Stereoselective Synthesis of 2,3-Diamino Acids. 2,3-Diamino-4-phenylbutanoic Acid

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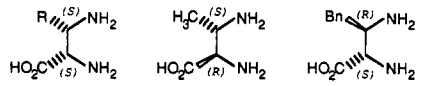
The synthesis of (2*S*,3*S*)- and (2*S*,3*R*)-2,3-diamino-4-phenylbutanoic acid (**1c** and **3**) from L-aspartic acid is described. The *N*-(phenylfluorenyl)-protected aspartic acid diesters **4** and **10** (α-*tert*-butyl, β-methyl), **18** (β-benzyl, α-*tert*-butyl), and **28** (β-benzyl, α-methyl) are regioselectively benzylated at C-3 by using KHMDS and benzyl bromide or iodide. Whereas the alkylation of compounds **4** and **28** proceeds in low to moderate diastereoselectivities, derivatives **10** and **18** gave the corresponding diastereomers in ratios of up to 30/1. Selective cleavage of the β ester followed by Curtius degradation using diphenyl phosphorazidate (DPPA) gives rise to 2,3-diamino derivatives that are subsequently transformed into **1c** or **3**. Depending on the nature of the ester groups and the N-protection, substrates **4**, **18**, and **28** can serve for different purposes. Whereas **4** leads to a mixture of both diastereomers, which are easily separated as the cyclic ureas **7a** and **7b**, use of diester **18** allows the direct preparation of the 2*S*,3*S* isomer in high selectivity. Finally, compound **28** permits the preparation of esters of 2,3-diamino acids with differentially protected amino groups. Since we have demonstrated previously that the C-3 alkylation of *N*-(phenylfluorenyl)aspartates is a general reaction, this method provides general access to 2,3-diamino acids.

Introduction

2,3-Diamino carboxylic acids are uncommon, naturally occurring amino acids that have attracted considerable recent interest. (*S*)-2,3-Diaminopropanoic acid (**1a**) is a constituent of several antibiotics[1] as well as other biologically active molecules.[2] 2,3-Diaminobutanoic acids **1b** and **2** are present in the peptide antibiotics aspartocin[3] and glumamycin (2*S*,3*S* isomer only).[4] The metal complexing abilities of (*S*)-2,3-diaminopropanoic acid (**1a**) are well documented,[1c,5] and the synthesis of chiral ethylenediamine derivatives is of interest to prepare *cis*-Platin analogues.

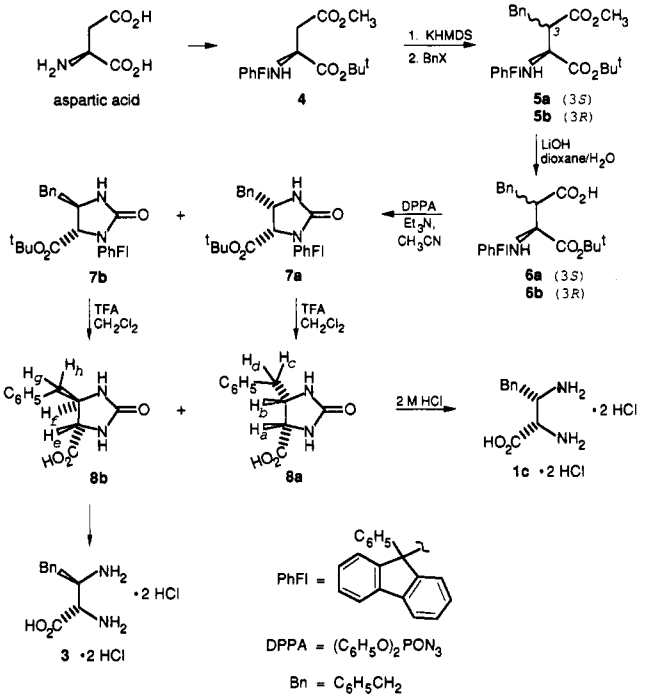


1a R = H **1b** R = CH_3 **1c** R = Bn **2** **3**

A number of efficient syntheses of 2,3-diaminopropanoic acid (**1a**) have been reported from aspartic acid[1a,d,2c,6] or L-serine.[1d,7] The preparation of 2,3-diaminobutanoic acid is reported from threonine.[3b] Clearly these syntheses result in a product that either has no substituent at C-3 or one dependent on the individual amino acid and hence are not useful for the preparation of other 3-substituted 2,3-diamino acids.[8] The importance of these compounds and the lack of a generally applicable method for their preparation prompted us to develop an efficient chirospecific synthesis of 4-phenyl-2,3-diaminobutanoic acids (**1c** and **3**) from aspartic acid. Furthermore we also report methodology for alkylation of an aspartic acid derivative that, compared to recent literature reports,[9] is highly diastereoselective.

Three different routes to these 2,3-diamino acids are presented. In Scheme I, (2*S*,3*S*)- and (2*S*,3*R*)-2,3-diamino

Scheme I. Synthesis of 2,3-Diamino Acids via the Cyclic Urea



(1) (a) Waki, M.; Kitajima, Y.; Izumiya, N. *Synthesis* **1981**, 266 and references cited therein. (b) Kittaka, A.; Sugano, Y.; Otsuka, M.; Ohno, M.; Sugiura, Y.; Umezawa, H. *Tetrahedron Lett.* **1986**, *27*, 3631. Sugano, Y.; Kittaka, A.; Otsuka, M.; Ohno, M.; Sugiura, Y.; Umezawa, H. *Ibid.* **1986**, *27*, 3635. Otsuka, M.; Kittaka, A.; Ohno, M.; Suzuki, T.; Kuwahara, J.; Sugiura, Y.; Umezawa, H. *Ibid.* **1986**, *27*, 3639. (c) Iitaka, Y.; Nakamura, H.; Nakatani, T.; Muraoka, Y.; Fujii, A.; Takita, T.; Umezawa, H. *J. Antibiot.* **1978**, *31*, 1070. Takita, T.; Muraoka, Y.; Nakatani, T.; Fujii, H.; Iitaka, Y.; Umezawa, M. *Ibid.* **1978**, *31*, 1073. (d) Otsuka, M.; Kittaka, A.; Iimori, T.; Yamashita, H.; Kobayashi, S., Ohno, M. *Chem. Pharm. Bull.* **1985**, *33*, 509.

(2) (a) Andruszkiewicz, R.; Chmara, H.; Milewski, S.; Borowski, E. *Int. J. Pept. Protein Res.* **1986**, *27*, 449. (b) Baldwin, J. E.; Adlington, R. M.; Birch, D. J. *Tetrahedron Lett.* **1985**, *26*, 5931. (c) Baldwin, J. E.; Adlington, R. M.; Birch, D. J. *J. Chem. Soc., Chem. Commun.* **1985**, 256. (d) Kjaer, A.; Larsen, P. O. *Acta Chem. Scand.* **1959**, *13*, 1565.

(3) (a) Atherton, E.; Meienhofer, J. *Hoppe-Seyler's Z. Physiol. Chem.* **1973**, *354*, 689. (b) Martin, J. H.; Hausmann, W. K. *J. Am. Chem. Soc.* **1960**, *82*, 2079.

(4) (a) Inoue, M.; Hitomi, H.; Mizuno, K.; Fujino, M.; Miyake, A.; Nakazawa, K.; Shibata, M.; Kanzaki, T. *Bull. Chem. Soc. Jpn.* **1960**, *33*, 1014. (b) Fujino, M.; Inoue, M.; Ueyanagi, J.; Miyake, A. *Bull. Chem. Soc. Jpn.* **1961**, *34*, 740. (c) Inoue, M. *Ibid.* **1961**, *o4*, 885. (d) Inoue, M. *Ibid.* **1962**, *35*, 1556. (e) Fujino, M.; Inoue, M.; Ueyanagi, J.; Miyake, A. *Ibid.* **1965**, *38*, 515.

(5) (a) Sivasankaran Nair, M. *Indian J. Chem.* **1985**, *24A*, 717. (b) Ley, H.; Hegge, H. *Chem. Ber.* **1915**, *48*, 70.

(6) (a) Karrer, P.; Schlosser, A. *Helv. Chim. Acta* **1923**, *6*, 411. (b) Karrer, P. *Ibid.* **1923**, *6*, 957. (c) Schneider, F. *Justus Liebig's Annu. Chem.* **1937**, *529*, 1.

(7) Moore, S.; Patel, R. P.; Atherton, E.; Kondo, M.; Meinhofer, J.; Blau, L.; Bittman, R.; Johnson, K. R. *J. Med. Chem.* **1976**, *19*, 766.

(8) For a recent preparation of 2,3-diaminobutanoic acid via amination of a 3-aminobutanoic acid derivative, see: Estermann, H.; Seebach, D. *Helv. Chim. Acta* **1989**, *71*, 1824.

(9) (a) Wolf, J.-P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 3164. (b) Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 3382. (c) Gmeiner, P.; Feldman, P. L.; Chu-Moyer, M.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 3608. (d) Baldwin, J. E.; Moloney, M. G.; North, M. *Tetrahedron* **1989**, *45*, 6309.

0022-3263/90/1955-5017$02.50/0

acids are prepared and easily separated by chromatography of the cyclic urea intermediate. Scheme III provides an access to (2*S*,3*S*)-2,3-diamno acids that is both chirospecific and highly diastereoselective. Scheme IV gives diamino acids in which the two amino functions are differentiated, thus allowing subsequent regioselective modification of these groups.

Results and Discussion

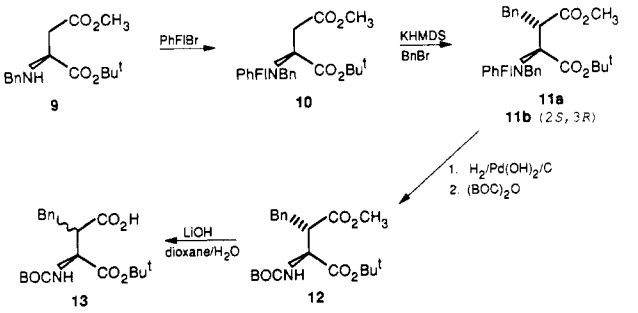
Our basic plan was to take a suitable N-protected aspartic acid derivative in which the two carboxyl groups were differentially protected and to alkylate this derivative at C-3 without affecting the stereochemistry at C-2. The function of the N-protecting group was to maintain steric integrity at C-2 and influence diastereomeric selectivity at C-3. This selective introduction of a substituent at C-3, which in principle could involve the use of any electrophile, was to be followed by specific deprotection of the 4-carboxyl group, which would then allow introduction of the 3-amino group by a Curtius reaction.

The 9-phenylfluoren-9-yl group was chosen as the N-protecting group. This mode of N-protection efficiently blocks the C-2 center in aspartic acid derivatives and leads to exclusive deprotonation at C-3. Therefore, the aspartic acid derivative **4**, which had previously been prepared in three steps from aspartic acid,[9a] presented a logical starting point. We selected (2*S*,3*S*)- and (2*S*,3*R*)-2,3-diamino-4-phenylbutanoic acid (**1c** and **3**) as targets. Previous work[9a-c] had demonstrated that the introduction of an alkyl group at C-3 of an *N*-(9-phenylfluoren-9-yl) diester such as **4** was a general reaction.

