Chirospecific Synthesis of (1S,3R)-1-Amino-3-(hydroxymethyl)cyclopentane, Precursor for Carbocyclic Nucleoside Synthesis. Dieckmann Cyclization with an α-Amino Acid

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Received November 24, 1992

Carbocyclic nucleosides are important isosteres of nucleosides possessing a variety of antiviral and antineoplastic activities. We report here a new method for the chirospecific synthesis of (1S,3R)-1-amino-3-(hydroxymethyl)cyclopentane. This compound is a key precursor for the synthesis of some carbocyclic nucleosides. The method involves (1) an improved synthesis of (S)-2-aminoadipic acid; (2) Dieckmann cyclization of this α-amino acid to an aminocyclopentanone; and (3) elaboration of the latter to the target (1S,3R)-1-amino-3-(hydroxymethyl)cyclopentane. The starting (S)-2-aminoadipic acid δ-methyl ester was prepared enantiomerically pure from (S)-aspartic acid in 51% overall yield. Dieckmann condensation converted this amino acid to a (methoxycarbonyl)-cyclopentanone, and reduction of the ketone followed by elimination yielded (S)-3-[N-(9-phenylfluoren-9-yl)amino]-1-(methoxycarbonyl)cyclopentene. Reduction of the double bond gave a mixture of the cis and trans diastereomers. This mixture was converted to a single diastereomer by epimerization and trapping of the cis isomer as (1S,4R)-2-(9-phenylfluoren-9-yl)-2-azabicyclo[2.2.1]heptan-3-one. Hydrolytic cleavage of the lactam followed by reduction gave (1S,3R)-1-amino-3-(hydroxymethyl)-cyclopentane.

Introduction

Carbocyclic nucleosides are important isosteres of nucleosides. Both chemically and enzymatically they are more stable than nucleosides, and this stability can offer distinct advantages in the therapeutic use of carbocyclic nucleosides. They possess a variety of antiviral[1] and antineoplastic activities.[2] In recent years these nucleosides have seen potential application as antiviral agents.[3,4] Most carbocyclic nucleosides are synthetic in origin; however, two examples from nature are neplanocin A[5] and aristeromycin.[6] Since the biological activity of these compounds usually resides in only one enantiomer, the development of enantiospecific syntheses is of great importance.

Two general methods for the preparation of carbocyclic nucleosides have been widely used.[7] The first is the condensation of adenine with a substituted cyclopentane (or pentene) containing an appropriate leaving group. Other types of electrophilic sites on the cyclopentane such as epoxides and vinyl nitro functions also have served for coupling to the heterocyclic base. Methods for the chiral syntheses of these ribose isosteres have been reviewed.[8] A particular problem with this route is the poor yield of coupled products. This is often due to alkylation at other sites on the base, hindrance at the electrophilic site, and accompanying elimination.

A second general method for the synthesis of carbocyclic nucleosides is the conversion of a cyclopentylamine to a carbocyclic nucleoside.[9] The purine nucleosides have been prepared via the Traube method[10] and the pyrimidines have been prepared by the method of Shaw and Warrener.[11] This method avoids problems inherent in the use of the base as a displacing nucleophile at the cost of additional steps in the synthesis. The asymmetric synthesis of the requisite substituted cyclopentylamines has recently been reviewed.[12] It is of interest to note that several syntheses in this class make use of substituted cyclopentanes which are then treated with an NH_2^- synthon such as N_3^-.[13] Reduction or deprotection then yields the aminocyclopentane. An additional route to the chiral preparation of carbocyclic nucleosides is the enzymatic resolution of carbocyclic nucleotides; thus the use of calf liver alkaline phosphatase or snake venom 5′-nucleotidase has been reported to resolve the monophosphate of some N-substituted carbocyclic adenosine derivatives.[14]

We now report a new method for the preparation of hydroxymethyl-substituted cyclopentylamines which can

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(7) Marquez, V. E.; Lim, M.-I. *Med. Res. Rev.* **1986**, *6*, 1.
(8) Reviewed in: Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571. Some other recent examples are: (a) Copp, R. R.; Marquez, V. E. *J. Med. Chem.* **1991**, *34*, 208. (b) Saville-Stones, E. A.; Lindell, S. D.; Jennings, N. S.; Head, J. C.; Ford, M. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2603. (c) Roberts, S. M.; Shoberu, K. A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2605. (d) Jones, M. F.; Myers, P. L.; Robertson, C. A.; Storer, R.; Williamson, C. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2479. (e) Peel, M. R.; Sternbach, D. D.; Johnson, M. R. *J. Org. Chem.* **1991**, *56*, 4990. (f) Wolfe, M. S.; Anderson, B. L.; Borcherding, D. R.; Borchardt, R. T. *J. Org. Chem.* **1990**, *55*, 4712.
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(10) Lister, J. H. In *Fused Pyrimidines*; Brown, D. W.; Ed.; Wiley, 1971; Part II, p 31.
(11) (a) Shaw, G.; Warrener, R. N. *J. Chem. Soc.* **1958**, 153. (b) Shaw, G.; Warrener, R. N. *J. Chem. Soc.* **1958**, 157.
(12) (a) Reviewed in ref. 8. Other more recent articles are: (b) Coe, D. M.; Parry, D. M.; Roberts, S. M.; Storer, R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2373. (c) Vanhessche, K.; Gonzalez Bello, C.; Vandewalle, M. *Synlett.* **1991**, 921.
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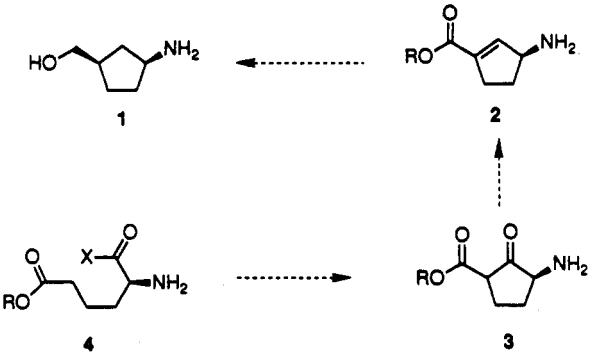
(14) Daluge, S. M. Eur. Pat. Appl. 434450, June 26, 1991.

0022-3263/93/1958-2369$04.00/0

Scheme I. Projected Synthesis of (1S,3R)-1-Amino-3-(hydroxymethyl)cyclopentane (1)



be used in the synthesis of carbocyclic nucleosides. This method involves (1) an improved synthesis of (*S*)-2-aminoadipic acid; (2) Dieckmann cyclization of this α-amino acid to an aminocyclopentanone; and (3) elaboration of the latter to the target (2*S*,3*R*)-1-amino-3-(hydroxymethyl)cyclopentane (1). All reactions proceeded with total enantiomeric integrity. Our planned synthesis of the cyclopentanes is shown in Scheme I.

We projected that the cyclopentane ring could be formed via a Dieckmann condensation of a substituted α-amino acid **4**. Although no Dieckmann cyclizations of α-amino esters have been reported, the advent of the 9-phenylfluoren-9-yl protecting group for nitrogen presaged that such an anionic reaction could occur with no loss of enantiomeric integrity. The β-keto ester **3** obtained from the Dieckmann reaction then could be readily converted to the cyclopentane **1** via the cyclopentene **2**. The requisite amino acid needed for the Dieckmann cyclization was (*S*)-2-aminoadipic acid.

Results and Discussion

Synthesis of (*S*)-2-Aminoadipic Acid. The published syntheses of (*S*)-2-aminoadipic acid proved limiting[15] and required development of a new method. Our synthesis starts with aspartic acid (**5**) as shown in Scheme II and used the α-*tert*-butyl aspartic ester derivative **10** as starting material. Since the reported preparation of this compound proceeds in only 24% yield from aspartic acid,[16] a better synthesis was clearly needed if it were to be the starting material for a practical synthesis of aminoadipic acid **17**. Thus, using the same protocol developed for the synthesis of the β-methyl ester of aspartic acid, the β-benzyl ester was prepared[17] via the dibenzyl ester **6**, accomplished in 95% yield with benzyl alcohol and pTSA in benzene. The Cu(II)-assisted hydrolysis of the α-ester proceeded to give monoester **7** in 98% yield. This compound was shown to be enantiomerically pure as detailed below. The reported preparation of **7** produces the ester in only 40–45% yield.[18]

The amino group was protected as the BOC derivative, and esterification of the free acid was done with O-*tert*-butyl-*N*,*N*′-diisopropylisourea[19] to yield the triprotected aspartate derivative **9**. Then the β-benzyl ester was cleaved by hydrogenolysis to give β-acid **10** in quantitative yield, the overall yield for the conversion of aspartic acid to **10** being 83% (lit.[16] yield, 24%). Next, a better yielding route to the aldehyde **12** was needed. An overall yield of 54% has been reported[15k] for **12** via the reduction of acid **10** ($ClCO_2Et/NaBH_4$) followed by CrO_3/pyridine oxidation. Other combinations of reducing agents and oxidants in our hands failed to improve the yield for this transformation. We considered that reduction of a thioester might provide a high yielding route to **12** and this was applied to thioester **11** using a deactivated Raney-Ni which gave a 62% yield of **12**; however, triethylsilane/Pd/C[20] gave the aldehyde **12** in 83–97%.[21]

Wittig reaction with [(methoxycarbonyl)methylene]-triphenylphosphorane gave the α,β-unsaturated ester **13**. This useful intermediate could be converted to δ-methyl ester hydrochloride **16** with essentially a single isolation. The double bond was reduced to give adipic acid diester **14**, which was usually not isolated but the catalyst removed and the crude product treated with anhydrous HCl. After 24 h the hydrochloride salt of the δ-ester α-amino acid **16** was obtained in quantitative yield. If the deprotection reaction is halted after 3 h, the amine hydrochloride **15** can be obtained. Since the use of the hydrochloride salt **16** gave erratic results in the following step, the salt was converted to the zwitterion **17** in 77% yield by treatment with propylene oxide. Our synthesis of **16** proceeds in 60% overall yield from aspartic acid and is a scalable, convenient route using readily available reagents.

