Stereospecific Synthesis of the (2*R*,3*S*)- and (2*R*,3*R*)-3-Amino-2-hydroxy-4-phenylbutanoic Acids from D-Glucono-δ-lactone

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The enantiomerically pure (2*R*,3*S*)- and (2*R*,3*R*)-3-amino-2-hydroxy-4-phenylbutanoic acids (AHPBA) **1** and **3** are readily obtained from D-glucono-δ-lactone. Both AHPBAs are the structural key units of KMI derivatives which are the potent inhibitors of BACE 1 (β-secretase) and HIV protease. Additionally, the obtained AHPBAs **1** and **3** are converted to dipeptides of bestatin stereoisomers **2** and **4**.

Key Words : α-Hydroxy-β-amino acid, (2*R*,3*S*)-AHPBA, BACE 1, Bestatin stereoisomer, D-Glucono-δ-lactone.

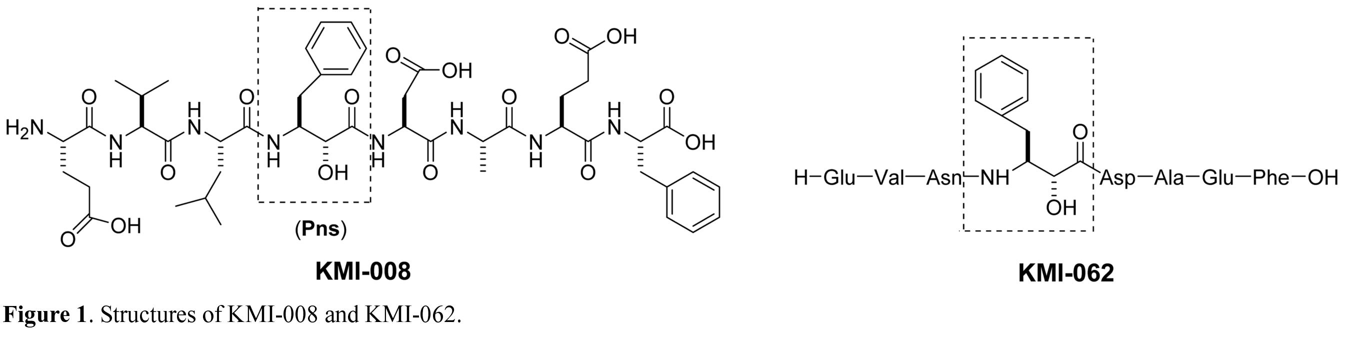
Introduction

α-Hydroxy-β-amino acids are key components of numerous organic substances. These important compounds have been shown to act as substrates for the synthesis of peptide isosteres[1] and are constituents of several natural products that exhibit potent biological activity such as bestatin, dideoxykanamycin A, microginin, and paclitaxel.[2] The synthesis of α-hydroxy-β-amino acids has therefore attracted a considerable amount of interest in recent years and several approaches have been developed to effect their synthesis.[3] A particularly important set of α-hydroxy-β-amino acids, the diastereomers of 3-amino-2-hydroxy-4-phenybutanoic acid (AHPBA), are very attractive because of their biological and medicinal roles,[2a,4] and because they are chiral synthons for many bioactive compounds.[2a,5] (2*R*,3*S*)-AHPBA, phenylnorstatine (Pns) **1**, is an important component of BACE1 (β-secretase) inhibitor such a KMI-008 and KMI-370 (Figure 1).[6] In addition, it is the key component of KMI-062, which is an octapeptide containing a hydroxymethyl carbonyl (HMC) isostere as a transition-state analogue (Figure 1).[7] A wide range of synthetic routes to AHPBA have been attempted using chiral glyoxylate methodology,[2b] cyanohydrin chemistry of α-aminoaldehydes,[3b,8] epoxide opening by azide ion,[9] and hydroxamination of a substituted alkene,[10] respectively. Unfortunately, these protocols were unable to control the absolute configuration within C-2 and C-3, leading to low overall yields. In our previous paper, we described the stereoselective synthesis of (2*S*,3*R*)-, (2*S*,3*S*)-AHPBA, and (–)-bestatin from sugar.[11] In this paper, to further demonstrate of the versatility of the above synthetic strategy, we describe the synthesis of (2*R*,3*S*)- and (2*R*,3*R*)-AHPBAs **1** and **3** *via* synthetic techniques from enantiopure D-glucono-δ-lactone. The enantiomerically pure AHPBAs **1** and **3**, thus obtained were easily used to effect simple the syntheses of (–)-bestatin stereoisomers **2** and **4** (Figure 2).

Results and Discussion

The absolute configuration within C2 and C3 in the target molecules **1** and **3** were transferred from those of C2 and C3 in D-glucono-δ-lactone, the starting material. The absolute stereochemistry within C2 of the target molecule was controlled through the stereodivergent formation of an oxirane ring. The formation of the benzyl unit in the target molecules **1** and **3** were carried out *via* nucleophilic addition of phenylmagnesium bromide to the oxirane ring.

(2*R*,3*S*)-AHPBA 1 and *N*-[(2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoyl]-L-leucine 2. The synthesis commenced from glucitol **5** which was easily accessed *via* reduction of D-glucono-δ-lactone with $NaBH_4$ reported in the previous manuscript.[11] To effect the stereodivergent synthesis of (2*R*,3*S*)-AHPBA **1** and (2*R*,3*R*)-AHPBA **3** from the glucitol **5**, the most important transformation was the inversion of



KMI-008 **KMI-062**

Figure 1. Structures of KMI-008 and KMI-062.

