Enantioselective Synthesis of (1*R*,4*S*)-1-Amino-4-(hydroxymethyl)-2-cyclopentene, a Precursor for Carbocyclic Nucleoside Synthesis

Ki Hun Park and Henry Rapoport*

Department of Chemistry, University of California, Berkeley, California 94720

Received September 13, 1993®

(1*R*,4*S*)-1-Amino-4-(hydroxymethyl)-2-cyclopentene, an important precursor for the synthesis of carbocyclic nucleosides, has been prepared from D-glucono-δ-lactone in enantiomerically pure form (er > 99/1). The synthesis proceeded from the lactone via the diisopropylidene-2-amino-2-deoxymannonate and hydrolysis of the terminal isopropylidene group. Selective oxidation of the primary alcohol and esterification gave the corresponding mannarate which was deoxygenated at C5. Further transformations by regiospecific eliminative cleavage of the ketal and hydrogenation gave dimethyl (2*S*,3*R*)-2-amino-3-hydroxyadipate. Dieckmann cyclization through specific carbanion formation at C5 led to the aminohydroxy(methoxycarbonyl)cyclopentanone which was readily converted in a series of high-yielding steps to the target cyclopentene. Throughout the synthesis, stereo- and regioselectivities were strongly influenced by the sterically demanding 9-phenyl-9-fluorenyl protecting group on nitrogen.

Introduction

Carbocyclic nucleosides, which show potential antitumor[1] and antivirial[2] activities, have been the object of increasing interest. Most current synthetic approaches[3] involve the construction of the pyrimidine or purine base from the functionalized cyclopentylamine which, with very few exceptions,[4] is used as the racemate. Since the biological properties of the enantiomeric carbocyclic nucleosides are expected to be different,[5] the development of enantiospecific syntheses would provide a significant advantage. Present procedures for the synthesis of the carbocyclic portion, including utilization of the bicyclo[2.2.1]heptene[6] and azabicyclo[2.2.1]heptene systems,[7] have largely overcome the problem of diastereoselectivity, but still have the disadvantage of being nonenantioselective. The problem of enantioselectivity in the carbocyclic portion has been solved in a few cases by invoking other chiral precursors or by enzymatic or chemical resolution of a racemic intermediate.[8,9]

Our objective was to develop a synthetic route to enantiomerically pure (1*R*,4S)-1-amino-4-(hydroxymethyl)-2-cyclopentene (**6**). This cyclopentene can be used to prepared carbovir[10] and aristeromycin[11] which show potent and selective anti-HIV activity. The process we planned is outlined in Scheme 1. It begins with the very inexpensive D-glucono-δ-lactone (**1**) and proceeds via a substituted adipate to the cyclopentanone **3** by Dieckmann cyclization with anticipated total regio- and stereointegrity.[12] The intermediate cyclopentyl derivatives with their multiple functionalities should offer a broad scope of possibilities, among which is the target 1-amino-4-(hydroxymethyl)-2-cyclopentene **6**.

Results and Discussion

As our chiral educt we chose D-glucono-δ-lactone (**1**) which supplies the complete C_6-unit of the final (hydroxymethyl)cyclopentene. It also provides two chiral centers of adipate **14** and subsequent cyclopentyl derivatives as shown in Scheme 2. At C2 is the stereochemistry, with inversion, required for the amino group, and at C3 is another potentially useful chiral center; those at C4 and C5 will be expended. We chose the 9-phenyl-9-fluorenyl group for protection of the amine since this protecting group has been shown to inhibit deprotonation at the α-position of an α-amino ester.[12,13]

The key intermediate to be synthesized was α-amino-β-hydroxyadipate **14** which then would be cyclized to

® Abstract published in *Advance ACS Abstracts,* January 1, 1994.

(1) (a) Vince, R.; Brownell, J.; Daluge, S. *J. Med. Chem.* **1984**, *27*, 1358. (b) MacCoss, M.; Robins, M. J. In *Chemistry of Antitumor Agents*; Wilman, D. E. V., Ed.; Blackie and Sons: U.K., 1990; p 261.

(2) (a) Suhadolnik, R. J. *Nucleosides as Biological Probe*; Wiley: New York, NY, 1979; p 147. (b) Marquez, V. E.; Lim, M.-I. *Med. Res. Rev.* **1986**, *6*, 1. (c) Robins, R. K.; Revanker, G. R. In *Antiviral Drug Development*; De Clercq, E.; Walker, R. T.; Plenum: New York, 1988; p 11.

(3) (a) Cookson, R. C.; Dudfield, P. J.; Newton, R. F.; Ravenscroft, P.; Scopes, D. I. C.; Cameron, J. M. *Eur. J. Med. Chem.-Chim Ther.* **1985**, *20*, 375. (b) Herdewijn, P.; De Clercq, E.; Balzarini, J.; Vanderhaeghe, *J. Med. Chem.* **1985**, *28*, 550. (c) Borthwick, A. D.; Butt, S.; Biggadike, K.; Exall, A. M.; Roberts, S. M.; Youds, P. M.; Kirk, B. E.; Booth, B. R.; Cameron, J. M.; Cox, S. W.; Marr, C. L. P.; Shill, M. D. *J. Chem. Soc., Chem. Commun.* **1988**, 656. (d) Exall, A. M.; Jones, M. F.; Mo, C.-L.; Myers, P. L.; Paternoster, I. L.; Singh, H.; Storer, R.; Weingarten, G. G.; Williamson, C.; Brodie, A. C.; Cook, J.; Lake, D. E.; Meerholz, A.; Turnbull, P. J.; Highcock, R. M. *J. Chem. Soc. Perkin Trans. 1* **1991**, 2467.

(4) (a) Jones, M. F.; Myers, P. L.; Robertson, C. A.; Storer, R.; Williamson, C. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2479. (b) Balzarini, J.; Baumgartner, H.; Bodenteich, M.; De Clercq, E. D.; Griengl, H. *Nucleoside Nucleotides* **1989**, *8*, 855. (c) Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571.

(5) Vince, R.; Brownell, J. *Biochem. Biophys. Res. Commun.* **1990**, *168*, 912.

(6) (a) Shealy, Y. F.; Clayton, J. D. *J. Am. Chem. Soc.* **1966**, *88*, 3885. (b) Shealy, Y. F.; Clayton, J. D. *J. Am. Chem. Soc.* **1969**, *91*, 3075.

(7) (a) Cermak, R. C.; Vince, R. *Tetrahedron Lett.* **1981**, *22*, 2331. (b) Kam, B. L.; Oppenheimer, N. J. *J. Org. Chem.* **1981**, *46*, 3268. (c) Daluge, S.; Vince, R. *Tetrahedron Lett.* **1976**, 3005. (d) Daluge, S.; Vince, R. *J. Org. Chem.* **1978**, *43*, 2311.

