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Enantiospecific Synthesis of Carbapentostatins

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In this paper we describe enantioselective syntheses of (+)-carbapentostatin (**8**) and its cyclopentyl analogue **12b**. A new and efficient one-pot, two-step preparation of aldehyde **15** has been developed, based on the borane reduction of *N*-Pf-protected L-aspartic acid γ-methyl ester (**13**) and Swern oxidation of the resulting alcohol. Homologation to diester **18** and ring formation by Dieckman cyclization, followed by reduction and dehydration steps, afford the 4-amino-1-cyclopentenemethanol derivative **22**. Hydroboration and oxidation transform this compound stereospecifically into aminocyclopentanol **26**, the key aminocyclitol component for an asymmetric synthesis of (+)-carbapentostatin.

Introduction

Pentostatin (**1**),[1] coformycin (**2**),[2] 2-chloropentostatin (adechlorin, **3**),[3] and adecypenol (**4**)[4] (Figure 1) are natural products of microbial origin with profound anticancer activity, particularly against certain leukemias.[5] The biological activity of these unusual homopurine, or imidazodiazepine, structures have stimulated a number of syntheses.[6] All these efforts, with one exception, have involved formation of the 8-keto analogues, which were subsequently reduced to a diastereomeric mixture of alcohols. The one exception was an asymmetric synthesis of the aglycon itself.[7]

Our desire to synthesize a carbon analogue of **1** was based on its enhanced chemical and enzymatic stability relative to that of the parent nucleoside. Earlier work in our laboratory had established an excellent method for the enantiocontrolled synthesis of the aglycon with the natural *R* configuration of the hydroxyl group at C-8.[7]

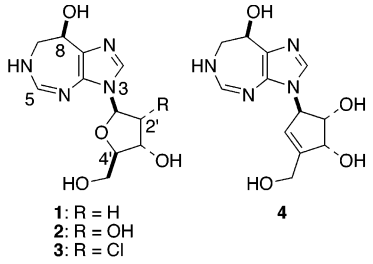

FIGURE 1.

Both regiochemical and stereochemical problems can arise when a nucleoside aglycon is coupled with ribose or ribose analogues; these problems could be avoided if an appropriately substituted cyclopentylamine could serve as the source of the N-3 nitrogen in the synthesis of the aglycon. We now report the enantiospecific synthesis of cyclopentylamine **25** from natural L-aspartic acid, and its incorporation into the pentostatin aglycon synthesis to afford carbapentostatin **8**.

Results and Discussion

Our retrosynthetic analysis of **7** led to the functionalized nitrile **5** and cyclopentylamine **6**, each of which would be available from an L-amino acid (Scheme 1). This sequence would thus allow enantiocontrol over all of the asymmetric centers in the target molecule. The synthesis of nitrile **5** (R = ethyl) from L-methionine via L-vinylglycine has been described previously in the enantiospecific synthesis of the aglycon, in which the 8(*R*)-hydroxyl group of the heterocycle arises from the 3(*R*)-silyloxy group of **5**.[7] We envisaged a synthesis of amine **6** in which the stereocenter in L-aspartic acid would give rise to the desired amine configuration in the sugar mimic and, in turn, control the remaining stereocenters of the final target.

The feasibility of introducing the N-3 moiety as a functionalized amine, and hence the value of developing a synthesis of **6**, was first explored with cyclopentylamine

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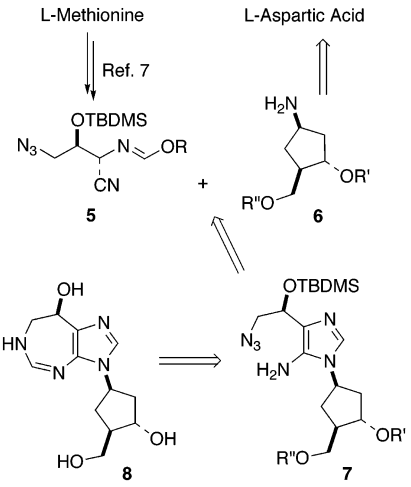
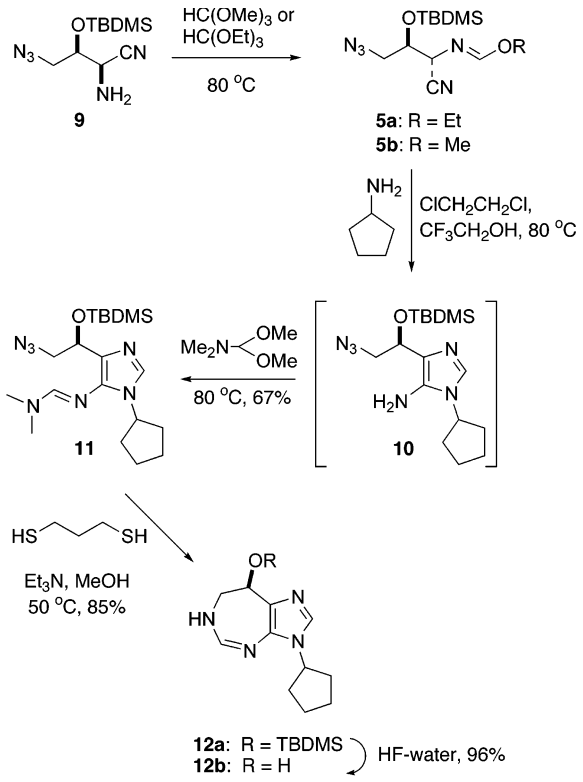
SCHEME 1. Proposed Route to Carbapentostatin