Dieckmann Cyclization. Two regio-modes of Dieckmann cyclization are possible. In order to direct the cyclization to the required regio-orientation, two modifications to the molecule were carried out. The first was protection of the amine as the *N*-(9-phenylfluoren-9-yl) derivative **19** (Scheme III). This protecting group previously has been shown to inhibit deprotonation at the carbon to which the nitrogen is attached.[17,22] An alternate route to **19** is first to selectively remove the BOC group from **14** to yield primary amine **15**. The *N*-(9-phenylflu-

(15) The reported preparations of (*S*)-2-aminoadipic acid can be classed into five groups: (1) The oxidation of lysine and lysine derivatives: (a) Mochizuki, K.; Yamazaki, Y.; Maeda, H.; Suzuki, H. Jpn. Kokai Tokkyo Koho JP 01 98,495 [89 98,495], *Chem. Abstr.* **1989**, *111*, 152190k. (b) Yoshifuji, S.; Tanaka, K.-I.; Kawai, T.; Nitta, Y. *Chem. Pharm. Bull.* **1985**, *33*, 5515. (c) Sakuri, N.; Hirose, K.; Hashimoto, T. *Chem. Pharm. Bull.* **1986**, *34*, 3506. (d) Buckley, T. F.; Rapoport, H. *J. Am. Chem. Soc.* **1982**, *104*, 4446. (e) Jensen, S. E.; Westlake, D. W. S.; Bowers, J. R.; Ingold, C. F.; Jouany, M.; Lyubechansky, L.; Wolfe, S. *Can. J. Chem.* **1984**, *62*, 2712. (f) Baldwin, J. E.; Killin, S. J.; Adlington, R. M.; Speigel, U. *Tetrahedron* **1988**, *44*, 2633. (g) Scott, A. I.; Wilkinson, T. J. *Synth. Commun.* **1980**, *10*, 127. (h) Kondo, M.; Miyazaki, K.; Kodama, H.; Horimoto, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1171. (2) The homologation of glutamic or aspartic acid: (i) Rudinger, J.; Farkasova, H. *Coll. Czech. Chem. Commun.* **1963**, *28*, 2941. (j) Pellicciari, R.; Natalini, B.; Marinozzi, M. *Synth. Commun.* **1988**, *18*, 1707. (k) Ramsamy, K.; Olsen, R. K.; Emery, T. *Synthesis* **1982**, 42. (3) The resolution of 2-aminoadipic acid: (l) Wolfe, S.; Jokinen, M. G. *Can. J. Chem.* **1979**, *57*, 1388. (m) Greenstein, J. P.; Birnbaum, S. M.; Otey, M. C. *J. Am. Chem. Soc.* **1953**, *73*, 1994. (n) Shostakavskii, M. F.; Rabinovich, M. S.; Preobrazhenskaya, E. V.; Zykova, G. N. *Z. Obsch. Khim.* **1960**, *30*, 67. (o) Rabinovich, M. S.; Shostakovskii, M. F.; Preobrazhenskaya, E. V. *Z. Obs. Khim.* **1960**, *30*, 71. (p) Claesen, M.; Laridon, G.; Vanderhaeghe, H. *Bull. Soc. Chim. Belges* **1968**, *77*, 579. (q) Claesen, M.; Vlietinck, A.; Vanderhaeghe, H. *Bull. Soc. Chim. Belges.* **1968**, *77*, 587. (r) Khan, N. H.; Ali, M.; Panda, H. *J. Indian Chem. Soc.* **1982**, *59*, 1077 (*Chem. Abstr.* **98**, 161132h). (4) An enzymatic reductive amination: (s) Matos, J. R.; Wong, C. H. *J. Org. Chem.* **1986**, *51*, 2388. (5) An Ugi reaction: (t) Kunz, H.; Pfrengle, W. *J. Am. Chem. Soc.* **1988**, *110*, 651. (u) Kunz, H.; Pfrengle, W. *Tetrahedron* **1988**, *44*, 5487.

(16) Yang, C. C.; Merrifield, R. B. *J. Org. Chem.* **1976**, *44*, 5487.

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

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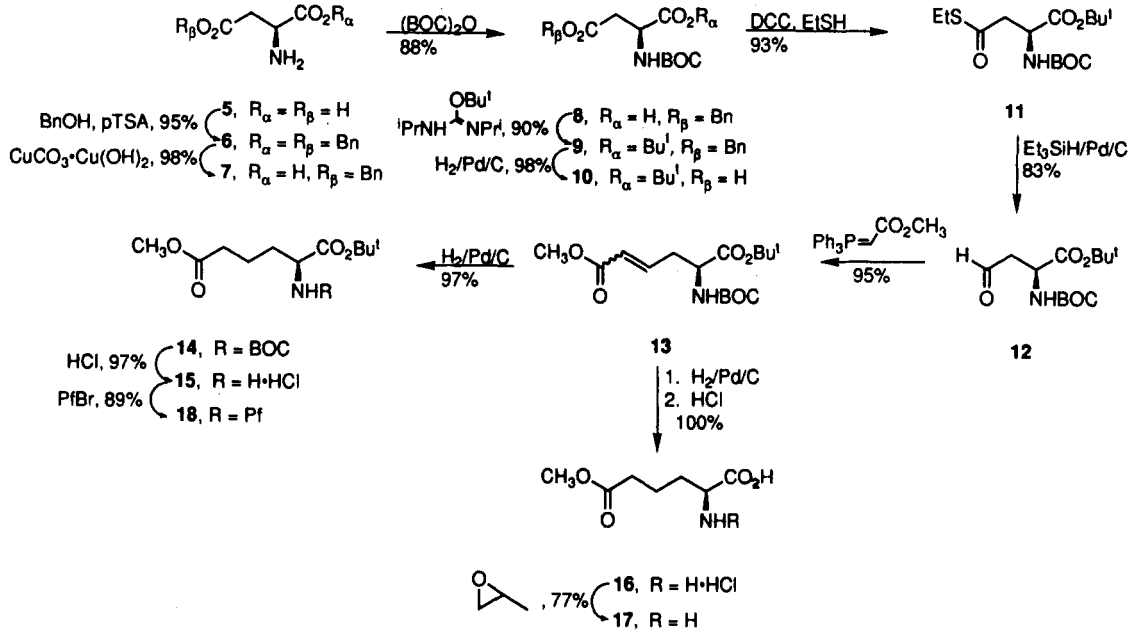
(19) Mathias, L. J. *Synthesis* **1979**, 561.

(20) Fukuyama, T.; Lin, S.-C.; Li, L. *J. Am. Chem. Soc.* **1990**, *112*, 7050.

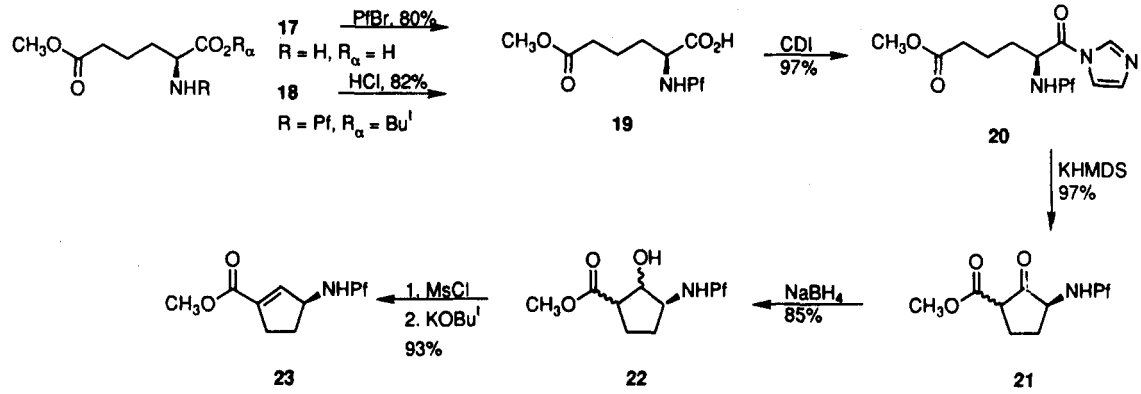
(21) On a scale of 10 mmol of thioester **11**, a yield of 97% was obtained. Upon scaling up the reaction to 45 mmol, the yield dropped to 83%. Intermediate scale reactions (16 and 28 mmol) gave yields of 92 and 88%, respectively. This may be due to difficulty in controlling the temperature of the reaction upon addition of the Et_3SiH in the larger scale reactions. If the temperature is not kept below 20 °C, the yield of the reaction is dramatically decreased (approx. 50%) irrespective of the scale of the reaction.

(22) (a) Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1987**, *109*, 236. (b) Dunn, P. J.; Häner, R.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 5017. (c) Wolf, J.-P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 3164.

Scheme II. Synthesis of (*S*)-2-Aminoadipic Acid from Aspartic Acid



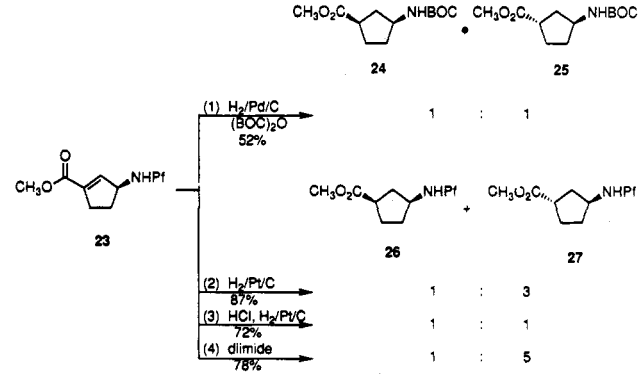
Scheme III. Dieckmann Cyclization of α-Aminoadipic Acid Derivative and Conversion to a Cyclopentene



orene) group then can be introduced to give protected amine **18** in 89% yield. This preparation of a *N*-(9-phenylfluorene) derivative avoids the use of $Pb(NO_3)_2$ as a bromide scavenger by carrying out the reaction in CH_3NO_2. Treatment of **18** with anhydrous HCl in EtOAc gives **19** in 82% yield. While the yields of the two routes are similar, operationally the latter route is preferred due to ease of manipulation.