(8) Roberts, S. M.; Shoberu, K. A. *J. Chem. Soc. Perkin Trans. 1* **1991**, 2605.

(9) Daluge, S. M. Eur. Pat. Appl. 434450, June 26, 1991, reported enzymatic resolution of the monophosphates of some N-substituted carbocyclic adenosine derivatives and chemical resolution of racemic *cis*-1-amino-4-(hydroxymethyl)-2-cyclopentene as the dibenzoyl-D-tartrate.

(10) Vince, R.; Hua, M.; Brownell; J.; Daluge, S.; Lee, F.; Shannon, W. M.; Lavell, G. C.; Qualls, J.; Weislow, O. S.; Kiser, R.; Canonico, P. G.; Schultz, R. H.; Narayanan, V. L.; Mayo, J. G.; Shoemaker, R. H.; Boyd, M. R. *Biochem. Biophys. Res. Commun.* **1988**, *156*, 1046.

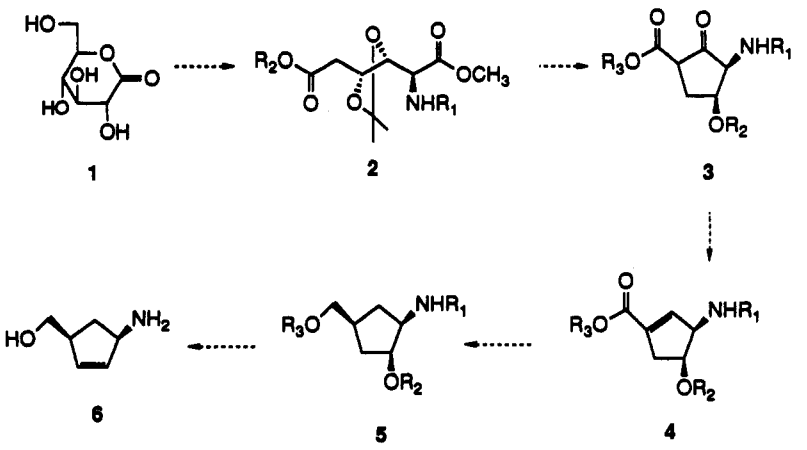
(11) Kusaka, T.; Tamamoto, H.; Shibaata, M.; Muroi, M.; Hicki, T.; Mizuno, K. *J. Antibiot.* **1968**, *21*, 255.

(12) Bergmeier, S. C.; Cobas, A. A.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 2369.

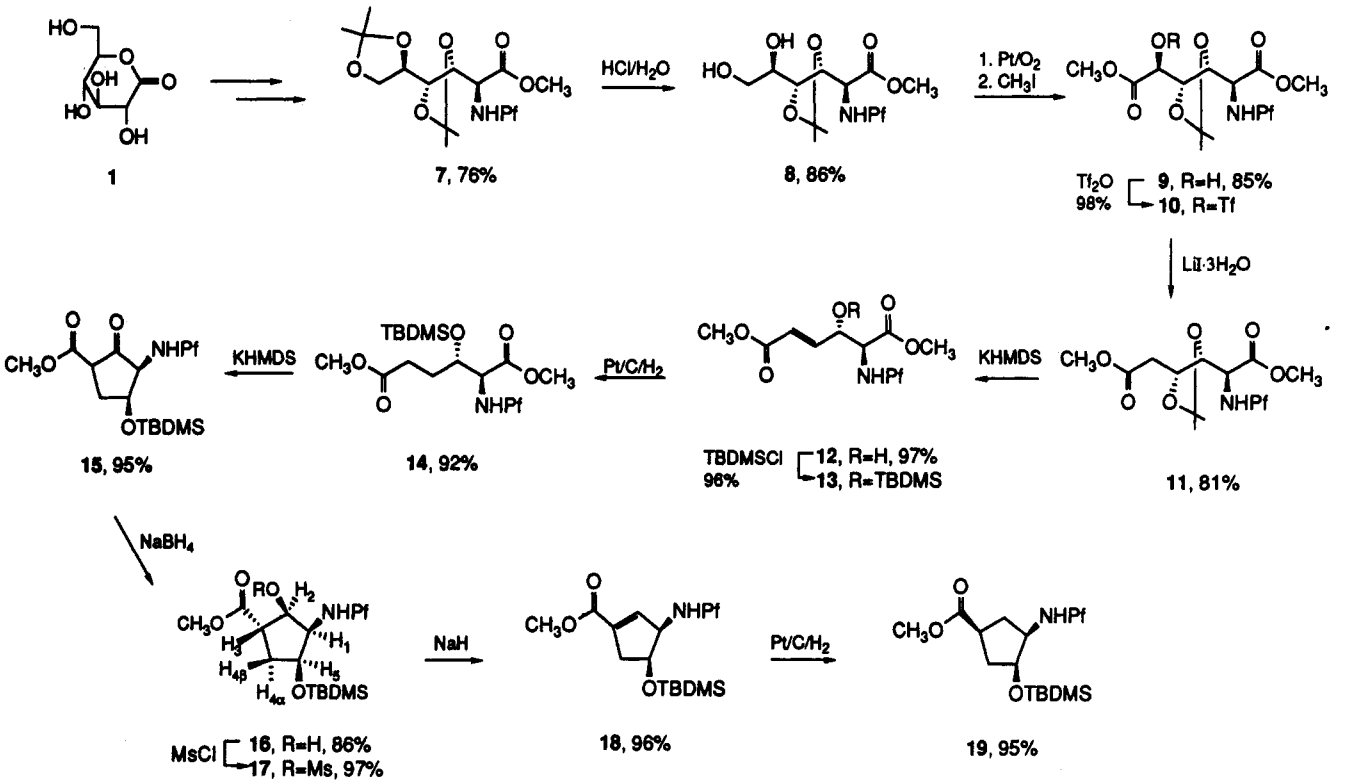
(13) Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1987**, *109*, 236.

0022-3263/94/1959-0394$04.50/0

Scheme 1



Scheme 2



cyclopentanone β-keto ester **15** via a Dieckmann condensation. The diisopropylidenemannonate **7** was synthesized in four easy, high-yielding steps from D-glucono-δ-lactone **1** as described;[14] the overall yield for this conversion was 76%. Proceeding from the resulting mannonate **7**, the terminal isopropylidene group was selectively cleaved by treatment with water (300 mol %) and HCl in ether producing **8** in 86% yield,[14c] and the primary alcohol group of **8** was oxidized by Pt/O_2[15] to give carboxylic acid in 85% yield.