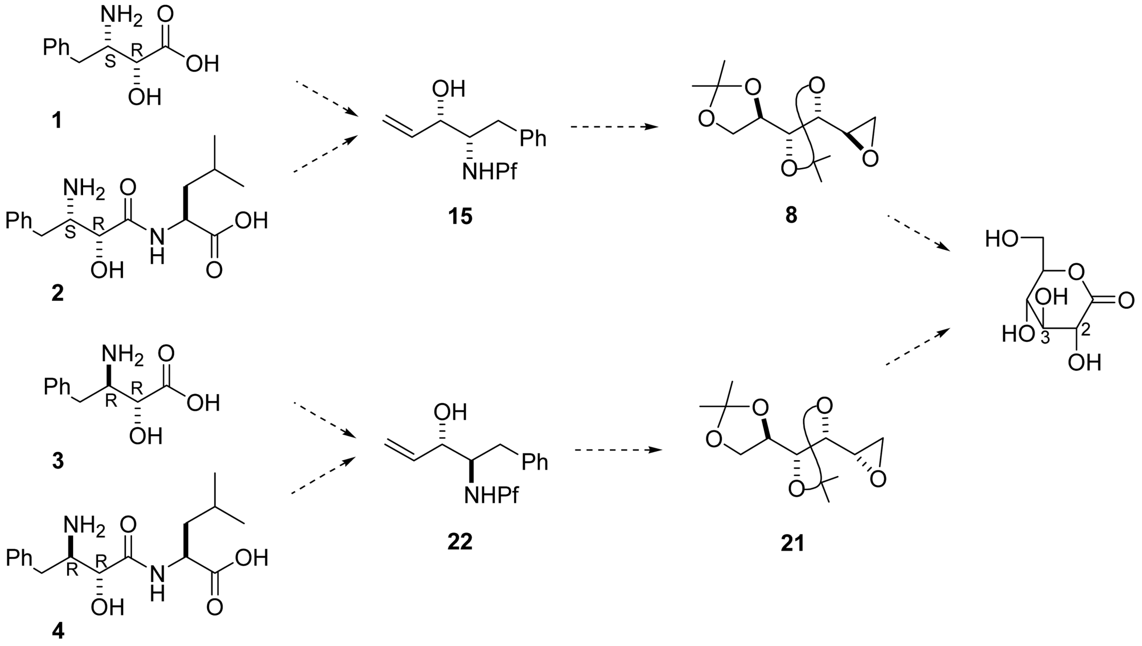
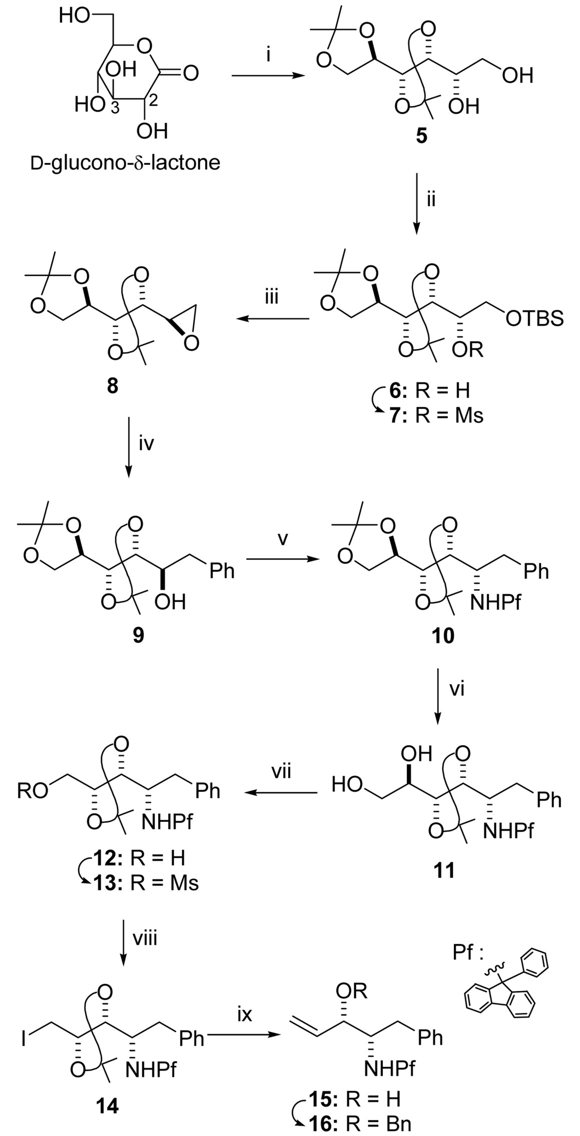


Figure 2. Retrosynthesis of Target Molecules **1**-**4**.

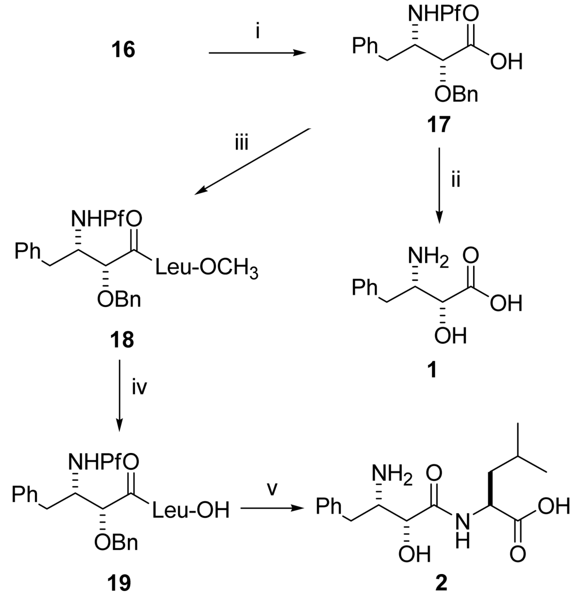
the configuration of C3 in AHPBA numbering. This was started from the selective silylation of the primary hydroxyl group in diols **5**. Treatment of TBDMSCl to the diol **5** in CH_2Cl_2 gave the secondary alcohol **6** in 94% yield. Subsequent mesylation of the hydroxyl group gave **7**, which when reacted with Bu_4NF at room temperature enacted desilyation/intramolecular mesylate displacement to give the epoxide **8** in 88% yield. The epoxide **8** was then reacted with PhMgBr in the presence of CuI at –40 °C to give the alcohol **9** regioselectively in 94% yield. The *N*-Pf protected amine **10** was prepared in 63% yield from the secondary alcohol **9** according to our recently published methodology,[11] involving the use of a pre-cooled solution of Tf_2O in CH_2Cl_2 at –10 °C, which suppressed epimerization during the reaction. The 9-phenyl-9-fluorenyl (Pf) group was chosen to protect the amino group as it is to be not only stable under basic conditions but also stable to organometallic reagents (Scheme 1).[12] The terminal isopropylidene group was selectively cleaved by treating diisopropylidene **10** with Dowex 50-X8 resin to give the diol **11** in 92% yield.[13] The diol **11** was then treated with $NaIO_4$ in EtOH-H_2O (2 : 1) at room temperature, and the resulting aldehyde was reduced with $NaBH_4$, leading to the formation of the alcohol **12** in 90% overall yield. After mesylation of the alcohol **12** with MsCl in THF, the resulting mesylate **13** was treated with LiI at 80 °C to give the iodide **14** in 92% yield. Treatment of the iodide **14** with *n*-BuLi in THF at –40 °C generated (3*S*,4*S*) chiral aminoalcohol **15** {$[\alpha]_D^{20}$ –4.9° (*c* 1.35, $CHCl_3$)} in 90% yield through simultaneous dealkoxyhalogenation (Scheme 1).[13]

The secondary hydroxyl group of the aminoalcohol **15** was easily protected with BnBr in THF to give the benzylate **16** in 91% yield. Ozonolysis of the olefin within benzylate **16** and subsequent H_2O_2-mediated oxidation afforded protected (2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoic acid **17**. To remove the Pf and Bn protecting groups, protected (2*R*,3*S*)-AHPBA **17** was treated with H_2 and 10% Pd/C in MeOH at 70 °C and subsequently purified by ion-exchange chromatography through Dowex 50W-X8 resin. To the free base **1** was added conc. HCl and co-evaporated with toluene to give (2*R*,3*S*)-AHPBA **1** as its hydrochloride salt. This methodology has been applied to the synthesis of (−)-bestatin stereoisomer **2** which requires the coupling of two structural units, *N*-terminal α-hydroxy-β-amino acid [(2*R*,3*S*)-AHPBA **1**] and C-terminal amino acid leucine. The coupling reaction of **17** with (*S*)-leucine methyl ester was carried out in the presence of DCC to afford the dipeptide product **18** in 89% yield. Treatment of **18** with LiOH followed by exposure to H_2 over Pd/C gave (2*R*,3*S*)-bestatin stereoisomer **2** in 89% yield (Scheme 2).