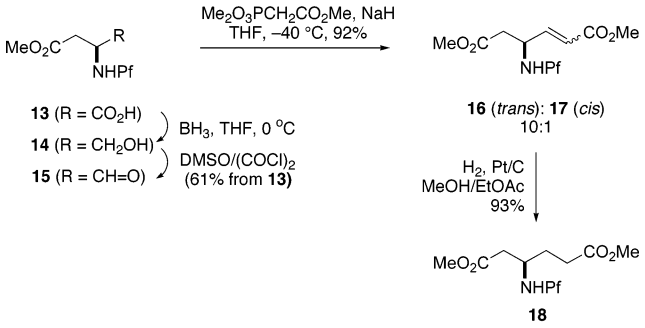


SCHEME 2. Synthesis of the Cyclopentyl Analogue of Pentostatin



(Scheme 2). The synthesis was initiated by reacting azide **9** with triethyl orthoformate (or trimethyl orthoformate) to give **5a** (or **5b**) in good yield.[7] Reaction of **5b** with cyclopentylamine afforded the aminoimidazole **10**, which was treated directly with *N*,*N*-dimethylformamide dimethyl acetyl at 80 °C to provide the stable amidine **11**. Reduction of the azide of **11** immediately resulted in cyclization to the bicyclic derivative **12a**. Deprotection of the *tert*-butyldimethylsilyl ether yielded the carbapentostatin analogue **12b** in pure form. These straightforward condensation and cyclization reactions thus demonstrated that the N-3 nitrogen and its substituent could be readily incorporated into the synthesis of the aglycon, thus avoiding the regiochemical or stereochemical ambiguity arising from alkylation of the free aglycon.[7]

SCHEME 3. Enantiospecific Synthesis of Dimethyl (3*R*)-3-[*N*-(9-Fluorenyl)amino]adipate from L-Aspartic Acid *β*-Methyl Ester



The development of a stereoselective synthesis of the substituted aminocyclopentane of carbapentostatin was justified by the successful preparation of **12b** and our conviction that the additional substituents on the cyclopentane ring would not interfere with the addition or ring-closure reactions. L-Aspartic acid derivative **13**[8] served as the chiral starting material (Scheme 3). We chose the *N*-phenylfluorenyl (Pf)[9] protecting group because of its known ability to minimize epimerization at the α position under basic conditions.[8] Selective reduction of the acid group of **13** was effected with 250 mol % BH_3 in THF at 0 °C for 60 h to furnish the alcohol **14**. Longer reaction times or a greater excess of BH_3 resulted in the reduction of both acid and methyl ester groups of **13** to give a diol. The hydroxy ester **14** is very susceptible to lactonization, for example, during attempted purification by chromatography on silica gel, so this material was carried on directly to the aldehyde **15** by Swern oxidation.[10] Aldehyde **15** can be purified by silica gel chromatography without the competing lactonization, in an overall yield of 61% for the two steps. Alternative oxidation procedures, such as Corey−Kim,[11] Dess−Martin,[12] TEMPO,[13] or TPAP[14] oxidations, gave lower yields than the Swern method. Olefination of aldehyde **15** with the Horner−Emmons reagent gave a 10:1 ratio of the *trans* and *cis* unsaturated esters **16** and **17**. Although the isomers could be separated by chromatography, the mixture was reduced directly to the saturated diester **18**.

The key issue with respect to formation of the five-membered ring from diester **18** was the regioselectivity of the Dieckmann cyclization (Scheme 4). The desired keto ester was **19**, which after reduction and dehydration would afford the 4-amino-1-cyclopentenecarboxylate derivative **21a**. We studied several strong bases in optimizing this process, with the results summarized in Table 1. Lithium 2,2,6,6-tetramethylpiperidine (LiTMP) proved to be the most selective among those investigated, af-

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SCHEME 4. Regioselective Dieckmann Condensation of 3-Aminoadipate 18 with Lithium Tetramethylpiperidide

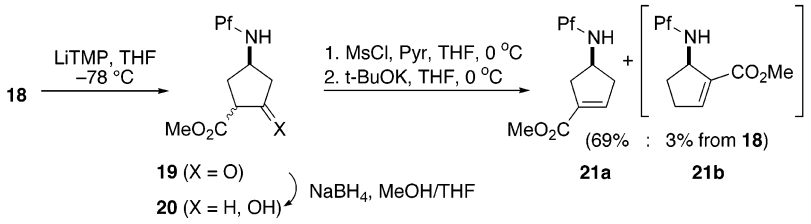
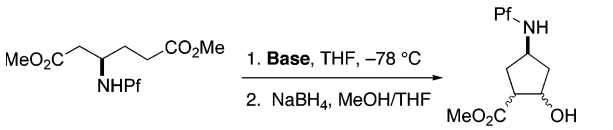


TABLE 1. Regioselective Dieckmann Condensation of Dimethyl (3*R*)-3[*N*-(9-Phenyl-9-fluorenyl)amino]adipate (18) with Various Bases



base	base concn (mol %)	yield of **20**[a] (%)	base	base concn (mol %)	yield of **20**[a] (%)
t-BuLi	200	20	$LiN(^iPr)_2$	250	60
$KN(TMS)_2$	220	49	LTMP	300	88[b]