Our first route to these 2,3-diamino acids proceeds following Scheme I. Deprotonation of the diester **4**, with KHMDS at −78 °C, followed by addition of benzyl bromide gave the benzylated compounds **5a** and **b** in 75% yield as a 2/1 mixture of diastereomers. Previous results had indicated that increasing the reactivity of the electrophile would result in better diastereomeric ratios.[9a,c] Indeed, substituting benzyl bromide with benzyl iodide improved the diastereoselectivity to 7/1. Hydrolysis of the mixture of esters **5a** and **5b** was accomplished by treatment with lithium hydroxide (water/dioxane, 45 °C) to give a mixture of the crude acids **6a** and **6b** that was used directly for the Curtius degradation. No epimerization at the β-center occurred in this basic hydrolysis step. This was proved by subjecting a single diastereomer, **5a**, obtained by careful chromatography of a mixture of **5a** and **5b**, to the same reaction conditions, followed by remethylation with diazomethane. No formation of isomer **5b** occurred under these conditions. The Curtius reaction with diphenyl phosphorazidate (DPPA)[10] proceeded smoothly at 50 °C, affording the cyclic ureas **7a** and **7b**,[11] which were easily separated by chromatography. The overall yield from C-benzylated aspartate **5** to cyclic urea **7** was 65%. Treatment of either diastereomer **7a** or **7b** with trifluoroacetic acid gave the acids **8a** and **8b** in 97 and 98% yield, respectively. Upon hydrolysis with 2 N hydrochloric acid, the acids **8a** and **8b** yielded the corresponding 2,3-diamino acids **1c** and **3** as the dihydrochlorides in quantitative yield.

The relative stereochemistry at C-3 of the diamines **1c** and **3** was determined by NOESY studies on their precursors **8a** and **8b**. The major isomer, **8a**, shows strong dipolar exchange of magnetism between the protons H_a and H_b, indicating that these protons are cis; therefore the absolute configuration of **8a** is 4*S*,5*S*. This NOE is stronger than the NOE's between the proton H_b and the benzylic protons H_c and H_d as would be expected. The minor isomer **8b** shows a much weaker dipolar exchange of magnetism between protons H_e and H_f, weaker also than the NOE between H_f and its adjacent benzylic protons H_g and H_h. This indicates that protons H_e and H_f are trans and thus the configuration of **8b** is 4*S*,5*R*.

Scheme II



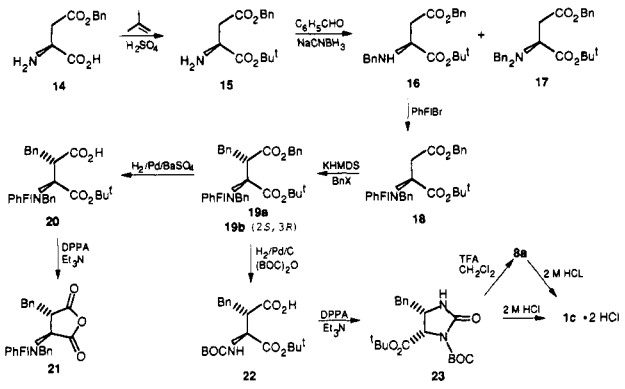
Clearly, route 1 provides a simple and effective chirospecific synthesis of the diamino acids **1c** and **3**. The route combines the advantages of efficiency (eight steps from aspartic acid) and practicality, yielding both diastereomers that are easily separated by chromatography of the cyclic urea intermediate. The disadvantages are that the two amino groups are not differentiated and that the diastereoselectivity is moderate (4/1–7/1). Hence we decided to investigate the possibility of performing the same sequence of reactions on a derivative in which both hydrogens of the amino group are replaced with protecting groups. In such a protected compound intramolecular trapping of the intermediate isocyanate, formed in the Curtius reaction, by the 2-amino group is no longer possible and hence intermolecular trapping leading to a differentially protected diamine should occur. The effect of the additional N-protecting group on the alkylation at C-3 was also of interest. For practical reasons (easy preparation, deprotection possible under the same conditions as required for the removal of the *N*-phenylfluorenyl group, hence no additional steps), we decided to substitute the nitrogen additionally with a benzyl group.

This is shown in Scheme II, which begins with *N*-benzylaspartate **9**. Subsequent phenylfluorenation yielded **10**. Deprotonation of **10** with KHMDS (200 mol %) at −23 °C followed by addition of benzyl bromide afforded the crystalline alkylated compound **11a** in 80% yield. The stereochemical assignment of **11a** was confirmed as described below. If the reaction was carried out at lower temperature or using less base, some of the starting material **10** was always recovered. The ratio of diastereomers was 30/1, thus providing the best example of an aspartic acid derivative being alkylated in high chemical yield and with high diastereoselectivity. Unfortunately, however, attempts to hydrolyze the methyl ester failed under a variety of basic and nucleophilic methods.[12] Removal of the nitrogen-protecting groups by hydrogenation followed by reprotection with di-*tert*-butyl dicarbonate gave **12**, which could be hydrolyzed to the acid **13** in high yield but, in striking contrast to the *N*-phenylfluorenyl-protected compound **5a**, epimerization at C-3 (40–80%) now occurred.

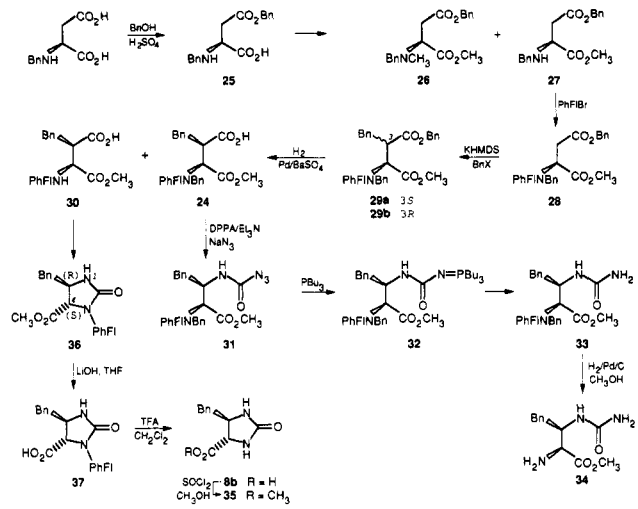
Encouraged by the high diastereoselectivities obtained in the alkylation described above, we decided to replace

(10) Ninomiya, K.; Shiori, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151.
(11) Intramolecular trapping of an isocyanate by a vicinal acyl-protected amino group was observed in a similar case, see ref 6a.
(12) (a) McMurray, J. E. *Organic Reactions*; Wiley: London, Vol. 24, Ch 2. (b) Haslam, E. *Tetrahedron* **1980**, 2409.

Scheme III



Scheme IV. Synthesis of 2,3-Diamino Acids via the 3-Carbamoyl Azide



the β-methyl ester with the β-benzyl ester. This would enable us to remove the β ester under nonbasic conditions, thus avoiding the observed epimerization. This sequence, route 2, is shown in Scheme III. β-Benzyl aspartate (**14**)[13] was esterified with isobutylene and sulfuric acid[14] to give diester **15** in 75% yield. Reductive amination with benzaldehyde, followed by sodium cyanoborohydride in methanol/acetic acid (4/1), yielded the *N*-benzylamine **16** (73%) as a pale yellow oil along with 11% of the dibenzylamine **17**. Phenylfluorenation to give the highly hindered tertiary amine **18** proceeded smoothly in 88% yield at room temperature. Alkylation using conditions analogous to those used on compound **10** gave the crystalline compounds **19a** and **19b** in 73% yield as a 12/1 mixture of diastereomers. In a second experiment, benzyl iodide (200 mol %) was used instead of benzyl bromide and essentially the same yield of **19a** and **19b** was obtained (75%) but the ratio of diastereomers improved to 25/1. The result was reproduced successfully on six occasions. In striking contrast, alkylation of the dibenzylamine **17** proceeded in poor diastereoselectivity (less than 1.6/1) with either benzyl iodide or benzyl bromide.

Selective catalytic reduction of the *O*-benzyl ester of **19a** to give the carboxylic acid **20** was achieved in 78% yield with palladium on barium sulfate in ethyl acetate. With the desired carboxylic acid **20** in hand, the stage was set to introduce the 3-amino substituent via the Curtius reaction with intermolecular trapping by methanol or benzyl alcohol to give the 3-amine protected as the carbamate. However, the attempted Curtius degradation of the acid **20** unexpectedly resulted in the formation of the cyclic anhydride **21**. The reaction was particularly facile and occurred at room temperature in the presence or absence of any alcohol as trapping reagent. Any question of reagent purity was dispelled by repurification and performing identical, parallel Curtius experiments on the acids **6a** and **20**. Whereas the acid **6a** reacted as expected to give the cyclic urea **8a**, acid **20** gave the crystalline anhydride in 55% yield in a much more rapid reaction. Infrared experiments indicated that the anhydride **21** was being formed without any build up in concentration of an acyl azide. A plausible explanation for the formation of **21** would involve activation of the β-carboxyl group followed by intramolecular anhydride formation with less of the *tert*-butyl cation.

The difference in the reactions of **6a** and **20** with DPPA was puzzling. Proton NMR of the diester **19a** (the acid **20** gave a second-order spectrum, making interpretation difficult) exhibited a coupling constant between the α and β protons of approximately 12 Hz, indicating that there is substantially restricted rotation about the C_2–C_3 bond, probably induced by the extreme bulkiness of the protecting groups and the *tert*-butyl ester, and that the α and β protons are approximately trans to each other.[15] In such a conformation the two carboxyl groups are in close proximity and hence may react more readily, once the β-carboxyl group is activated, than the carboxyl groups of acid **6a**. As we were not able to observe discrete formation of an acyl azide, this pathway was abandoned; however, we wanted to make use of the high diastereoselectivities obtained in the alkylation of **18**. A new and successful route shown in Scheme III involved removal of all of the hydrogen-sensitive groups from **19a** with concomitant protection of the amino group as its *tert*-butoxycarbonyl derivative **22**. This was achieved by performing the reduction at a hydrogen pressure of 60 psi in the presence of di-*tert*-butyl dicarbonate; the yield was 86%. Curtius reaction on acid **22** now gave the protected urea **23** in 91% yield. Deprotection with trifluoroacetic acid gave the urea **8a**, thus proving the stereochemistry at C-3 for route 2. Hydrolysis of the urea **8a** quantitatively gave the diamino acid **1c**, which had identical properties with that obtained in route 1.[16]

Clearly, route 2 provides a good procedure for diastereoselective alkylation of an aspartic acid derivative and a means for converting the products of such reactions into diamino acids; however, the problem of differentiating between the two amino groups still remained. The successful differentiation of the two amino groups in α,β-diaminopropionic acid is described;[2d] however, when applied to compounds **1c** and **3**, these procedures proved to be unreliable or proceeded in low yields. Furthermore, since it added additional steps to this method, we felt the need to find a direct way to solve this problem. Our proposed mechanism for the formation of anhydride **21** from the acid **20** requires loss of a stable *tert*-butyl cation. We reasoned that if we changed the α ester from *tert*-butyl to methyl, formation of an anhydride by this mechanism would be suppressed since the analogous reaction would now require loss of an unstable methyl cation.

Thus, the desired compound for the Curtius degradation was the acid **24**, which was prepared as shown in Scheme

(13) Benoiton, L. *Can. J. Chem.* **1962**, *40*, 570.
(14) Yang, C. C.; Merrifield, R. B. *J. Org. Chem.* **1976**, *41*, 1032.

(15) In comparison the NMR of the diester **5a** showed a smaller coupling constant (9.3) between the α and β protons.
(16) With the stereochemistry of acid **20** being established, the stereochemical assignment of **11a** was now confirmed by transformation of **20** into ester **11a** via methylation with diazomethane, see Experimental Section.

IV. N-Benzylation of aspartic acid (reductive amination in 82% yield) followed by selective esterification of the β-carboxyl group with benzyl alcohol and sulfuric acid gave the monoester **25** in 85% yield. Methylation of the α-carboxylic acid was achieved with *N,N'*-diisopropyl-*O*-methylisourea. In this reaction N-methylation[17] to give the dimethyl compound **26** was a problem, but by limiting the amount of esterifying reagent and removing the insoluble starting material by filtration followed by further treatment under the same conditions, yields of 71% of the secondary amine **27** could be obtained. Phenylfluorenation gave the tertiary amine **28** in 87% yield. Surprisingly, when **28** was alkylated by using KHMDS/benzyl iodide (same conditions as for **18**), the ratio of diastereomers was reducd and reversed from 25/1 to now 1/1.5, thus indicating that the nature of the α ester is of paramount importance in its effect on diastereoselectivity. Benzyl bromide at −23 °C or 0 °C gave very similar results (1/1.3–1.6, **29a**/**29b**), but with benzyl iodide at −78 °C, the selectivity was reversed, giving 2.5 parts of **29a** and 1 part of **29b** (80% overall).

