An Efficient Procedure for the Preparation of (1*S*,3*R*)- and (1*S*,3*S*)-1-Amino-3-(hydroxymethyl)cyclopentanes

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Enantiomerically pure (1*S*,3*S*)- and (1*S*,3*R*)-1-amino-3-(hydroxymethyl)cyclopentanes have been efficiently synthesized from L-aspartic acid. The title compounds are isosteres of ribose and may be used to construct nucleoside analogs with important antiviral and antineoplastic activities as demonstrated by a concise total synthesis of (+)-4′-deoxycarbapentostatin nucleoside.

Key words amino acid; heterocycle; carbocycle; enantioselectivity; nucleoside

Methods for the synthesis of carbanucleoside building blocks have drawn considerable attention[1—3] because carbocyclic nucleosides exhibit greater chemical and enzymatic stability relative to their analogs with sugar moities.[4—7] (1*S*,3*R*)- and (1*S*,3*S*)-1-amino-3-(hydroxymethyl)cyclopentane (**1**, **2**) (Fig. 1) have been used as ribose motifs for the preparation of many biologically active compounds, such as inosine analogs,[8] nucleobases for DNA polymerase,[9] human immunodeficiency virus (HIV) inhibitors,[10] purine nucleosides,[11] thimine nucleosides,[12] carbocyclic thymidines,[13] and others.[14—17]

Previously, compound **1** was prepared from L-aspartic acid *via* 2-aminoadipic acid using a 15-step sequence with less than 10% overall yield.[18] An alternate route[19] that involved an activated aziridine intermediate resulted in a similar yield for **1**. Cyclopentane **2** was also generated as a minor product during the synthesis of **1**. To the best of our knowledge, there is no specific preparation of (1*S*,3*S*)-1-amino-3-(hydroxymethyl)cyclopentane (**2**). In our preparation of carbapentostatine, we developed an efficient method to synthesize enantiomerically pure **4** (36% overall yield) from L-aspartic acid derivative **3** (Chart 1).[20] This prompted us to develop a procedure to use **4** as a precursor to obtaining either **1** or **2** as a major product.

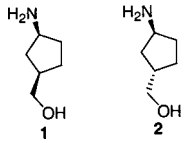
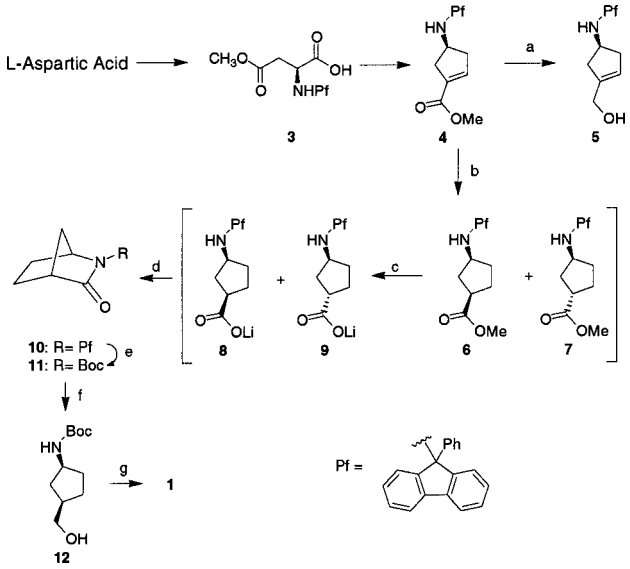


Fig. 1



Reagents and conditions: (a) DIBAL-H, THF, 94%; (b) H_2, Pd/C, MeOH, 99%, **6**:**7**=1:1; (c) LiOH, water, MeOH; (d) Ac_2O, AcONa, 95% from 4; (e) Boc_2O, H_2, Pt/C, MeOH, 97%, (f) $NaBH_4$, MeOH, 91%; (g) 1.0 M HCl in ether, 99%.