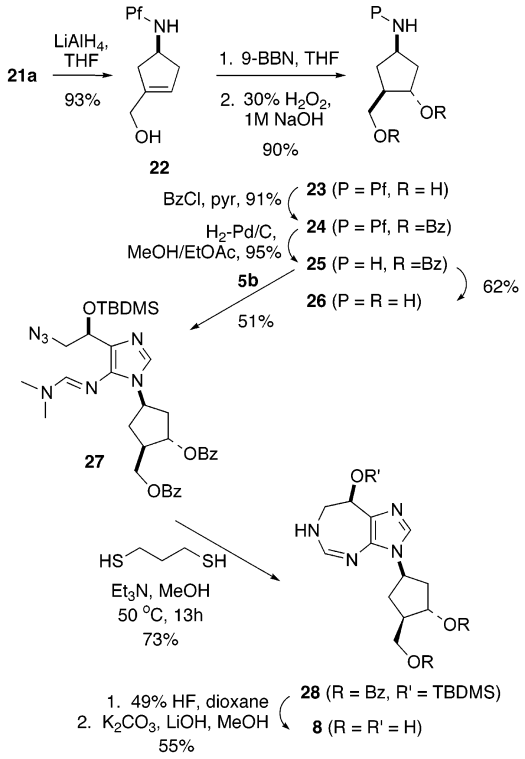
[a] Yields were determined after $NaBH_4$ reduction to hydroxy ester **20**. [b] The regioselectivity was at least 15:1, as shown by subsequent isolation of **21a** and **21b**.

fording almost exclusively the desired product **19** as a mixture of *cis* and *trans* isomers. This material was reduced with $NaBH_4$ to a mixture of four diastereomeric hydroxy esters, **20**, which were mesylated and eliminated with potassium *tert*-butoxide in THF at 0 °C to afford a single unsaturated ester, **21a**, in 69% overall yield from **18**. The isomeric ester **21b** constituted only 3% of the product.

Conversion of ester **21a** to the functionalized aminocyclopentanol began with $LiAlH_4$ reduction to alcohol **22** in 93% yield (Scheme 5). We speculated that steric interactions with the Pf protecting group would direct hydroboration of the double bond to the opposite face of the cyclopentene ring, especially with a bulky reagent such as 9-BBN. Indeed, the desired diol **23** was obtained in 90% yield with >99% diastereomeric excess. Benzoylation of the diol **23** followed by hydrogenation to remove the Pf group provided **25** in excellent yield. Removal of the benzoyl groups afforded the stereochemically pure (1*S*,2*R*,4*R*)-4-amino-2-(hydroxymethyl)-1-cyclopentanol (**26**). The amino diol **26** is a known compound,[15] having been prepared from (+)-*cis*-2-oxabicyclo[3.3.0]oct-6-en-3-one in 12 steps with an overall yield of 0.7%. The new route to **26** involves only nine steps and proceeds in 19% overall yield from the readily accessible aspartic acid derivative **13**.

The synthesis of carbapentostatin **8** was completed by coupling amine **25** and imidate **9b** to give imidazole **27** in 51% yield, which in turn was reduced and cyclized in 73% yield, in analogy to the synthesis of **10** described above. The yields for these steps were slightly lower than observed for the unsubstituted cyclopentylamine, most

SCHEME 5. Enantiospecific Synthesis of Carbapentostatin



likely as a consequence of the increased steric bulk of **25**. Final deprotection of the silyl and benzoate protecting groups afforded carbapentostatin **8**.

In conclusion, we have accomplished the stereocontrolled synthesis of carbapentostatin **8** and its analogue **12b**. This synthesis entailed the development of efficient and novel procedures for preparing aldehyde **15**, an amino acid derivative with a number of potential applications, and the highly functionalized intermediate **26**.

Experimental Section[16]

(2*S*,3*R*)-4-Azido-3-[(*tert*-butyldimethylsilyl)oxy]-2-[(methoxymethylene)amino]butanitrile (5b). A solution of amino nitrile **9** (255 mg, 1 mmol) in trimethyl orthoformate (1 mL, 9.2 mL) was heated at 80 °C for 4 h. The excess orthoformate was evaporated to give **5b** as an oil, which solidified upon storage at room temperature: mp 98−99 °C; ^{1}H NMR δ 0.12 (s, 3H), 0.16 (s, 3H), 0.91 (s, 9H), 3.37 (dd, 1H, J = 14.0, 5.8

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(16) All reactions were conducted under a nitrogen atmosphere. Unless otherwise noted, all NMR data were obtained at 400 MHz for ^{1}H and 100 MHz for ^{13}C, in $CDCl_3$ using TMS as an internal standard. Optical rotations were measured at 25 °C. Melting points are uncorrected. Column chromatography was performed using 230−400 mesh silica gel.

Hz), 3.54 (dd, 1H, J = 14.0, 4.1 Hz), 3.73 (m, 1H), 3.75 (s, 3H), 4.40 (d, 1H, J = 5.2 Hz), 7.75 (s, 1H); ^{13}C NMR δ −4.9, −4.7, 17.9, 25.6, 53.2, 54.0, 55.5, 72.2, 116.9, 159.7. Anal. Calcd for $C_{12}H_{23}N_5O_2Si$: C, 48.48; H, 7.74; N, 23.57. Found: C, 48.48; H, 7.74; N, 23.57.

4-[(1*R*)-2-Azido-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-1-cyclopentyl-5-[dimethylaminomethylene]amino]imidazole (11). A solution of imidate **5b** (297 mg, 1 mmol) and cyclopentylamine (80 μL, 69 mg, 0.81 mmol) in 2,2,2-trifluoroethanol (1 mL) and 1,2-dichloroethane (10 mL) was stirred at 80 °C for 4 h to yield **10**. An analytical sample was obtained by flash chromatography (EtOAc:Et_3N = 99:1): ^{1}H NMR δ 0.01 (s, 3H), 0.20 (s, 3H), 0.09 (s, 9H), 1.6−2.20 (m, 8H), 3.30−3.45 (m, 4H), 4.25−4.30 (m, 1H), 4.97 (t, J = 4.2 Hz, 1H), 7.13 (s, 1H). Anal. Calcd for $C_{16}H_{30}N_6OSi$: C, 54.82; H, 8.63; N, 23.97. Found: C, 55.11; H, 8.76; N, 24.01.