The less polar diastereomer **29b** was reduced (H_2, 1 atm, $Pd/BaSO_4$, ethyl acetate) to give the acids **24** and **30** in 63 and 19% yields, respectively. Once again the Curtius reaction on **24**, with DPPA (130 mol %) and attempted trapping with benzyl alcohol or methanol, did not give the expected carbamate. It was noted that the Curtius degradation proceeded at an unusually low temperature (50% complete in 4 h at 26 °C). Infrared monitoring experiments showed that the acyl azide (2140 cm^{-1}) and the isocyanate (2260 cm^{-1}) were formed, indicating that changing the α ester had indeed resulted in avoiding the formation of the cyclic anhydride **21**. However, the product finally isolated (35–60%) was the carbamoyl azide **31**, formed by trapping the intermediate isocyanate with hydrazoic acid.[18] If the reaction was performed by using a deficiency of DPPA (80 mol %) in methanol as cosolvent, a small amount (15%) of the methyl carbamate was formed, but still the major product was the carbamoyl azide **31**. Eventually we decided to exploit the tendency to form **31** by performing the reaction with an excess of DPPA (250 mol %) followed by addition of sodium azide (250 mol %). This resulted in an 88% yield of **31**, a readily crystallized solid (mp 172–173 °C), whose stability to nucleophiles is demonstrated by its successful recrystallization from methanol. It is slowly decomposed by methanol in boiling xylene to give a complex mixture of products. The carbamoyl azide **31** was converted to the ylide **32** with tributylphosphine in dry ether by using the Staudinger procedure.[19] Without isolation, the ylide **32** was directly hydrolyzed with water in THF to give the acyclic urea **33** in 76% yield from **31**.

Thus by a rather unusual but potentially useful variant of the Curtius reaction, we now had the two amino groups differentially protected as had been our aim. Selective N-deprotection of the hydrogen-sensitive groups gave the primary amine **34**. That the major product was indeed the amine **34** and not the cyclic urea **35** was proven by preparing **35** through quantitative esterification of the urea **8b** with methanol and thionyl chloride.

The stereochemical configuration at C-3 was determined by subjecting the acid **30** to a Curtius degradation, yielding 90% of the cyclic urea **36**. Alkaline hydrolysis of the methyl ester (LiOH, THF/H_2O, 25 °C) followed by removal of the phenylfluorenyl group (TFA, CH_2Cl_2, 25 °C) gave the known urea **8b**, thus proving that the configuration of the less polar alkylation product **29b** is 2*S*,3*R*.

Conclusions

In summary, a number of versatile routes provide a general synthesis of 2,3-diamino acids. In principle these methods should be amenable to introducing a number of electrophilic sustituents at C-3. The three routes answer nearly all synthetic requirements by yielding either one or both diastereomers and differentiating the two nitrogens if required. The key strategy to all of these sequences is the protection of the configuration at the α-center by the *N*-(9-phenylfluoren-9-yl) group, which is well established by previous precedent.[9a-c,20] The sensitivity of the alkylation and Curtius reactions to seemingly small changes in substrate structure is particularly noteworthy.

Experimental Section

General. All reactions involving air- and moisture-sensitive reagents were conducted under a dry nitrogen atmosphere. Tetrahydrofuran (THF) was distilled from sodium benzophenone; methanol was distilled from magnesium; acetonitrile, diphenyl phosphorazidate (DPPA, in vacuo), dioxane, and triethylamine were distilled from CaH_2. Benzyl iodide was recrystallized from methanol and benzyl bromide was distilled prior to use. Commercial KHMDS was used as 0.5 M solution in toluene. Thin-layer chromatography (TLC) was done on silica/F-254 aluminum-backed plates (E. Merck). Low pressure chromatography (LPC) utilized 230–400-mesh silica gel (E. Merck). Melting points (Büchi melting point apparatus, open capillary) are uncorrected. Chemical shifts for ^1H and ^{13}C NMR spectra are reported in ppm (δ) downfield from tetramethylsilane in $CDCl_3$ or from sodium 3-(trimethylsilyl)propionate-d_4 in D_2O, and coupling constants (*J*) are given in hertz. Elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley. All final organic product solutions were dried over $MgSO_4$, filtered, and rotary-evaporated in vacuo.

(2*S*,3*S*)- and (2*S*,3*R*)-1-*tert*-Butyl 4-Methyl *N*-(9-Phenylfluoren-9-yl)-3-benzylaspartate (5a and 5b). The diester **4** (665 mg, 1.5 mmol)[9c] in THF (2 mL) was added dropwise to a solution of KHMDS (1.8 mmol) in a mixture of THF (3 mL) and toluene (9 mL) at −78 °C. After being stirred for 50 min, benzyl iodide (0.392 g, 1.8 mmol) in THF (4 mL) was added. The resulting solution was stirred for 4 h at −78 °C and partitioned between ether and phosphate buffer (pH 7), and the aqueous layer was extracted with ether (3 × 25 mL). The combined organic phase was washed with saturated aqueous $Na_2S_2O_3$ and brine, dried, and evaporated. The residue was purified by LPC and CH_2Cl_2/hexane (3/2) eluted 173 mg (22%) of **5a**: mp 143 °C; R_f 0.53 (CH_2Cl_2); ^1H NMR δ 1.16 (s, 9 H, Bu^t), 2.58 (dd, 1 H, *J* = 13.2, 3.5, PhCH_2), 2.76–2.88 (m, 1 H, C$_\beta$H), 2.93 (d, 1 H, *J* = 13.2, PhCH_2), 2.95 (s, 1 H, NH), 3.23 (d, 1 H, *J* = 9.3, C2-H), 3.50 (s, 3 H, CO_2CH_3), 7.10 (d, *J* = 6.6, Ar H), 7.12–7.39 (m, Ar H), 7.66 (d, 1 H, *J* = 7.5, Ar H), 7.68 (d, 1 H, *J* = 7.5, Ar H), total 18 Ar H. Anal. Calcd for $C_{35}H_{35}NO_4$: C, 78.8; H, 6.6; N, 2.6. Found: C, 79.0; H, 6.7; N, 2.6. Continued elution with CH_2Cl_2/hexane (3/2) gave 284 mg (36%) of a 10/1 mixture of **5a** and **5b**. Further elution gave an additional 91 mg (11%) of a 1/1 mixture of the two diastereomers: total yield of **5a** and **5b** 0.548 g (69%), overall ratio of diastereomers (7:1). ^1H NMR of the **5a**/**5b** mixture: δ 1.16 and 1.23 (2 s, 18 H, 2 × Bu^t), 2.58 (dd, 1 H, *J* = 13.7, 3.8, PhCH_2), 2.71–2.76 (m, 1 H, PhCH_2), 2.77–2.80 and 2.80–2.83 (2 m, 2 H, PhCH_2), 2.92–2.97 (m, 4 H, 2 × C3-H and C2-H), 3.21 and 3.53 (2 s, br, 2 × 1 H, 2 × NH), 3.42 and 3.51 (2 s, 2 × 3 H, 2 × CO_2CH_3), 7.01 (d, *J* = 6.9), 7.10 (d, *J* = 7.0), 7.13–7.42 (m), 7.63 (dd, *J* = 13.3, 7.6), 7.60 (t, *J* = 7.5). Finally, CH_2Cl_2 eluted the starting diester **4** (30 mg, 5%).

(17) Musich, J. A.; Rapoport, H. *J. Org. Chem.* **1977**, *42*, 139.
(18) Oliveri-Mandala, E.; Noto, F. *Gazz. Chim. Ital.* **1913**, *43*, 304.
(19) (a) Gololobov, Yu. G.; Zhmurova, I. N.; Kasukhin, L. F. *Tetrahedron* **1981**, *37*, 437. (b) Staudinger, H.; Hauser, E. *Helv. Chim. Acta* **1921**, *4*, 861.
(20) (a) Christie, B. D.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1239. (b) Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1987**, *109*, 236.

Repeating the above experiment using excess benzyl iodide (0.49 g, 2.25 mmol) gave the benzylated diester in 81% yield as a 3/1 mixture of **5a** and **5b** along with 8% of the dibenzylated material (2*S*)-1-*tert*-butyl 4-methyl *N*-(9-phenylfluoren-9-yl)-3,3-dibenzylaspartate: R_f 0.61 (CH_2Cl_2); ^1H NMR δ 1.17 (s, 9 H, Bu^t), 2.45 (d, 1 H, J = 15.1), 2.73 (d, 1 H, J = 15.0), 3.10 (AB quartet, 2 H, J = 15.0), 3.31 (d, 1 H, J = 15.0), 3.59 (s, 3 H, CO_2CH_3), 3.73 (d, 1 H, J = 15.1), 6.95–7.33 (m, 21 H, Ar H), 7.61 (d, 1 H, J = 7.5, Ar H), 7.67 (d, 1 H, J = 7.5).

(2*S*,3*S*)-1-*tert*-Butyl *N*-(9-Phenylfluoren-9-yl)-3-benzylaspartate (6a). A mixture of diester **5a** ( ) mg, 0.13 mmol) and 1 M LiOH (1.2 mL, 1.2 mmol) in dioxane (5.8 mL) was stirred at 45 °C. After 63 h, 1 M NaOH (8 mL) and THF (1 mL) were added, and the mixture was extracted with hexane (6 × 10 mL). The combined hexane extracts were evaporated to give recovered diester **5a** (20 mg, 29%). The aqueous layer was adjusted to pH 3 with 1 M H_3PO_4 and extracted with ether (3 × 15 mL), and the combined ether phase was washed with brine, dried, and evaporated to give 45 mg (66%) of acid **6a**: ^1H NMR δ 1.15 (s, 9 H, Bu^t), 2.58–3.00 (m, 4 H, C2-H, C3-H CH_2Ph), 7.03–7.69 (m, 18 H, Ar H). Reesterification of **6a** with diazomethane gave **5a** containing <1% of **5b** (NMR analysis).

When a 1/1 mixture of diesters **5a** and **5b** (1.05 g, 2.02 mmol) and 1 M LiOH (17.4 mL, 17.4 mmol) in dioxane (86 mL) was stirred at 45 °C for 7 days and the reaction product isolated as described above, acids **6a** and **6b** (0.96 g, 94%) resulted as 1/1 mixture of diastereomers: ^1H NMR δ 1.15 (s, 9 H, Bu^t), 1.33 (s, 9 H, Bu^t) 2.4–3.0 (m, 8 H, C2-H, C3-H, CH_2Ph), 6.74 (m, 2 H, Ar H), 7.0–7.4 (m, 30 H, Ar H), 7.55 (d, 2 H, J = 7, Ar H), 7.70 (d, 2 H, J = 7, Ar H).

(4*S*,5*S*)- and (4*R*,5*S*)-5-(*tert*-Butoxycarbonyl)-1-(9-phenylfluoren-9-yl)-4-benzylimidazolidin-2-one (7a and 7b). The above 1/1 mixture of crude acids **6a** and **6b** (605 mg, 1.16 mmol) was dissolved in acetonitrile (6 mL), and DPPA (390 mg, 1.4 mmol) and triethylamine (195 μL, 1.4 mmol) were added. After being stirred for 15 h at 60 °C, the reaction mixture was evaporated and the brown residue was purified by LPC. Ethyl acetate/hexane (1/2) eluted 215 mg (36%) of **7a**: mp 213 °C; R_f 0.53 (EtOAc/hexane, 1/1); IR (CCl_4) 3420 w (NH), 3060 w, 2980 w, 1730 s (CO), 1450 w, 1405 m, 1370 w, 1150 s cm^{-1}; ^1H NMR δ 1.21 (s, 9 H, Bu^t), 2.42 (dd, 1 H, J = 13.0, 10.3, $PhCH_2$), 2.84 (dd, 1 H, J = 13.0, 2.3), 4.09 (m, 2 H, C4-H and C5-H), 4.36 (1 H, br s, NH), 7.09 (d, 2 H, J = 7.0, Ar H), 7.15–7.39 (m, 11 H, Ar H), 7.53 (d, 1 H, J = 7.6, Ar H), 7.64 (t, 2 H, J = 7.3, Ar H), 7.86 (d, 2 H, J = 7, Ar H); ^{13}C NMR δ 27.7, 37.3, 55.2, 62.8, 72.4, 82.1, 119.4, 120.0, 125.2, 126.8, 126.9, 127.0, 128.0, 128.1, 128.3, 128.5, 128.6, 128.76, 128.83, 128.9, 137.1, 139.9, 140.1, 142.4, 147.0, 147.8, 161.1 (NCO), 168.1 (OCO). Anal. Calcd for $C_{34}H_{32}N_2O_3$: C, 79.0; H, 6.2; N, 5.4. Found: C, 79.0; H, 6.2; N, 5.4.