The second modification of the amino acid was to increase the reactivity of the α-carbonyl. This was done by treating the α-carboxylic acid with carbonyl diimidazole to form imidazolide **20** which was used directly in the Dieckmann condensation[23] to give the keto ester **21** in excellent yield as a 3/2 mixture of diastereomers as determined by ^1H NMR. Purification of **21** proved difficult, as this compound decomposed on attempted silica gel chromatography as well as on storage. Thus the crude keto ester was immediately reduced with $NaBH_4$ to the hydroxy ester **22** as a mixture of all four possible diastereomers in a ratio of 1/3/3/1. The stereochemistry of the individual diastereomers was not determined as both stereocenters were to be eliminated in the next step. Using other reducing agents (DIBALH, L-Selectride) gave poorer overall yields of alcohol **22**. Elimination from

Scheme IV. Attempted Diastereoselective Reduction of 23



hydroxy ester **22** to α,β-unsaturated ester **23** was carried out by sequential treatment with methanesulfonyl chloride followed by $KOBu^t$ to give cyclopentene **23** in 93% yield; isolation of the intermediate mesylate gave much poorer overall yields of **23**.

Cyclopentene Reduction. A stereoselective hydrogenation of cyclopentene **23** from the less hindered face of the molecule to yield a *cis*-amino ester proved more difficult than anticipated. Our initial plan (Scheme IV) was first to reduce the double bond of **23**, then to remove the phenylfluorenyl group and replace it with a BOC protecting group without isolating intermediates. This sequence gave a 1/1 mixture of **24** and **25** in a disappointing

(23) A corresponding Dieckmann cyclization has been carried out with the dimethyl ester to give enantiomerically pure β-keto ester in excellent yield; Park, K.-H., this laboratory.

52% yield. It suggested, however, that retaining the very bulky phenylfluorenyl group might aid in directing hydrogenation to the less hindered face of the molecule. A variety of solvents and catalysts were examined for the conversion of **23** to **26**. The combination of 5% Pt/C in EtOAc gave the best yields of the reduced material without loss of the phenylfluorenyl group, an 87% yield of **26/27** in a 1/3 ratio. NOESY experiments (Figure 1) showed that the minor isomer was the desired **26**. Apparently the NHPf group has an unexpected directing effect, inducing hydrogenation from the seemingly more hindered side of the molecule. Attempts to influence the cis/trans ratio by varying the catalyst or solvent proved limited. We thought that perhaps changing the complexing ability of the NHPf group might influence the cis/trans ratio. To this end **23** was protonated and the hydrogenation carried out as before. Reduction of this acidic solution gave a 72% yield of **26** and **27** and did change the ratio to 1/1. Reduction of the double bond with diimide (generated from dipotassium azodicarboxylate and AcOH)[24] heavily favored the trans isomer, giving a 78% yield of **26** and **27** in a ratio of 1/5 (Scheme IV).

We then examined the reduction of the allylic alcohol **28**, which could be prepared from ester **23** in 94% yield (Scheme V). Once again catalytic hydrogenation using 5% Pt/C gave the *trans*-alcohol **30** as the major product, although only in a ratio of 2/1. The relative stereochemistry of **29** and **30** was assigned based on NOESY experiments (Figure 1) and were confirmed by an X-ray crystallographic structure determination of **30** (Figure 2).[25] This clearly shows that the major alcohol **30** has the NHPf group trans to the hydroxymethyl group. Further confirmation of the stereochemical assignments was obtained by reduction of the ester **26** with $LiAlH_4$ to yield the alcohol **29**, and similar reduction of **27** gave the alcohol **30** (Scheme V). Thus the major isomer from the hydrogenation of α,β-unsaturated ester **23** is the *trans*-ester **27** and the major isomer in the hydrogenation of allylic alcohol **28** is *trans*-alcohol **30**. Reduction of the hydrochloride salt of **28** gave a 1/1 mixture of **29** and **30** in only 32% yield, the remainder being polymeric material. Again, reduction of **28** using diimide resulted primarily in the trans isomer, giving **29** and **30** in a ratio of 1/10 and an overall yield of 73%.

Since hydrogenation of either **23** or **28** would not provide an acceptable yield of the cis product, we turned to an isomerization of the trans isomer that might give an acceptable conversion to the cis product (Scheme VI). Treatment of *trans*-ester **27** with catalytic NaOMe in refluxing MeOH gave a 91% yield of **26** and **27** in a ratio of 1/5, thus establishing that equilibration had occurred. To examine whether kinetic capture of the enolate of **27** would give a better cis/trans ratio, *trans*-ester **27** first was treated with LDA followed by a variety of quenching agents (AcOH, camphorsulfonic acid, 2,6-di-*tert*-butyl-4-methylphenol); all gave a 1/1 ratio of **26/27** in 90–95% yield. By separating *cis*- and *trans*-esters from the hydrogenation of the hydrochloride of **23** (Scheme IV, entry 3) and epimerizing the *trans*-ester **27** (LDA followed by an AcOH quench), an overall 69% yield of the desired *cis*-ester **26** can be obtained from **23**.

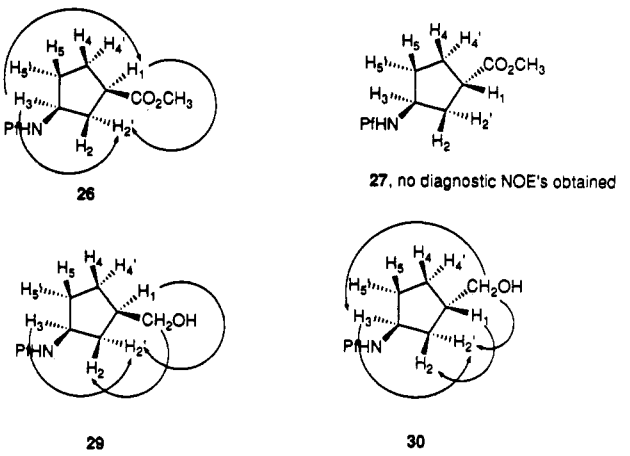


Figure 1. NOE interactions derived from NOESY experiments.

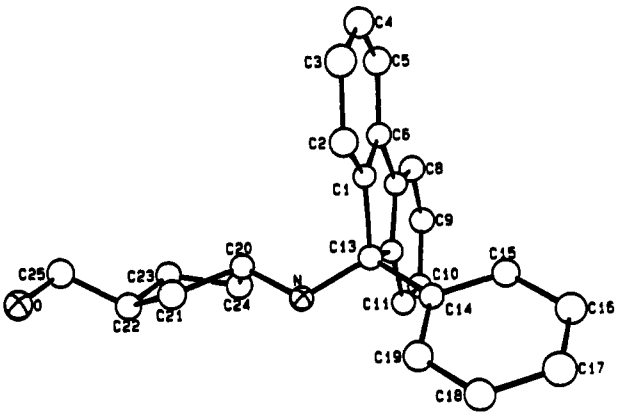


Figure 2. Structure of (1*S*,3*S*)-1-[*N*-(9-phenylfluoren-9-yl)-amino]-3-(hydroxymethyl)cyclopentane (**30**) as determined by X-ray crystallography.

An alternative method for the conversion of **23** to a compound with cis stereochemistry is outlined in Scheme VI. Our plan was to prepare a mixed anhydride of the acid obtained from the mixture of **26/27** without acylating the secondary amino group, since such acylation would preclude lactam formation. The phenylfluorenyl protecting group does function in exactly that way; all attempts at intermolecular alkylation or acylation of phenylfluorenylamines have failed. Also, preparing the mixed anhydride would enhance the acidity of the α-proton, allowing epimerization to be effected by a mild base. Thus the isomerized mixed anhydride would trap the cis compound as the lactm since such intramolecular acylation would not be inhibited by the phenylfluorenyl group. Operationally the 1/3 mixture of **26** and **27** from the hydrogenation was hydrolyzed with LiOH to yield the lithium carboxylate **31** which was dried and treated with NaOAc in refluxing Ac_2O to yield the bicyclic lactam **32** in 97% yield. In this way the unfavorable 1/3 mixture of esters **26** and **27** was converted to the single *cis*-lactam **32**. Hydrolysis of the lactam in refluxing AcOH/6 M HCl (2/1) gave the crude amino acid **33**, which was directly reduced to the amino alcohol **1**[26] in 76% yield. The alcohol **35** can be obtained in 89% yield by reductive removal of the phenylfluorenyl group from **30**.

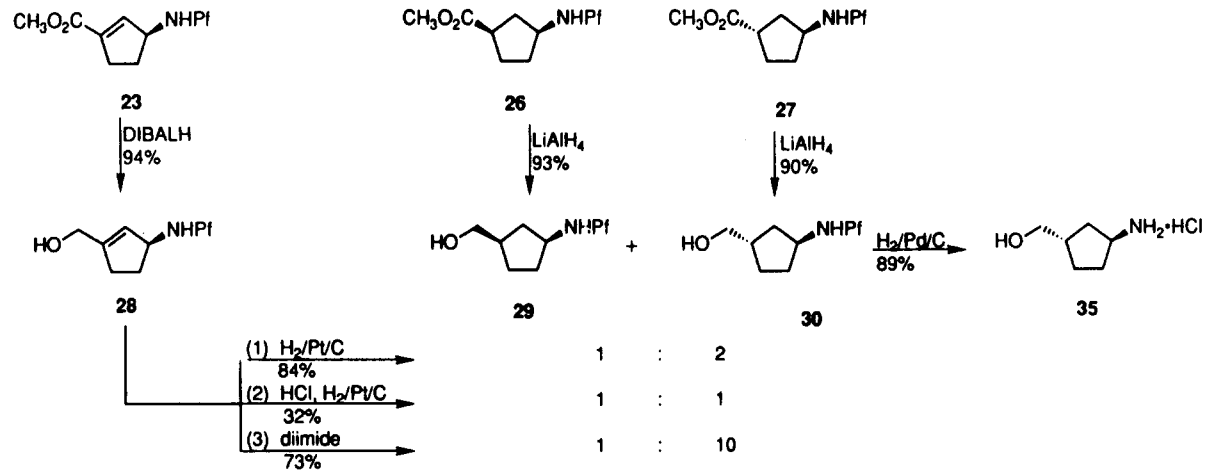
Determination of Enantiomeric Ratios. The dibenzyl ester **6** was prepared as reported for the synthesis of

(24) Pasto, D. J.; Taylor, R. T. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1991; Vol. 40, Chapter 2, pp 91–156.