Without purification of **10**, *N*,*N*-dimethylformamide dimethyl acetal (0.5 mL, 3.77 mmol) was added, and the resulting mixture was heated at reflux temperature for 13 h. Purification by flash chromatography on SiO_2 (EtOAc:hexane:Et_3N = 30:70:0.1) gave imidazole **11** (220 mg, 67%): $[\alpha]_D$ +68.5 (*c* 0.11, $CHCl_3$); ^{1}H NMR δ −0.11 (s, 3H), −0.02 (s, 3H), 0.84 (s, 9H), 1.77 (m, 6H), 2.07 (m, 2H), 3.00 (s, 6H), 3.34 (dd, 1H, J = 12.4, 4.9 Hz), 3.64 (dd, 1H, J = 12.4, 8.5 Hz), 4.49 (quintet, 1H, J = 7.2 Hz), 4.76 (dd, 1H, J = 8.5, 4.9 Hz), 7.22 (s, 1H), 7.79 (s, 1H); ^{13}C NMR δ −4.9, −4.4, 18.4, 24.3, 26.2, 33.1, 33.4, 55.3, 56.0, 69.9, 123.9, 129.2, 139.1, 155.5. Anal. Calcd for $C_{19}H_{35}N_7OSi$: C, 56.14; H, 8.78; N, 24.12. Found: C, 56.24; H, 8.68; N, 24.11.

(8*R*)-8-[(*tert*-Butyldimethylsilyl)oxy]-3-cyclopentyl-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepine (12a). A solution of imidazole **11** (206 mg, 0.5 mmol), propanedithiol (0.5 mL, 5 mmol), and triethylamine (1 mL, 7.2 mmol) in methanol (5 mL) was heated at 50 °C. After 13 h, the solvent was evaporated to give a yellow oil which was purified by flash chromatography (EtOAc:hexane:Et_3N = 50:50:0.1) to afford diazepine **12a** (145 mg, 85%): $[\alpha]_D$ +72.5 (*c* 0.12, $CHCl_3$); ^{1}H NMR δ −0.10 (s, 3H), 0.14 (s, 3H), 0.85 (s, 9H), 1.70 (m, 6H), 2.13 (m, 2H), 3.40 (m, 1H), 4.73 (quintet, 1H, J = 7.1 Hz), 5.20 (m, 1H), 5.43 (br s, 1H), 7.07 (d, 1H, J = 4.2 Hz), 7.29 (s, 1H); ^{13}C NMR δ −4.4, −4.1, 18.6, 24.1, 24.2, 26.1, 33.6, 50.2, 54.9, 69.2, 129.6, 130.4, 145.9. Anal. Calcd for $C_{19}H_{35}N_7OSi$: C, 61.08; H, 8.98; N, 16.77. Found: C, 61.16; H, 8.75; N, 16.72.

(8*R*)-3-Cyclopentyl-8-hydroxy-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepine (12b). A solution of silyl ether **12a** (132 mg, 0.4 mmol) in 1,4-dioxane (30 mL) in a Teflon container was cooled in an ice bath as aq HF (49%, 10 mL) was added slowly. The mixture was stirred at room temperature for 3 h, diluted with $CHCl_3$ (100 mL), and washed with saturated aq Na_2CO_3 (200 mL). The aq phase was extracted with $CHCl_3$/isopropyl alcohol (3:1, 100 mL × 5), and the combined organic layers were dried (Na_2SO_4) and concentrated to a yellow oil. Purification was effected by flash chromatography (IPA:$CHCl_3$:Et_3N = 10:90:0.1) to give **12b** (183 mg, 96%): $[\alpha]_D$ +85.0 (*c* 0.14, $CHCl_3$); ^{1}H NMR δ 1.77 (m, 6H), 2.13 (m, 2H), 3.42 (m, 2H), 4.73 (quintet, 1H, J = 7.5 Hz), 4.94 (br s, 1H), 5.14 (m, 1H), 6.08 (br s, 1H), 7.09 (s, 1H), 7.41 (s, 1H); ^{13}C NMR δ 23.3, 32.6, 54.9, 66.9, 72.1, 128.4, 135.5, 148.1, 148.2. Anal. Calcd for $C_{19}H_{35}N_7OSi$: C, 55.44; H, 7.61; N, 23.51. Found: C, 55.26; H, 8.00; N, 23.11.

Methyl (3*S*)-3-[*N*-(9-Phenyl-9-fluorenyl)amino]-4-oxobutanoate (15). A stirred solution of **13**[8] (7.0 g, 19 mmol) in THF (60 mL) was cooled to −78 °C as BH_3 (1.0 M solution in THF, 45 mL, 4.5 mmol) was added. The solution was warmed to 0 °C and stirred for 60 h. Aqueous NH_4Cl (80 mL) was added, and the mixture was extracted twice with CH_2Cl_2 (100 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to about 40 mL, which was immediately used in the next step without purification. A small amount of alcohol **14** was purified by flash chromatography (EtOAc:hexane = 30:70) in a cold room (<4 °C):

mp 105−107 °C; ^{1}H NMR δ 2.14 (dd, 2H, J = 15.5, 5.7 Hz, 2.59 (quintet, 1H, J = 5.1 Hz), 2.99 (dd, 1H, J = 11.0, 4.8 Hz), 3.16 (dd, 1H, J = 11.0, 4.8 Hz), 3.62 (s, 3H), 7.15−7.85 (m, 13H); ^{13}C NMR δ 37.8, 51.1, 51.9, 64.7, 72.7, 120.4, 125.3, 125.5, 126.2, 126.4, 127.6, 128.2, 128.5, 128.7, 128.8, 128.9, 140.4, 140.9, 145.2, 150.0, 150.2, 173.2. Anal. Calcd for $C_{24}H_{23}NO_3$: C, 77.21; H, 6.22; N, 3.75. Found: C, 76.95; N. 6.21; N, 3.77.