After the methyl ester **9** was prepared using iodomethane, deoxygenation at C5 was accomplished by treating **10**, the triflate of **9**, with lithium iodide trihydrate[16] to produce isopropylideneaminoadipate **11** in 81% yield. On treatment of **11** with KHMDS, regiospecific elimination took place leading to α-amino-β-hydroxy unsaturated ester **12**. The C3 hydroxy group had a crucial role in the synthetic sequence since it provided the means to introduce the double bond in the cyclopentene and conceivably could be converted to other functionality. Protection of the hydroxyl group and reduction with Pt/C in ethyl acetate gave protected dimethyl α-amino-β-hydroxyadipate **14** in 92% yield, with retention of the *N*-phenylfluorenyl group.

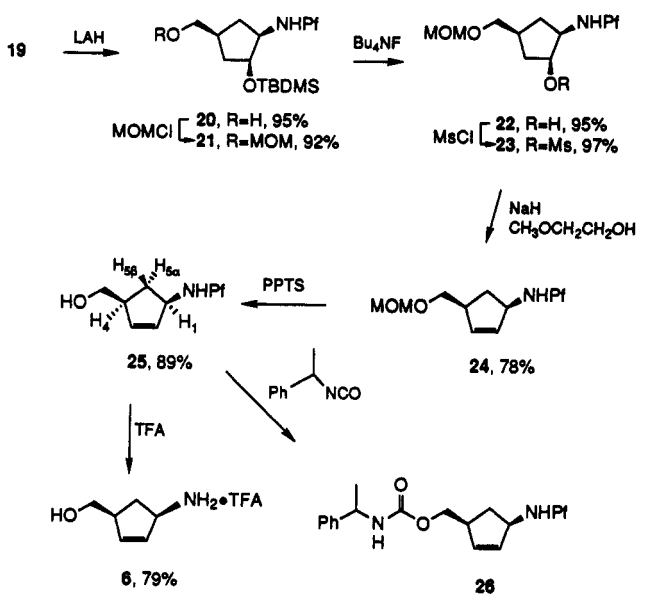
Condensation to the cyclic β-keto ester was to be the next step. Previously,[12] the Dieckmann reaction was applied to an ester imidazolide in order to further bias the regiochemistry of ring closure. In the present case, however, we proceeded with the dimethyl ester **14** and obtained a single, regioisomeric cyclic β-keto ester, cyclopentanone **15**, in 95% yield. The keto ester **15** was a 12/1 mixture of diastereomers as determined by ^{1}H-NMR analysis. Treatment of ketone **15** with $NaBH_4$ at 0 °C

(14) (a) Regeling, H.; de Rouville, E.; Chittenden, G. J. F. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 461. (b) Csuk, R.; Hugener, M.; Vasella, A. *Helv. Chim. Acta* **1988**, *71*, 609. (c) Gerspacher, M.; Rapoport, H. *J. Org. Chem.* **1991**, *56*, 3700.

(15) Roemmele, R. C.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 1866.

(16) Elliott, R. P.; Fleet, G. W. J.; Gyoung, Y. S.; Ramsden, N. G.; Smith, C. *Tetrahedron Lett.* **1990**, *31*, 3785.

Scheme 3



gave the alcohols **16** in 86% yield as a mixture of diastereomers in the ratio 96/4, from which alcohol **16** was separable in 86% yield by chromatography on silica gel. The configuration of the major isomer, hydroxy ester **16**, was established by a 2D-NOESY experiment which showed that H_1 was trans to H_3.

To set a cis relationship between the ester and amino groups, we chose to eliminate the alcohol, forming the α,β-unsaturated ester, and hydrogenate the resulting double bond. We reasoned that hydrogenation should occur from the less-hindered bottom face of the cyclopentene. This was achieved by treatment of **16** with MsCl in THF giving the mesylate **17** in quantitative yield. Using KOtBu to effect the elimination led only to a 30% yield of **18**. When the reaction was carried out at 0 °C using NaH as the base, however, elimination to **18** was quantitative. The next transformation was to reduce the double bond without hydrogenolyzing the *N*-9-phenyl-9-fluorenyl group. This regio- and stereoselective hydrogenation of unsaturated ester **18** was accomplished with 5% Pt/C in ethyl acetate at room temperature under hydrogen at 1 atm to give cyclopentane ester **19** as the single cis diastereomer in 95% yield.

With the necessary relative and absolute stereochemistry now established in amino ester **19**, we proceeded to complete the synthesis as shown in Scheme 3. Reduction of the ester was nearly quantitative, and the resulting carbinol **20** was converted to its methoxymethyl ether **21**. The three nucleophilic groups in amino diol **21** are differentially protected and offer the possibility of various succeeding sequences. Most effective for the preparation of Δ^2-cyclopentene **6** was first to cleave the silyl ether at C2 to alcohol **22** and then to prepare its mesylate **23**. Although a trans elimination might also occur to C1, the known inhibition of deprotonation at carbon bearing a phenylfluorenylamino group[13] should minimize elimination in that direction.

Thus, when mesylate **23** was treated with sodium methoxyethanolate, the desired $\Delta^{2,3}$-cyclopentene **24** was isolated in 78% yield. The methoxymethyl group was removed easily with pyridinium *p*-toluenesulfonate in *tert*-butyl alcohol,[17] giving stable, N-protected amino(hydroxymethyl)cyclopentene **25**. Confirmation of the previously assigned conformation was obtained by 2D NOESY experiments on **25**. Strong NOE cross peaks were observed between H_1–$H_{5\alpha}$ and H_4–$H_{5\alpha}$; none were observed with $H_{5\beta}$. To demonstrate the enantiomeric purity of **25**, it was derivatized to the carbamate **26** with (+)-α-methylbenzyl isocyanate after demonstrating with the (±)-isocyanate that the carbamates were easily formed and separated. Analysis by HPLC established the enantiomeric ratio in **25** to be >99/1.

Remaining was deprotection of *N*-phenylfluorenyl cyclopentylcarbinol **25** to the primary amine **6**. While **6** has been employed in various carbocyclic nucleoside syntheses,[18] it has not been characterized as such. We have prepared (1*R*,4*S*)-1-amino-4-(hydroxymethyl)-2-cyclopentene (**6**) trifluoroacetate from **25** by cleavage of the phenylfluorenyl group with TFA; **6** trifluoroacetate is an oil, reasonably stable on oxygen-free storage at 0 °C.

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, and DMF was distilled from BaO. 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 NOESY experiments were conducted using a phase-sensitive NOESY pulse program on a Bruker AM-500 spectrometer. Final solutions before evaporation were dried over $MgSO_4$.

Methyl 2-[(9-phenyl-9-fluorenyl)amino]-2-deoxy-3,4:5,6-di-*O*-isopropylidene-D-mannonate (7) was prepared from D-glucono-δ-lactone as described:[14c] yield, 76%; mp 114–115 °C (lit.[14c] mp 113 °C).