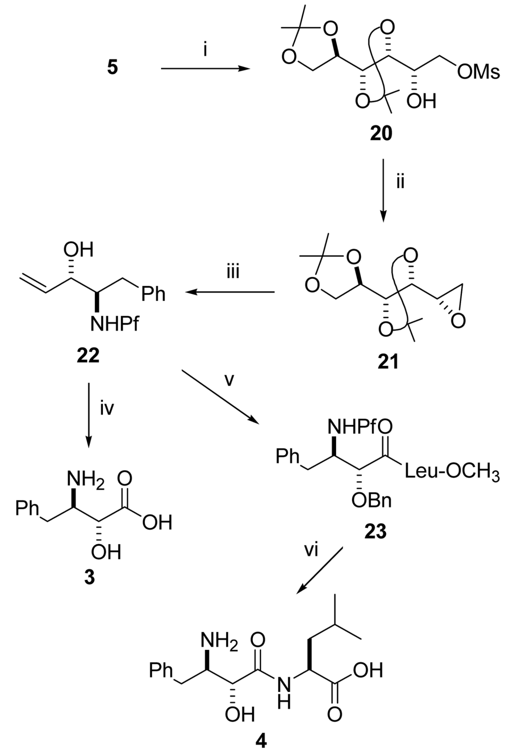
(2*R*,3*R*)-AHPBA 3 and *N*-[(2*R*,3*R*)-3-amino-2-hydroxy-4-phenylbutanoyl]-L-leucine 4. The effect the synthesis of (2*R*,3*R*)-AHPBA **3**, conversion of diol **5** to the corresponding epoxide **21** with retention of C2 stereochemistry was required. Thus, the diol **5** was treated with MsCl in CH_2Cl_2 at –40 °C to give the primary mesylate **20**. The treatment of the monomesylate **20** with K_2CO_3 in methanol afforded the epoxide **21** in quantitative yield (Scheme 3). Oxirane **21** was then subjected to the same reaction conditions to those already described above (compound **8** → compound **15**) to afford (3*R*,4*R*)-aminoalcohol **22** {$[\alpha]_D^{20}$ –8.2° (*c* 2.00, $CHCl_3$)}. After *O*-benzylation of the chiral aminoalcohol **22**, the resulting benzylate was subjected to ozonolysis followed by hydrogenolysis employing the same protocol to that used to convert the compound **1** to (2*R*,3*R*)-AHPBA **3**. After protection of the secondary alcohol **22** with BnBr, vinyl group in the protected alcohol was converted to phenylbutanoic acid by ozonolysis. The



Scheme 1. Reagents and conditions; (i) ref. 11, 14 ii) a) TBDMSCl, imidazole, CH_2Cl_2, rt, 94%, c) MsCl, Et_3N, THF, 0 °C, 94%; (iii) Bu_4NF, THF, rt, 88%; (iv) PhMgBr, CuI, THF, –40 °C, 94%; (v) a) Tf_2O, Pyridine, CH_2Cl_2, –10 °C, 96%, b) NaN_3, DMF, rt, 96%, c) H_2, Pd/C, EtOAc, rt, 85%, d) Pf-Br, $Pb(NO_3)_2$, Et_3N, CH_2Cl_2, rt, 80%; (vi) Dowex 50W-X8, MeOH, rt, 92%; (vii) a) $NaIO_4$, $EtOH-H_2O$ (2 : 1), rt, $NaBH_4$, 0 °C, 90%, b) MsCl, Et_3N, THF, 0 °C, 97%; (viii) LiI, DMF, 80 °C, 92%, (ix) a) *n*-BuLi, THF, –40 °C, 90%, b) BnBr, 60% NaH, Bu_4NI, THF, 0 °C, 91%.



Scheme 2. Reagents and conditions; (i) O_3, MeOH, –78 °C, 30% H_2O_2, rt, 94%; (ii) H_2, 10% Pd/C, MeOH, 70 °C, 85%; (iii) (*S*)-Leu-OCH_3, HOBT, TsOH, DCC, Et_3N, THF, 0 °C, 89%; (iv) LiOH, THF-H_2O (2 : 1), 0 °C, 89%; (v) H_2, 10% Pd/C, MeOH, 70 °C, 89%.



Scheme 3. Reagents and conditions; (i) MsCl, Et_3N, CH_2Cl_2, –40 °C, 81%; (ii) K_2CO_3, MeOH, rt, 92%; iii) ref. 11; (iv) a) BnBr, 60% NaH, Bu_4NI, THF, 0 °C, b) O_3, MeOH, –78 °C, 30% H_2O_2, rt, c) H_2, 10% Pd/C, MeOH, 70 °C; (v) a) BnBr, 60% NaH, Bu_4NI, THF, 0 °C, b) O_3, MeOH, –78 °C, 30% H_2O_2, rt, c) (*S*)-Leu-OCH_3, HOBT, TsOH, DCC, Et_3N, THF, 0 °C; (vi) a) LiOH, THF-H_2O (2 : 1), 0 °C, b) H_2, 10% Pd/C, MeOH, 70 °C.

reaction of the protected AHPBA with leucine methyl ester was carried out *via* coupling reaction. The product dipeptide **23** was subjected to the deprotection sequence already described above (compound **18** → compound **2**) methods to afford (2*R*,3*R*)-bestatin stereoisomer (**4**) (Scheme 3).