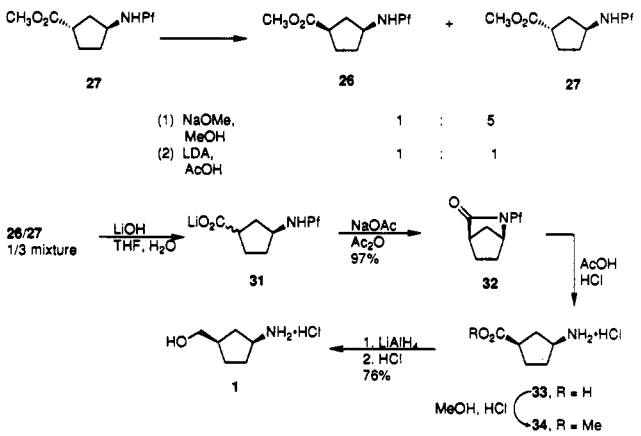
(25) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(26) Compound **1** was prepared in racemic form and the ^1H NMR reported: Hronowski, L. J. J.; Szarek, W. A. *Can. J. Chem.* **1988**, *66*, 61. For other preparations of **1** in which no spectral data are reported, see ref 3 (racemic) and 9 (1*S*,3*R*).

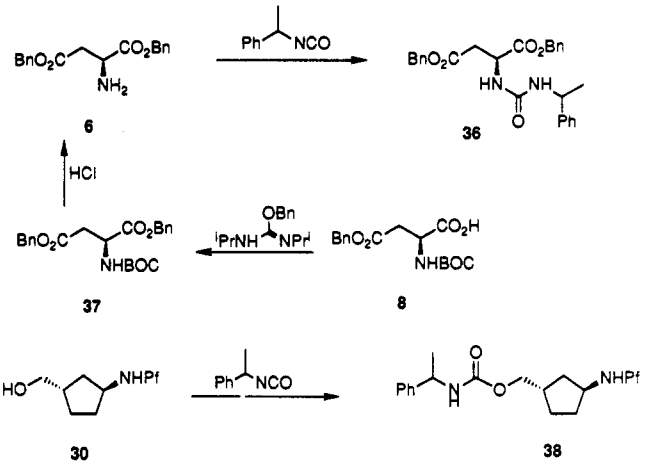
Scheme V. Preparation and Transformations of 28



Scheme VI. Epimerization and Conversion of 26/27 to (1*S*,3*R*)-1-Amino-3-(hydroxymethyl)cyclopentane (1)



Scheme VII. Derivatization to Determine Enantiomeric Ratios



dibenzyl glutamate.[27] This procedure calls for removal of water from a mixture of the amino acid, pTSA, and benzyl alcohol in refluxing benzene. After the appropriate reaction time a 98% yield of the diester **6** was obtained. The reaction time and amount of pTSA are critical to the success of the reaction. Using 105 mol% of pTSA the reaction is only 80% complete after 3.5 h. Continuing the reaction for 24 h gives a 90% yield of the diester **6**. The enantiomeric ratio (er) for this material was determined by derivatization with (*R*)-1-phenethyl isocyanate[28] to yield the urea **36**. Analysis of this urea by HPLC showed an er of 85/15. When the amount of pTSA was increased to 125 mol% and the reaction time shortened to 3.5 h, a yield of 95% was obtained, and the er was >99.5/0.5 (limits of detection). Apparently the long reaction time (24 h) under the acidic conditions causes the high degree of racemization; shortening the reaction time and increasing the amount of pTSA led to no detectable racemization.

In order to ascertain if any loss of enantiomeric integrity had occurred during the selective hydrolysis of the α-ester, monobenzyl ester **8** was treated with *O*-benzyl-*N*,*N*′-diisopropylisourea[19] to yield dibenzyl ester **37** (Scheme VII). The BOC group was removed with HCl to yield amine **6** as the hydrochloride salt. Derivatization with the isocyanate, followed by HPLC analysis showed an er of >99.5/0.5.

The diastereomeric purity of **30** was determined by preparing the carbamate **38** with (*R*)-1-phenethyl isocyanate, and its er also was shown to be >99.5/0.5, indicating the same er for cis isomer **29**, prepared by an identical sequence of transformations.

Conclusion

We report the first asymmetric synthesis of **1** by a novel Dieckmann cyclization of an α-amino acid. This compound is an important precursor for the asymmetric synthesis of carbocyclic nucleosides. Additionally we have reported the first asymmetric synthesis of the *trans*-amino alcohol **35**. We have also reported an improved synthesis of (*S*)-2-aminoadipic acid and derivatives.

Experimental Section

General. All reactions were conducted under an atmosphere of dry nitrogen unless otherwise noted. THF was distilled from Na/benzophenone; CH_3OH was distilled from Mg; CH_2Cl_2 and benzene were distilled from CaH_2. Chromatography was carried out using 230–400 mesh silica gel. NMR spectra were taken in $CDCl_3$ unless otherwise noted; coupling constants are reported in hertz; and 2D NOESY experiments were conducted using a phase-sensitive NOESY pulse program on a Bruker AM-500 spectrometer. Final solutions before evaporation were dried over $MgSO_4$.

(*S*)-Dibenzyl Aspartate *p*-Toluenesulfonate (6). A mixture of (*S*)-aspartic acid (10.1 g, 75.9 mmol), *p*-toluenesulfonic acid (18 g, 94.6 mmol), benzyl alcohol (50 mL, 483 mmol), and benzene (75 mL) was heated at reflux with a Dean–Stark trap for 3.5 h. The reaction mixture was cooled to room temperature and evaporated, CH_3OH (200 mL) was added and warmed to dissolve the residue, then Et_2O (800 mL) was added, and the resulting suspension was stirred for 20 min and then filtered.

(27) Zervas, L.; Winitz, M.; Greenstein, J. P. *J. Org. Chem.* **1957**, *22*, 1515.

(28) Cairns, T. L. *J. Am. Chem. Soc.* **1941**, *63*, 871.

The filter cake was washed three times with Et_2O and dried to give 35.0 g (95% yield) of **6** as a white solid: $[\alpha]^{20}_D$ +5.2° (*c*, 1, $CHCl_3$); mp 155–156 °C, (lit.[27] mp 159–160 °C); ^1H NMR δ 8.41 (br s, 3 H), 7.71 (d, *J* = 8.1, 2 H), 7.27–7.14 (m, 10 H), 7.00 (d, *J* = 8, 2 H), 4.99 (d, *J* = 6, 2 H), 4.89 (s, 2 H), 4.47 (m, 1 H), 3.15 (dd, *J* = 18, 4.8, 1 H), 3.05 (dd, *J* = 18, 5.2, 1 H), 2.25 (s, 3 H); ^{13}C NMR δ 169.7, 167.9, 141.3, 140.1, 135.1, 134.5, 128.8, 128.4, 128.3, 128.2, 128.2, 126.0, 68.1, 67.0, 49.6, 33.8, 21.3.

(*S*)-Aspartic Acid β-Benzyl Ester *p*-Toluenesulfonate (7). The dibenzyl ester *p*-toluenesulfonate **6** (4.73 g, 10.0 mmol) was dissolved in hot EtOH (75 mL), and H_2O (250 mL) and $CuCO_3$·Cu$(OH)_2$ (11.1 g, 50 mmol) were added. The mixture was vigorously stirred and heated at 70 °C for 2 h after which it was cooled to room temperature, H_2S was passed through until the pH was 2.3, the mixture was filtered through Celite, and the filtrate was evaporated and dried to give 3.77 g (98% yield; when the scale was increased to 60 mmol, the yield was 95%) of **7**: $[\alpha]^{20}_D$ +6.3° (*c*, 0.5, MeOH); ^1H NMR (D_2O) δ 7.51 (d, *J* = 8.2, 2 H), 7.25 (m, 5 H), 7.17 (d, *J* = 8.2, 2 H), 5.03 (s, 2 H), 4.07 (t, *J* = 5.6, 1 H), 2.93 (d, *J* = 5.6, 2 H), 2.2 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 169.7, 169.5, 145.4, 137.8, 135.7, 128.4, 128.1, 128.0, 125.5, 66.1, 49.0, 34.6, 20.8.

β-Benzyl (*S*)-*N*-(*tert*-Butoxycarbonyl)aspartate (8). To a solution of **7** (1.083 g, 2.7 mmol) in H_2O/THF, 1/1 (25 mL) were added triethylamine (1.3 mL, 30 mmol) and $(BOC)_2O$ (1.2 g, 5.5 mmol). After being stirred for 12 h at rt, the reaction mixture was diluted with EtOAc (50 mL), the organic layer was extracted with water (2 × 25 mL), the aqueous layer was acidified to pH 3 with 3 M HCl and extracted with EtOAc (2 × 50 mL), and the combined organic phase was dried and evaporated to give 748 mg (88% yield; on a 41 mmol scale, the yield was 90%) of **8** as a white solid: $[\alpha]^{20}_D$ −19.6° (*c*, 0.25, DMF); mp (EtOAc) 112–114 °C; IR ($CHCl_3$) 1730 cm^{-1}; ^1H NMR δ 7.34 (m, 5 H), 5.60–5.57 (m, 1 H), 5.13 (s, 2 H), 4.62–4.57 (m, 1 H), 3.10–3.04 (m, 1 H), 2.89 (dd, *J* = 17.1, 4.6, 1 H); ^{13}C NMR δ 175.4, 171.0, 155.5, 135.2, 128.5, 128.3, 128.2, 80.3, 66.9, 50.0, 36.7, 28.3. Anal. Calcd for $C_{16}NO_6H_{21}$: C, 59.4; H, 6.5; N, 4.3. Found: C, 59.3; H, 6.5; N, 4.3.