Methyl 2-[(9-Phenyl-9-fluorenyl)amino]-2-deoxy-3,4-*O*-isopropylidene-D-mannonate (8). A solution of diisopropylidene derivative **7** (12 g, 25 mmol) in 500 mL dry diethyl ether was cooled to 0 °C, and a solution of HCl in diethyl ether (saturated at 0 °C, 10 mL) and 1.5 mL (300 mol %) of H_2O was added. After stirring for 3 h, reaction mixture was poured into a solution of $NaHCO_3$ and Na_2CO_3 (3.0 g and 4.0 g, respectively, in 400 mL of water) and stirred for 30 min. The reaction mixture was extracted with EtOAc (3 × 300 mL), and the combined organic layers were washed with water and brine, dried, and evaporated. The crude residue was chromatographed on silica gel (hexane/EtOAc, 1/1) to give 10.5 g (86%) of monoisopropylidene derivative **8** as a white solid: mp 68–70 °C; $[\alpha]^{20}_D$ −102° (*c* 1.40, $CHCl_3$); ^1H NMR δ 1.07 (s, 3H), 1.25 (s, 3H), 2.59 (d, 1H), 3.25 (s, 3H), 3.48 (dd, 1H), 3.66 (m, 1H), 3.71 (dd, 1H), 3.84 (dd, 1H), 3.91 (dd, 1H), 7.06–7.50 (m, 11H), 7.73 (d, 2H); ^{13}C NMR δ 26.1, 26.5, 29.6, 52.2, 58.4, 64.4, 72.6, 72.8, 76.7, 80.1, 81.4, 109.8, 120.2, 120.3, 125.5, 125.9, 126.2, 127.5, 127.6, 128.4, 128.7, 128.8, 129.2, 140.6, 141.0, 142.0, 147.1, 147.3, 174.6. Anal. Calcd for $C_{29}H_{31}NO_6$: C, 70.8; H, 6.4; N, 2.6. Found: C, 71.1; H, 6.4: N, 2.9.

Dimethyl (2*S*,3*S*,4*R*,5*S*)-2-[(9-Phenyl-9-fluorenyl)amino]-3,4,5-trihydroxy-3,4-*O*-isopropylideneadipate (9). To a solution of diol **8** (1.2 g, 2.55 mmol) in 50 mL of water/EtOAc (50 mL, 1/5) was added 5 mL of iPrOH and 0.6 g of PtO_2 which had been reduced immediately beforehand by shaking under H_2 (45 psi) for 20 min in H_2O (20 mL). The reaction mixture was stirred under an oxygen atmosphere at 40 °C, cooled to rt, and filtered. After the organic layer of the filtrate was separated, dried, and evaporated, the crude residue was chromatographed (hexane/EtOAc, 1/1) to give 0.76 g (60%) of acid and 0.36 g of recovered diol **8** (29%). The crude acid (0.76 g, 1.5 mmol) was dissolved in 30 mL of dry DMF, K_2CO_3 (0.7 g, 5.15 mmol) and iodomethane (1.17 g, 8.24 mmol) were added, the solution was stirred for 12

(17) Monti, H.; Leandri, G.; Klos-Ringuet, M.; Corriol, C. *Synth. Commun.* **1983**, *13*, 1021.

(18) (a) Katagiri, N.; Muto, M.; Nomura, M.; Higashikawa, T.; Kaneko, C. *Chem. Pharm. Bull.* **1991**, *39*, 1112. (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) See refs 4, 8, and 9.

h at rt, 50 mL of diethyl ether was added, and the mixture was extracted with water (3 × 70 mL). The aqueous layer was back-extracted with diethyl ether (2 × 50 mL) and the combined organic layer was washed with a 0.5 M sodium thiosulfate solution (25 mL), dried, and evaporated. The residue was chromatographed (hexane/EtOAc, 4/1) on silica gel to give 0.75 g (98%) of diester **9** as a white solid: mp 63–65 °C; $[\alpha]^2 10_D$ −112.5° (*c* 1.14, $CHCl_3$); ^1H NMR δ 1.05 (s, 3H), 1.25 (s, 3H), 2.60 (d, 1H), 3.25 (s, 3H), 3.82 (s, 3H), 3.91 (dd, 1H), 4.08 (dd, 1H), 4.43 (d, 1H); ^{13}C NMR δ 26.4, 26.6, 52.0, 52.5, 58.8, 72.6, 73.1, 79.5, 81.3, 110.6, 120.1, 120.3, 125.7, 126.0, 126.1, 127.5, 128.57, 128.6, 128.7, 130.0, 140.3, 141.1, 142.8, 147.5, 147.6, 172.4, 172.6. Anal. Calcd for $C_{30}H_{31}NO_7$: C, 69.6; H, 6.0; N, 2.7. Found: C, 69.3; H, 6.0; N, 2.7.

Dimethyl (2*S*,3*S*,4*R*)-2-[(9-Phenyl-9-fluorenyl)amino]-3,4-dihydroxy-3,4-*O*-isopropyldeneadipate (11). A solution of hydroxy diester **9** (1.2 g, 2.3 mmol) in methylene chloride (30 mL) was cooled to −15 °C, and precooled pyridine (1 mL) was added. A solution of Tf_2O (0.85 g, 3.0 mmol) was added over 5 min with vigorous stirring and the solution was stirred for 1 h and then neutralized at 0 °C with saturated $NaHCO_3$ solution. The organic layer was washed with brine, dried, and evaporated to afford 1.46 g (98%, brownish crystals) of triflate **10** which were used without further purification. To a solution of lithium iodide trihydrate (3.5 g, 19.9 mmol) in THF (5 mL) was added acetic acid (3 mL) and a solution of **10** (1.46 g, 2.24 mmol) in THF (5 mL). This reaction mixture was refluxed for 2 days, allowed to cool to rt, and poured into a mixture of EtOAc (50 mL) and saturated $NaHCO_3$ solution (100 mL) with rapid stirring. The organic layer was washed with brine, dried, and evaporated, and the resulting crude residue was chromatographed on silica gel (hexane/EtOAc, 3/1) to give 0.97 g (81%) of crystalline **11**: mp 128–130 °C; $[\alpha]^{20}_D$ −187° (*c* 1.04, $CHCl_3$); ^1H NMR δ 1.09 (s, 3H), 1.28 (s, 3H), 2.64 (m, 1H), 2.65 (dd, 1H), 3.06 (dd, 1H), 3.07 (s, 3H), 3.73 (m, 1H), 3.78 (s, 3H), 4.20 (m, 1H), 7.36–7.11 (m, 11H); ^{13}C NMR δ 26.7, 27.1, 40.1, 51.8, 51.9, 58.7, 72.6, 76.6, 81.4, 109.9, 120.1, 125.4, 125.9, 126.0, 127.3, 127.4, 128.4, 128.5, 128.7, 140.0, 141.3, 143.8, 148.1, 148.2, 171.1, 174.3. Anal. Calcd for $C_{30}H_{31}O_6N$: C, 71.8; H, 6.2; N, 2.8. Found: C, 71.7; H, 6.2; N, 6.7.