To establish the relative configuration within amino alcohols **15** and **22**, they were separately converted to the corresponding oxazolidinone **15a** and **22a** by reaction with carbonydiimidazole after Pd-mediated hydrogenolysis of the *N*-Pf group. The relative stereochemistry within the oxazolidinones **15a** and **22a** was shown by analysis of the coupling constants: a large coupling constant was shown by **15a** ($J_{3,4}$ = 11-13 Hz), consistent with a 3,4-*syn* relationship whereas **22a** exhibited a smaller coupling constant ($J_{3,4}$ = 6-

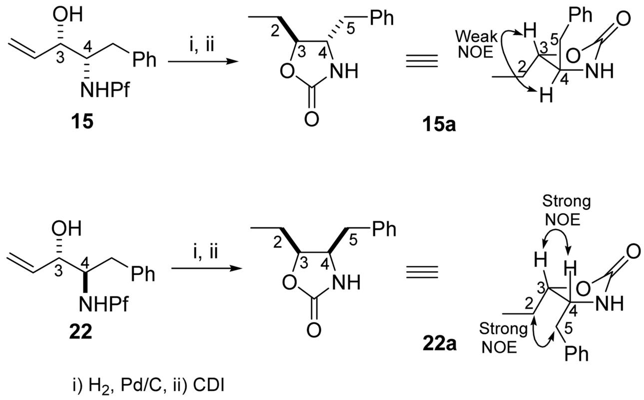


Figure 3. Stereochemistry of compounds **15** and **22**.

8 Hz), consistent with a 3,4-*anti* arrangement. NOESY experiments were also consistent with this analysis: strong correlation was observed between H_3–H_4 and H_2–H_5 in compound **22a**, whereas weak correlation was observed between H_3–H_4 in compound **15a** (Figure 3).

Conclusions

The amino alcohols **15** and **22**, important precursors of α-hydroxy-β-amino acids, have been prepared from D-glucono-δ-lactone *via* simultaneous dealkoxyhalogenation and stereodivergent formation of the oxirane. Chiral synthons **15** and **22** were used to effect the synthesis of enantiomerically pure (2*R*,3*S*)- and (2*R*,3*R*)-AHPBAs **1** and **3**. Furthermore successful coupling of the protected AHPBAs with leucine methyl ester and ensuing deprotection furnished the stereoisomers of bestatin **2** and **4**.

Experimental Section

General. All non-aqueous reaction was carried out under an inert nitrogen atmosphere. THF was distilled from Na/benzophenone; 2,2-dimethoxypropane, DMF, and methylene chloride were distilled from CaH_2. Column chromatography was carried out using 230-400 mesh silica gel. The final solution before evaporation was washed with brine and dried over anhydrous Na_2SO_4. All melting points were measured on a Thomas Scientific Capillary Melting point apparatus and are uncorrected. IR spectra were recorded on a Bruker IFS66 infrared Fourier transform spectrophotometer. ^{1}H-NMR and ^{13}C-NMR experiments were conducted on Bruker AW-500 spectrometer. EIMS data were collected on a JEOLJMS-700 mass spectrometer. Optical rotations were measured on a JASCO DIP-1000 polarimeter and $[\alpha]_D$-values are given in units of 10^{-1} deg cm^{2}g^{-1}.

3,4;5,6-Di-*O*-isopropylidene-D-glucitol (5). This was prepared from D-glucono-δ-lactone through previously reported method.[11] The spectroscopic data of **5** was consistent with that of the reported.[14]

3,4;5,6-Di-*O*-isopropylidene-1-*O*-*tert*-butyldimethylsilyl-D-glucitol (6). To a solution of the diol **5** (3.00 g, 11.44 mmol) in CH_2Cl_2 (57 mL) were added imidazole (1.56 g, 22.87 mmol) and TBDMSCl (3.45 g, 22.87 mmol) at room temperature. After stirring the mixture for 1 h, saturated aqueous $NaHCO_3$ (60 mL) was added and the mixture was extracted with CH_2Cl_2 (60 mL × 3). After concentration of the combined extracts, the residue was chromatographed on silica gel [hexane-EtOAc (4 : 1)] to give compound **6** (4.05 g, 94%) as an oil, $[\alpha]_D^{20}$ +1.7° (*c* 2.65, $CHCl_3$); IR (neat): 3517, 3056, 3012 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.00 (s, 6H), 0.83 (s, 9H), 1.25-1.33 (m, 12H), 2.29 (d, J = 7.8 Hz, 1H), 3.58 (dd, J = 10.1, 6.2 Hz, 1H), 3.62 (dd, J = 10.1, 6.3 Hz, 1H), 3.69 (m, 1H), 3.86 (dd, 1H, J = 8.3, 5.0 Hz, 1H), 3.90-3.99 (m, 3H), and 4.05 (dd, J = 8.3, 5.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ –5.0, –5.0, 18.7, 25.7, 26.2, 27.0, 27.3, 27.5, 65.1, 68.2, 70.7, 77.6, 77.7, 80.1, 109.9, and 110.0 (Found; C, 57.41; H, 9.63. $C_{18}H_{36}O_6Si$ requires C, 57.41; H, 9.64%).

3,4;5,6-Di-*O*-isopropylidene-2-*O*-methanesulfonyl-1-*O*-*tert*-butyldimethylsilyl-D-glucitol (7). To a solution of compound **6** (3.50 g, 9.29 mmol) in THF (45 mL) were added triethylamine (2.60 mL, 18.59 mmol) and MsCl (1.44 mL, 18.59 mmol) at 0 °C. The reaction mixture was stirred for 10 min at room temperature, and then was quenched with saturated aqueous $NaHCO_3$ (50 mL). The reaction mixture was extracted with EtOAc (50 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (40 mL × 3). After concentration of the combined extracts, the resulting residue was chromatographed on silica gel [hexane-EtOAc (6 : 1)] to give compound **7** (3.98 g, 94%) as an oil; $[\alpha]_D^{20}$ –0.5 ° (*c* 3.30, $CHCl_3$); IR (neat): 3056, 3011, 2968 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.00 (s, 6H), 0.81 (s, 9H), 1.24 (s, 3H), 1.28 (s, 3H), 1.31 (s, 3H), 1.34 (s, 3H), 3.01 (s, 3H), 3.77 (dd, J = 11.1, 5.1 Hz, 1H), 3.82-3.86 (m, 2H), 3.89 (dd, J = 14.9, 7.4 Hz, 1H), 3.99 (m, 1H), 4.05-4.07 (m, 2H), and 4.70 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ –5.4, –5.4, 18.4, 25.3, 25.9, 26.3, 26.7, 27.3, 38.9, 63.1, 67.6, 76.8, 77.1, 77.4, 78.4, 81.3, 110.0, and 110.3 (Found; C, 50.19; H, 8.43. $C_{19}H_{38}O_8SSi$ requires C, 50.19; H, 8.42%).