Chart 1

Results and Discussion

In the synthesis of **1** (Chart 1), hydrogenation of **4** led to a 1 : 1 ratio of *syn* and *anti* esters **6** and **7**. Without separation, the mixture was hydrolyzed with aqueous LiOH to form a mixture of lithium carboxylate **8** and **9**, which was treated with acetic anhydride in the presence of sodium acetate. Epimerization of **9** to **8** followed by cyclization to form lactam **10** in an excellent yield. The Pf-group was replaced with an *N*-Boc group to form lactam **11**. The amide carbonyl group of **11** had a great deal of imide character, as evidenced by its reduction to alcohol **12** using $NaBH_4$. Upon treatment with HCl, compound **12** was transformed to the desired product **1**.[21]

To synthesize **2**, DIBAL reduction of **4** gave the allyllic alcohol **5** (Chart 1). A variety of reduction methods was then attempted to convert **5** to **14** selectively (Table 1). Hydrogenation with different catalysts proceeded rapidly; however, the *cis*-isomer **13** was usually the predominant product except in the case of the nickel catalyst which yielded an 18 : 82 ratio of *cis* : *trans* products. Reductions with diimide and ionic hydrogenation with $nBuSiH_3$ gave higher selectivity for the *trans*-isomer **14** with better overall yields. Hydrogenation of **14** with 5% Pt/C resulted in the removal of *N*-Pf protecting group to give the desired product **2** (Table 1).

The utility of **1**, was demonstrated by the synthesis of deoxycarbapentostatin (Chart 2). Protection of **12** with

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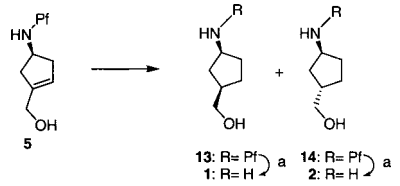
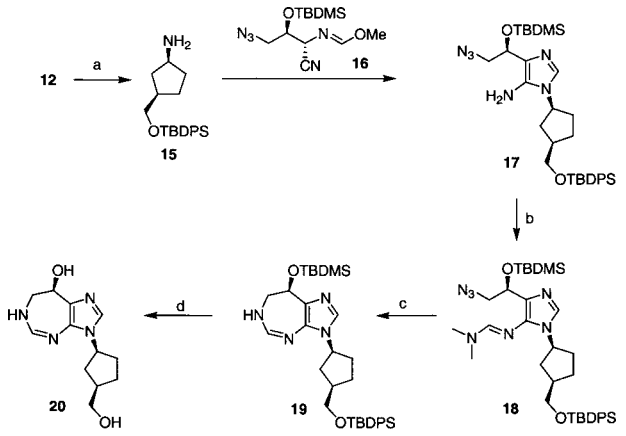
Table 1



Run	Method	**13** : **14**	Yield of **13** (%)	Yield of **14** (%)
1	H_2, Pd/C, MeOH	55 : 45	46	40
2	H_2, Rh/C, MeOH	34 : 66	29	52
3	H_2, Ni, PhH	18 : 82	11	78
4	Diimide	3 : 97	1	92
5	TFA, $nBuSiH_3$	2 : 98	1	93

Reagents and conditions: (a) H_2, Pt/C, MeOH, 98%.



Reagents and conditions: (a) TBDPS-Cl, pyr, rt, 18 h, then 1.0 M HCl in ether, 12 h, 83%; (b) $ClCH_2CH_2Cl$, CF_3CH_2OH, 80 °C, 4 h, then, DMF dimethyl acetyl, 80 °C, 74% from **15**; (c) Propanedithiol, Et_3N, 67%; (d) Aqueous HF (49%), 1,4-dioxane, 3 h, 72%.

Chart 2

TBDPS-Cl followed by Boc removal with HCl in ether afforded amine **15** which was treated with enantiomerically pure nitrile **16**[20] to give imidazole **17**. Treatment of **17** with *N*,*N*-dimethylformamide dimethyl acetal yielded stable amidine **18**. The azide was reduced and cyclized to azepine **19**, which upon removal of the silyl groups with aqueous HF furnished deoxycarbapentostatin (**20**).

In summary, an efficient approach to cyclopentane amino alcohols **1** and **2** was developed using a common intermediate **4** derived from L-aspartic acid. By employing D-aspartic acid, this route would also provide access to enantiomerically pure (1*R*,3*S*)-, and (1*R*,3*R*)-1-amino-3-(hydroxymethyl)cyclopentanes.

Experimental

General All reactions were conducted under a nitrogen atmosphere. All NMR data were obtained at 400 MHz for proton and 100 MHz for carbon spectra, in $CDCl_3$ unless otherwise noted, using TMS as an internal standard. Specific rotations were measured at 25 °C. Melting points are uncorrected. Column chromatography was performed using 230—400 mesh silica gel. Enantiomeric excess was determined by chiral HPLC (Chiralpak AD column 250×4.6) with isoocratic mobile phase (hexane : isopropanol = 97 : 3).