Dimethyl (2*S*,3*S*)-(*E*)-2-[(9-Phenyl-9-fluorenyl)amino]-3-hydroxy-4-hexenedioate (12). To a solution of 0.1 M KHMDS (5.8 mL, 6.2 mmol, 400 mol %, in THF) in THF (15 mL) at −78 °C was added dropwise over 5 min via syring pump a solution of **11** (0.77 g, 1.53 mmol) in THF (20 mL). The reaction mixture was stirred an additional 1 h at −78 °C, cold 1 M KH_2PO_4 (100 mL) was added, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined extracts were washed with brine, dried, and evaporated, and the residue was chromatographed (hexane/EtOAc, 3/1) to give 0.66 g (97%) of **12** as a white solid: mp 55–57 °C; $[\alpha]^{20}_D$ −181° (*c* 0.72, $CHCl_3$); ^1H NMR δ 2.79 (d, 1H), 3.32 (s, 3H), 3.74 (s, 3H), 4.16 (m, 1H), 6.01 (dd, 1H), 6.38 (dd, 1H), 7.16–7.39 (m, 11H), 7.69 (m, 2H); ^{13}C NMR δ 29.7, 51.6, 51.9, 59.7, 71.7, 72.6, 120.0, 120.2, 121.4, 125.1, 125.9, 126.0, 127.53, 127.55, 128.3, 128.5, 128.6, 128.8, 140.0, 141.1, 143.6, 146.3, 147.8, 148.2, 166.5, 173.3. Anal. Calcd for $C_{27}H_{25}O_5N$: C, 73.1; H, 5.7; N, 3.2. Found: C, 73.3; H, 6.1; N, 2.9.

Dimethyl (2*S*,3*S*)-(*E*)-2-[(9-Phenyl-9-fluorenyl)amino]-3-[(*tert*-butyldimethylsilyl)oxy]-4-hexenedioate (13). To a solution of **12** (2.1 g, 4.7 mmol) in dry DMF (30 mL) were added imidazole (0.97 g, 14.2 mmol) and TBDMSCl (1.42 g, 9.4 mmol) at rt. The reaction mixture was stirred for 12 h at rt and then 40 mL of saturated $NaHCO_3$ was added followed by extraction with EtOAc (3 × 75 mL). The combined organic layer was washed with water and brine, dried, and evaporated, and the crude residue was chromatographed (hexane/EtOAc, 4/1) to give 2.52 g (96%) of **13**: mp 56–58 °C; $[\alpha]^{20}_D$ −185° (*c* 1.50, $CHCl_3$); ^1H NMR δ 0.00, 0.03 (2s, 6H), 0.83 (s, 9H), 2.62 (d, 1H), 3.25 (s, 3H), 3.84 (s, 3H), 4.31 (m, 1H), 5.94 (dd, 1H), 7.09 (dd, 1H), 7.17–7.44 (m, 11H, Pf), 7.72 (m, 2H); ^{13}C NMR δ −5.3, −4.5, 17.9, 25.5, 51.5, 51.6, 61.3, 72.7, 74.5, 119.97, 120.04, 121.1, 125.80, 125.84, 126.0, 127.3, 127.4, 127.8, 128.3, 128.36, 128.43, 139.9, 141.3, 144.2, 148.2, 148.4, 149.3, 166.6, 174.8. Anal. Calcd for $C_{33}H_{39}O_5NSi$: C, 71.1; H, 7.0; N, 2.5. Found: C, 70.9; H, 7.1; N, 2.3.

Dimethyl (2*S*,3*S*)-2-[(9-Phenyl-9-fluorenyl)amino]-3-[(*tert*-butyldimethylsilyl)oxy]hexanedioate (14). To a solution of **13** (1.8 g, 3.2 mmol) in 65 mL of EtOAc was added 5% Pt/C (0.18 g). The mixture was hydrogenated at 40 psi for 15 h and then filtered, and the filtrate was evaporated. Chromatography of the residue on silica gel (hexane/EtOAc, 6/1) gave 1.64 g (92%) of **14** as a thick oil: $[\alpha]^{20}_D$ −173° (*c* 1.6, $CHCl_3$); ^1H NMR δ 0.00, 0.65 (s, 6H), 0.81 (s, 9H), 1.69 (m, 1H), 1.91 (m, 1H), 2.21 (m, 1H), 2.36 (m, 1H), 2.57 (m, 1H), 2.99 (m, 1H), 3.21 (s, 3H), 3.74 (s, 3H), 3.86 (m, 1H), 7.18–7.46 (m, 11H), 7.73 (m, 2H); ^{13}C NMR δ −5.3, −4.5, 17.8, 25.6, 27.5, 27.9, 51.3, 51.4, 58.5, 72.6, 73.7, 119.99, 120.04, 125.4, 126.0, 126.1, 127.3, 127.4, 128.0, 128.2, 128.3, 128.4, 140.1, 141.2, 144.3, 148.55, 148.58, 174.2, 178.5. Anal. Calcd for $C_{33}H_{41}NO_5Si$: C, 70.8; H, 7.4; N, 2.5. Found: C, 70.8; H, 7.4; N, 2.3.

(2*S*,3*S*)-2-[(9-Phenyl-9-fluorenyl)amino]-3-[(*tert*-butyldimethylsilyl)oxy]-5-(methoxycarbonyl)cyclopentanone (15). To 1.0 M KHMDS (12.5 mL, 500 mol %, in THF) in THF (15 mL) at −78 °C was added dropwise over 5 min via syringe pump a solution of **14** (1.4 g, 2.5 mmol) in THF (5 mL). The reaction mixture was stirred an additional 30 min at −78 °C and then quenched with cold 1 M KH_2PO_4 solution (100 mL), and the aqueous layer was extracted with EtOAc (3 × 75 mL). The combined extracts were washed with brine, dried, and evaporated, and the crude residue was chromatographed on silica gel (hexane/EtOAc, 8/1) to give 1.25 g (95%) of **15** as a 12/1 mixture of diastereomers at *C*-5 as assigned by ^1H NMR: mp 58–61 °C; $[\alpha]^{20}_D$ −25.5° (*c* 1.15, $CHCl_3$); ^1H NMR δ 0.00, 0.06 (2s, 6H), 0.84 (s, 9H), 1.92 (m, 1H), 2.01 (m, 1H), 2.74 (d, 1H), 3.17 (m, 1H), 3.57 (s, 3H), 3.67 (m, 1H), 7.16–7.44 (m, 11 H), 7.64 (m, 2H); ^{13}C NMR δ −4.53, −4.49, 18.0, 25.7, 32.1, 48.5, 52.4, 66.8, 70.5, 71.6, 73.0, 76.7, 119.8, 120.0, 125.3, 125.5, 126.3, 126.4, 127.1, 127.7, 127.8, 128.1, 128.2, 128.4, 139.8, 140.8, 144.3, 149.5, 150.2, 169.5, 208.1. Anal. Calcd for $C_{32}H_{37}O_4NSi$: C, 72.8; H, 7.1; N, 2.7. Found: C, 72.7; H, 7.1; N, 2.5.