1,2-Anhydro-3,4;5,6-di-*O*-isopropylidene-D-mannitol (8). To a solution of compound **7** (4.00 g, 8.80 mmol) in THF (44 mL) was added Bu_4NF (3.45 g, 13.20 mmol). After stirring for 3 h at room temperature, the reaction mixture was quenched with H_2O (50 mL) and extracted with EtOAc (50 mL × 3). The combined extracts were evaporated, and then the residue was chromatographed on silica gel [hexane-EtOAc (12 : 1)] to give compound **8** (1.90 g, 88%) as an oil; $[\alpha]_D^{20}$ +4.2 (*c* 1.15, $CHCl_3$); IR (neat): 3051, 3016, 2982 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35-1.42 (m, 12H), 2.82 (m, 2H), 3.20 (m, 1H), 3.83 (m, 1H), 3.95 (dd, J = 10.54, 4.85 Hz, 1H), 4.05 (m, 1H), and 4.11 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.2, 26.6, 26.7, 27.1, 44.2, 51.9, 67.4, 76.7, 78.7, 78.9, 109.8, and 110.7 (Found; C, 59.01; H, 8.24. $C_{12}H_{20}O_5$ requires C, 59.00; H, 8.25%).

1-Deoxy-3,4;5,6-di-*O*-isopropylidene-1-phenyl-D-mannitol (9). To a solution of CuI (0.94 g, 4.91 mmol) in THF (30 mL) at –40 °C under N_2 was added dropwise 1.0 M PhMgBr (24.56 mL, 24.56 mmol, 200 mol%) over 15 min. After stirring for 10 min, a solution of epoxide **8** (4.50 g, 18.42 mmol) in THF (50 mL) was added dropwise over a period of 20 min at the same temperature. After additional stirring for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (60 mL). The mixture was extracted with EtOAc (50 mL × 3), and the combined organic layer was concentrated. The resulting residue was chromatographed on silica gel [hexane-EtOAc (12 : 1)] to give compound **9** (3.70 g, 94%) as an oil, $[\alpha]_D^{20}$ +2.88° (*c* 2.00, $CHCl_3$); IR (neat): 3502, 3027, 2968, 1604 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.2-1.4 (m, 12H), 2.75 (dd, *J* = 13.9, 8.4 Hz, 1H), 3.09 (dd, *J* = 13.9, 3.0 Hz, 1H), 3.73-3.79 (m, 2H), 3.88 (m, 1H), 3.99 (m, 1H), 4.06 (m, 1H), 4.17 (dd, *J* = 8.5, 6.1 Hz, 1H), and 7.20-7.46 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.2, 26.5, 26.9, 27.0, 39.7, 67.9, 73.1, 76.4, 81.1, 82.8, 109.3, 110.2, 126.2, 128.2, 129.8, and 138.5 (Found; C, 67.04; H, 8.13. $C_{18}H_{26}O_5$ requires C, 67.06; H, 8.13%).

1,2-Dideoxy-3,4;5,6-di-*O*-isopropylidene-1-phenyl-2-[(9-phenyl-9-fluorenyl)-amino]-D-glucitol (10). To a solution of mannitol **9** (0.70 g, 2.17 mmol) in CH_2Cl_2 (10 mL) at –10 °C were added pyridine (0.52 mL, 6.51 mmol) dropwisely over a period of 5 min and an ice-cooled solution of Tf_2O (0.55 mL, 3.26 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 10 min at –10 °C, and then was quenched with saturated aqueous $NaHCO_3$ (15 mL). The organic layer was washed with saturated aqueous $CuSO_4$ (12 mL) and was evaporated to give the triflate (0.96 g, 96%), which was used without further purification. The mixture of the triflate (0.96 g, 2.10 mmol) and NaN_3 (0.41 g, 6.27 mmol) in DMF (10 mL) was stirred for 2 h at room temperature. The reaction mixture was quenched with H_2O (50 mL) and extracted with EtOAc (40 mL × 3). After evaporation of the organic layer, the remaining residue was chromatographed to give the azido compound (0.70 g, 96%). This compound was directly hydrogenated with 10% Pd/C (0.07 g) in EtOAc (10 mL) to the corresponding free amine (0.55 g, 85%). To the solution of the free amine (0.55 g, 1.71 mmol) in CH_2Cl_2 (12 mL) was added 9-phenyl-9-fluorenyl bromide (Pf-Br) (0.83 g, 2.57 mmol), $Pb(NO_3)_2$ (0.85 g, 2.57 mmol), and Et_3N (0.47 mL, 3.42 mmol). After stirring for 24 h at room temperature, the mixture was filtrated, poured into excess H_2O, and the organic layer was separated, then the aqueous layer was extracted with CH_2Cl_2 (20 mL × 3). After concentration of the combined extracts, the resulting residue was chromatographed on silica gel [hexane-EtOAc (25 : 1)] to give compound **10** (0.80 g, 80%) as a solid, mp 53-57 °C; $[\alpha]_D^{20}$ +84.4° (*c* 6.00, $CHCl_3$); IR (KBr): 3309, 3027, 2992, 1602 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.14 (s, 3H), 1.17 (s, 3H), 1.23 (s, 3H), 1.49 (s, 3H), 2.31 (dd, *J* = 12.6, 5.1 Hz, 1H), 2.43 (dd, *J* = 12.6, 9.0 Hz, 1H), 2.49 (m, 1H), 3.43 (m, 1H), 3.53 (dd, *J* = 6.0, 1.3 Hz, 1H), 3.70-3.46 (m, 2H), 4.14 (m, 1H), and 6.66-7.20 (m, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.3, 26.1, 26.6, 27.4, 40.4, 54.4, 66.5, 72.3, 76.1, 78.8, 99.3, 108.5, 109.1, 119.8, 120.1, 125.5, 125.6, 125.9, 126.6, 127.0, 127.7, 128.0, 128.0, 128.1, 128.2, 128.3, 129.3, 139.7, 140.4, 145.8, 149.9, and 151.2 (Found; C, 79.11; H, 6.98; N, 2.51. $C_{37}H_{39}NO_4$ requires C, 79.11; H, 7.00; N, 2.49%).

1,2-Dideoxy-3,4-*O*-isopropylidene-1-phenyl-2-[(9-phenyl-9-fluorenyl)-amino]-D-glucitol (11). To a solution of the *N*-protected compound **10** (4.00 g, 7.12 mmol) in 90% MeOH (40 mL) was added Dowex 50W-X8 resin (0.40 g) at room temperature. After stirring for 24 h, the reaction mixture was filtered, and then the filtrate was evaporated. The resulting residue was chromatographed on silica gel [hexane-EtOAc (3 : 1)] to give the diol **11** (3.40 g, 92%) as a solid, mp 72-74 °C; $[\alpha]_D^{20}$ +60.7° (*c* 1.66, $CHCl_3$); IR (KBr): 3487, 3347, 3053, 3004, 1600 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.03 (s, 3H), 1.31 (s, 3H), 2.43 (dd, *J* = 13.6, 10.9 Hz, 1H), 2.69 (dt, *J* = 10.8, 2.8 Hz, 1H), 3.05 (dd, *J* = 13.6, 2.5 Hz, 1H), 3.20 (dd, *J* = 8.7, 3.0 Hz, 1H), 3.55 (m, 1H), 3.78 (m, 1H), 3.85-3.92 (m, 2H), and 5.75-7.71 (m, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.3, 26.9, 36.3, 54.7, 64.8, 71.8, 72.8, 76.1, 80.7, 100.7, 107.8, 119.6, 120.4, 124.5, 125.6, 126.3, 126.7, 127.4, 128.1, 128.5, 128.7, 128.9, 129.0, 129.7, 137.8, 140.2, 140.9, 143.4, 147.5, and 148.3 (Found; C, 78.30; H, 6.77; N, 2.69. $C_{34}H_{35}NO_4$ requires C, 78.28; H, 6.76; N, 2.69%).