A solution of oxalyl chloride (2.0 M, 23 mL, 46 mmol) in CH_2Cl_2 (60 mL) was cooled at −78 °C as DMSO (7 mL in 17 mL of CH_2Cl_2) was added via a syringe pump at such a rate (1 mL/min) that the temperature remained below −60 °C. The mixture was cooled to −78 °C for 1 h, freshly prepared **14** in CH_2Cl_2 (ca. 40 mL) was added slowly, and stirring was continued at −78 °C for 1 h. Et_3N (25 mL, 180 mmol) was added, the resulting mixture was stirred at −78 °C for 0.5 h, and 1% aq HCl (150 mL) was added. The solution was warmed to room temperature and extracted with CH_2Cl_2 (100 mL × 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated to dryness, and the residue was immediately purified by flash chromatography (EtOAc:hexane = 15:85) to give the aldehyde **15** (4.4 g, 61%): mp 105−107 °C; ^{1}H NMR δ 2.21 (dd, 1H, J = 11.9, 5.7 Hz), 2.51 (dd, 1H, J = 11.9, 4.3 Hz), 2.82 (ddd, 1H, J = 6.1, 5.7, 4.3 Hz), 3.46 (d, 1H, J = 6.1 Hz), 3.65 (s, 3H), 7.20−7.43 (m, 11H), 7.69 (m, 2H), 9.44 (s, 1H); ^{13}C NMR δ 36.6, 51.8, 58.7, 72.8, 120.0, 120.2, 125.2, 125.3, 126.1, 127.4, 128.0, 128.2, 128.4, 128.6, 128.7, 140.1, 144.2, 149.0, 149.3, 171.6, 201.7. Anal. Calcd for $C_{24}H_{21}NO_3$: C, 77.60; H, 5.71; N, 3.77. Found: C, 77.55; H, 5.95; N, 3.68.

Methyl (3*S*)-5-Methoxycarbonyl-3-[*N*-(9-phenyl-9-fluorenyl)amino]-4-pentenoate (16 and 17). A suspension of NaH (60% suspension in mineral oil, 2.8 g, 70 mmol) in THF (1500 mL) was stirred at 0 °C as trimethyl phosphonoacetate (11 mL, 68 mL) was added, and the resulting mixture was stirred at 0 °C for 2 h. The mixture was cooled to −40 °C, and a solution of aldehyde **15** (8.6 g, 23.2 mmol) in THF (100 mL) was added over 10 min. The resulting mixture was stirred at −40 °C for 2 h. Aqueous KH_2PO_4 (1 M, 600 mL) and EtOAc (400 mL) were added, and the particulates were filtered. The aq phase was extracted with EtOAc (100 mL × 2), and the combined organic layers were washed with water (200 mL × 2) and brine (100 mL), dried ($MgSO_4$), and filtered. The solvent was evaporated, and the residue was purified by flash chromatography (EtOAc:hexane = 15:85) to give a 10:1 mixture (8.96 g, 92%) of *trans* olefin **16** and *cis* olefin **17**. Analytical samples were prepared by an additional chromatography (EtOAc:hexane = 10:90).

Data for **16** (*E* isomer): $[\alpha]_D$ +43.0 (*c* 0.04, $CHCl_3$); ^{1}H NMR δ 2.24 (dd, J = 15.4, 5.1 Hz, 1H), 2.37 (dd, J = 15.4, 7.5 Hz, 1H), 2.82 (br s, 1H), 3.15−3.20 (m, 1H), 3.59 (s, 3H), 3.65 (s, 3H), 5.15 (d, J = 15.6 Hz, 1H), 6.37 (dd, J = 15.6, 8.3 Hz, 1H), 7.28 (m, 11H), 7.60 (d, J = 7.5 Hz, 1H), 7.69 (d, J = 7.5 Hz, 1H); ^{13}C NMR δ 40.4, 51.2, 51.6, 51.9, 72.5, 119.1, 119.7, 120.0, 125.1, 125.6, 126.0, 127.2, 127.7, 127.8, 128.3, 128.5, 140.3, 140.6, 144.9, 148.9, 150.0, 166.4, 171.4. Anal. Calcd for $C_{27}H_{25}NO_4$: C, 75.85; H, 5.91; N, 3.28. Found: C, 75.54; H, 6.03; N, 3.23.

Data for **17** (*Z* isomer): $[\alpha]_D$ +36.0 (*c* 0.02, $CHCl_3$); ^{1}H NMR δ 2.38 (m, 2H), 2.95 (br s, 1H), 3.39 (s, 3H), 3.68 (s, 3H), 4.24 (m, 1H), 4.98 (dd, J = 10.6, 1.0 Hz, 1H), 5.73 (dd, J = 10.6, 9.3 Hz, 1H), 7.28 (m, 11H), 7.56 (d, J = 7.5 Hz, 1H), 7.61 (d, J = 7.5 Hz, 1H); ^{13}C NMR δ 40.5, 48.3, 50.8, 51.6, 72.5, 116.6, 119.5, 119.7, 125.3, 125.6, 126.0, 127.1, 127.3, 127.8, 128.1, 128.2, 128.3, 140.5, 140.8, 144.9, 148.9, 150.7, 151.9, 165.7, 172.1. Anal. Calcd for $C_{27}H_{25}NO_4$: C, 75.85; H, 5.91; N, 3.28. Found: C, 76.05; H, 5.99; N, 3.20.