(1*R*,2*S*,4*S*,5*R*)-1-[(9-Phenyl-9-fluorenyl)amino]-2-[(*tert*-butyldimethylsilyl)oxy]-4-(methoxycarbonyl)-5-hydroxycyclopentane (16). To a solution of **15** (1.0 g, 1.9 mmol) in iPrOH (20 mL) was added $NaBH_4$ (0.1 g, 26 mmol) at 0 °C. After stirring for 3 h at 0 °C, 5% citric acid (30 mL) was added and the mixture was extracted with EtOAc (3 × 50 mL). The combined extract was washed with brine, dried, and evaporated, and the residue was chromatographed (hexane/EtOAc, 8/1) to give 0.86 g (86%) of **16** (and 30 mg of a diastereomer of **16**) as white solid: mp 47–49 °C; $[\alpha]^{20}_D$ +88.8° (*c* 1.53, $CHCl_3$); ^1H NMR δ 0.00 (s, 6H), 0.89 (s, 9H), 1.48 (m, 1H) 1.82 (m, 1H), 2.45 (m, 1H), 2.88 (m, 1H), 3.16 (bs, 1H), 3.38 (m, 1H), 3.58 (s, 3H), 3.79 (m, 1H), 4.62 (bs, 1H), 7.18–7.39 (m, 11H), 7.68 (m, 2H); ^{13}C NMR δ −5.0, −4.1, 17.9, 25.8, 34.4, 50.5, 51.7, 58.0, 72.2, 72.4, 74.4, 119.95, 119.98, 124.4, 125.2, 125.9, 127.2, 127.9, 128.2, 128.4, 128.5, 140.0, 140.7, 143.8, 149.4, 150.5, 175.2. Anal. Calcd for $C_{32}H_{39}O_4NSi$: C, 72.5; H, 7.4; N, 2.6. Found: C, 72.8; H, 7.6; N, 2.3.

(1*S*,2*S*,4*S*,5*R*)-1-[(9-Phenyl-9-fluorenyl)amino]-2-[(*tert*-butyldimethylsilyl)oxy]-4-(methoxycarbonyl)-5-[(methanesulfonyl)oxy]cyclopentane (17). To a solution of **16** (750 mg, 1.4 mmol) in THF (10 mL) were added triethylamine (286 mg, 2.8 mmol) and methanesulfonyl chloride (192 mg, 1.7 mmol) at 0 °C. After stirring for 2 h at 0 °C, 15 mL of 5% citric acid was added and the mixture was extracted with EtOAc (3 × 25 mL). The combined extracts were washed with brine, dried, and evaporated, and the residue was chromatographed (hexane/EtOAc, 4/1) to give 820 mg (97%) of **17**: mp 62–64 °C; $[\alpha]^{20}_D$ +400° (*c* 1.35, $CHCl_3$); ^1H NMR δ 0.00 (s, 6H), 0.86 (s, 9H), 1.44 (m, 1H), 1.91 (m, 1H), 2.61 (m, 1H), 3.00 (s, 3H), 3.17 (m, 1H), 3.56 (s, 3H), 3.61 (m, 1H), 4.79 (m, 1H), 7.17–7.43 (m, 11H), 7.65 (m, 2H); ^{13}C NMR δ −4.8, −4.1, 17.9, 25.6, 35.2, 38.6, 48.3, 52.2, 60.1, 72.6, 73.3, 83.6, 119.9, 120.0, 125.0, 125.6, 126.3, 127.1, 127.8, 127.27, 127.34, 127.37, 128.5, 139.9, 140.4, 144.2, 150.0, 150.9, 173.6. Anal. Calcd for $C_{33}H_{41}O_6NSSi$: C, 65.2; H, 6.8; N, 2.3. Found: C, 65.3; H, 6.9; N, 2.0.

(1*R*,2*S*)-1-[(9-Phenyl-9-fluorenyl)amino]-2-[(*tert*-butyldimethylsilyl)oxy]-4-(methoxycarbonyl)-4-cyclopentene (18). A suspension of NaH (100 mg, 2.5 mmol) in THF (8 mL) was cooled to 0 °C and a solution of **17** (760 mg, 1.25 mmol) in THF (4 mL) was added. The reaction mixture was stirred for 3 h at 0 °C and then quenched with 10 mL of 5% citric acid, and the aqueous layer was extracted with EtOAc (3 × 25 mL). The

combined extracts were washed with brine, dried, and evaporated, and the residue was chromatographed (hexane/EtOAc, 5/1) to give 610 mg (96%) of **18**: mp 129–131 °C; $[\alpha]^{20}_D$ –33° (*c* 1.0, $CHCl_3$); ^1H NMR δ 0.00, 0.17 (2s, 6H), 0.83 (s, 9H), 2.41 (m, 2H), 3.15 (s, 1H), 3.18 (m, 1H), 3.60 (s, 3H), 4.05 (m, 1H), 5.96 (s, 1H), 7.12–7.37 (m, 11H), 7.64 (d, 2H); ^{13}C NMR δ –4.8, –4.3, 18.1, 25.8, 39.3, 51.4, 61.6, 72.7, 73.6, 119.8, 120.0, 124.8, 125.6, 126.2, 127.0, 127.9, 128.0, 128.2, 128.3, 132.2, 140.1, 140.7, 144.7, 146.1, 150.4, 150.9, 165.7. Anal. Calcd for $C_{32}H_{37}O_3NSi$: C, 75.1; H, 7.3; N, 2.7. Found: C, 75.2; H, 7.3; N, 2.5.

(1*R*,2*S*,4*S*)-1-[(9-Phenyl-9-fluorenyl)amino]-2-[(*tert*-butyldimethylsilyl)oxy]-4-(methoxycarbonyl)cyclopentane (19). To a solution of **18** (630 mg, 1.23 mmol) in 25 mL of EtOAc was added 5% Pt/C (63 mg). The reaction mixture was stirred for 5 h under a hydrogen atmosphere and then filtered, the filtrate was evaporated, and the residue was chromatographed (hexane/EtOAc, 8/1) to give 660 mg (95%) of **19** as an oil: $[\alpha]^{20}_D$ –37.3° (*c* 1.5, $CHCl_3$); ^1H NMR δ 0.00, 0.02 (2s, 6H), 0.85 (s, 9H), 1.38 (m, 1H), 1.66 (m, 1H), 1.75 (m, 1H), 1.88 (m, 1H), 2.35 (m, 1H), 2.40 (m, 1H), 2.64 (bs, 1H), 3.59 (s, 3H), 3.73 (m, 1H), 7.14–7.38 (m, 11H), 7.65 (m, 2H); ^{13}C NMR δ –4.9, –4.4, 18.1, 25.8, 34.7, 35.6, 39.2, 51.6, 58.3, 72.6, 74.2, 119.7, 119.8, 124.9, 125.6, 126.2, 126.8, 127.7, 127.8, 128.0, 128.06, 128.11, 140.2, 140.3, 145.4, 150.8, 151.3, 176.0. Anal. Calcd for $C_{32}H_{39}O_3NSi$: C, 74.8; H, 7.7; N, 2.7. Found: C, 74.4; H, 7.7; N, 2.7.