α-*tert*-Butyl β-Benzyl (*S*)-*N*-(*tert*-Butoxycarbonyl)aspartate (9). *O*-*tert*-Butyl-*N*,*N*′-diisopropylisourea (36 g, 180 mmol) was added to a solution of monoacid **8** (39.3 g, 121 mmol) in CH_2Cl_2 (250 mL). The reaction mixture was slowly warmed to reflux and maintained at reflux for 12 h. *O*-*tert*-Butyl-*N*,*N*′-diisopropylisourea (36 g, 180 mmol) was added again and reflux was continued for an additional 24 h. Cooling, filtering, and evaporating left a residue which was dissolved in 10% EtOAc/hexane and filtered through silica gel (230–400 mesh). Evaporation of the filtrate gave 41.6 g (90% yield) of **9** as a white solid: $[\alpha]^{20}_D$ +21.8° (*c*, 0.27, $CHCl_3$); mp (hexane) 64–65 °C; IR ($CHCl_3$) 1720 cm^{-1}; ^1H NMR δ 7.37–7.30 (m, 5 H), 5.41 (d, *J* = 8.2, 1 H), 5.08–4.98 (m, 2 H), 4.40–4.34 (m, 1 H), 2.90 (dd, *J* = 4.5, 16.7, 1 H), 2.73 (dd, *J* = 4.8, 16.7, 1 H), 1.35 (s, 9 H), 1.32 (s, 9 H); ^{13}C NMR δ 170.8, 169.8, 155.3, 135.5, 128.5, 128.3, 128.2, 82.3, 79.8, 66.6, 50.5, 37.0, 28.3, 27.8. Anal. Calcd for $C_{20}H_{29}NO_6$: C, 63.2; H, 7.7; N, 3.4. Found: C, 63.6; H, 7.8; N, 3.5.

α-*tert*-Butyl (*S*)-*N*-(*tert*-Butoxycarbonyl)aspartate (10). A mixture of the ester **9** (38.8 g, 102.2 mmol) and 5% Pd/C (2.8 g) in 95% EtOH (250 mL) was shaken with hydrogen at 60 psi for 2 h. The mixture was then filtered and evaporated to give 29.0 g (98% yield) of **10** as a white crystalline solid: $[\alpha]^{20}_D$ −17.2° (*c*, 1.7, EtOH) [lit.[16] $[\alpha]^{20}_D$ −14° (*c*, 1, EtOH)]; mp (hexane) 99–100 °C [lit.[17] 97–98 °C]; ^1H NMR δ 5.47 (d, *J* = 7.9 Hz, 1 H), 4.47–4.40 (m, 1 H), 3.01 (dd, *J* = 17.1, 4.0, 1 H), 2.82 (dd, *J* = 17.1, 4.4, 1 H), 1.45 (s, 18 H); ^{13}C NMR δ 176.3, 169.7, 155.5, 82.4, 80.1, 50.2, 36.8, 28.2, 27.8.

α-*tert*-Butyl β-*S*-Ethyl (*S*)-*N*-(*tert*-Butoxycarbonyl)thioaspartate (11). To a solution of **10** (17.5 g, 60.6 mmol) in CH_2Cl_2 (120 mL) was added DCC (15.0 g, 73 mmol), ethanethiol (11.3 g, 182.0 mmol), and DMAP (700 mg, 6 mmol). The reaction mixture was stirred at room temperature for 3 h, then filtered, evaporated, and chromatographed (10% EtOAc/hexane) to give 18.9 g (93% yield) of **11** as a clear oil: $[\alpha]^{20}_D$ +41.7° (*c*, 1, $CHCl_3$); IR (film) 1720 cm^{-1}; ^1H NMR δ 5.41 (d, *J* = 7.8, 1 H), 4.40 (m, 1 H), 3.15 (dd, *J* = 16.4, 4.6, 1 H), 3.02 (dd, *J* = 16.2, 4.6 1 H), 2.95–2.84 (m, 2 H), 1.45 (s, 9 H), 1.44 (s, 9 H), 1.24 (t, *J* = 7.4, 3 H); ^{13}C NMR δ 196.9, 169.6, 155.2, 82.2, 79.7, 50.8, 45.5, 28.2, 27.8, 23.4, 14.6. Anal. Calcd for $C_{15}H_{27}NO_5S$: C, 54.0; H, 8.2; N, 4.2. Found: C, 53.9; H, 8.1; N, 4.2.

***tert*-Butyl (*S*)-2-[*N*-(*tert*-Butoxycarbonyl)amino]-4-oxobutanoate (12).** Triethylsilane (15.7 g, 135 mmol) was quickly added to a solution of **11** (15.0 g, 45 mmol) and 10% Pd/C (960 mg, 0.90 mmol) in CH_2Cl_2 (90 mL) cooled in an ice bath to maintain the internal temperature between 15–20 °C. The reaction was monitored for 20 min after which the temperature no longer increased (if the temperature is not monitored and kept below 20 °C the yield drops to 56%). The reaction mixture was then filtered, evaporated, and chromatographed (15% EtOAc/hexane) to give 10.3 g (83% yield) of **12** as a clear oil: $[\alpha]^{20}_D$ −24.3° (*c*, 1.5, EtOH), [lit.[15k] $[\alpha]^{20}_D$ −21.6° (*c*, 1.5, EtOH)]; ^1H NMR δ 9.73 (s, 1 H), 5.37–5.34 (m, 1 H), 4.49–4.46 (m, 1 H), 3.00–2.84 (m, 2 H), 1.45 (s, 9 H), 1.44 (s, 9 H); ^{13}C NMR δ 175.9, 169.8, 155.5, 82.5, 80.0, 50.3, 36.8, 28.3, 27.9, 27.8.

1-*tert*-Butyl 6-Methyl (*S*)-2-[*N*-(*tert*-Butoxycarbonyl)amino]hex-4-enedioate (13). A solution of aldehyde **12** (14.8 g, 54.1 mmol) and [(methoxycarbonyl)methylene]triphenylphosphorane (27.2 g, 81.2 mmol) in THF (160 mL) was heated at reflux for 18 h. The reaction mixture was evaporated and the residue was chromatographed (10% EtOAc/hexane) to give 16.9 g (95% yield) of **13** as a white solid: $[\alpha]^{25}_D$ +2.3° (*c*, 1.2, EtOH); mp 73–75 °C; ^1H NMR δ 6.87–6.80 (m, 1 H), 5.87 (d, *J* = 15.6, 1 H), 5.13 (d, *J* = 7.2, 1 H), 4.32 (m, 1 H), 3.71 (s, 3 H), 2.67–2.66 (m, 1 H), 2.62–2.56 (m, 1 H), 1.45 (s, 9 H), 1.41 (s, 9 H); ^{13}C NMR δ 170.3, 166.3, 155.0, 143.0, 124.2, 82.6, 79.9, 52.9, 51.5, 35.5, 28.3, 28.0. Anal. Calcd for $C_{16}H_{27}NO_6$: C, 58.3; H, 8.3; N, 4.3. Found: C, 58.2; H, 8.5; N, 4.3.

1-*tert*-Butyl 6-Methyl (*S*)-2-[*N*-(*tert*-Butoxycarbonyl)amino]hexanedioate (14). A solution of **13** (1.2 g, 3.6 mmol) and 10% Pd/C (120 mg) in EtOAc (10 mL) was stirred under a H_2 atmosphere (balloon) for 12 h, then filtered, and evaporated to give 1.2 g (97% yield) of **14** as a clear oil: R_f 0.30 (10% EtOAc/hexane): $[\alpha]^{25}_D$ −7.4° (*c*, 3.3, EtOAc); ^1H NMR δ 5.04 (bd, *J* = 8.2, 1 H), 4.18–4.10 (m, 1 H), 3.63 (s, 3 H), 2.33–2.28 (m, 2 H), 1.80–1.72 (m, 1 H), 1.70–1.58 (m, 3 H), 1.44 (s, 9 H), 1.40 (s, 9 H); ^{13}C NMR δ 173.5, 171.6, 155.3, 81.9, 79.6, 53.6, 51.5, 33.4, 32.2, 28.3, 28.0, 20.6. Anal. Calcd for $C_{16}H_{29}NO_6$: C, 58.0; H, 8.8; N, 4.2. Found: C, 57.9; H, 8.7; N, 4.2.

(*S*)-2-Aminohexanedioic Acid γ-Methyl Ester (17). A mixture of **13** (19.2 g, 58.2 mmol) and 10% Pd/C (0.96 g) were stirred in EtOAc (120 mL) under an atmosphere of H_2 (balloon) for 16 h. The reaction mixture was filtered through Celite, and a solution of HCl in EtOAc [prepared by adding acetyl chloride (103 mL, 1450 mmol) to an ice-cooled solution of CH_3OH (59 mL, 1450 mmol) in EtOAc (60 mL)] was added to the filtrate, which was stirred at room temperature for 24 h and then evaporated to give 12.3 g (100%) of **16**: mp 157–160 °C; $[\alpha]^{20}_D$ +20.5° (*c*, 1.1, CH_3OH); IR (KBr) 3200, 1730 cm^{-1}; ^1H NMR (D_2O) δ 3.90 (t, *J* = 5.0, 1 H), 3.54 (s, 3 H), 2.32 (t, *J* = 8.1, 2 H), 1.88–1.76 (m, 2 H), 1.66–1.52 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 172.9, 170.8, 51.6, 51.3, 32.6, 29.2, 20.0 The hydrochloride **16** (12.3 g, 58 mmoL) was suspended in EtOH (120 mL), propylene oxide (16.8 g, 290 mmol) was added, the reaction mixture was heated at reflux for 6 h, cooled, and filtered, and the precipitate was washed with Et_2O to give 7.8 g (77% yield) of **17**: mp 177–179 °C; $[\alpha]^{25}_D$ −15.2° (*c*, 1.6, H_2O); IR (KBr) 3200, 1730 cm^{-1}; ^1H NMR (D_2O) δ 3.57 (t, *J* = 6.1, 1 H), 3.53 (s, 3 H), 2.30 (t, *J* = 7.3, 2 H), 1.75–1.68 (m, 2 H), 1.58–1.47 (m, 2 H); ^{13}C NMR (D_2O) δ 176.5, 174.5, 54.6, 52.2, 33.1, 28.8, 20.0. Anal. Calcd for $C_7H_{13}NO_4$: C, 48.0; H, 7.5; N, 8.0. Found: C, 47.9; H, 7.4; N, 7.8.