Dimethyl (3*R*)-3-[*N*-(9-Phenyl-9-fluorenyl)amino]adipate (18). A slurry of a 10:1 mixture of esters **16** and **17** (8.96 g, 21 mmol), EtOAc (100 mL), MeOH (50 mL), and 5% Pt/C (1 g) was hydrogenated in a Parr shaker under 20 psi of H_2 at room temperature for 30 h. The reaction mixture was filtered,

and the filtrate was evaporated. Purification of the residue by flash chromatography (EtOAc:hexane = 20:80) afforded **18** (8.33 g, 93%) as a white solid: mp 65−66 °C; $[\alpha]_D$ +113.9 (*c* 0.04, $CHCl_3$); ^{1}H NMR δ 1.45 (m, 1H), 1.67 (m, 1H), 1.82 (dd, J = 15.7, 5.7 Hz, 1H), 1.93 (dd, J = 15.7, 4.2 Hz, 1H), 2.35 (m, 1H), 2.48 (m, 2H), 2.71 (br s, 1H), 3.56 (s, 3H), 3.61 (s, 3H), 7.15−7.71 (m, 13H); ^{13}C NMR δ 31.0, 31.2, 39.2, 49.5, 51.2, 51.4, 72.5, 119.9, 120.0, 125.1, 125.5, 126.0, 127.0, 127.7, 127.8, 128.1, 128.2, 128.3, 140.0, 140.5, 145.5, 149.4, 151.0, 172.5, 174.2. Anal. Calcd for $C_{27}H_{27}NO_4$: C, 75.49; H, 6.40; N, 3.15. Found: C, 75.64; H, 6.63; N, 3.26.

Methyl (1*RS*,4*R*)-2-Oxo-4-[*N*-(9-phenyl-9-fluorenyl)-amino]cyclopentanecarboxylate (19). A solution of freshly distilled 2,2,6,6-tetramethylpiperidine (LTMP; 10 mL, 59.3 mmol) in THF (100 mL) was stirred at −78 °C as ^{n}BuLi (1.6 M solution in hexane, 37 mL, 59.2 mmol) was added at such a rate that the internal temperature remained below −60 °C. The solution was warmed to 0 °C for 1 h and then cooled to −78 °C, and a solution of diester **18** (8.3 g, 19.3 mmol) in THF (300 mL) at −78 °C was added over 20 min. The resulting mixture was stirred at −78 °C for 0.5 h, and KH_2PO_4 (1 M, 200 mL) was added. The mixture was warmed to room temperature, and the aq phase was extracted with EtOAc (2 × 250 mL). The combined organic layers were washed with brine (2 × 100 mL), dried, filtered, and evaporated to afford β-ketoester **19** (6.7 g, 88%).

Methyl (1*RS*,2*RS*,4*R*)-2-Hydroxy-4-[*N*-(9-phenyl-9-fluorenyl)amino]cyclopentanecarboxylate (20). A solution of β-ketoester **19** in CH_3OH/THF (500 mL, 1/1) was stirred at 0 °C while $NaBH_4$ (1.46 g, 38.6 mmol) was added in 20 portions over 20 min. The reaction mixture was stirred at 0 °C for 1 h, and most of the solvent was evaporated. The residue was partitioned between saturated aq KH_2PO_4 (500 mL) and EtOAc (250 mL), and the aq phase was extracted with EtOAc (200 mL). The combined organic layers were washed with water (200 mL) and brine (100 mL), dried, and filtered. The filtrate was evaporated to give β-hydroxy ester **20** as an oil (6.4 g, 84% from **18**).

Methyl (4*S*)-4-[*N*-(9-Phenyl-9-fluorenyl)amino]-1-cyclopentenecarboxylate (21a) and Methyl (5*S*)-5-[*N*-(9-Phenyl-9-fluorenyl)amino]-1-cyclopentenecarboxylate (21b). A solution of hydroxy ester **20** (6.4 g, 18 mmol) and DMAP (47 mg, 0.39 mmol) in THF (500 mL) was stirred at 0 °C as Et_3N (5 mL, 36 mmol) and methanesulfonyl chloride (2 mL, 25.9 mmol) were added sequentially. The reaction mixture was stirred at 0 °C for 7 h and then filtered. Potassium *tert*-butoxide (6.2 g, 55.3 mmol) was added to the filtrate, and the mixture was stirred at 0 °C for 2 h. Saturated aq KH_2PO_4 (500 mL) and EtOAc (250 mL) were added, and the aq layer was extracted with EtOAc (150 mL). The combined organic layer was washed with water (2 × 500 mL) and brine (100 mL), dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was purified by flash chromatography (EtOAc:hexane = 15:85) to give **21a** (4.4 g, 69% from **18**) and **21b** (0.19 g, 3% from **18**). Data for **21a**: $[\alpha]_D$ −117 (*c* 0.038, $CHCl_3$); ^{1}H NMR δ 2.15 (m, 3H), 2.37 (m, 1H), 3.07 (q, 1H, J = 7.7 Hz), 3.64 (s, 3H), 6.46 (m, 1H), 7.25 (m, 11H), 7.68 (d, 1H, J = 3.5 Hz), 7.70 (d, 1H, J = 3.5 Hz); ^{13}C NMR δ 40.4, 42.5, 51.3, 54.2, 73.2, 119.9, 125.0, 126.2, 127.1, 127.7, 127.9, 128.2, 128.3, 134.2, 140.4, 141.8, 145.1, 150.3, 165.3. Anal. Calcd for $C_{26}H_{23}NO_2$ $0.5H_2O$: C, 79.60; H, 6.22; N, 3.57. Found: C, 79.42; H, 5.90; N, 3.87. Data for **21b**: ^{1}H NMR δ 1.61 (m, 2H), 2.07 (m, 1H), 2.35 (m, 1H), 3.05 (m, 1H), 3.63 (s, 3H), 6.45 (m, 1H), 7.35 (m, 10H), 7.69 (m, 2H). Anal. Calcd for $C_{26}H_{23}NO_2$: C, 81.89; H, 6.03; N, 3.67. Found: C, 81.53; H, 5.73; N, 3.50.