Ethyl acetate/hexane, 1/2, eluted 205 mg (34%) of **7b**: mp 235 °C; R_f 0.39 (EtOAc/hexane, 1/1); IR ($CHCl_3$) 3440 w (NH), 3000 w, 1710 s (CO), 1450 w, 1410 m, 1370 w, 1150 s cm^{-1}; ^1H NMR δ 1.15 (s, 9 H, Bu^t), 2.36–2.50 (m, 2 H, $PhCH_2$), 3.43 (d, 1 H, J = 2.7, C5-H), 4.37 (m, 1 H, C4-H), 5.55 (br s, 1 H, NH), 6.94–6.96 (m, 2 H, Ar H), 7.11–7.31 (m, 11 H, Ar H), 7.41 (t, 1 H, J = 7.4, Ar H), 7.57 (d, 1 H, J = 7.7, Ar H), 7.61 (d, 1 H, J = 7.5, Ar H), 7.68–7.71 (m, 2 H, Ar H). Anal. Calcd for $C_{34}H_{32}N_2O_3$: C, 79.0; H, 6.2; N, 5.4. Found: C, 79.2; H, 6.3; N, 5.4.

(4*S*,5*S*)-4-Carboxy-5-benzylimidazolidin-2-one (8a). To a solution of *tert*-butyl ester **7a** (1.28 g, 2.48 mmol) in dichloromethane (25 mL) was added trifluoroacetic acid (5 mL). After being stirred at room temperature for 17 h, the reaction mixture was evaporated and the residue was partitioned between water and ether. The ether layer was extracted twice with water and the combined aqueous portions were evaporated to give 530 mg (97%) of **8a**, which was pure by ^1H NMR. A sample was recrystallized from methanol (−30 °C): mp 187 °C; ^1H NMR (CD_3OD) δ 2.57 (dd, 1 H, J = 13.5, 10.1, $PhCH_2$), 2.96 (dd, 1 H, J = 13.5, 3.7, $PhCH_2$), 4.16 (ddd, 1 H, J = 10.1, 9.0, 3.7, C5-H), 4.42 (d, 1 H, J = 9.0, C4-H), and 7.22 (m, 5 H, Ar H); ^{13}C NMR (CD_3OD) δ 38.6, 57.0, 59.5, 127.8, 129.7, 130.2, 138.7, 165.5, 173.3. Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 60.0; H, 5.5; N, 12.7. Found: C, 59.7; H, 5.5; N, 12.6.

(4*S*,5*R*)-4-Carboxy-5-benzylimidazolidin-2-one (8b). The cyclic urea **8b** was obtained as described for **8a** in 98% yield: mp 210 °C; ^1H NMR (CD_3OD) δ 2.92 (AB quartet of doublets, 2 H, J_{AB} = 13.4, J_{AX} = 6.1), 3.98 (d, 1 H, J = 4.2, C4-H), 4.06 (m, 1 H, C5-H), 7.26 (m, 5 H, Ar H); ^{13}C NMR (CD_3OD) δ 42.6, 58.6, 59.4, 127.8, 129.6, 130.6, 137.8, 164.8, 174.7. Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 60.0; H, 5.5; N, 12.7. Found: C, 59.7; H, 5.5; N, 12.6.

(2*S*,3*S*)-2,3-Diamino-4-phenylbutanoic Acid Dihydrochloride (1c·2HCl). The carboxyimidazolidinone **8a** (145 mg, 0.66 mmol) in 2 M HCl (2 mL) was heated at reflux for 2.5 h; the resulting solution was evaporated and the residue was dried for 17 h at room temperature (0.5 mmHg) and then for 17 h at 40 °C (0.5 mmHg) to give 176 mg (100%) of **1c**·2HCl as a white crystalline solid: mp 170–172 °C; $[\alpha]^{20}_D$ +1.8° (*c* 1.3, MeOH); ^1H NMR (D_2O) δ 2.90 (dd, 1 H, J = 14.3, 10.0, $PhCH_2$), 3.14 (dd, 1 H, J = 14.3, 5.5, $PhCH_2$), 3.94–3.98 (m, 1 H, C3-H), 4.07 (d, 1 H, J = 5.6, C2-H), 7.21–7.31 (m, 5 H, Ar H). Anal. Calcd for $C_{10}H_{16}N_2O_2Cl_2$: C, 45.0; H, 6.0; N, 10.5. Found: C, 44.7; H, 6.2; N, 10.4.

(2*S*,3*R*)-2,3-Diamino-4-phenylbutanoic Acid Dihydrochloride (3·2HCl). The carboxyimidazolidinone **8b** (125 mg, 0.57 mmol) was treated as described above to give 154 mg (99%) of 3·2HCl: mp 206–207 °C; $[\alpha]^{20}_D$ +18.8° (*c* 1.4, MeOH); ^1H NMR (CD_3OD) δ 2.75 (dd, 1 H, J = 13.5, 11.5, CH_2Ph), 3.40 (d, 1 H, J = 13.7, CH_2Ph), 4.21 (d, 1 H, J = 10, C3-H), 4.62 (s, 1 H, C2-H), 7.27–7.43 (m, 5 H, Ar H). Anal. Calcd for $C_{10}H_{16}N_2O_2Cl_2·0.5H_2O$: C, 43.5; H, 6.2; N, 10.1. Found: C, 43.7; H, 6.2; N, 10.1.

(2*S*)-1-*tert*-Butyl 4-Methyl *N*-Benzylaspartate (9). The diester **4** (12.0 g, 27.0 mmol) was dissolved in methanol/acetic acid (100 mL, 4/1), 10% palladium on carbon (1.20 g) was added, and the mixture was stirred at room temperature under hydrogen (1 atm) for 16 h, then filtered through Celite, and washed with methanol/acetic acid (20 mL, 4/1). Benzaldehyde (3.0 mL, 30.0 mmol) was added to the filtrate. After being stirred for 30 min at room temperature, the solution was cooled to 0 °C and sodium cyanoborohydride (1.88 g, 30.0 mmol) was added in portions over 1 h followed by stirring for an additional 15 min and repetition of the above procedure with benzaldehyde and sodium cyanoborohydride. The clear solution was then cautiously partitioned between saturated aqueous $NaHCO_3$ and dichloromethane, and the aqueous phase was twice extracted with CH_2Cl_2. The combined organic phase was dried and evaporated and the residue was purified by LPC (hexane/EtOAc, 7/1 to 4/1) to give 3.12 g (30%) of **(2*S*)-1-*tert*-butyl 4-methyl *N*,*N*-dibenzylaspartate** and 4.10 g (52%) of mono-*N*-benzyl compound **9**. The *N*,*N*-dibenzyl derivative is a colorless, viscous liquid: R_f 0.50 (hexane/EtOAc, 4/1); ^1H NMR δ 1.55 (s, 9 H), 2.62 (dd, 1 H, J = 7.4, 15.5), 2.79 (dd, 1 H, J = 8.0, 15.5), 3.58 (s, 3 H), 3.60 (d, 2 H, J = 14.0), 3.75 (t, 1 H, J = 7.65), 3.83 (d, 2 H, J = 13.7), 7.22–7.34 (m, 10 H). The mono-*N*-benzyl compound **9** is a colorless liquid: R_f 0.29 (hexane/EtOAc, 4/1); ^1H NMR δ 1.47 (s, 9 H), 2.1 (s, br, 1 H), 2.60–2.72 (m, 2 H), 3.55 (t, 1 H, J = 6.5), 3.68 (s, 3 H), 3.72 (d, 1 H, J = 13.0), 3.88 (d, 1 H, J = 13.0), 7.23–7.32 (m, 5 H).

(2*S*)-1-*tert*-Butyl 4-Methyl *N*-Benzyl-*N*-(9-phenylfluoren-9-yl)aspartate (10). A mixture of **9** (4.10 g, 14.0 mmol), $Pb(NO_3)_2$ (3.70 g, 11.2 mmol), K_3PO_4 (5.94 g, 28.0 mmol) and 9-phenylfluoren-9-yl bromide (4.94 g, 15.4 mmol) in acetonitrile was stirred at room temperature in a Morton flask for 16 h and then filtered, and the precipitate was washed with dichloromethane. The combined filtrate and washings were evaporated and the residue was dissolved in Et_2O, washed (2×) with 5% aqueous citric acid and water, dried, evaporated, and purified by LPC (hexane/EtOAc, 10/1) to give 6.87 g (92%) of **10**: mp 125–126 °C (from MeOH); ^1H NMR δ 1.13 (s, 9 H), 1.93 (dd, 1 H, J = 2.7, 15.7), 2.54 (dd, 1 H, J = 10.9, 15.7), 3.41 (s, 3 H), 3.84–3.90 (m, 2 H), 4.20 (d, 1 H, J = 13.8), 7.18–7.39 (m, 10 H), 7.47 (d, 2 H, J = 7.5), 7.56 (d, 1 H, J = 7.6), 7.66–7.74 (m, 3 H), 7.81 (m, 2 H). Anal. Calcd for $C_{35}H_{35}NO_4$: C, 78.8; H, 6.6; N, 2.6. Found C, 78.8; H, 6.6; N, 2.6.

Benzylation of 10. Formation of (2*S*,3*S*)- and (2*S*,3*R*)-1-*tert*-Butyl 4-Methyl *N*-Benzyl-*N*-(9-phenylfluoren-9-yl)-3-benzylaspartate (11a and 11b). The N,N-disubstituted diester **10** (4.27 g, 8.0 mmol) was dissolved in THF (90 mL) at −20 °C, and KHMDS (16.0 mmol) in toluene (30 mL) was added. After completion of the addition, benzyl bromide (1.9 mL, 16.0 mmol) was added, and the solution was stirred for 2 h at −20 °C and poured on phosphate buffer (pH 7). The mixture was extracted with EtOAc and the combined organic phase was

dried and evaporated. ^{1}H NMR analysis revealed a diastereomeric ratio of 30/1 and LPC (hexane/EtOAc, 10/1) gave a mixture of the two diastereomers and a trace of starting material (1%) as a white foam. Addition of 20 mL of absolute ethanol gave a solution from which **11a** and **11b** precipitated spontaneously in a combined yield of 3.87 g (78%) as a white powder of unchanged diastereomeric ratio. Recrystallization from methanol gave the pure major diastereomer **11a**: mp 185–186 °C (from MeOH); ^{1}H NMR δ 1.02 (s, 9 H), 2.49 (t, br, 1 H, J = 12.6), 2.79 (dt, 1 H, J = 4.1, 12.2), 3.05 (s, 3 H), 3.61 (dd, 1 H, J = 4.1, 13.0), 3.75 (d, 1 H, J = 11.1), 4.44 (d, 1 H, J = 13.3), 4.56 (d, 1 H, J = 13.3), 6.47–6.48 (m, 2 H), 7.07–7.08 (m, 3 H), 7.23–7.40 (m, 9 H), 7.47–7.49 (m, 1 H), 7.63–7.67 (m, 3 H), 7.77–7.78 (m, 5 H). Anal. Calcd for $C_{42}H_{41}NO_4$: C, 80.9; H, 6.6; N, 2.3. Found: C, 81.0; H, 6.6; N, 2.2. The minor diastereomer **11b** was isolated by LPC as a white foam: ^{1}H NMR δ 1.08 (s, 9 H), 2.21 (dd, 1 H, J = 9.8, 13.2), 2.43 (dd, 1 H, J = 4.1, 13.5), 2.92 (dt, 1 H, J = 4.1, 10.1), 3.35 (s, 3 H), 3.95 (d, 1 H, J = 11.2), 3.34 (d, 1 H, J = 13.4), 4.62 (d, 1 H, J = 13.4), 6.72–6.73 (m, 2 H), 7.07–7.08 (m, 3 H), 7.16–7.34 (m, 10 H), 7.47 (t, 1 H, J = 14.8), 7.57–7.69 (m, 6 H), 7.78 (d, 1 H, J = 7.5).