1-*tert*-Butyl 6-Methyl (*S*)-2-Aminohexanedioate Hydrochloride (15). Acetyl chloride (3.9 g, 49 mmol) was added to an ice-cooled solution of CH_3OH (1.6 g, 49 mmol) in EtOAc (40 mL) and the solution was stirred at 0 °C for 10 min and then warmed to room temperature for 30 min. The solution was recooled to 0 °C, a solution of **14** (960 mg, 2.9 mmol) in EtOAc (9 mL) was added, and the reaction mixture was warmed to room temperature, stirred for 3 h, and then evaporated. The residual white solid was suspended in dry Et_2O and filtered to give 750 mg (97% yield) of **15**: $[\alpha]^{20}_D$ +14.2° (*c*, 1.0, CH_3OH); mp 125–127 °C; ^1H NMR (D_2O) δ 3.86 (t, *J* = 6.2, 1 H), 3.54 (s, 3 H), 2.32 (t, *J* = 7.2, 2 H), 1.80–1.77 (m, 2 H), 1.63–1.56 (m, 1 H), 1.56–1.48 (m, 1 H); ^{13}C NMR (D_2O) δ 176.3, 169.0, 85.9, 53.2, 52.4, 32.9, 29.3, 27.2, 19.8. Anal. Calcd for $C_{11}H_{22}ClNO_4$: C, 49.3; H, 8.3; N, 5.2. Found: C, 49.2; H, 8.3; N, 4.9.

(*S*)-2-[*N*-(9-Phenylfluoren-9-yl)amino]hexanedioic Acid, γ-Methyl Ester (19). Trimethylsilyl chloride (1.7 g, 15.9 mmol) was added to a suspension of **17** (2.7 g, 15.1 mmol) in CH_2Cl_2 (30 mL) and after 10 min the now clear solution was heated at reflux for 2 h. The reaction mixture was cooled to room temperature, Et_3N (3.2 g, 31.8 mmol) was added with stirring for 15 min, and then $Pb(NO_3)_2$ (3.6 g, 10.9 mmol) followed by a solution of 9-bromo-9-phenylfluorene[29] (7.0 g, 21.7 mmol) in CH_2Cl_2 (30 mL) were added. After vigorous stirring for 96 h, CH_3OH (15 mL) was added and stirring continued for an additional 2 h, the mixture was filtered and evaporated, and the residue was chromatographed (5% iPrOH/$CHCl_3$) to yield 5.0 g (80% yield) of **19** as a foam: $[\alpha]^{20}_D$ −54° (*c*, 1, CH_3OH); ^1H NMR δ 7.66 (m, 2 H), 7.41 (m, 2 H), 7.39 (m, 3 H), 7.20 (m, 6 H), 3.63 (s, 3 H), 2.59 (dd, *J* = 7.1, 5.2, 1 H), 2.11 (m, 2 H), 1.62 (m, 2 H), 1.51 (m, 1 H), 1.38 (m, 1 H); ^{13}C NMR δ 178.8, 173.7, 148.5, 147.6, 143.7, 140.8, 140.3, 128.7, 128.6, 128.3, 127.9, 127.4, 125.9, 125.1, 120.0, 119.9, 72.8, 55.1, 51.5, 33.5, 33.2, 20.4. Anal. Calcd for $C_{26}H_{25}NO_4$: C, 75.2; H, 6.1; N, 3.4. Found: C, 75.1; H, 6.1; N, 3.4.

1-*tert*-Butyl 6-Methyl (*S*)-2-[*N*-(9-Phenylfluoren-9-yl)amino]hexandioate (18). A solution of **15** (0.60 g, 2.2 mmol), 9-bromo-9-phenylfluorene[29] (0.84 g, 2.6 mmol), and K_3PO_4 (0.93 g, 4.4 mmol) in CH_3NO_2 (4 mL) was stirred at room temperature for 72 h, after which CH_3OH (2 mL) was added and stirring continued for 1 h. Filtration, evaporation, and chromatography of the residue (10% EtOAc/hexane) gave 0.92 g (89% yield) of **18** as a clear oil: $[\alpha]^{25}_D$ −180° (*c*, 4.4, $CHCl_3$); ^1H NMR δ 7.66 (t, *J* = 7.1, 2 H), 7.42–7.16 (m, 11 H), 3.63 (s, 3 H), 2.49 (m, 1 H), 2.13 (m, 2 H), 1.71–1.62 (m, 2 H), 1.43–1.37 (m, 1 H), 1.35–1.25 (m, 1 H), 1.17 (s, 9 H); ^{13}C NMR δ 175.2, 173.8, 149.4, 144.9, 140.9, 140.0, 129.0, 128.4, 128.1, 127.8, 126.2, 125.6, 124.8, 120.0, 119.8, 80.5, 73.0, 55.4, 51.4, 35.0, 33.7, 27.8, 20.8. Anal. Calcd for $C_{30}H_{33}NO_4$: C, 76.4; H, 7.0; N, 3.0. Found: C, 76.7; H, 6.7; N, 2.6.

(*S*)-2-[*N*-(9-Phenylfluoren-9-yl)amino]hexanedioic Acid γ-Methyl Ester (19). The ester **18** (0.10 g, 0.21 mmol) was added to a solution of HCl in EtOAc [prepared by adding acetyl chloride (0.60 mL, 8.5 mmol) to CH_3OH (0.34 mL, 8.5 mmol) in EtOAc (4 mL)]. The reaction mixture was stirred at room temperature for 24 h and then evaporated. The residue was partitioned between EtOAc and pH 5 phosphate buffer, which in turn was extracted with EtOAc. The organic layer was dried, filtered, and evaporated. Chromatography (5% iPrOH/$CHCl_3$) of the residue gave 78 mg (89% yield) of **19** as a thick oil which was identical spectrally with material previously prepared by the phenylfluorenylation of **17**.

Imidazolide 20. Carbonyl diimidazole (0.96 g, 5.9 mmol, freshly recrystallized from THF) was added to a solution of the acid **19** (2.1 g, 4.9 mmol) in THF (10 mL) and stirred at room temperature for 20 h. The solution was evaporated and the residue filtered through a plug of silica gel eluting with 50% EtOAc/hexane. Evaporation gave 2.2 g (97% yield) of **20** as a foam: R_f 0.29, 50% EtOAc/hexane; ^1H NMR δ 7.60 (d, *J* = 7.5, 1 H), 7.40 (m, 7 H), 7.25 (m, 3 H), 7.11 (m, 1 H), 7.05 (m, 2 H), 6.83 (d, *J* = 9.6, 2 H), 3.62 (s, 3 H), 3.25 (bd, *J* = 9.1, 1 H), 3.08 (bs, 1 H), 2.11 (m, 2 H), 1.88 (m, 1 H), 1.59 (m, 2 H), 1.44 (m, 1 H); ^{13}C NMR δ 173.8, 173.3, 148.5, 147.6, 143.6, 140.7, 139.9, 135.6, 130.6, 128.9, 127.5, 126.0, 125.4, 120.0, 119.8, 115.6, 72.8, 54.7, 51.5, 34.1, 33.1, 20.9.

(1*S*,3*R*/*S*)-1-[*N*-(9-Phenylfluoren-9-yl)amino]-2-oxo-3-(methoxycarbonyl)cyclopentane (21). A solution of the imidazolide **20** (2.2 g, 4.8 mmol) in THF (24 mL) was added to a −78 °C solution of KHMDS (24 mL of a 1 M solution in THF, 24 mmol) in THF (48 mL) over 1 h. The reaction mixture was stirred an additional 1 h at −78 °C and then poured into an ice-cold mixture of EtOAc (100 mL) and 1 M KH_2PO_4 (100 mL). The aqueous phase was further extracted with EtOAc (3 × 50 mL), and the combined EtOAc phase was washed with brine, dried, and evaporated. The residue was filtered through a plug of silica gel, eluting with 10% EtOAc/hexane to give 1.8 g (97%) of **21** as an unstable oil, which was used immediately: R_f 0.20, 10% EtOAc/hexane; ^1H NMR δ 7.73–7.65 (m, 2 H), 7.42–7.10 (m, 11 H), 3.72 (s, 1.2 H), 3.64 (s, 1.8 H), 3.12 (d, *J* = 7.8, 0.4 H), 3.01 (dd, *J* = 11.4, 8.9, 0.6 H), 2.91–2.89 (m, 0.4 H), 2.69–2.64 (m, 0.6 H), 2.11–2.08 (m, 0.4 H), 2.01–1.95 (m, 0.6 H), 1.71–1.67 (m, 0.6 H), 1.62–1.53 (m, 1.4 H), 1.32–1.20 (m, 1 H); ^1C NMR δ 169.3, 149.9, 149.1, 148.7, 144.5, 141.4, 139.4, 128.6-124.6 (many peaks), 119.9, 72.7, 61.8, 52.5, 52.0, 50.2, 34.1, 31.5, 30.6, 23.9, 22.5, 22.0; HRMS calcd for $C_{26}H_{24}NO_3$ (MH+): 398.1756. Found: 398.1759.