(4*S*)-4-[*N*-(9-Phenyl-9-fluorenyl)amino]-1-cyclopentenemethanol (22). A solution of $LiAlH_4$ (1.0 M solution in THF, 12 mL) was added to a solution of ester **21a** (1.5 g, 3.94 mmol) in CH_2Cl_2 (100 mL) at −78 °C, and the reaction mixture was stirred at −78 °C for 1 h. NaOH (6 M, 0.5 mL) was added, the precipitate was removed by filtration, and the filtrate was partitioned between water (150 mL) and EtOAc (150 mL). The aq phase was extracted with EtOAc (100 mL × 2), and the combined organic layer was washed with water (100 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (EtOAc:hexane = 30:70) to give alcohol **22** as a thick oil (1.3 g, 93%): $[\alpha]_D$ −4.4 (*c* 0.037, $CHCl_3$); ^{1}H NMR δ 2.01 (m, 4H), 3.07 (q, 1H, J = 7.7 Hz), 3.95 (s, 3H), 5.31 (m, 1H), 7.33 (m, 11H), 7.69 (d, 2H, J = 7.5 Hz); ^{13}C NMR δ 41.5, 41.6, 54.7, 62.1, 73.2, 119.8, 119.9, 123.5, 125.2, 126.2, 127.0, 127.6, 127.7, 128.0, 128.1, 128.2, 142.3, 145.3, 150.5. Anal. Calcd for $C_{25}H_{23}NO$: C, 84.95; H, 6.56; N, 3.96. Found: C, 84.64; H, 6.48; N, 3.80.

(1*R*,2*S*,4*R*)-4-[*N*-(9-Phenyl-9-fluorenyl)amino]-2-hydroxycyclopentanemethanol (23). A solution of 9-BBN (1.0 M in THF, 2 mL, 2 mmol) was added to a solution of alcohol **22** (300 mg, 0.85 mmol) in THF (2 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 48 h. The solution was cooled to 0 °C as aq NaOH (1.0 m, 5 mL) and 30% aq H_2O_2 (5 mL) were added. After 1 h at room temperature, the mixture was extracted with EtOAc (250 mL × 2) and the combined organic layer was washed with brine (50 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography to yield diol **23** (285 mg, 90%): $[\alpha]_D$ +0.88 (*c* 0.09, $CHCl_3$); ^{1}H NMR δ 0.93 (m, 1H), 1.40 (m, 1H), 1.55 (m, 2H), 1.74 (m, 1H), 2.88 (m, 1H), 3.50 (dd, 1H, J = 16.0 8.0 Hz), 3.70 (dd, 1H, J = 16.0, 8.0 Hz) 4.15 (m, 1H), 7.30 (m, 14H), 7.71 (d, 2H, J = 9 Hz); ^{13}C NMR δ 36.9, 43.9, 48.9, 52.5, 60.4, 73.1, 75.1, 119.9, 125.0, 125.2, 125.8, 125.9, 127.1, 127.7, 127.8, 128.1, 128.2, 128.3, 140.2, 140.3, 144.9, 149.7, 149.8. Anal. Calcd for $C_{25}H_{25}NO_2$: C, 79.02; H, 7.08; N, 3.51. Found: C, 79.22; H, 7.11; N, 3.56.

(1*S*,2*R*,4*R*)-1-Benzoyloxy-2-(benzoyloxy)methyl-4-[*N*-(9-phenyl-9-fluorenyl)amino]cyclopentane (24). Benzoyl chloride (0.5 mL, 4.8 mmol) was added to a solution of diol **23** (100 mg, 0.27 mmol) in pyridine (3 mL), and the mixture was stirred at room temperature for 18 h. Glycine (100 mg, 1.33 mmol) was added, and the mixture was stirred for another 6 h. The solvent was evaporated, and the residue was purified by flash chromatography (EtOAc:hexane = 20:80) to afford dibenzoate **24** (142 mg, 91%) as a thick oil: $[\alpha]_D$ +38.4 (*c* 1, $CHCl_3$); ^{1}H NMR δ 1.20−1.3 (m, 1H), 1.95 (m, 1H), 2.26 (m, 1H), 2.51 (m, 1H), 2.65 (m, 1H), 4.28 (m, 1H), 4.40 (m, 2H), 4.68 (d, J = 7.5 Hz, 1H), 5.36 (q, J = 3.7 Hz, 1H), 7.60 (m, 23H). Anal. Calcd for $C_{39}H_{33}NO_4$: C, 80.81; H, 5.74; N, 2.42. Found: C, 81.02; H, 5.71; N, 2.32.