(1*R*,2*S*,4*S*)-1-[(9-Phenyl-9-fluorenyl)amino]-2-[(*tert*-butyldimethylsilyl)oxy]-4-(hydroxymethyl)cyclopentane (20). To a solution of LAH (32 mg, 1.6 mmol) in THF (5 mL) was added a solution of **19** (420 mg, 0.81 mmol) in THF (2 mL) at 0 °C. After stirring for 2 h at 0 °C, 10 mL of aqueous citric acid was added and the mixture was extracted with EtOAc (3 × 20 mL). The combined extracts were washed with brine, dried, and evaporated, and the crude residue was chromatographed (hexane/EtOAc, 4/1) to give 373 mg (95%) of **20** as an oil: $[\alpha]^{20}_D$ +116° (*c* 1.72, $CHCl_3$); ^1H NMR δ 0.00, 0.06 (2s, 6H0, 0.87 (s, 9H), 0.98 (m, 1H, C5-H_β), 1.24 (m, 1H, C5-H_α), 1.74 (m, 1H, C3-H_β), 1.85 (m, 1H, C3-H_α), 2.05 (m, 1H, C1-H), 3.83 (m, 2H, C5-H), 2.48 (m, 2H, C6-5), 7.14–7.50 (m, 11H), 7.67 (m, 2H); ^{13}C NMR δ –4.7, –4.66, 18.2, 25.9, 33.5, 36.4, 56.3, 65.8, 72.6, 75.5, 119.6, 119.9, 125.0, 125.9, 126.4, 127.0, 127.8, 127.9, 128.4, 140.0, 141.1. Anal. Calcd for $C_{31}H_{39}O_2NSi$: C, 76.6; H, 8.1; N, 2.9. Found: C, 76.3; H, 8.1; N, 2.6.

(1*R*,2*S*,4*S*)-1-[(9-Phenyl-9-fluorenyl)amino]-2-[(*tert*-butyldimethylsilyl)oxy]-4-[(methoxymethoxy)methyl]cyclopentane (21). To a solution of **20** (320 mg, 0.66 mmol) in methylene chloride (5 mL) was added diisopropylethylamine (597 mg, 4.6 mmol) and chloromethyl methyl ether (213 mg, 2.6 mmol) at rt. After stirring for 3 h at rt, the reaction mixture was quenched with 1 M KH_2PO_4 solution (20 mL) and extracted with EtOAc (3 × 20 mL). The combined extracts were washed with brine, dried, and evaporated, and the residue was chromatographed (hexane/EtOAc, 5/1) to give 320 mg (93%) of **21** as a bright yellow oil: $[\alpha]^{20}_D$ –174° (*c*, 1.3, $CHCl_3$); ^1H NMR δ 0.00, 0.02 (s, 6 H), 0.86 (s, 9H), 0.98 (m, 1H, C5-H_α), 1.29 (m, 1H, C5-H_β), 1.63 (m, 1H, C3-H_α), 1.79 (m, 1H, C3-H_β), 2.45 (m, 1H, C4-H), 2.60 (m, 1H, C1-H), 3.26 (s, 3H), 3.31 (m, 2H, C6-H), 3.76 (m, 1H, C2-H), 5.53 (s, 2H), 7.13-7.38 (m, 11H), 7.65 (m, 2H); ^{13}C NMR δ –4.8, –4.2, 18.1, 25.9, 34.7, 35.5, 36.0, 55.0, 58.4, 72.6, 73.7, 75.1, 96.4, 119.7, 119.9, 125.0, 125.5, 126.3, 126.8, 127.6, 127.7, 127.9, 128.1, 140.2, 140.4, 145.5, 150.9, 151.6. Anal. Calcd for $C_{33}H_{43}NO_3Si$: C, 74.8; H, 8.2; N, 2.6. Found: C, 74.5; H, 8.2; N, 2.3.

(1*R*,2*S*,4*S*)-1-[(9-Phenyl-9-fluorenyl)amino]-2-hydroxy-4-[(methoxymethoxy)methyl]cyclopentane (22). To a solution of **21** (300 mg, 0.62 mmol) in THF (10 mL) was added 1.0 M Bu_4NF (3 mL, 3.3 mmol, in THF). After stirring for 10 h, the reaction mixture was quenched with water (25 mL) and extracted with EtOAc (3 × 25 mL). The combined extracts were washed with brine, dried, and evaporated. The crude residue was chromatographed (hexane/EtOAc, 2/1) to give 245 mg (95%) of **22** as an oil: $[\alpha]^{20}_D$ –225° (*c* 1.3, $CHCl_3$); ^1H NMR δ 1.25 (m, 1H), 1.34 (m, 1H), 1.65 (m, 2H), 1.85 (m, 1H), 2.32 (m, 1H), 3.0 (m, 1H), 3.30 (s, 3H), 3.37 (m, 2H), 3.64 (s, 1H), 4.55 (s, 2H), 7.20–7.40 (m, 11H), 6.75 (m, 2H); ^{13}C NMR δ 34.4, 35.3, 35.5, 55.1, 58.0, 70.8, 72.4, 72.7, 96.3, 119.8, 119.9, 124.2, 125.0, 125.9, 127.2, 127.9, 128.0, 128.3, 128.36, 139.7, 141.1, 144.5, 149.4, 150.1. Anal. Calcd for $C_{27}H_{29}NO_3$: C, 78.0; H, 7.04; N, 3.4. Found: C, 78.3; H, 7.3; N, 3.6.