(1*S*,2*R*/*S*,3*R*/*S*)-1-[*N*-(9-Phenylfluoren-9-yl)amino]-2-hydroxy-3-(methoxycarbonyl)cyclopentane (22). To an ice-cooled solution of **21** (1.8 g, 4.6 mmol) in CH_3OH/THF (50 mL, 1/1) was added $NaBH_4$ (0.18 g, 4.6 mmol). After stirring for 30 min the reaction mixture was concentrated, the residue was partitioned between EtOAc (50 mL) and 1 M KH_2PO_4 (50 mL), the aqueous phase was extracted with EtOAc (2 × 50 mL), and the combined organic phases were dried, filtered, and evaporated. Chromatography (25% EtOAc/hexane) gave 1.6 g (85%) of **22** as a 3:3:1:1 mixture of diastereomers as shown by ^1H NMR: R_f 0.38, 0.36, 0.29, 30% EtOAc/hexane; ^1H NMR (key resonances) δ 3.66 (s, 3 H), 3.62 (s, 3 H), 3.55 (s, 3 H). Anal. Calcd for $C_{26}H_{25}NO_3 \cdot 0.5H_2O$: C, 76.4; H, 6.4; N, 3.4. Found: C, 76.4; H, 6.4; N, 3.4.

(*S*)-3-[*N*-(9-Phenylfluoren-9-yl)amino]-1-(methoxycarbonyl)cyclopentene (23). Triethylamine (0.24 g, 4.0 mmol) was added to a solution of **22** (0.79 g, 2.0 mmol) and DMAP (49 mg, 0.4 mmol) in THF (4 mL) at 0 °C, followed by methanesulfonyl chloride (0.15 g, 2.4 mmol), and the reaction mixture was stirred for 3 h. It was filtered, the insoluble material was washed with cold THF (5 mL), the filtrate was diluted with THF (20 mL) and cooled in an ice bath, and KOBu^t (0.67 g, 6.0 mmol) was added. The reaction mixture was stirred for 15 min and then poured into a 5% aqueous citric acid solution (50 mL) and extracted with EtOAc (2 × 50 mL). Drying and evaporating left a residue which was chromatographed (10% EtOAc/hexane) to give 0.72 g (93%) of **23** as a hygroscopic oil: R_f 0.49 (25% EtOAc/hexane); $[\alpha]^{20}_D$ −60.7° (*c*, 1.6, $CHCl_3$); IR (neat) 1710 cm^{-1}; ^1H NMR δ 7.70 (m, 2 H), 7.50–7.15 (m, 11 H), 6.22 (m, 1 H), 3.64 (s, 3 H), 3.43 (m, 1 H), 2.47 (m, 1 H), 2.36 (m, 1 H), 2.02 (bs, 1 H, NH), 1.85 (m, 1 H), 1.46 (m, 1 H); ^{13}C NMR δ 165.7, 150.3, 150.1, 146.4, 144.7, 140.4, 135.6, 128.3, 128.2, 128.0, 127.8, 126.2, 125.2, 125.0, 120.0, 73.1, 60.0, 51.4, 34.6, 29.8. Anal. Calcd for $C_{26}H_{23}NO_2 \cdot H_2O$: C, 78.2; H, 6.3; N, 3.5. Found: C, 78.3; H, 6.1; N, 3.5.

(1*S*,3*R*)-1-[*N*-(9-Phenylfluoren-9-yl)amino]-3-(methoxycarbonyl)cyclopentane (26) and (1*S*,3*S*)-1-[*N*-(9-Phenylfluoren-9-yl)amino]-3-(methoxycarbonyl)cyclopentane (27). A mixture of **23** (340 mg, 0.90 mmol) and 5% Pt/C (34 mg) was stirred in EtOAc (45 mL) under a hydrogen atmosphere (1 atm) for 20 h. The mixture was filtered through Celite, the insoluble material was washed with EtOAc, the filtrate was evaporated, and the residue was chromatographed (5% EtOAc/hexane) to give first 75 mg (22%) of **26** as an oil, followed by 226 mg (65%) of **27** as an oil.

26: R_f 0.25, 10% EtOAc/hexane; $[\alpha]^{20}_D$ +5.5° (*c*, 1.3, EtOAc); ^1H NMR δ 7.71 (d, *J* = 7.5, 2 H), 7.45–7.19 (m, 11 H), 3.53 (s, 3 H), 2.83–2.76 (m, 2 H), 1.89–1.84 (m, 1 H), 1.63–1.58 (m, 1 H), 1.50–1.39 (m, 3 H), 1.26–1.10 (m, 1 H); ^{13}C NMR δ 176.8, 140.4, 140.2, 128.2, 127.8, 126.2, 125.3, 125.2, 119.9, 73.2, 54.9, 51.5, 41.7, 28.2. Anal. Calcd for $C_{26}H_{25}NO_2$: C, 81.4; H, 6.6; N, 3.6. Found: C, 81.6; H, 6.6; N, 3.6.

27: R_f 0.20, 10% EtOAc/hexane; $[\alpha]^{20}_D$ −35.8° (*c*, 3.8, EtOAc); ^1H NMR δ 7.68 (m, 2 H), 7.44–7.14 (m, 11 H), 3.60 (s, 3 H), 2.60–2.55 (m, 1 H), 2.46–2.38 (m, 1 H), 1.83–1.75 (m, 1 H), 1.64–1.56 (m, 1 H), 1.54–1.42 (m, 2 H), 1.32–1.23 (m, 2 H); ^{13}C NMR δ 176.8, 150.6, 145.4, 140.3, 128.1, 127.7, 126.9, 125.1, 119.8, 73.1, 55.3, 51.5, 41.5, 38.9, 34.3, 27.1. Anal. Calcd for $C_{26}H_{25}NO_2$: C, 81.4; H, 6.6; N, 3.6. Found: C, 81.1; H, 6.6; N, 3.5.

(*S*)-3-[*N*-(9-Phenylfluoren-9-yl)amino]-1-(hydroxymethyl)cyclopentene (28). DIBALH (3 mL of a 1 M solution in toluene, 3 mmol) was added to an ice-cooled solution of **23** (0.54 g, 1.4 mmol) in Et_2O (14 mL). The mixture was stirred in an ice bath for 2 h, CH_3OH (0.42 mL) was added, the solution was warmed to room temperature, and then a saturated $NaHCO_3$ solution (0.3 mL) was added and the stirring continued overnight. The dried mixture was filtered (Celite), the insoluble material was washed thoroughly with Et_2O, the filtrate was evaporated, and the residue was chromatographed (40% EtOAc/hexane) to give 0.46 g (94% yield) of **28** as an oil; $[\alpha]^{20}_D$ −63.8° (*c*, 2.4, $CHCl_3$); ^1H NMR δ 7.73 (m, 3 H), 7.45–7.18 (m, 11 H), 5.17 (bs, 1 H), 4.03 (dd, *J* = 14.2, 20.2, 2 H), 3.38–3.35 (m, 1 H), 2.23–2.18 (m, 1 H), 1.95–1.90 (m, 1 H), 1.83–1.76 (m, 1 H), 1.47–1.40 (m, 1 H); ^{13}C

(29) Jamison, T. F.; Lubell, W. D.; Dener, J. M.; Krisché, M. J.; Rapoport, H. *Organic Syntheses*; Wiley: New York, 1992; Vol. 71, p 220.

NMR δ 150.8, 150.5, 145.1, 140.4, 129.2, 128.2, 127.8, 127.0, 126.3, 125.3, 125.1, 119.9, 73.1, 62.0, 59.7, 34.7, 30.9. Anal. Calcd for $C_{25}H_{23}NO$: C, 84.9; H, 6.6; N, 4.0. Found: C, 84.5; H, 6.9; N, 3.9.

(1*S*,3*R*)-1-[*N*-(9-Phenylfluoren-9-yl)amino]-3-(hydroxymethyl)cyclopentane (29) and (1*S*,3*S*)-1-[*N*-(9-Phenylfluoren-9-yl)amino]-3-(hydroxymethyl)cyclopentane (30). A mixture of **28** (0.35 g, 0.98 mmol) and 5% Pt/C (34 mg) were stirred in EtOAc (50 mL) under a H_2 atmosphere for 24 h and then filtered, the filtrate was evaporated, and the residue was chromatographed (gradient elution, $CHCl_3 \rightarrow 2\%$ iPrOH/$CHCl_3$) to give first 98 mg (28%) of **29** followed by 199 mg (56%) of **30**.

29: $[\alpha]^{20}_D$ −4.2° (*c*, 2.4, EtOAc); ^{1}H NMR δ 7.70–7.67 (m, 2 H), 7.40–7.14 (m, 11 H), 3.52–3.46 (m, 2 H), 2.68–2.63 (m, 1 H), 2.01–1.97 (m, 1 H), 1.55–1.50 (m, 2 H), 1.49–1.42 (m, 1 H), 1.35–1.29 (m, 1 H), 1.23–1.18 (m, 1 H), 1.01–0.96 (m, 1 H); ^{13}C NMR δ 150.0, 149.5, 144.9, 140.7, 140.2, 128.3, 128.2, 127.8, 127.7, 127.1, 126.0, 125.5, 124.9, 119.9, 119.8, 73.2, 66.6, 54.9, 39.4, 38.9, 34.8, 25.8. Anal. Calcd for $C_{25}H_{25}NO \cdot H_2O$: C, 80.4; H, 7.3; N, 3.7. Found: C, 80.1; H, 7.0; N, 3.7.

30: mp 129–131 °C; R_f 0.20 (50% EtOAc/hexane); $[\alpha]^{20}_D$ −8.8° (*c*, 1.3, EtOAc); ^{1}H NMR δ 7.73 (d, *J* = 7.5, 2 H), 7.46 (d, *J* = 8.0, 2 H), 7.38 (m, 4 H), 7.25 (m, 5 H), 3.26 (d, *J* = 6.9, 2 H), 2.70 (quin, 1 H), 2.18 (m, 1 H), 1.80 (bs, 1 H, NH), 1.73 (m, 1 H), 1.38 (m, 2 H), 1.17 (m, 2 H), 0.94 (m, 1 H); ^{13}C NMR δ 150.6, 150.4, 145.5, 140.3, 128.1, 128.0, 127.6, 127.0, 126.1, 125.2, 119.8, 73.2, 67.2, 54.5, 39.8, 37.7, 35.4, 27.5. Anal. Calcd for $C_{25}H_{25}NO$: C, 84.5; H, 7.1; N, 3.9. Found: C, 84.3; H, 6.8; N, 4.0.