1,2-Dideoxy-3,4-*O*-isopropylidene-1-phenyl-2-[(9-phenyl-9-fluorenyl)-amino]-D-xylitol (12). To a solution of the diol **11** (3.50 g, 6.70 mmol) in EtOH : H_2O (50 mL : 25 mL) was added $NaIO_4$ (2.15 g, 10.06 mmol) at room temperature. After stirring for 3 h, the mixture was cooled to 0 °C, and then $NaBH_4$ (0.38 g, 10.06 mmol) was added and stirred for 10 min. After evaporation of EtOH, the mixture was poured into excess of H_2O and extracted with EtOAc (50 mL × 3). After concentration of the combined extracts, the residue was chromatographed on silica gel [hexane-EtOAc (8 : 1)] to give compound **12** (2.97 g, 90%) as a solid, mp 57-60 °C; $[\alpha]_D^{20}$ +103.6° (*c* 1.00, $CHCl_3$); IR (KBr): 3492, 3345, 3061, 3007, 1601 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.10 (s, 3H), 1.37 (s, 1H), 2.38 (dd, *J* = 13.3, 8.9 Hz, 1H), 2.52 (m, 1H), 2.87 (dd, *J* = 13.3, 5.1 Hz, 1H), 3.16 (dd, *J* = 8.7, 2.8 Hz, 1H), 3.41 (dd, *J* = 10.9, 7.5 Hz, 1H), 3.59 (dd, *J* = 10.9, 4.3 Hz, 1H), 4.10 (m, 1H), and 6.17-7.68 (m, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.6, 27.1, 37.6, 54.3, 62.5, 72.8, 75.9, 80.1, 107.7, 119.7, 120.2, 124.9, 125.8, 126.1, 126.4, 127.4, 127.9, 128.2, 128.3, 128.5, 128.7, 128.8, 129.5, 138.2, 140.2, 140.9, 144.0, 148.7, and 148.8 (Found; C, 80.62; H, 6.79; N, 2.85. $C_{33}H_{33}NO_3$ requires C, 80.62; H, 6.77; N, 2.85%).

1,2-Dideoxy-3,4-*O*-isopropylidene-5-*O*-methanesulfonyl-1-phenyl-2-[(9-phenyl-9-fluorenyl)-amino]-D-xylitol (13). To a solution of alcohol **12** (2.00 g, 4.07 mmol) in THF (20 mL) were added triethylamine (1.13 mL, 8.23 mmol) and methanesulfonyl chloride (0.63 mL, 8.23 mmol) at 0 °C. The reaction mixture was stirred for 10 min at room temperature, and then was quenched with saturated aqueous $NaHCO_3$ (40 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (40 mL × 3). After concentration of the combined extracts, the resulting residue was chromatographed on silica gel [hexane-EtOAc (12 : 1)] to give compound **13** (2.25 g, 97%) as a solid, mp 50-51 °C; $[\alpha]_D^{20}$ +115.7° (*c* 1.40, $CHCl_3$); IR (KBr): 3345, 3065, 3021, 2985, 1605 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.56 (s, 3H), 2.26-2.30 (m, 2H), 2.45 (m, 1H), 2.76 (s, 3H), 3.36 (d, *J* = 8.5 Hz, 1H), 3.70 (dd, *J* = 11.1, 6.2 Hz, 1H), 3.86 (dd, *J* = 11.1, 2.9 Hz, 1H), 4.52 (m, 1H), and 6.56-7.77 (m, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.7, 27.4, 37.3, 40.2, 53.6, 69.0, 72.4, 74.2, 76.9, 109.1, 120.0, 120.2, 125.4, 125.7, 126.0, 126.1, 127.3, 128.1, 128.2, 128.4, 128.4, 128.5, 128.7, 129.0, 138.9, 140.2, 140.8, 145.0, 148.9, and 151.1 (Found; C, 71.68; H, 6.20; N, 2.44. $C_{34}H_{35}NO_5S$ requires C, 71.68; H, 6.19; N, 2.46%).

1,2,5-Trideoxy-3,4-*O*-isopropylidene-5-iodo-1-phenyl-2-[(9-phenyl-9-fluorenyl)-amino]-D-xylitol (14). To a solution of the mesylate **13** (1.50 g, 2.63 mmol) in DMF (15 mL) was added LiI (1.06 g, 7.90 mmol). After stirring of the mixture for 12 h at 80 °C, saturated aqueous $NaHCO_3$ (40 mL) was added and the mixture was extracted with EtOAc (30 mL × 3). The extract was evaporated and the remaining residue was chromatographed on silica gel [hexane-EtOAc (20 : 1)] to give compound **14** (1.45 g, 92%) as a solid, mp 45-47 °C; $[\alpha]_D^{20}$ +115.1° (*c* 1.60, $CHCl_3$); IR (KBr): 3329, 3071, 3018, 2967, 1601 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.58 (s, 3H), 2.16-2.24 (m, 3H), 2.63 (dd, *J* = 10.5, 6.8 Hz, 1H), 2.72 (dd, *J* = 10.5, 4.2 Hz, 1H), 3.26 (d, *J* = 7.9 Hz, 1H), 4.25 (m, 1H), and 6.55-7.79 (m, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 5.8, 27.2, 27.6, 30.9, 40.7, 53.6, 72.4, 75.8, 77.6, 80.7, 108.4, 120.0, 120.1, 125.6, 125.7, 125.8, 126.1, 127.2, 128.1, 128.1, 128.2, 128.4, 128.5, 128.6, 129.1, 138.9, 140.2, 140.8, 145.2, 149.1, and 151.4 (Found; C, 65.90; H, 5.36; N, 2.35. $C_{33}H_{32}INO_2$ requires C, 65.89; H, 5.36; N, 2.33%).

