 1450 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.43 (t, J = 7.3 Hz, 3H), 1.34 (m, 1H), 2.10 (ddd, J = 3.3, 11.0, 11.0 Hz, 1H), 2.19 (m, 1H), 2.93 (s, 3H), 3.35 (s, 3H), 3.57 (d, J = 10.3 Hz, 1H), 4.31 (d, J = 13.4 Hz, 1H), 4.40 (d, J = 13.4 Hz, 1H), 7.22–7.77 (m, 18H). Anal. Calcd for $C_{34}H_{33}NO_4$: C, 78.59; H, 6.40; N, 2.70. Found: C, 78.81; H, 6.35; N, 2.46.

Alkylated Aspartate Derivative 12a. To 5.00 g (10.2 mmol) of **4** in 25 mL of THF at −78 °C was added rapidly dropwise 20.4 mL of a 1.0 M solution of LHMDS in THF. After the mixture was stirred for 20 min, 11.1 g (61.2 mmol) of 2-methyl-3-iodopropene was added rapidly, and the solution was stored at −78 °C for 20 h. The mixture was quenched with 20 mL of saturated aqueous NH_4Cl, 10 mL of ether was added, and the layers were separated. The aqueous portion was extracted with an additional 20 mL of ether. Combined organic portions were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. Crude NMR revealed a 10:1 ratio of diastereomers (**12a**:**12b**). The residue was chromatogrtaphed (1/10 ethyl acetete/hexanes) to provide pure **12a** and pure **12b**, both white solids, in a combined yield of 5.50 g (99%). **12a**: mp 76–80 °C; IR (thin film) 3064, 2945, 1730, 1446 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.49 (dd, J = 4.0, 13.2 Hz, 1H), 1.69 (dd, J = 11.3, 13.2 Hz, 1H), 2.79 (dt, J = 4.0, 11.3, 11.3 Hz, 1H), 2.93 (s, 3H), 3.51 (s, 3H), 3.80 (d, J = 11.3 Hz, 1H), 4.33 (s, 1H), 4.34 (obsc. d, J = 13.7 Hz, 1H), 4.46 (s, 1H), 4.61 (d, J = 13.7 Hz, 1H) 7.19–7.79 (m, 18 H); HRMS m/e calcd for $C_{36}H_{36}NO_4^+$ 546.2635, found 546.2623.

Alkylated Aspartate Derivative 12b. To 3.00 g (6.11 mmol) of **4** in 15 mL of THF at −23 °C was added rapidly dropwise 24.4 mL (12.2 mmol) of a 0.5 M solution of KHMDS in toluene, followed by 6.67 g (36.7 mmol) of 2-methyl-3-iodopropene. The solution was stored at −20 °C for 20 h. The mixture was then quenched with 15 mL of saturated aqueous NH_4Cl, 10 mL ether was added, and the layers were separated. The aqueous portion was extracted with an additional 15 mL of ether. Combined organic portions were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. Crude NMR revealed a 15:1 ratio of diastereomers (**12b**:**12a**). The orange residue was chromatographed (1/10 ethyl acetete/hexanes) to provide pure **12b** and pure **12a** in a combined yield of 3.16 g (95%). **12b** was crystallized from EtOAc/hexanes to give colorless needles: mp 170–173 °C; IR (thin film) 2947, 1732, 1446 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.21 (s, 3H), 1.95 (br m, 1H), 2.66 (dt, J = 3.6, 11.6 Hz, 1H), 2.87 (dd, J = 3.2, 13.4 Hz, 1H), 2.95 (s, 3H), 3.29 (s, 3H), 3.63 (d, J = 11.2 Hz, 1H), 4.27 (d, J = 13.4 Hz, 1H), 4.35 (s, 1H), 4.39 (d, J = 13.4 Hz, 1H), 4.51 (s, 1H), 7.2–7.8 (m, 18H); HRMS m/e calcd for $C_{36}H_{36}NO_4^+$ 546.2635, found 546.2625.

D-*cis*-2,3-Pyrrolidinedicarboxylic Acid (13a). To aldehyde **6a** (14.0 g, 26.3 mmol) in 30 mL of CH_2Cl_2 and 30 mL of EtOAc was added 6 mL of concd HCl in 60 mL of methanol and 7.0 g of 10% palladium on carbon. After hydrogenation at 52 psi for 24 h, the mixture was filtered and the solvent was removed under vacuum. The residue was dissolved in 40 mL of CH_2Cl_2 and extracted with three 40-mL portions of 6 M HCl. The aqueous extracts were heated to 60 °C for 12 h, and the solvent was then removed under vacuum at 60 °C. Residual HCl was removed by dissolving the sample in 20 mL of water and removing the water under vacuum. This process was repeated twice. The resulting light brown foam was then dissolved in a minimal amount of water and loaded to the top of an anion-exchange column containing 75 g (wet weight) of Bio Rad Ag-1-X2 anion-exchange resin. The column was washed with eight bed volumes of water, and the crude product was eluted with 1% acetic acid. Ninhydrin-positive fractions were concentrated in vacuo, and crystallization from water–ethanol afforded 1.32 g (35%) of pure **13a** as white crystals: mp 332–333 °C dec; $[\alpha]^{27}_D$ +42.2° (c 1.15, $CHCl_3$); IR (KBr) 3600–2200 (br), 3085, 1723, 1607, 1435 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 2.30 (m, 1H), 2.44 (m, 1H), 3.47 (m, 1H), 3.43–3.60 (m, 3H), 4.35 (d, J = 7.2 Hz, 1H). Anal. Calcd for $C_6H_9NO_4$: C, 45.28; H, 5.70; N, 8.80. Found: C, 45.08; H, 5.59; N, 8.82.

D-*trans*-2,3-Pyrrolidinedicarboxylic Acid (13b). A 8.54-g (26.3-mmol) portion of aldehyde **6b** was dissolved in 19 mL of CH_2Cl_2 and 19 mL of EtOAc. To the solution was added 3.7 mL of concd HCl in 37 mL of methanol and 4.2 g of 10% palladium on carbon. After subjection to 52 psi of hydrogen for 30 h, the mixture was filtered and the solvent removed in vacuo. The residue was dissolved in 30 mL of CH_2Cl_2 and extracted with three 30-mL portions of 6 M HCl. The aqueous extracts were heated at 60 °C for 12 h, and the solvent was then removed under vacuum. To remove any residual HCl, the residue was repeatedly (three times) dissolved into 20 mL of water and evaporated. The light-brown foam was then dissolved in a minimal amount of water and loaded to the top of an anion-exchange column containing 46 g (wet weight) of Bio Rad Ag-1-X2 acetate anion-exchange resin. The column was washed with eight bed volumes of water, and the crude product was eluted with 1% acetic acid. Ninhydrin-positive fractions were combined and concentrated in vacuo. Crystallization from water–ethanol afforded 998 mg (43%) of pure **13b** as white crystals: mp 333–335 °C dec; $[\alpha]^{26}_D$ −34.3° (c 1.00, $CHCl_3$); IR (KBr) 3600–2300 (br), 1705, 1610, 1440 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 2.28 (m, 1H), 2.37 (m, 1H), 3.38–3.50 (m, 3H), 4.48–4.49 (d, J = 5.8 Hz, 1H). Anal. Calcd for $C_6H_9NO_4$: C, 45.28; H, 5.70; N, 8.80. Found: C, 45.09; H, 5.58; N, 8.57.

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Supplementary Material Available: Proton NMR spectra for compounds not accompanied by combustion analysis data in the Experimental Section (7 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.