(2*S*,3*S*)-1-*tert*-Butyl 4-Methyl *N*-(*tert*-Butoxycarbonyl)-3-benzylaspartate (12). The amine **11a** (2.95 g, 4.75 mmol) was suspended in glacial acetic acid (30 mL) and Pd(OH)$_2$/C (20%, 0.90 g) was added. The mixture was stirred at room temperature under hydrogen (1 atm) for 24 h, the catalyst was removed by filtration through Celite and washed with glacial acetic acid (20 mL), the filtrate was evaporated, and the residue was partitioned between Et_2O and 1 M H_3PO_4. The ether phase was extracted again with 1 M H_3PO_4 (2×), and the combined aqueous phase was adjusted to pH 9 with solid K_2CO_3 and extracted with Et_2O (3×). The organic phases were combined, dried, and evaporated to give 1.25 g (90%) of the primary amine as a colorless oil: ^{1}H NMR δ 1.47 (s, 9 H), 2.85 (q, 1 H, J = 9.4), 3.03–3.09 (m, 2 H), 3.60 (s, 3 H), 3.68–3.69 (m, 1 H), 7.06–7.30 (m, 5 H). The crude primary amine was dissolved in acetonitrile (10 mL) and a solution of di-*tert*-butyl dicarbonate (1.20 g, 6.0 mmol) in acetonitrile (10 mL) was added. After 4 h at room temperature, the solvent was evaporated to give **12** as a pale yellow oil, which was directly used in the next reaction.

Hydrolysis of the β-Methyl Ester of Diester 12. Formation of (2*S*,3*S*)- and (2*S*,3*R*)-1-*tert*-Butyl *N*-(*tert*-Butoxycarbonyl)-3-benzylaspartate (13). To a solution of crude **12** in dioxane (50 mL) was added 0.5 M LiOH (20 mL), and then solid LiOH·H_2O was added until the solution remained alkaline. After 90 min at 60 °C, the solvent was evaporated and the residue was partitioned between Et_2O and 1 N NaOH. A third phase was formed, which was separated from the ether phase, together with the aqueous phase. The ether phase was again extracted (2×) with 1 N NaOH. The aqueous phases and the third phase were combined and acidified with 1 M H_3PO_4 to pH 2 and then extracted (3×) with Et_2O. The organic phases were combined, dried, and evaporated to give **13** as a white foam consisting of two diastereomers in 3/2 ratio by ^{1}H NMR analysis.

Hydrolysis at room temperature with 1 M LiOH (500 mol %) gave the two diastereomers in a 4/1 ratio.

(2*S*)-4-Benzyl 1-*tert*-Butyl Aspartate (15).[14] Isobutylene (80 mL) was condensed into a mixture of 4-benzyl aspartate[13] (**14**, 8.0 g, 36 mmol), dry dioxane (75 mL), and concentrated sulfuric acid (7.5 mL) in a 250-mL pressure bottle. The mixture was mechanically shaken at 25 °C for 4 h and then poured immediately into a cold mixture of 1 M NaOH (400 mL) and ether (200 mL). The aqueous phase was extracted (3×) with ether, and the combined organic portions were dried and evaporated to give 7.25 g (75%) of **15**: ^{1}H NMR δ 1.43 (s, 9 H, Bu^t), 1.90 (br s, 2 H, NH_2), 2.77 (AB quartet of doublets, 2 H, J_{AB} = 16, J_{AX} = 5, J_{BX} = 7, H-3), 3.73 (dd, 1 H, J = 5, 7, C2-H), 5.14 (br s, 2 H, PhCH_2), 7.35 (m, 5 H, Ar H).

(2*S*)-4-Benzyl 1-*tert*-Butyl *N*-Benzylaspartate (16). Freshly distilled benzaldehyde (3.18 g, 30 mmol) was added dropwise to a solution of the amino diester **15** (5.58 g, 20 mmol) in methanol (128 mL) and acetic acid (32 mL), and the resulting solution was stirred for 1.5 h at room temperature. After cooling to 0 °C, sodium cyanoborohydride (2.20 g, 35 mmol) was added in portions over 1 h. After being stirred for an additional 15 min, the reaction mixture was partitioned between saturated $NaHCO_3$ and dichloromethane, the aqueous phase was twice extracted with dichloromethane, the combined dichloromethane portions were dried and evaporated, and the residue was purified by LPC. Dichloromethane eluted 1.21 g (13%) of **(2*S*)-4-benzyl 1-*tert*-butyl *N*,*N*-dibenzylaspartate (17)** as a pale yellow oil: R_f 0.33 (CH_2Cl_2/hexane, 1/1); IR (neat) 1730 s (CO) and 1150 s cm^{-1}; ^{1}H NMR δ 1.56 (s, 9 H, Bu^t), 2.68 (dd, 1 H, J = 14, 7, C3-H), 2.88 (dd, 1 H, J = 14, 7, C3-H), 3.61 (d, 2 H, J = 12, NCH_2Ph), 3.82 (t, 1 H, J = 7, C2-H), 3.84 (d, 2 H, J = 12, NCH_2Ph), 4.95 (d, 1 H, J = 9.9, CO_2CH_2Ph), 5.14 (d, 1 H, J = 9.9 Hz, CO_2CH_2Ph), 7.20–7.40 (15 H, m, Ar H). Anal. Calcd for $C_{29}H_{33}NO_4$: C, 75.8; H, 7.2; N, 3.1. Found: C, 75.7; H, 7.3; N, 3.0. Ethyl acetate/dichloromethane, 1/4, eluted 5.39 g (73%) of **16** as a colorless oil: R_f 0.78 (EtOAc/dichloromethane, 1/9); IR (neat) 3340 w (NH), 1730 s (CO), 1150 s cm^{-1}; ^{1}H NMR δ 1.43 (s, 9 H, Bu^t), 2.09 (br s, 1 H, NH), 2.69 (septet, 2 H, J_{AB} = 15, J_{AX} = 7.5, C3-H), 3.57 (t, 1 H, J = 7.5, C2-H), 3.69 (d, 1 H, J = 12.9, NCH_2Ph), 3.85 (d, 1 H, J = 12.9, NCH_2Ph), 5.10 (q, 2 H, J_{AB} = 8, CO_2CH_2Ph), 7.22–7.32 (m, 10 H, Ar H). Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.5; H, 7.4; N, 3.8. Found: C, 71.2; H, 7.2; N, 3.8.

(2*S*)-4-Benzyl 1-*tert*-Butyl *N*-Benzyl-*N*-(9-phenylfluoren-9-yl)aspartate (18). A mixture of diester **16** (3.7 g, 10.0 mmol), K_3PO_4 (4.27 g, 20 mmol), $Pb(NO_3)_2$ (2.66 g, 8 mmol), and 9-phenylfluoren-9-yl bromide (3.55 g, 11 mmol) in acetonitrile (110 mL) was stirred at room temperature in a Morton flask for 17 h. Dichloromethane and solid Na_2SO_4 were added, the mixture was filtered through filter aid, the filtrate was evaporated, and the residue was purified by LPC. Dichloromethane/hexane, 6/4, eluted 5.37 g (88%) of **18**: colorless needles, mp 103–104 °c (from MeOH); R_f 0.27 (EtOAc/hexane, 1/9); IR ($CHCl_3$) 1727 s (CO), 1450 m, 1370 m, 1152 s cm^{-1}; ^{1}H NMR δ 1.07 (s, 9 H, Bu^t), 1.97 (dd, 1 H, J = 15.8, 2.4, C3-H), 2.61 (dd, 1 H, J = 15.8, 10.9, C3-H), 3.83 (d, 1 H, J = 13.8, NCH_2Ph], 3.92 (dd, 1 H, J = 10.9, 2.4, C2-H), 4.22 (d, 1 H, J = 13.8, NCH_2Ph), 4.82 (q, 2 H, J_{AB} = 12.5, CO_2CH_2Ph), 7.05–7.83 (m, 23 H, Ar H). Anal. Calcd for $C_{41}N_{39}NO_4$: C, 80.8; H, 6.5; N, 2.3. Found: C, 80.8; H, 6.6; N, 2.3.

(2*S*,3*S*)- and (2*S*,3*R*)-4-Benzyl 1-*tert*-Butyl *N*-Benzyl-*N*-(9-phenylfluoren-9-yl)-3-benzylaspartate (19a and 19b). The tertiary amine **18** (1.27 g, 2.09 mmol) in THF (4 mL) was added dropwise to a solution of KHMDS (8.36 mL, 0.5 M in toluene, 4.18 mmol) in THF (20 mL) at −20 °C. As soon as the addition was complete, a solution of benzyl iodide (911 mg, 4.18 mmol) in THF (4 mL) was added. After being stirred for 2 h at −20 °C, the reaction mixture was partitioned between phosphate buffer (pH 7) and ether, the aqueous layer was extracted (2×) with ether, and the combined ether portions were washed with saturated aqueous $Na_2S_2O_3$ and brine, dried, and evaporated. On LPC, EtOAc/hexane, 1/11.5, eluted 41 mg (3%) of **19b** (minor diastereomer): R_f 0.60 (EtOAc/hexane, 1/4); ^{1}H NMR δ 1.07 (s, 9 H, Bu^t), 2.23 (dd, 1 H, J = 13, 10, C3-CH_2Ph), 2.48 (dd, 1 H, J = 10, 2, C3-CH_2Ph), 3.00 (m, 1 H, C3-H), 3.99 (d, 1 H, J = 10, C2-H), 4.33 (d, 1 H, J = 13, NCH_2Ph), 4.66 (d, 1 H, J = 13, NCH_2Ph), 4.82 (br s, 2 H, CO_2CH_2Ph), 6.72 (m, 2 H, Ar H), 6.90–7.95 (m, 26 H, Ar H). Continued elution gave 1.05 g (72%) of **19a** (major diastereomer): mp 194–195 °C (from MeOH); R_f 0.58 (EtOAc/hexane, 1/4); IR ($CHCl_3$) 1725 s (CO), 1425 m, 1150 s cm^{-1}; ^{1}H NMR δ 0.97 (s, 9 H, Bu^t), 2.53 (1 H, J_{AB} = 12.6, C3-CH_2Ph), 2.88 (1 H, J_{AB} = 11.5, J_{AX} = 3.8, C3-CH_2Ph), 3.65 (dd, 1 H, J = 12.9, 3.8, C3-H), 3.84 (d, 1 H, J = 11.1, C2-H), 4.44 (d, 2 H, J = 12.9, NCH_2Ph and COCH_2), 4.63 (d, 1 H, J = 12.9, NCH_2Ph or CO_2CH_2Ph), 4.64 (d, 1 H, J = 12.6, NCH_2Ph or CO_2CH_2Ph), 6.39 (m, 2 H, Ar H), 6.68 (m, 2 H, Ar H), 7.00–7.80 (m, 24 H, Ar H); ^{13}C NMR δ 28.0, 37.1, 51.1, 52.1, 64.0, 65.9, 80.9, 81.1, 120.4, 120.9, 126.6, 126.9, 127.7, 127.9, 128.0, 128.2, 128.3, 128.5, 128.6, 128.9, 128.95, 129.2, 131.0, 136.0, 139.0, 140.3, 141.2, 142.5, 145.7, 146.4, 148.0, 170.5 (CO), 173.1 (CO). Anal. Calcd for $C_{48}H_{45}NO_4$: C, 82.4; H, 6.5; N, 2.0. Found: C, 82.1; H, 6.6; N, 2.0.