(3*S*,4*S*)-5-Phenyl-4-[(9-phenyl-9-fluorenyl)-amino]-penten-3-ol (15). A solution of the iodinate **14** (1.20 g, 1.99 mmol) in THF (12 mL) was cooled to –40 °C and 2.5 M *n*-BuLi (1.60 mL, 3.99 mmol, 200 mol%) was added dropwise over 10 min using a syring pump. The reaction mixture was stirred for an additional 15 min at –40 °C, then quenched with saturated aqueous NH_4Cl (20 mL). The mixture was extracted with EtOAc (20 mL × 3) and combined extracts were concentrated. The resulting residue was chromatographed on silica gel [hexane-EtOAc (8 : 1)] to give compound **15** (0.75 g, 90%) as a solid, mp 48-52 °C; $[\alpha]_D^{20}$ –4.9° (*c* 1.35, $CHCl_3$); IR (KBr): 3458, 3330, 3062, 3023, 2982, 2931, 1602 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.28 (m, 2H), 2.39 (m, 1H), 2.55 (m, 1H), 3.69 (br, 1H), 5.07 (m, 2H), 5.54 (m, 1H), and 6.71-7.70 (m, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 39.8, 59.7, 73.1, 73.7, 116.2, 120.9, 120.9, 126.5, 127.0, 127.0, 127.3, 128.2, 128.7, 128.9, 129.3, 129.3, 129.4, 129.5, 130.5, 140.1, 140.6, 141.4, 141.6, 146.3, 150.1, and 151.0 (Found; C, 86.30; H, 6.53; N, 3.34. $C_{30}H_{27}NO$ requires C, 86.30; H, 6.52; N, 3.35%).

(3*S*,4*S*)-3-*O*-Benzyl-5-phenyl-4-[(9-phenyl-9-fluorenyl)-amino]-penten-3-ol (16). Allylic alcohol **15** (1.00 g, 2.39 mmol) was dissolved in THF (15 mL) and treated with 60% NaH (0.19 g, 4.79 mmol) and Bu_4NI (0.27 g, 0.72 mmol) at 0 °C. After stirring for 10 min at the same temperature, BnBr (0.57 mL, 4.79 mmol) was added. The reaction mixture was stirred for 24 h at room temperature, and then quenched with saturated aqueous NH_4Cl (40 mL). The mixture was extracted with EtOAc (40 mL × 3). After concentration of the combined extracts, the residue was purified by silica gel column chromatography [hexane-EtOAc (15 : 1)] to give the compound **16** (1.10 g, 91%) as an oil, $[\alpha]_D^{20}$ +20.0° (*c* 3.00, $CHCl_3$); IR (neat) 3328, 3063, 3022, 2926, 2866, 1602 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.17 (dd, *J* = 13.4, 7.7 Hz, 1H), 2.53 (m, 1H), 2.74 (dd, *J* = 13.4, 6.0 Hz, 1H), 3.29 (m, 1H), 3.95 (d, *J* = 12.2 Hz, 1H), 4.24 (d, *J* = 12.2 Hz, 1H), 5.12 (m, 1H), 5.22 (m, 1H), 5.98 (ddd, *J* = 17.2, 10.6, 6.4 Hz, 1H), and 6.53-7.62 (m, 23H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 38.0, 58.4, 70.4, 72.7, 80.7, 117.3, 119.5, 119.8, 125.3, 125.6, 126.2, 126.2, 126.9, 127.2, 127.4, 127.4, 127.8, 127.9, 128.1, 128.1, 128.2, 129.5, 136.2, 138.9, 140.1, 140.1, 140.4, 145.8, 150.0, and 150.0 (Found; C, 87.56; H, 6.57; N, 2.76. $C_{37}H_{33}NO$ requires C, 87.54; H, 6.55; N, 2.76%).

(2*R*,3*S*)-2-*O*-Benzyl-4-phenyl-3-[(9-phenyl-9-fluorenyl)-amino]-phenylbutanoic acid (17). A solution of the benzylate **16** (1.00 g, 1.97 mmol) in CH_3OH (20 mL) was reacted with ozone at –78 °C until the solution turned blue, then the residual ozone was removed with N_2 gas. The reaction mixture was allowed to reach room temperature and then was added 30% H_2O_2 (20 mL) and stirred overnight. After concentration of the combined extracts, the residue was chromatographed on silica gel [hexane-EtOAc (3 : 1)] to give compound **17** (0.97 g, 94%) as a solid; mp 80-82 °C; $[\alpha]_D^{20}$ +74.8° (*c* 2.00, $CHCl_3$); IR (KBr) 3334, 3288, 3063, 3020, 2928, 1742, 1602 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.20 (dd, *J* = 13.5, 10.6 Hz, 1H), 2.65 (m, 1H), 3.05 (d, *J* = 12.1 Hz, 1H), 3.18 (d, *J* = 3.8 Hz, 1H), 4.02 (d, *J* = 12.2 Hz, 1H), 4.61 (d, *J* = 12.2 Hz, 1H), 5.94 (d, *J* = 5.4 Hz, 1H), and 6.77-7.64 (m, 23H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.0, 56.1, 72.2, 73.0, 77.3, 119.8, 120.5, 124.5, 125.4, 125.5, 127.0, 127.5, 127.7, 127.8, 128.3, 128.4, 128.5, 128.7, 128.8, 129.0, 129.4, 129.6, 136.7, 137.6, 139.7, 140.6, 146.8, 147.0, and 171.9 (Found; C, 82.25; H, 5.94; N, 2.66. $C_{36}H_{31}NO_3$ requires C, 82.26; H, 5.94; N, 2.66%).

(2*R*,3*S*)-3-Amino-2-hydroxy-4-phenylbutanoic acid hydrochloride (1·HCl). Protected AHPBA **17** (0.30 g, 0.57 mmol) was reacted with H_2 and 10% Pd/C (0.03 g) in CH_3OH (8 mL) at 70 °C for 12 h. After filtration of the catalyst with Celite, Dowex 50W-X8 was added to the filtrate. The mixture was filtered, and then washed with MeOH. The remaining residue was eluted with 3 N NH_4OH and the ammoniacal solution was evaporated. To the free base **1** was added conc. HCl. The mixture was evaporated, and then co-evaporated with toluene, to give compound **1** as its hydrochloride salt. mp 219-220 °C; $[\alpha]_D^{20}$ –25.3° (*c* 0.70, 1 N HCl); IR (KBr) 3434, 3048, 2939, 1608 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) δ 2.97 (dd, *J* = 14.0, 8.0 Hz, 1H), 3.12 (dd, *J* = 14.0, 7.0 Hz, 1H), 3.89 (ddd, *J* = 15.0, 7.5, 3.0 Hz, 1H), 4.26 (d, *J* = 3.0 Hz, 1H), and 7.31-7.41 (m, 5H); δ_C (125 MHz; D_2O) δ 35.5, 54.9, 69.2, 128.0, 129.5, 129.8, 135.3, and 175.0; MS m/z: 134, 120, 104, 91 (M^+); (Found; C, 51.84; H, 6.08; N, 6.06. $C_{10}H_{14}ClNO_3$ requires C, 51.84; H, 6.09; N, 6.05%).