(1*S*,3*S*)-1-[*N*-(9-Phenylfluoren-9-yl)amino]-3-(hydroxymethyl)cyclopentane (30). A solution of AcOH (123 μL, 2.1 mmol) in CH_3OH (1 mL) was added to a solution of **28** (75 mg, 0.21 mmol) and dipotassium azodicarboxylate (414 mg, 2.1 mmol) in CH_3OH (1 mL) via syringe pump over 6 h. The reaction was allowed to proceed with stirring for an additional 6 h, then it was evaporated, and the residue was chromatographed (40% EtOAc/hexane) to yield 50 mg (66%) of **30**, identical spectrally with material prepared by the hydrogenation of **28**.

(1*S*,3*R*)-1-[*N*-(9-Phenylfluoren-9-yl)amino]-3-(hydroxymethyl)cyclopentane (29). To an ice-cooled solution of **26** (160 mg, 0.42 mmol) in THF (4 mL) was added $LiAlH_4$ (32 mg, 0.84 mmol), the reaction mixture was warmed to room temperature, stirred for 1 h, and then quenched by the sequential addition of water (32 μL), 15% NaOH solution (32 μL), and water (96 μL). Filtration, evaporation of the filtrate, and chromatography of the residue (40% EtOAc/hexane) gave 139 mg (93%) of **29**, identical spectrally with material prepared by the hydrogenation of **28**.

(1*S*,3*S*)-1-[*N*-(9-Phenylfluoren-9-yl)amino]-3-(hydroxymethyl)cyclopentane (30). To an ice-cooled solution of **27** (106 mg, 0.28 mmol) in THF (3 mL) was added $LiAlH_4$ (22.8 mg, 0.6 mmol). The reaction was allowed to proceed, and the product was isolated as described for **29** to give 88.5 mg (90% yield) of **30**, identical spectrally with material prepared by the hydrogenation of **28**.

(1*S*,4*R*)-*N*-(9-Phenylfluoren-9-yl)-2-azabicyclo[2.2.1]heptan-3-one (32). Lithium hydroxide (26 mg, 0.62 mmol) was added to an ice-cooled solution of **26** and **27** (157 mg, 0.42 mmol, 1/3 mixture of **26**/**27**) in THF (2 mL) and water (0.7 mL). This mixture was stirred at 0 °C for 48 h and then evaporated, the residue was azeotroped with toluene, then Ac_2O (4 mL) and NaOAc (340 mg, 4.1 mmol) were added, and the mixture was heated at 105 °C for 4 h. After concentrating in vacuo, the residue was partitioned between EtOAc (10 mL) and saturated $NaHCO_3$ solution (10 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined EtOAc phase was evaporated and then filtered through a plug of silica gel, eluting with $CHCl_3$, to give 140 mg (97%) of **32**: mp 220 °C dec; $[\alpha]^{20}_D$ +492° (*c*, 0.9, $CHCl_3$); ^{1}H NMR δ 7.86 (d, *J* = 7.7, 1 H), 7.68 (t, *J* = 7.6, 2 H), 7.42 (t, *J* = 6.4, 1 H), 7.35–7.17 (m, 9 H), 3.64 (bs, 1 H), 2.82 (d, *J* = 3.8, 1 H), 2.00 (d, *J* = 9.2, 1 H), 1.71–1.63 (m, 1 H), 1.40–1.33 (m, 1 H), 1.25–1.18 (m, 2 H), 0.81–0.75 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 178.6, 148.6, 147.6, 141.7, 140.2, 139.0, 128.9, 128.6, 128.2, 128.0, 126.9, 124.9, 120.4, 119.6, 72.3, 60.6, 47.5, 40.1, 28.1, 23.4. Anal. Calcd for $C_{24}H_{21}NO$: C, 85.4; H, 6.0; N, 4.0. Found: C, 84.9; H, 6.2; N, 4.1.

(1*S*,3*R*)-1-Amino-3-(hydroxymethyl)cyclopentane Hydrochloride (1). To a solution of lactam **32** (42 mg, 0.12 mmol) in AcOH (2 mL) was added 6 M HCl (1 mL) and the solution heated at reflux for 18 h. After cooling and evaporating, 1 M HCl (10 mL) was added and washed with hexane. The aqueous layer was then evaporated and azeotroped with toluene to give amino acid **33**: ^{1}H NMR (D_2O) δ 3.62–3.59 (m, 1 H), 2.88–2.84 (m, 1 H), 2.28–2.23 (m, 1 H), 2.03–1.96 (m, 1 H), 1.95–1.91 (m, 1 H), 1.89–1.82 (m, 1 H), 1.79–1.73 (m, 1 H), 1.68–1.62 (m, 1 H). This solid was dissolved in CH_3OH (1 mL), 2,2-dimethoxypropane (5 mL) and 3 drops of concd HCl were added, and the solution was stirred for 18 h. Evaporation gave the ester **34**, which was dissolved in THF (5 mL), and $LiAlH_4$ (13 mg, 0.30 mmol) was added to the solution cooled in an ice bath, and stirring was continued for 3 h at 0 °C. Excess $LiAlH_4$ was quenched by the sequential addition of water (13 μL), 15% NaOH (13 μL), and water (39 μL), the resulting precipitate was separated (filtration), the filtrate was evaporated, and the residue was dissolved in 1 M HCl. Evaporation gave 13.6 mg (76%) of **1** as a glass (with the same spectral properties as reported[26]): $[\alpha]^{20}_D$ −7.4° (*c*, 2.7, 1 M HCl); ^{1}H NMR (D_2O) δ 3.54–3.51 (m, 1 H), 3.41 (d, *J* = 6.1, 2 H), 2.17–2.06 (m, 2 H), 1.95–1.89 (m, 1 H), 1.72–1.67 (m, 1 H), 1.59–1.52 (m, 1 H), 1.39–1.33 (m, 1 H), 1.18–1.12 (m, 1 H); ^{13}C NMR (D_2O) δ 65.2, 51.7, 39.9, 34.2, 29.8, 26.2. Anal. Calcd for $C_6H_{14}NO \cdot HCl \cdot 0.5H_2O$: C, 44.9; H, 8.8; N, 8.72. Found: C, 44.8; H, 8.6; N, 8.4.

(1*S*,3*S*)-1-Amino-3-(hydroxymethyl)cyclopentane Hydrochloride (35). The alcohol **30** (117 mg, 0.33 mmol) and 10% Pd/C (32 mg) were stirred in CH_3OH/EtOAc (4 mL/1 mL) under an atmosphere of hydrogen for 24 h. The mixture was filtered through Celite, the insoluble material was washed with CH_3OH, and the filtrate was evaporated. The residue was partitioned between hexane (10 mL) and 1 M HCl (10 mL), the hexane was extracted with 1 M HCl (2 × 10 mL), and the aqueous layers were evaporated to give 44 mg (89%) of **35** as an oil: $[\alpha]^{20}_D$ −2.7° (*c*, 2.2, 1 M HCl); ^{1}H NMR (D_2O) δ 3.60–3.53 (m, 1 H), 3.35 (d, *J* = 6.8, 2 H), 2.23–2.16 (m, 1 H), 2.05–1.97 (m, 1 H), 1.83–1.75 (m, 1 H), 1.68–1.63 (m, 2 H), 1.55–1.45 (m, 1 H), 1.27–1.17 (m, 1 H); ^{13}C NMR (D_2O) δ 65.2, 51.8, 39.4, 33.4, 30.5, 27.1. Anal. Calcd for $C_6H_{14}NO \cdot HCl \cdot 0.5H_2O$: C, 44.9; H, 8.8; N, 8.7. Found: C, 44.9; H, 8.8; N, 8.7.

Procedure for the Preparation of Urea Derivatives. 36: A solution or suspension of diester **6** in CH_2Cl_2 (0.1 M) was treated with iPr_2NEt (97 mol%) followed by 1-phenethyl isocyanate (150 mol%, either *R* or *R*/*S*) and stirred for 24 h. This solution was poured into 0.5 M HCl and extracted with CH_2Cl_2, and the organic phase was washed with 0.5 M HCl and saturated $NaHCO_3$, dried, and evaporated to give **36**, an aliquot of which was used directly for HPLC analysis: 4.6 × 250 mm, 5 μm silica column, 1.5% iPrOH/CH_2Cl_2, 0.5 mL/min, $t_{R(S)}$ = 14.5 min, $t_{R(R)}$ = 15.5 min, monitored at 254 nm.

Procedure for the Preparation of Carbamate Derivatives. 38: 1-Phenethyl isocyanate (105 mol%, either *R* or *R*/*S*) was added to a 1 M solution of the alcohol **30** in THF, the solution was stirred at room temperature for 24 h and then evaporated, and the residue was filtered through a small plug of silica gel, eluting with EtOAc, to give **38**. An aliquot was used directly for HPLC analysis: 4.6 mm × 250 mm, 5 μm silica column, 2.5% iPrOH/CH_2Cl_2, 0.5 mL/min, $t_{R(S)}$ = 38 min, $t_{R(R)}$ = 41 min, monitored at 254 nm; ^{1}H NMR ($CDCl_3$, key resonances) δ (*S*) 1.04 (d, *J* = 6.8, 3 H, CH_3), (*R*) 1.01 (d, *J* = 6.8, 3 H).

Acknowledgment. We thank T.F. Jamison (Undergraduate Research Participant) for performing some initial experiments, Dr. B.J. McNelis for determining the conditions for 9-phenylfluorenylation in the absence of $Pb(NO_2)_3$, and Dr. F.J. Hollander of the CHEXRAY facility at the University of California, Berkeley for the X-ray crystallographic determination. A.A.C. is grateful to the Xunta de Galicia and the Ministereo de Educacion y Ciencia (Spain) for fellowship support. Burroughs Wellcome Co. provided generous financial support.