(2*S*,3*S*)-1-*tert*-Butyl *N*-Benzyl-*N*-(9-phenylfluoren-9-yl)-3-benzylaspartate (20). To a solution of diester **19a** (450 mg, 0.64 mmol) in ethyl acetate (20 mL) was added 5% palladium on barium sulfate (200 mg). The mixture was stirred at room temperature under hydrogen (1 atm) for 18 h, and the catalyst was removed by filtration through Celite and washing with methanol and dichloromethane. The combined filtrate and

washings were evaporated, and the residue was dissolved in cold 1 M NaOH containing 10% THF. After quick extraction (3×) with hexane, the aqueous and interface layers were acidified to pH 3 with 1 M H_3PO_4 and extracted (3×) with ether. The hexane layers were evaporated and the residue was resubjected to identical hydrogenation conditions for a further 18 h. The catalyst was removed and washed as before. The combined filtrates, washings, and ether portion from the initial extraction were evaporated and the residue was purified by LPC. Ethyl acetate/hexane (2/3) eluted 306 mg (78%) of **20**: IR (Nujol) 1725 (CO, ester), 1710 sh (CO, acid) cm^{-1}; ^1H NMR δ 0.89 (s, 9 H, Bu^t), 2.40 (q, 1 H, J = 13, C3-CH_2Ph), 2.75 (1 H, J_{AB} = 12, J_{AX} and J_{BX} = 3, C3-CH_2Ph), 3.60 (m, 2 H, C2-H and C3-H), 4.47 (AB quartet, 2 H, J_{AB} = 13.5, NCH_2Ph), 6.40 (m, 2 H, Ar H), 7.02 (m, 4 H, Ar H), 7.20–7.75 (m, 17 H, Ar H). Methylation of the acid **20** with diazomethane quantitatively gave diester **11a**, identical with that described previously.

Attempted Curtius Degradation of Carboxylic Acid 20. To a solution of carboxylic acid **20** (213 mg, 0.35 mmol) in acetonitrile (6 mL) were added DPPA (103 mg, 0.37 mmol) and triethylamine (59 μL, 0.42 mmol). After being stirred at 50 °C for 3 h, the reaction mixture was evaporated and the residue purified by LPC. Ethyl acetate/hexane (1/10) eluted 103 mg (55%) of **(2*S*,3*S*)-2-[(9-phenylfluoren-9-yl)benzylamino]-3-benzylsuccinic anhydride (21)**: mp 208–209 °C (from hexane/dichloromethane); R_f 0.65 (EtOAc/hexane, 1/4); IR ($CHCl_3$) 1785 cm^{-1}; ^1H NMR δ 1.92 (dd, 1 H, J = 13.7, 6, CCH_2Ph), 2.57 (dd, 1 H, J = 13.7, 4.5, CH_2Ph), 3.10 (q, 1 H, J = 5.5, C3-H), 3.81 (d, 1 H, J = 5.6, C2-H), 4.19 (d, 1 H, J = 13.7, NCH_2Ph), 4.30 (br d, 1 H, J = 13.7, NCH_2Ph), 6.46 (d, 2 H, J = 6.6, ArH), 7.08 (t, 2 H, Ar H), 7.12 (d, 1 H, Ar H), 7.25–7.90 (m, 18 H, Ar H); ^{13}C NMR δ 43.68, 43.74, 60.1, 60.3, 79.0, 120.3, 120.5, 120.8, 121.0, 126.8, 127.0, 127.8, 128.1, 128.4, 128.5, 128.9, 129.0, 129.4, 129.6, 129.8, 135.1, 136.1, 139.6, 140.9, 142.6, 146.1, 147.0, 170.6, 171.4. Anal. Calcd for $C_{37}H_{29}NO_3$: C, 83.0; H, 5.5; N, 2.6. Found: C, 82.7; H, 5.3; N, 2.6.

(2*S*,3*S*)-1-*tert*-Butyl *N*-(*tert*-Butoxycarbonyl)-3-benzylaspartate (22). A mixture of tertiary amine diester **19a** (3.50 g, 5 mmol), di-*tert*-butyl dicarbonate (5.46 g, 25 mmol), and 10% palladium on carbon (1 g) in methanol (40 mL) was shaken under an atmosphere of hydrogen (60 psi) for 48 h. The reaction mixture was filtered and the filtrate partitioned between ether and 1 M NaOH. The ether layer was washed twice with 1 M NaOH and the combined aqueous layers were acidified to pH 2 with 1 M H_3PO_4 and extracted with ether (3×). The combined ether phases were washed with brine, dried, and evaporated to give 1.40 g (74%) of **22**. Digestion of the catalyst with methanol and then chloroform gave an additional 220 mg (12%) of **22**: mp 132–135 °C; ^1H NMR δ 1.43 (br s, 9 H, Bu^t), 1.47 (s, 9 H, Bu^t), 2.80–3.18 (m, 4 H, C2-H, C3-H, and CH_2Ph), 4.67 (d, 0.5 H, J = 7, NH, rotamer), 5.40 (d, 0.5 H, J = 7, NH, rotamer), 7.13–7.31 (m, 5 H, Ar H). Anal. Calcd for $C_{20}H_{29}NO_6$: C, 63.3; H, 7.7; N, 3.7. Found: C, 63.6; H, 8.0; N, 3.6.

(4*S*,5*S*)-4-Benzyl-1,5-bis(*tert*-butoxycarbonyl)-imidazolidin-2-one (23). To a solution of the acid **22** (1.20 g, 3.16 mol) in acetonitrile (20 mL) were added diphenyl phosphorazidate (921 mg, 3.79 mmol) and triethylamine (0.53 mL, 3.80 mmol). After being stirred at 55 °C for 16 h, the reaction mixture was concentrated and the residue partitioned between ether and saturated aqueous $NaHCO_3$. The organic phase was washed with 1 M H_3PO_4 and brine, dried, and evaporated to give 1.08 g (91%) of **23**: mp 180–182 °C (from MeOH, −20 °C); ^1H NMR δ 1.52 (s, 9 H, Bu^t), 1.55 (s, 9 H, Bu^t), 1.70 (br s, 1 H, NH), 2.52 (dd, 1 H, J = 13.2, 11.5, CCH_2Ph), 3.06 (dd, 1 H, J = 13.2, 2.8, CCH_2Ph), 4.01–4.11 (m, 1 H, C4-H), 4.66 (br s, 1 H, NH), 4.67 (d, 1 H, J = 9.3, C5-H), 7.16–7.38 (m, 5 H, Ar H); ^{13}C NMR δ 27.9 (Bu^t), 28.0 (Bu^t), 28.1 (Bu^t), 37.5 (CH_2Ph), 51.6 and 60.6 (C4 and C5), 82.90 [$C(CH_3)_3$], 83.1 [$C(CH_3)_3$], 127.3 (Ph), 128.8 (Ph), 129.0 (Ph), 136.2 (Ph), 149.6 (CO), 154.2 (CO), 167.0 (CO). Anal. Calcd for $C_{20}H_{28}N_2O_5$: C, 63.8; H, 7.5; N, 7.4. Found: C, 63.7; H, 7.6; N, 7.5.

(4*S*,5*S*)-4-Benzyl-5-carboxyimidazolidin-2-one (8a). To a solution of cyclic urea **23** (70 mg, 0.185 mmol) in dichloromethane (1 mL) was added trifluoroacetic acid (0.25 mL). After being stirred at room temperature for 36 h, the reaction mixture was evaporated and the residue partitioned between ether and water. The ether layer was extracted twice with water, and the combined aqueous portions were evaporated to give 38 mg (94%) of **8a**, identical with that described above.

(2*S*)-*N*-Benzylaspartic Acid. A solution of aspartic acid (123.8 g, 0.93 mol) in 3 M NaOH (600 mL) was placed in a 3-L Morton flask equipped with an overhead stirrer. The solution was deoxygenated by passage of a vigorous stream of nitrogen for 20 min; then benzaldehyde (300 mL, 2.97 mol) was added to the solution over 30 min. After stirring for another 1.5 h, the pH was adjusted to 9.2 with concentrated hydrochloric acid, the flask was cooled in an ice bath, and sodium cyanoborohydride (62.8 g, 1.0 mol) was added in small portions while maintaining the temperature below 25 °C. After the completion of the addition, stirring was continued for 1.5 h at room temperature and the reaction mixture was filtered through Celite. The filtrate was washed with dichloromethane and then ether, the pH was adjusted to 2.8, and the solution was cooled to 0 °C. *N*-Benzylaspartic acid (170 g, 82%) was collected by filtration, washed with acetone, and dried overnight in a vacuum oven at 70 °C: ^1H NMR (D_2O) δ 2.83 (m, 2 H, C3-H), 3.81 (t, 1 H, J = 7, C2-H), 4.20 (2 H, J = 11.5, NCH_2Ph), 7.36 (s, 5 H, Ar H). Proton NMR indicated that the material obtained from different batches contained between 3 and 15% aspartic acid (proven by a spiking experiment). Attempts to remove this impurity by recrystallization from water or redissolving the product in 2 M NaOH followed by reprecipitation by adjusting the pH to 2.8 were unsuccessful.

(2*S*)-4-Benzyl *N*-Benzylaspartate (25). Concentrated sulfuric acid (20 mL) was added carefully to ether (200 mL) followed by benzyl alcohol (200 mL). The ether was removed in vacuo and *N*-benzylaspartic acid (44.6 g, 0.2 mmol) was added in several portions, while the mixture was magnetically stirrd. The ensuing solution was left at room temperature for 48 h. Ethanol (400 mL) was added, followed by pyridine (100 mL), which was added dropwise while the solution was stirred. The mixture was cooled overnight and benzyl ester **25** (53.1 g, 85%) was collected by filtration, washed with ether, and dried in a vacuum oven. The product was purified further by recrystallization from methanol/pyridine (3/1): ^1H NMR (d_6-DMSO) δ 2.72 (qd, 2 H, J_{AB} = 16.1, J_{AX} = 6.1, J_{BX} = 7.2, C-3H), 3.50 (t, 1 H, J = 7, C-2H), 3.76 (d, 1 H, J = 13.4, NCH_2Ph), 3.90 (d, 1 H, J = 13.4, NCH_2Ph), 5.09 (s, 2 H, COCH_2Ph), 7.25–7.34 (m, 10 H, Ar H).

(2*S*)-4-Benzyl 1-Methyl *N*-Benzylaspartate (27). To a solution of 4-benzyl *N*-benzylaspartate (**25**) (16.6 g, 53 mmol) in acetonitrile (160 mL) was added *N,N'*-diisopropyl-*O*-methylisourea (11.4 g, 72 mmol), and the reaction mixture was heated at reflux for 2 h, then cooled to 25 °C, and filtered. The solid was resubjected to the same reaction conditions with an equal batch of isourea reagent for a further 2 h. After filtration, the acetonitrile filtrates were combined and evaporated, and the residue was purified by LPC. Ethyl acetate/hexane, 3/17, eluted **(2*S*)-4-benzyl 1-methyl *N*-benzyl-*N*-methylaspartate (26)** (1.81 g, 10%) as a colorless oil: ^1H NMR δ 2.23 (s, 3 H, NCH), 2.73 (dd, 1 H, J = 15.8, 7.3, C-3H), 2.94 (dd, 1 H, J = 15.8, 7.9, C3-H), 3.6–3.8 (m, 2 H, NCH_2Ph), 3.73 (s, 3 H, CO_2Me), 3.93 (t, 1 H, J = 7.6, C2-H), 5.13 (2 H, J_{AB} = 12.3, OCH_2Ph), 7.26 (s, 10 H, Ar H). Ethyl acetate/hexane, 1/4, eluted 12.31 g (71%) of **27** as a colorless oil: R_f 0.39 (EtOAc/hexane, 1/3); IR (neat) 3340 w (NH), 1740 s (CO), 1170 m cm^{-1}; ^1H NMR δ 2.09 (br s, 1 H, NH), 2.76 (heptet, 2 H, J_{AB} = 13, J_{AX} = 6.2, J_{BX} = 5.3, C3-H), 3.76 (s, 3 H, CO_2CH_3), 3.68 (m, 1 H, C2-H), 3.70 (d, 1 H, J = 13.0, NCH_2Ph), 3.85 (d, 1 H, J = 13.0, NCH_2Ph), 5.11 (s, 2 H, OCH_2Ph), 7.21–7.32 (m, 10 H, Ar H); ^{13}C NMR δ 38.1, 51.9, 52.0, 56.9, 66.4, 127.0, 128.1, 128.2, 128.4, 135.5, 139.3, 170.5, 173.8. Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.7; H, 6.5; N, 4.3. Found: C, 69.7; H, 6.5; N, 4.3.