(1*S*,2*R*,4*R*)-4-Amino-1-benzoyloxy-2-(benzoyloxy)methylcyclopentane (25). A slurry of **24** (100 mg, 0.17 mmol) and 10% Pd/C (50 mg) in EtOAc (5 mL) and methanol (5 mL) was stirred under hydrogen (balloon) at room temperature for 12 h. The reaction mixture was filtered, the filtrate was concentrated, and the residue was purified by flash chromatography (CH_2Cl_2:MeOH:Et_3N = 80:20:0.1) to give amine **25** (56 mg, 95%) as a thick oil: ^{1}H NMR δ 1.28 (m, 1H), 1.95 (m, 1H), 2.20 (m, 1H), 2.42 (m, 3H), 2.75 (m, 1H), 3.70 (quint, 1H, J = 7.8 Hz), 4.48 (m, 2H), 5.40 (m, 1H), 7.60 (m, 10H); ^{13}C NMR δ 38.0, 42.5, 44.6, 51.3, 66.5, 77.8, 128.6, 129.9, 130.3, 130.5, 133.3, 166.4, 166.8. Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.80; H, 6.19; N, 4.13. Found: C, 71.02; H, 6.11; N, 4.33.

(1*R*,2*S*,4*R*)-4-Amino-2-hydroxycyclopentanemethanol (26). A solution of dibenzoate **25** (100 mg, 0.41 mmol) and NaOH (160 mg, 4 mmol) in methanol/THF (10 mL, 1:1) was stirred at 50 °C for 12 h. The solvent was removed, and the residue was purified by flash chromatography (MeOH:1.0 M NH_3 = 30:1) to afford 24.5 mg (62% yield) of amino diol **26** as a thick oil: $[\alpha]^{25}_D$ +37.0 (*c* 1, DMF) {lit.[15] $[\alpha]^{26}_D$ +34.0 (*c* 1, DMF)}; ^{1}H NMR (DMSO-d_6) δ 0.87−0.97 (m, 1H), 1.38−1.56 (m, 1H), 1.55−1.63 (m, 1H), 1.75−1.83 (m, 1H), 1.91−2.00 (m, 1H), 3.25−3.40 (m, 3H), 3.85−3.90 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 39.44, 44.44, 45.49, 50.61, 64.16, 73.42. Anal. Calcd for $C_6H_{15}NO_2$: C, 54.96; H, 9.92; N, 10.69. Found: C, 54.79; H, 9.66; N, 10.84.

1-[(1*S*,2*R*,4*R*-4-Amino-2-(benzoyloxymethyl)-1-benzoyloxycyclopentyl]-4-[(1*R*)-[(2-azido-1-*tert*-butyldimeth-

ylsilyl)oxy]ethyl]-5-[(dimethylaminomethylene)amino]-imidazole (27). Condensation of **5b** (100 mg, 0.34 mmol) and amine **25** (50 mg, 0.34 mmol) as described for imidazole **10** gave imidazole **27** (49 mg, 51%): ^{1}H NMR δ −0.09 (s, 3H), −0.01 (s, 3H), 0.85 (s, 9H), 1.93 (m, 1H), 2.53 (m, 2H), 2.75 (m, 1H), 2.85 (m, 1H), 3.03 (s, 6H), 3.20 (m, 1H), 2.58 (m, 1H), 4.48 (m, 2H), 4.85 (m, 1H), 5.50 (m, 1H), 7.26 (s, 1H), 7.45 (m, 6H), 7.85 (s, 1H), 8.01 (m, 4H). Anal. Calcd for $C_{34}H_{45}N_7O_5Si$: C, 61.91; H, 6.83; N, 14.87. Found: C, 61.73; H, 6.50; N, 14.96.

(8*R*)-3-[(1*S*,2*R*,4*R*)-4-Amino-2-(benzoyloxymethyl)-1-benzoyloxycyclopentyl]-8-[(*tert*-butyldimethylsilyl)oxy]-3,6,7,8-tetrahydroimidazo[4.5-*d*][1.3]diazep ine (28). Cyclization of **27** (40 mg, 0.06 mmol) as described for **11** gave **28** (26 mg, 73%) as a thick oil: $[\alpha]_D$ +55.2 (*c* 0.06, $CHCl_3$); ^{1}H NMR δ −0.15 (s, 3H), 0.08 (s, 3H), 0.79 (s, 9H), 1.90 (m, 1H), 2.35 (m, 1H), 2.58 (m, 2H), 2.75 (m, 1H), 3.30 (m, 2H), 4.50 (m, 2H), 4.01 (m, 1H), 5.25 (m, 2H), 5.55 (m, 1H), 7.04 (d, 1H, J = 6.0 Hz), 7.33 (s, 1H), 7.72 (m, 10H). Anal. Calcd for $C_{32}H_{40}N_4O_5Si$: C, 65.31; H, 6.80; N, 9.52. Found: C, 65.16; H, 6.55; N, 9.76.

(8*R*)-3-[(1*S*,2*R*,4*R*-(3-Hydroxy-4-hydroxymethyl)cyclopentyl]-8-hydroxy-3, 6,7,8-tetrahydroimidazo[4.5-*d*][1,3]-diazepine (8). Benzoate **28** (20 mg, 0.034 mmol) was deprotected as described for **12**. Purification by flash chromatography (IPA:CH_2Cl_2:Et_3N = 20:80:0.1) gave **8** (5 mg, 55%): $[\alpha]_D$ +43.4 (*c* 0.03, $CHCl_3$); ^{1}H NMR δ 2.20 (m, 2H), 3.40 (m, 2H), 3.54 (m, 2H), 3.76 (m, 2H), 4.84 (m, 2H), 5.13 (m, 2H), 5.33 (br s, 3H), 6.13 (br s, 1H), 7.17 (s, 1H), 7.62 (s, 1H). Anal. Calcd for $C_{12}H_{18}N_4O_3$: C, 47.67; H, 7.33; N, 18.53. Found: C, 47.47; H, 7.47; N, 18.70.

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