Synthesis of (1*S*)-1-[*N*-(9-Phenyl-9-fluorenyl)amino]-3-(hydroxymethyl)-cyclopentene (5) A solution of DIBAL-H (1.0 M solution in THF, 21 ml, 21 mmol) was added to a solution of ester **4**[20] (4.0 g, 10.5 mmol) in THF (100 ml) at 0 °C, and the reaction mixture was stirred at room temperature for 4 h. NaOH (6 M, 3 ml) was added and mixture was partitioned between water (300 ml) and EtOAc (200 ml). Aqueous phase was extracted with EtOAc (200 ml×2). Combined organic layers were washed with water (100 ml) and brine (50 ml), dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (30% EtOAc : hexane = 30 : 70) to give alcohol **5** as a thick oil (3.3 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, 217.0, 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.

Synthesis of (1*S*,3*R*)-1-(*N*-Boc-amino)-3-(hydroxymethyl)cyclopentane (12) A slurry of **4** (4 g, 10.5 mmol), MeOH (50 ml), and 10% Pd/C (0.5 g) was hydrogenated in a Parr shaker under 45 psi of H_2 at rt for 24 h. The reaction mixture was filtered, and the filtrate was evaporated to give a 1 : 1 mixture (3.95 g, 99%) of *cis* ester **6** and *trans* ester **7**. Lithium hydroxide (1.0 M solution, 11 ml, 11 mmol) was added to a solution of **6** and **7** (3.95 g, 10.4 mmol) in THF (40 ml). The mixture was stirred at rt for 4 h then concentrated. Toluene (5 ml×3) was used to azeotrope water. Ac_2O (50 ml) and NaOAc (5 g, 61 mmol) were added and the mixture was heated at its reflux temperature under nitrogen atmosphere. After 18 h, the mixture was concentrated then saturated $NaHCO_3$ (100 ml) was added. The aqueous phase was extrated with EtOAc (100 ml×3). The combined organic layer was washed with brine (100 ml), dried ($MgSO_4$), filtered, and concentrated to dryness. Purification of this residue by flash chromatography (EtOAc : hexane = 15 : 85) afforded **10** (3.4 g, 95% from **4**) as a white solid (mp 222 °C; lit[18] mp 220 °C). A mixture of **10** (3.4 g, 10.0 mmol), Boc_2O (3.0 g, 13.8 mmol) and 5% Pt/C (0.5 g) was hydrogenated in a Parr shaker under 15 psi of H_2 at rt for 24 h. The reaction mixture was filtered, and filtrate was evaporated. Purification of the residue by flash chromatography (EtOAc : hexane = 15 : 85) afforded **11** (3.3 g, 97%): $[\alpha]_D^{25}$ −30.3° (c=1.7, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 1.40 (d, J=6.0 Hz, 1H), 1.52 (s, 9H), 1.78 (m, 5H), 2.84 (s, 1H), 4.52 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ: 23.8, 28.1, 28.4, 37.8, 46.7, 58.9, 149.4, 175.6; *Anal.* Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.55; H, 8.31; N, 6.88. A solution of **11** (3.0 g, 14.2 mmol) in MeOH (100 ml) was cooled in an ice bath as $NaBH_4$ (1.1 g, 28.9 mmol) was added in 3 portions. The mixture was warmed to room temperature and stirred for 3 h. Solvent was evaporated under vacuum, and the mixture was partitioned between saturated aq KH_2PO_4 (500 ml) and EtOAc (250 ml). Aqueous phase was extracted with EtOAc (200 ml) twice and combined organic layers were washed with brine (100 ml), dried, and filtered. The filtrate was evaporated and purified by flash chromatography (EtOAc : hexane = 30 : 70) to give alcohol **12** as an oil (2.9 g, 97%): $[\alpha]_D^{25}$ −21.2° (c=1.3, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 1.11 (m, 1H), 1.38 (m, 12H), 1.69 (m, 2H), 1.92 (m, 2H), 2.13 (m, 2H), 3.70 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ: 26.3, 28.4, 33.0, 36.3, 39.8, 52.0, 66.4, 79.0, 155.6; *Anal.* Calcd for $C_{11}H_{21}NO_3$: C, 61.37; H, 9.83; N, 6.51. Found: C, 61.28; H, 9.85; N, 6.35.