(2*S*)-4-Benzyl 1-Methyl *N*-Benzyl-*N*-(9-phenylfluoren-9-yl)aspartate (28). The *N*-benzylamine **27** (4.36 g, 13.3 mmol) was phenylfluorenated as described for the benzylamine **16**. Ethyl acetate/hexane, 1/9, eluted 9-phenylfluoren-9-ol (0.51 g, 15%) followed by 6.57 g (87%) of **28**: mp 72–73 °C (from MeOH); R_f 0.53 (EtOAc/hexane, 1/4); ^1H NMR δ 1.88 (dd, 1 H, J = 16.1, 2.6, C3-H), 2.60 (dd, 1 H, J = 16.1, 10.7, C3-H), 3.15 (s, 3 H, CO_2CH_3), 3.91 (d, 1 H, J = 13.7, NCH_2Ph), 3.95 (dd, 1 H, J = 10.7, 2.6, C2-H), 4.26 (d, 1 H, J = 13.7, NCH_2Ph), 4.82 (s, 2 H, CO_2CH_2Ph), 7.08–7.81 (m, 23 H, Ar H); ^{13}C NMR δ 33.2, 51.3, 51.7, 56.1, 65.7, 79.1, 119.9, 120.4, 126.3, 126.4, 126.9, 127.1, 127.2,

127.4, 127.6, 127.7, 127.8, 128.1, 128.3, 128.4, 128.5, 129.3, 135.6, 138.0, 139.8, 140.6, 143.3, 145.8, 147.1, 170.7, 172.4. Anal. Calcd for $C_{38}H_{33}NO_4$: C, 80.4; H, 5.9; N, 2.5. Found: C, 80.5; H, 5.9; N, 2.4.

Benzylation of 28. Formation of (2*S*,3*S*)- and (2*S*,3*R*)-4-Benzyl 1-Methyl *N*-Benzyl-*N*-(9-phenylfluoren-9-yl)-3-benzylaspartate (29a and 29b). A solution of tertiary amine **28** (3.7 g, 6 mmol) in THF (12 mL) was benzylated as described for **18**. Ethyl acetate/hexane, 1/9, eluted 2.01 g (51%) of **29b** as the less polar diastereomer: mp 77–79 °C (from MeOH); R_f 0.67 (EtOAc/hexane, 1/4); ^{1}H NMR δ 2.13 (dd, 1 H, J = 13.2, 10.4, C3-CH_2Ph), 2.29 (dd, 1 H, J = 13.2, 4.5, C3-CH_2Ph), 2.90 (m, 1 H, C3-H), 2.96 (s, 3 H, CO_2Me), 3.92 (d, 1 H, J = 11.2, C2-H), 4.32 (d, 1 H, J = 13.8, NCH_2Ph), 4.61 (d, 1 H, J = 13.8, NCH_2Ph), 4.79 (2 H, J_{AB} = 12.3, OCH_2Ph), 6.66 (m, 2 H, Ar H), 6.98–7.66 (m, 25 H, Ar H), 7.78 (d, 1 H, J = 6.7, Ar H); ^{13}C NMR δ 36.0, 48.8, 50.7, 51.2, 61.9, 65.8, 80.2, 119.3, 119.9, 126.1, 126.7, 126.8, 127.2, 127.3, 127.5, 127.6, 127.7, 127.88, 127.90, 128.1, 128.3, 128.5, 129.8, 135.6, 137.4, 139.1, 140.7, 142.2, 144.3, 146.9, 170.6, 172.2. Anal. Calcd for $C_{45}H_{39}NO_4$: C, 82.2; H, 6.0; N, 2.1. Found: C, 82.1; H, 5.8; N, 2.2. Ethyl acetate/hexane, 1/9, eluted 1.34 g (34%) of **29a** as the more polar diastereomer: mp 90–91 °C; R_f 0.58 (EtOAc/hexane, 1/4); ^{1}H NMR δ 2.46 (br t, 1 H, J = 12, C3-CH_2Ph), 2.80–2.95 (m, 1 H, C3-H), 2.83 (s, 3 H, CO_2Me), 3.64 (dd, 1 H, J = 13.3, 4.0, C3-CH_2Ph), 3.77 (d, 1 H, J = 11.2, C2-H), 4.42 (q, 2 H, NCH_2Ph), 4.52 (q, 2 H, OCH_2Ph), 6.42–6.45 (m, 2 H, Ar H), 6.68–6.71 (m, 2 H, Ar H), 7.01–7.84 (m, 24 H, Ar H); ^{13}C NMR δ 36.1 (t), 49.4 (d), 51.0 (q), 62.5 (d), 65.4 (t), 80.26 (s), 120.16 (d), 120.24 (d), 126.0 (d), 126.2 (d), 126.88 (d), 126.9 (d), 127.3 (d), 127.4 (d), 127.7 (d), 127.9 (d), 127.95 (d), 128.3 (d), 128.4 (d), 128.5 (d), 128.6 (d), 128.7 (d), 130.3 (d), 135.6 (s), 138.4 (s), 139.9 (s), 140.3 (s), 141.9 (s), 144.5 (s), 145.1 (s), 147.3 (s), 171.1 (s), 173.0 (s). Anal. Calcd for $C_{45}H_{35}NO_4$: C, 82.2; H, 6.0; N, 2.1. Found: C, 82.1; H, 6.0; N, 2.2.

(2*S*,3*R*)-1-Methyl *N*-Benzyl-*N*-(9-phenylfluoren-9-yl)-3-benzylaspartate (24). To a solution of the diester **29b** (1.55 g, 2.36 mmol) in ethyl acetate (80 mL) was added 5% palladium on barium sulfate (1 g). The mixture was stirred at room temperature under hydrogen (1 atm) for 30 h and then filtered through Celite, and the precipitate was washed with methanol and dichloromethane. The combined filtrates and washings were evaporated, and the residue was dissolved in cold 1 M NaOH containing 10% THF. After quick extraction three times with hexane, the combined aqueous and interface layers were acidified to pH 3 (1 M H_3PO_4) and extracted with ether (3×). The combined ether portions were washed with brine and dried. The combined hexane layers were evaporated, and the residue was resubjected to identical reduction conditions for a further 30 h. After the catalyst was removed by filtration and washed as before, the combined filtrates, washings, and ether portions were evaporated and the residue was purified by LPC. Ethyl acetate/hexane, 1/9, eluted 9-phenylfluorene (82 mg, 14%); EtOAc/hexane, 1/4, eluted unchanged diester **29b** (0.37 g, 24%); and EtOAc/hexane, 2/3, eluted 0.642 g (48%) of **24** as a colorless solid: mp 183–184 °C (from MeOH); R_f 0.29 (EtOAc/hexane, 1/3); IR (Nujol) 1740 s (ester CO), 1710 s (acid CO), 1160 s cm^{-1}; ^{1}H NMR δ 2.29 (dd, 1 H, J = 14.4, 7.6, C3-CH_2Ph), 2.49 (dd, 1 H, J = 14, 4.4, C3-CH_2Ph), 2.75 (ddd, 1 H, J = 11.7, 7.5, 4.3, C3-H), 2.96 (s, 3 H, CO_2Me), 3.77 (d, 1 H, J = 11.7, C2-H), 4.47 (d, 1 H, J = 13.3, NCH_2Ph), 4.69 (d, 1 H, J = 13.3, NCH_2Ph), 6.69–6.73 (m, 2 H, Ar H), 6.98 (m, 20 H, Ar H), 7.79 (d, 1 H, J = 7.4, Ar H); ^{13}C NMR δ 34.9, 47.7, 51.0, 51.4, 61.4, 80.4, 119.5, 120.1, 126.3, 126.8, 126.9, 127.3, 127.5, 127.6, 127.9, 128.1, 128.4, 128.6, 128.7, 130.3, 137.2, 139.4, 139.6, 142.3, 143.7, 143.9, 146.5, 170.0, 177.7. Anal. Calcd for $C_{38}H_{33}NO_4$: C, 80.4; H, 5.9; N, 2.5. Found: C, 80.4; H, 6.0; N, 2.5.

Methanol/ethyl acetate, 1/4, eluted **1-methyl *N*-(9-phenylfluoren-9-yl)-3-benzylaspartate (30)** (161 mg, 14%): R_f 0.45 (EtOAc/hexane, 1/1); ^{1}H NMR δ 2.46 (dd, 1 H, J = 12, 3.2, CH_2Ph), 2.75–2.86 (m, 1 H, C3-H), 2.89 (dd, 1 H, J = 12, 3.9, CH_2Ph), 2.98 (d, 1 H, J = 8.9, C2-H), 3.12 (s, 3 H, CO_2CH_3), 7.01–7.38 (m, 16 H, Ar H), 7.69 (d, 1 H, J = 7.8), 7.72 (d, 1 H, J = 7.7, Ar H). The yields of the acids **24** and **30** based on recovered starting material, were 63 and 19%, respectively.

(2*S*,3*R*)-Methyl 3-[(Azidocarbonyl)amino]-2-[benzyl(9-phenylfluoren-9-yl)amino]-4-phenylbutanoate (31). To a solution of acid **24** (514 mg, 0.9 mmol) in acetonitrile (8 mL) were added DPPA (622 mg, 2.3 mmol) and triethylamine (228 mg, 2.3 mmol). After being stirred at room temperature for 0.5 h, the solution was heated to 50 °C for 3 h and then cooled to room temperature. Sodium azide (147 mg, 2.3 mmol) and *tert*-butyl alcohol (400 mg) were added, and the reaction mixture was heated at 50 °C for 12 h and finally at 80 °C for 2 h. Evaporation left a residue, which was purified by LPC, eluting with EtOAc/hexane, 1/9, to give 480 mg (88%) of **31** as colorless needles: mp 172–173 °C (from MeOH); R_f 0.44 (EtOAc/hexane, 1/4); IR (Nujol) 3365 m (NH), 2145 s (N_3), 1740 s (ester CO), 1725 s (carbamoyl azide CO) cm^{-1}; ^{1}H NMR δ 2.22 (dd, 1 H, J = 14.3, 4, C3-CH_2Ph), 2.66 (dd, 1 H, J = 14.4, 4.4, C3-CH_2Ph), 3.02 (s, 3 H, CO_2Me), 3.31–3.46 (m, 2 H, C2-H and C3-H), 4.36 (2 H, J_{AB} = 13.3, NCH_2Ph), 5.23 (br d, 1 H, J = 4.3, NH), 6.59 (d, 2 H, J = 6.6, Ar H), 6.94–7.80 (m, 21 H, Ar H); ^{13}C NMR δ 35.1, 51.3, 51.9, 60.6, 61.0, 80.0, 120.1, 120.3, 126.0, 126.9, 127.1, 127.6, 127.8, 127.9, 127.98, 128.04, 128.1, 128.3, 128.6, 128.7, 128.8, 129.5, 129.7, 130.1, 135.8, 138.9, 139.4, 141.9, 143.7, 144.5, 146.8, 154.9 (CON_3), 170.4 (ester CO). Anal. Calcd for $C_{38}H_{33}N_5O_3$: C, 75.1; H, 5.5; N, 11.5. Found: C, 75.0; H, 5.6; N, 11.3.