(1*R*,2*S*,4*S*)-1-[(9-Phenyl-9-fluorenyl)amino]-2-[(methanesulfonyl)oxy]-4-[(methoxymethoxy)methyl]cyclopentane (23). To a solution of **22** (200 mg, 0.48 mmol) in 5 mL of dry THF were added triethylamine (97 mg, 0.96 mmol) and methanesulfonyl chloride (66 mg, 0.57 mmol) at 0 °C. After stirring for 2 h at 0 °C, 10 mL of 1 M citric acid was added and the mixture was extracted with EtOAc (3 × 20 mL). The combined extracts were washed with brine, dried, and evaporated, and the residue was chromatographed on silica gel (hexane/EtOAc, 2/1) to give 270 mg (97%) of **23** as an oil: ^1H NMR δ 1.08 (m, 1H), 1.48 (m, 1H), 1.72 (m, 1H), 1.80 (m, 1H), 2.55 (m, 1H), 3.04 (s, 3H), 3.28 (s, 3H), 3.32 (m, 1H), 3.34 (d, 1H), 4.53 (s, 2H), 4.61 (m, 1H), 7.16–7.41 (m, 11H), 7.69 (m, 2H); ^{13}C NMR δ 33.6, 34.4, 35.4, 35.6, 38.8, 55.2, 57.7, 58.1, 72.3, 72.5, 86.8, 96.4, 119.7, 120.0, 125.0, 125.1, 125.2, 126.0, 126.1, 127.2, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 140.5, 149.8, 150.7.

(1*R*,4*S*)-1-[(9-Phenyl-9-fluorenyl)amino]-4-[(methoxymethoxy)methyl]-2-cyclopentene (24). To a magnetically stirred suspension of sodium hydride (58 mg, 2.4 mmol) in 2 mL of dry DMF was added 2-methoxyethanol (183 mg, 2.4 mmol) dropwise. The mixture was stirred for 30 min then cooled to 0 °C. A solution of **23** (150 mg, 0.3 mmol) in 1.5 mL of dry DMF was added, and stirring at 0 °C was continued for 5 h. The mixture was diluted with water (30 mL), the crude product was extracted into ethyl acetate (3 × 30 mL), and the organic extract was washed with brine, dried, and evaporated. Chromatography (hexane/EtOAc, 3/1) of the crude residue gave 92 mg (78%) of **24** as an oil: $[\alpha]^{2}10_D$ –15.4° (*c* 1.1, $CHCl_3$); ^1H NMR δ 1.08 (m, 1H, C5-H_α), 1.91 (m, 1H, C5-H_β), 2.54 (m, 1H, C1-H), 3.31 (s, 3H0, 3.33 (m, 1H, C4-H), 3.39 (d, J = 6.1, 2H, C6-H), 4.58 (s, 2H), 5.34 (m, 1H, vinyl-H), 5.55 (m, 1H, vinyl-H), 7.17–7.42 (m, 11H0, 7.69 (m, 2H); ^{13}C NMR δ 38.1, 44.6, 55.1, 59.4, 71.6, 73.1, 96.4, 119.9, 125.2, 125.3, 126.3, 127.0, 127.7, 127.8, 128.0, 128.1, 128.2, 132.2, 136.6, 140.3, 140.4, 145.1, 150.7, 150.9. Anal. Calcd for $C_{27}H_{27}NO_2$: C, 81.6; H, 6.9; N, 3.5. Found: C, 81.3; H, 7.3; N, 3.4.

(1*R*,4*S*)-1-[(9-Phenyl-9-fluorenyl)amino]-4-(hydroxymethyl)-2-cyclopentene (25). To a solution of **24** (90 mg, 0.22 mmol) in 3 mL of *tert*-ButOH was added PPTS (56 mg, 2.26 mmol). After the reaction mixture was refluxed for 3 h, water (10 mL) was added to the cooled solution and the mixture was extracted with ether (3 × 10 mL). The ether layer was washed with water (10 mL), dried, and evaporated, and the residue was chromatographed on silica gel (hexane/EtOAc, 4/1) to give 70 mg (89%) of **25** as an oil: $[\alpha]^{20}_D$ +133° (*c* 1.5, $CHCl_3$); ^1H NMR δ 1.17 (m, 1H, C5-H_α), 1.17 (m, 1H, C5-H_β), 2.66 (m, 1H, C1-H), 3.20 (m, 1H, C4-H), 3.58 (d, 2H), 5.35 (m, 1H, vinyl-H), 5.65 (m, 1H, vinyl-H), 7.15–7.68 (m, 11H), 7.70 (m, 2H); ^{13}C NMR δ 36.8, 46.8, 57.7, 63.9, 73.1, 119.9, 120.0, 124.8, 125.7, 126.0, 127.2, 127.8, 128.0, 128.3, 128.35, 128.41, 134.5, 134.7, 140.1, 140.1, 140.8, 144.5, 149.1, 149.8. Anal. Calcd for $C_{25}H_{23}NO$: C, 85.0; H, 6.6; N, 4.0. Found: C, 84.7; H, 6.8; N, 4.1.

(1*R*,4*S*)-1-Amino-4-(hydroxymethyl)-2-cyclopentene (6) Trifluoroacetate Salt. To a solution of **25** (120 mg, 0.34 mmol) in CH_2Cl_2 (2 mL) was added TFA (1 mL). After refluxing for 8 h, the reaction mixture was concentrated, water (2 mL) was added, and the mixture was extracted with Et_2O (5 × 5 mL). The aqueous layer was evaporated and the residue was dired at 40 °C (0.1 Torr) to give 30 mg (79%) of the trifluoroacetate salt of **6** as an oil: $[\alpha]^{20}_D$ +113° (*c* 0.72, H_2O); ^1H NMR (D_2O, 400 MHz) δ 1.53 (m, 1H, C5-H_β), 2.52 (m, 1H, C5-H_α), 2.79 (m, 1H, C1-H), 3.57 (m, 2H, CH_2O), 4.27 (m, 1H, C4-H), 5.82 (m, 1H, C2-H), 6.07 (m, 1H, C3-H); ^{13}C NMR (D_2O, 100 MHz) δ 31.4, 46.6, 56.0, 62.7, 128.0, 139.6. Anal. Calcd for $C_6H_{11}NO{\cdot}CF_3CO_2H{\cdot}0.5H_2O$: C, 40.7; H, 5.5; N, 5.9. Found: C, 41.2; H, 5.7; N, 5.6.

Preparation of Urea Derivative 26. To a solution of **25** in THF (0.1 M) was added α-methylbenzyl isocyanate (150 mol %, either *R* or *R*/*S*). After stirring for 10 h at rt, the reaction mixture was added to water (10 mL) and extracted with EtOAc (2 × 10 mL). The organic phase was washed with brine, dried, and evaporated to give **26** which was used directly for HPLC

analysis: 4.6 × 250 mm, 5-μm silica column, 1.5% iPrOH/CH_2Cl_2, 1 mL/ min; $t_R(S)$ = 8.25 min, $t_R(R)$ = 10.5 min.

Acknowledgment. We thank Dr. S. C. Bergmeier for his assistance throughout this work. The Burroughs Wellcome Co. provided generous financial support.

Supplementary Material Available: ^1H and ^{13}C NMR spectra of compounds **6–9, 11–21, 23, 24, 25**; 2D-NOESY spectra of compounds **16** and **25**; HPLC analysis of carbamate **26** (39 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.