Synthesis of (1*S*,3*R*)-1-Amino-3-(hydroxymethyl)cyclopentane (1) A solution of **12** (2.8 g, 13.2 mmol) in CH_2Cl_2 (40 ml) was cooled in an ice bath as HCl (1.0 M solution in ether, 26.5 ml, 26.5 mmol) was added. The mixture was stirred at room temperature for 18 h, and concentrated to a white solid **1** (1.75 g, 99%) with 100% ee. The spectral data were identical with those previously reported.[18]

Generation Procedure for Hydrogenation A slurry of **5**, MeOH (10 ml), and catalyst (0.1 g) was hydrogenated in a Parr shaker under 45 psi of H_2 at rt for 24 h. The reaction mixture was filtered, and the filtrate was evaporated to give an oil. The ratio of **13** : **14** in the reaction mixture was determined by analytical RPHPLC (Zorbax RX C-18 column; MeCN : water : TFA = 49 : 51 : 0.1).

Synthesis of (1*S*,3*R*)-1-[*N*-(9-Phenyl-9-fluorenyl)amino]-3-cyclopentanemethanol (13) and (1*S*,3*S*)-1-[*N*-(9-Phenyl-9-fluorenyl)amino]-3-cyclopentanemethanol (14) The title compounds were prepared from **5** (353 mg) by the procedure mentioned above with 10% Pd/C as catalyst, and the ratio of **13** : **14** in the reaction mixture was 55 : 45. Compound **13** and **14** were then separated by preparative RP-HPLC (Zorbax RX C-18 column; MeCN : water : TFA = 42 : 58 : 0.1) to give **13** (163 mg, 46%), and **14** (141 mg, 40%). For compound **13**: $[\alpha]_D^{25}$ −7.1° (c=1.6, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 0.98 (m, 1H), 1.20 (m, 1H), 1.33 (m, 1H), 1.45 (m, 1H), 1.58 (m, 2H), 1.98 (m, 1H), 2.65 (m, 1H), 3.50 (m, 2H), 7.35 (m, 13H), 7.68 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ: 25.7, 34.7, 38.8, 39.4, 84.7, 66.7, 73.1, 119.7, 119.8, 124.8, 125.5, 125.6, 125.9, 127.1, 127.7, 127.8, 127.9, 128.2, 128.3, 128.4, 140.1, 140.8, 144.8, 145.6, 150.1. Calcd for $C_{25}H_{25}NO$: C, 84.47; H, 7.09; N, 3.94. Found: C, 84.11; H, 7.39; N, 3.66. For compound **14**: $[\alpha]_D^{25}$ −16.3° (c=1.6, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 0.94 (m, 1H), 1.18 (m, 2H), 1.39 (m,

2H), 1.72 (m, 1H), 1.82 (br s, 2H), 2.18 (m, 1H), 2.70 (m, 1H), 3.25 (d, J=7.0 Hz, 2H), 7.25 (m, 5H), 7.40 (m, 4H), 7.45 (d, J=7.8 Hz, 2H), 7.75 (d, J=7.5 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ: 27.3, 35.4, 37.6, 39.9, 54.5, 67.2, 73.3, 119.8, 119.9, 125.1, 125.2, 125.3, 126.2, 127.0, 127.6, 127.7, 128.0, 128.1, 128.2, 140.3, 140.4, 145.5, 150.5, 150.6. Calcd for $C_{25}H_{25}NO$: C, 84.47; H, 7.09; N, 3.94. Found: C, 84.17; H, 6.99; N, 4.04.

Hydrogenation of 5 with Rh/C as a Catalyst Compounds **13** and **14** were prepared from **5** (353 mg) by the general procedure mentioned above with Rh/C as catalyst, and the ratio of **13** : **14** in reaction mixture was 34 : 66. Compound **13** and **14** were separated by preparative RP-HPLC to give **13** (102 mg, 29%), and **14** (184 mg, 52%).

Hydrogenation of 5 with Re Ni as a Catalyst Compounds **13** and **14** were prepared from **5** (353 mg) by the general procedure mentioned above with Re Ni as catalyst, and the ratio of **13** : **14** in reaction mixture was 18 : 82. Compound **13** and **14** were separated by preparative RP-HPLC to give **13** (39 mg, 11%), and **14** (276 mg, 78%).