(2*S*,3*R*)-Methyl 2-[Benzyl(9-phenylfluoren-9-yl)amino]-4-phenyl-3-ureidobutanoate (33). A suspension of carbamoyl azide **31** (589 mg, 0.97 mmol) in dry ether (15 mL) was added to tributylphosphine (0.24 mL, 0.97 mmol) in dry ether (5 mL). Vigorous evolution of nitrogen was observed, and after stirring for 15 min, further tributylphosphine (0.24 mL) was added. After 30 min the reaction mixture was evaporated and the residue was dissolved in THF (20 mL). Water (20 mL) was added and the resulting mixture was heated at reflux for 16 h. Evaporation followed by chromatography (LPC) of the residue (EtOAc/hexane, 1/5) gave unchanged carbamoyl azide **31** (24 mg, 4%). Ethyl acetate/hexane, 3/1, eluted 415 mg (74%) of urea **33** as a white fluffy solid: mp 203–204 °C (from MeOH); R_f 0.69 (EtOAc); ^{1}H NMR δ 2.08 (d, 2 H, C3-CH_2Ph), 2.58 (d, 1 H, J = 10.5, C2-H), 3.57 (m, 3 H, NH_2, NH), 3.98 (m, 1 H, C3-H), 4.32 (2 H, J_{AB} = 13, NCH_2Ph), 6.65 (d, 2 H, J = 6.9, Ar H), 6.99–7.73 (m, 21 H, Ar H). Anal. Calcd for $C_{38}H_{35}N_3O_3$: C, 78.46; H, 6.06; N, 7.22. Found: C, 78.45; H, 6.06; N, 7.21.

(2*S*,3*R*)-Methyl 2-Amino-4-phenyl-3-ureidobutanoate (34). To a solution of urea **33** (137 mg, 0.24 mmol) in dry methanol (15 mL) was added 10% palladium on carbon (50 mg). The mixture was shaken under an atmosphere of hydrogen (55 psi) for 15 h, filtered through Celite, and evaporated. The residue was dissolved in chloroform and extracted with 1 M H_3PO_4 (6×), and the combined aqueous portions were extracted with chloroform/2-propanol (3/1, 6×). The combined organic portions were dried and evaporated to give 44 mg (62%) of the free amine **34**: ^{1}H NMR (CD_3OH) δ 2.82 (qd, 2 H, J_{AB} = 13.7, J_{AX} = 8.2, J_{BX} = 7.3, CH_2Ph), 3.29 (d, 1 H, J = 2.6, C2-H), 3.67 (s, 3 H, CO_2Me), 4.28 (m, 1 H, C3-H), 7.15–7.31 (m, 5 H, Ar H).

(4*R*,5*S*)-4-Benzyl-5-(methoxycarbonyl)-1-(9-phenylfluoren-9-yl)imidazolidin-2-one (36). To a solution of acid **30** (65 mg, 0.136 mmol) in acetonitrile (1.5 mL) were added DPPA (49 mg, 0.177 mmol) and triethylamine (25 μL, 0.177 mmol). After being stirred at 50 °C for 12 h, the reaction mixture was evaporated and the residue was purified by LPC. EtOAc/hexane, 1/1, eluted 58 mg (90%) of **36**: R_f 0.23 (EtOAc/hexane, 1/1); ^{1}H NMR δ 2.41 (dd, 1 H, J = 13.5, 7.9, CH_2Ph), 2.62 (dd, 1 H, J = 13.5, 4.9, CH_2Ph), 3.32 (s, 3 H, CO_2CH_3), 3.55 (d, 1 H, J = 3.4, C5-H), 3.58–3.61 (m, 1 H, C4-H), 4.54 (br s, 1 H, NH), 7.02 (d, 1 H, J = 7.3, Ar H), 7.03 (d, 1 H, J = 7.7, Ar H), 7.14–7.72 (m, 16 H, Ar H).

(4*R*,5*S*)-4-Benzyl-5-carboxy-1-(9-phenylfluoren-9-yl)-imidazolidin-2-one (37). To a solution of ester **36** (51 mg, 0.107 mmol) in THF (0.75 mL) was added 1 M LiOH, (0.75 mL, 0.75 mmol). After stirring at room temperature for 3 days, 1 M NaOH (5 mL) was added, and the solution was washed with ether (3×), acidified to pH 3 with 1 M H_3PO_4, and extracted three times with ethyl acetate. The combined ethyl acetate portions were dried and evaporated to give 45 mg (90%) of **37**: ^{1}H NMR δ 2.38 (dd, 1 H, J = 13.3, 6.9, CH_2Ph), 2.48 (dd, 1 H, J = 13.3, 5.2, CH_2Ph), 3.49 (d, 1 H, J = 2.7, C5-H), 3.65 (m, 1 H, C4-H), 5.95 (br s, 1 H, NH), 6.96 (d, 2 H, J = 7, Ar H), 7.08 (t, 1 H, J = 7.5 Hz), 7.12–7.27 (m, 9 H, Ar H), 7.32 (d, 1 H, J = 7.6, Ar H), 7.41 (t, 1 H, J = 7.3, Ar H), 7.49 (d, 1 H, J = 7.7, Ar H), 7.58 (t, 2 H, J

= 8.2, Ar H), 7.67 (d, 1 H, J = 7.4 Hz, Ar H).

(4*S*,5*R*)-5-Benzyl-4-carboxyimidazolidin-2-one (8b). The urea **37** (30 mg, 0.065 mmol) was deprotected as described for compound **7b** to give 13.7 mg (96%) of **8b**, identical with that described earlier.

(4*S*,5*R*)-5-Benzyl-4-(methoxycarbonyl)imidazolidin-2-one (35). The acid **8b** (22 mg, 0.1 mmol) was stirred in a mixture of methanol (20 mL) and thionyl chloride (5 drops) at room temperature for 12 h. The reaction mixture was concentrated to give the methyl ester **35** in quantitative yield: ^{1}H NMR (CD_3OD) δ 2.91 (d, 2 H, J = 5.8, CH_2Ph), 3.69 (s, 3 H, CO_2CH_3), 4.09–4.15 (m, 2 H, C4-H and C5-H), 7.21–7.34 (m, 5 H, Ar H).

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Enantiodivergent Synthesis of (+)- and (−)-Anatoxin from L-Glutamic Acid

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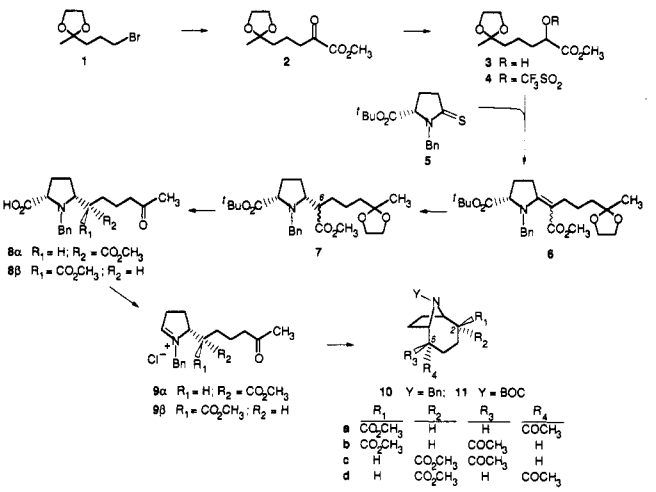
The optically pure 2,5-difunctionalized homotropane **11**, prepared from L-glutamic acid, serves as the common, advanced intermediate for the synthesis of either natural (+)-anatoxin (**30**, 18% overall yield) or unnatural (−)-anatoxin (**33**, 30% overall yield) by selective manipulation of either the C-2 ester or C-5 acetyl functionalities. Side-chain substitution in the decarbonylative iminium ion cyclization of a substituted proline enhanced the yield by 25% as compared to the unsubstituted parent system. The additional substitution at C-5 of the 9-azabicyclo[4.2.1]nonane ring system allows access to analogues of anatoxin not available through other syntheses.

Anatoxin-a, a strong nerve-depolarizing agent isolated from strains of the fresh water blue-green alga *Anabaena flos-aquae* (Lyng.) de Breb,[1] has played a central role in neurotransmission research during the last decade, since it is the most potent agonist known for the nicotinic acetylcholine receptor (nAChR).[2] In our previous publications,[3] we have presented the enantiospecific synthesis of (+)-anatoxin from D-glutamic acid as well as that of a number of its analogues. We have also summarized the synthetic activity of others in this field, all of which led to racemic material.[3f] We now report an enantiodivergent synthesis of either (+)- or (−)-anatoxin proceeding along a common path from L-glutamic acid.

Results and Discussion

Synthesis of 2,5-Difunctionalized Homotropanes 11. The synthesis of our first key intermediate, vinylogous methyl carbamate **6**, follows closely that reported for its benzyl ester analogue[3a] and is presented in Scheme I. The required methyl α-hydroxy ester **3** was prepared from bromo ketal **1**. Thus the Grignard reagent from **1** reacted with dimethyl oxalate to give α-keto ester **2**, which was hydrogenated (Pt/C) to give hydroxy ester **3**. The sulfide-contraction reaction between α-triflate **4** and thiolactam **5** proceeded as previously to give vinylogous carbamate **6** as a 4/1 mixture of double-bond isomers. Strict temperature control during the sulfide-contraction step is critical for the success of this reaction: below −10 °C little or no reaction occurs, while above 0 °C some racemization is observed.[4] Hydrogenation of the carbon–carbon double bond in **6** was achieved over Pd/C in methanol. The initial product contained some N-debenzylated material, and rebenzylation gave proline ester **7** as a 4/1 mixture of epimers at C-6.

Scheme I. Synthesis of 2,5-Difunctionalized Homotropanes



In the previous synthesis,[3] where the vinylogous carbamate was present as its benzyl ester, hydrogenation proceeded by initial O-debenzylation, decarboxylation, and double-bond reduction in a highly stereoselective process.[3a,b,4] The present substitution pattern, in which the ester function is retained at C-6, gave identical results; none of *trans*-pyrrolidine **7** could be detected in the crude product. Acidic hydrolysis then afforded a chromatographically resolvable mixture of keto acids 8α and 8β. Although the stereochemistry at C-6 could not be established at this stage, the stereochemical outcome of the two subsequent steps allowed assignment of 8β (6*R*) to the minor, less polar product and 8α (6*S*) to the major, more polar product.

(1) (a) Carmichael, W. W.; Biggs, D. F.; Gorham, P. R. *Science* **1975**, *187*, 542. (b) Devlin, J. P.; Edwards, O. E.; Gorham, P. R.; Hunter, N. R.; Pike, R. K.; Stavric, B. *Can. J. Chem.* **1977**, *55*, 1367.

(2) (a) Aronstam, R. S.; Witkop, B. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 4639. (b) Swanson, K. L.; Allen, C. N.; Aronstam, R. S.; Rapoport, H.; Albuquerque, E. X. *Mol. Pharmacol.* **1986**, *29*, 250 and references therein.

(3) (a) Petersen, J. S.; Fels, G.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 4539. (b) Koskinen, A. M. P.; Rapoport, H. *J. Med. Chem.* **1985**, *28*, 1301. (c) Petersen, J. S.; Toteberg-Kaulen, S.; Rapoport, H. *J. Org. Chem.* **1984**, *49*, 2948. (d) Sardina, F. J.; Howard, M. H.; Koskinen, A. M. P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 4654. (e) Howard, M. H.; Sardina, F. J.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 2829. (f) Recently (Stjernlöf, P.; Trogen, L.; Andersson, Å, *Acta Chem. Scand.* **1989**, *43*, 917) a resolution of racemic anatoxin has been reported to yield the (+) and (−) enantiomers, $[\alpha]^{20}_D$ +37.0 and −39.7° (lit.[3a] $[\alpha]^{24}_D$ +43.2°, −46.3°).

(4) Shiosaki, K.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1229.

0022-3263/90/1955-5025$02.50/0