Reduction of 5 with Diimide A solution of acetic acid (1.23 ml, 21 mmol) in MeOH (10 ml) was added to a solution of **5** (353 mg, 1.0 mmol) and dipotassium azodicarboxylate (4.1 g, 21 mmol) in MeOH (10 ml) using a syringe pump over 6 h. The resulting mixture was stirred at room temperature for 18 h. Solvent was evaporated under vacuum, and the mixture was partitioned between saturated aq KH_2PO_4 (500 ml) and EtOAc (250 ml). Aqueous phase was extracted with EtOAc (200 ml) twice and combined organic layers were washed with brine (100 ml), dried, and filtered. The ratio of **13** : **14** in reaction mixture was 3 : 97. The filtrate was evaporated and **13** and **14** were separated by preparative RP-HPLC to give **13** (3 mg, 1%), and **14** (327 mg, 92%).

Reduction of 5 with nBuSiH$_3$ A solution of $nBuSiH_3$ in THF (0.5 M, 5 ml, 2.5 mmol) was added to a solution of **5** (353 mg, 1.0 mmol) and TFA (123 μl, 2 mmol) in THF (10 ml) using a syringe pump over 2 h. The resulting mixture was stirred at rt for 18 h. Solvent was evaporated under vacuum, and the mixture was partitioned between saturated aq. KH_2PO_4 (500 ml) and EtOAc (250 ml). Aq phase was extracted with EtOAc (200 ml) twice and combined organic layers were washed with brine (100 ml), dried, and filtered. The ratio of **13** : **14** in reaction mixture was 2 : 98. The filtrate was evaporated and **13** and **14** were separated by preparative RP-HPLC to give **13** (3 mg, 1%), and **14** (330 mg, 93%).

Synthesis of (1*S*,3*R*)-1-Amino-3-(hydroxymethyl)cyclopentane (1) from Hydrogenation of 13 A slurry of **13** (355 mg, 1 mmol), MeOH (10 ml), HCl (1.0 M solution in ether, 2 ml, 2 mmol) and 5% Pt/C (0.1 g) was hydrogenated in a Parr shaker under 45 psi of H_2 at room temperature for 24 h. The reaction mixture was filtered, and the filtrate was evaporated to give **1** (149 mg, 98%). Chiral HPLC analysis (Chiralpak AD column 250×4.6; hexane : isopropanol=97 : 3) indicated that enantiomeric excess for **1** was 99.9%.

Synthesis of (1*S*,3*S*)-1-Amino-3-(hydroxymethyl)cyclopentane (2) A slurry of **14** (355 mg, 1 mmol), MeOH (10 ml), HCl (1.0 M solution in ether, 2 ml, 2 mmol) and 5% Pt/C (0.1 g) was hydrogenated in a Parr shaker under 45 psi of H_2 at rt for 24 h. The reaction mixture was filtered, and the filtrate was evaporated to give **2** (149 mg, 98%). Chiral HPLC analysis indicated that enantiomeric excess for **2** was 100%. A solution of BDCS silylation reagent (Aldrich, 0.5 M TBDMS-Cl and 1.0 M imidazole solution in DMF, 37 ml) was added to a solution of **12** (2 g, 9.3 mmol) in DMF (10 ml). The mixture was stirred at rt for 18 h then partitioned between saturated aq KH_2PO_4 (500 ml) and EtOAc (250 ml). Aq phase was extracted with EtOAc (200 ml×2) and combined organic layers were washed with brine (100 ml), dried, and filtered. Solvent was removed and HCl (5.0 M solution in EtOAc, 10 ml) was added. After the mixture was stirred at rt for 12 h, solvent was evaporated to give **15** as HCl salts (1.4 g, 83%): $[\alpha]_D^{25}$ −4.1° (c=1.2, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 1.05 (s, 9H), 1.35 (m, 2H), 1.55 (m, 2H), 1.71 (m, 1H), 1.86 (m, 1H), 2.11 (m, 2H), 2.75 (br s, 2H), 3.32 (q, J=7.0 Hz, 1H), 3.60 (d, J=7.0 Hz, 1H), 7.55 (m, 10H). Calcd for $C_{22}H_{31}NOSi$: C, 74.73; H, 8.84; N, 3.96. Found: C, 74.39; H, 8.98; N, 4.11.

Synthesis of 4-[(1*R*)-2-Azido-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-1-[3-(*tert*-butyldiphenylylsilyl)oxy]methyl]-cyclopentyl-5-[(dimethylaminomethylene)amino]-imidazole (18) A solution of **15** (360 mg, 1 mmol) and imidate **16**[20] (297 mg, 1 mmol) in 2,2,2-trifluoroethanol (1 ml) and 1,2 dichlorethane (10 ml) was stirred at 80 °C for 4 h to yield **17**. An analytical sample was obtained by flash chromatography (EtOAc : Et_3N= 99 : 1): $[\alpha]_D^{25}$ +2.9° (c=1.0, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 0.09 (s, 9H), 0.12 (s, 3H), 0.91 (s, 9H), 1.03 (s, 3H), 1.30—2.20 (m, 7H), 3.34 (m, 3H), 3.70 (m, 3H), 4.25 (m, 1H), 4.95 (m, 1H), 7.11 (s, 1H), 7.38—7.72 (m, 10H). Calcd for $C_{33}H_{50}N_6O_2Si_2$: C, 64.04; H, 8.14; N, 13.58. Found: C, 64.04; H, 8.14; N, 13.58. Without purification of **17**, *N*,*N*-dimethylformamide dimethyl acetal (0.5 ml, 3.77 mmol) was added and the resulting mixture was heated at 80 °C for 13 h. Purification by flash chromatography on SiO_2 (EtOAc : hexane : Et_3N=30 : 70 : 0.1) gave imidazole **18** (510 mg, 74% from **15**): $[\alpha]_D^{25}$ +4.8° (c=0.6, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: −0.10 (s, 3H), 0.01 (s, 3H), 0.85 (s, 9H), 1.05 (s, 9H), 1.45—2.30 (m, 6H), 3.30 (s, 6H), 3.35 (m, 2H), 3.64 (m, 3H), 4.50 (m, 1H), 4.82 (m, 1H), 7.12 (s, 1H), 7.19—7.66 (m, 10H), 7.78 (s, 1H). Calcd for $C_{36}H_{55}N_7O_2Si_2$: C, 64.15; H, 8.22; N, 14.55. Found: C, 64.50; H, 8.13; N, 14.37.

Synthesis of (8*R*)-3-[3-(*tert*-Butyldiphenylylsilyl)oxy]methyl]cyclopentyl-8-[(*tert*-butyldimethylsilyl)oxy]-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]-diazepine (19) A solution of imidazole **18** (500 mg, 0.72 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 **19** (291 mg, 67%): $[\alpha]_D$ +11.2° (c=0.5, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.09 (s, 3H), 0.14 (s, 3H), 0.92 (s, 9H), 1.06 (s, 9H), 1.27—2.20 (m, 6H), 3.36—3.50 (m, 3H), 3.60 (m, 3H), 4.25 (m, 1H), 4.95 (m, 1H), 7.11 (s, 1H), 7.38—7.65 (m, 10H), 7.72 (s, 1H). Calcd for $C_{34}H_{50}N_4O_2Si_2$: C, 67.73; H, 8.36; N, 9.29. Found: C, 67.44; H, 8.01; N, 9.62.

Synthesis of (8*R*)-3-[3-(Hydroxymethyl)]cyclopentyl-8-hydroxy-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepine (20) A solution of silyl ether **19** (250 mg, 0.42 mmol) in 1,4-dioxane (30 ml) in a Teflon container was cooled by an ice bath as aqueous HF (49%, 10 ml) was added slowly. The mixture was stirred at rt for 3 h, diluted with $CHCl_3$ (100 ml), and washed with saturated aqueous Na_2CO_3 (200 ml). The aqueous phase was extracted with $CHCl_3$/IPA (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) followed by RP-HPLC (Zorbax RX C-18 column; MeCN : water : TFA=34 : 66 : 0.1) to give **20** (83 mg, 72%): $[\alpha]_D$ +14.1° (c=0.4, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.26 (m, 2H), 1.74 (m, 3H), 2.16 (m, 2H), 3.43 (m, 2H), 3.70 (br s, 2H), 4.02 (m, 2H), 4.77 (m, 1H), 5.10 (m, 1H), 5.60 (br s, 1H), 7.13 (s, 1H), 7.36 (s, 1H). *Anal.* Calcd for $C_{12}H_{18}N_4O_2 \cdot H_2O$: C, 53.72; H, 7.51; N, 20.88. Found: C, 53.58; H, 7.90; N, 20.96.

Acknowledgments J.Z.H. dedicates this paper to his Ph.D. advisor, Professor Robert M. Coates, Ph.D., Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801, U.S.A., on the occasion of his 65th birthday. J.Z.H thanks Dr. Charles S. Elmore and Dr. Terry A. Lyle who have assisted greatly in the use of clear and proper written English.

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