Methyl *N*-[(2*R*,3*S*)-2-*O*-benzyl-4-phenyl-3-{(9-phenyl-

9-fluorenyl)-amino}-butano-yl]-L-leucinate (18). To a solution of compound **17** (0.54 g, 1.03 mmol) in THF (22 mL) were added (*S*)-Leu-OCH$_3$ (0.0.38 g, 2.06 mmol), HOBT (0.15 g, 1.13 mmol), TsOH (0.19 g, 1.03 mmol), DCC (0.24 g, 1.15 mmol) and Et$_3$N (0.22 mL, 1.54 mmol). After stirring the mixture for 2 h at 0 °C, the mixture was quenched with saturated aqueous NaHCO$_3$ (25 mL) and the mixture was extracted with EtOAc (25 mL × 3). After evaporation of the combined extracts, the remaining residue was chromatographed on silica gel [hexane-EtOAc (10 : 1)] to give compound **18** (0.60 g, 89%) as a solid. mp 42-44 °C; $[\alpha]_D^{20}$ −120.6° (*c* 2.00, CHCl$_3$); IR (KBr) 3412, 3324, 3063, 3019, 2957, 2929, 1743, 1667, 1602 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.91 (d, *J* = 6.3 Hz, 6H), 1.26 (m, 1H), 1.47-1.66 (m, 3H), 2.28 (dd, *J* = 14.3, 10.5 Hz, 1H), 2.66 (m, 1H), 3.32 (d, *J* = 7.9 Hz, 1H), 3.44 (d, *J* = 2.9 Hz, 1H), 3.71 (s, 3H), 3.93 (m, 1H), 4.62 (m, 1H), and 6.23-7.65 (m, 23H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 22.4, 23.2, 25.3, 38.4, 42.0, 50.5, 52.6, 57.5, 72.9, 73.0, 80.4, 119.7, 120.1, 125.9, 126.1, 126.6, 126.7, 127.2, 128.1, 128.1, 128.3, 128.3, 128.4, 128.4, 128.7, 128.8, 130.3, 137.9, 140.1, 140.5, 140.9, 146.0, 150.0, 151.3, 171.8, and 173.3 (Found; C, 79.09; H, 6.81; N, 4.29. $C_{43}H_{44}N_2O_4$ requires C, 79.11; H, 6.79; N, 4.29%).

***N*-[(2*R*,3*S*)-2-*O*-Benzyl-4-phenyl-3-{(9-phenyl-9-fluorenyl)-amino}-butano-yl]-L-leucine (19).** To a solution of the protected dipeptide **18** (0.44 g, 0.67 mmol) in THF : H$_2$O (8 mL : 4 mL) was added LiOH (0.03 g, 1.02 mmol) at 0 °C. After stirring for 3 h at room temperature, 3% HCl (8 mL) was added and the mixture was extracted with (CH$_3$)$_2$CHOH : CH$_2$Cl$_2$ (10 mL : 30 mL). After concentration of the combined extracts, the residue was chromatographed on silica gel [hexane-EtOAc (6 : 1)] to give compound **19** (0.38 g, 89%) as a solid. mp 228-230 °C; $[\alpha]_D^{20}$ −96.4° (*c* 3.00, CHCl$_3$); IR (KBr) 3416, 3326, 3063, 3018, 2959, 1720, 1662, 1603 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.91 (m, 6H), 1.52-1.58 (m, 2H), 1.70 (ddd, *J* = 13.0, 7.5, 5.4, .3 Hz), 2.28 (dd, *J* = 12.9, 8.9 Hz, 1H), 2.62-2.70 (m, 2H), 3.44 (d, *J* = 3.0 Hz, 1H), 3.94 (m, 2H), 4.56 (m, 1H), and 6.25-7.58 (m, 23H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 21.8, 22.8, 24.9, 37.9, 41.0, 50.4, 57.2, 72.5, 72.7, 79.9, 119.3, 119.8, 125.4, 125.7, 126.1, 126.2, 126.9, 127.6, 127.8, 127.9, 127.9, 128.0, 128.0, 128.3, 128.4, 129.8, 137.3, 139.8, 139.8, 140.4, 145.4, 149.6, 150.5, 172.1, and 176.8 (Found; C, 79.00; H, 6.62; N, 4.39. $C_{42}H_{42}N_2O_4$ requires C, 78.97; H, 6.63; N, 4.39%).

***N*-[(2*R*,3*S*)-3-Amino-2-hydroxy-4-phenylbutanoyl]-L-leucine (2).** The protected leucine **19** (0.30 g, 0.47 mmol) was reacted with H$_2$ and 10% Pd/C (0.07 g) in CH$_3$OH (10 mL) at 70 °C for 10 h. The reaction mixture was filtered through Celite, and the remaining solid was subjected to ion-exchange chromatography (Dowex 50W-X8, eluting with 3 N NH$_3$ in water) to give compound **2** (0.13 g, 89%) as a solid. mp 231-232 °C; $[\alpha]_D^{20}$ −6.6° (*c* 0.85, AcOH); IR (KBr) 3421, 3211, 3063, 2957, 2869, 1667, 1647, 1611 cm^{-1}; ^{1}H NMR (500 MHz, D$_2$O) δ 0.86 (d, *J* = 6.4 Hz, 3H), 0.90 (d, *J* = 6.4 Hz, 3H), 1.59-1.75 (m, 3H), 3.00 (dd, *J* = 14.2, 8.1 Hz, 1H), 3.11 (dd, *J* = 14.2, 7.3 Hz, 1H), 3.86 (m, 1H), 4.24 (d, *J* = 3.7 Hz, 1H), 4.41 (dd, *J* = 9.1, 5.5 Hz, 1H), and 7.32-7.43 (m, 5H); ^{13}C NMR (125 MHz, D$_2$O) δ 21.0, 22.6, 24.9, 35.5, 39.5, 51.9, 55.5, 69.8, 128.2, 129.7, 129.8, 135.4, 173.5, and 176.8 (Found; C, 62.31; H, 7.84; N, 9.09. $C_{16}H_{24}N_2O_4$ requires C, 62.32; H, 7.84; N, 9.08%).

3,4;5,6-Di-*O*-isopropylidene-1-*O*-methanesulfonyl-D-glucitol (20). To a solution of glucitol **5** (0.20 g, 0.76 mmol) in CH$_2$Cl$_2$ (3.5 mL) was added diluted Et$_3$N (0.11 mL, 0.76 mmol) in CH$_2$Cl$_2$ (1.7 mL) and MsCl (0.06 mL, 0.76 mmol) in CH$_2$Cl$_2$ (2 mL) at −40 °C. After stirring for 5 min, the mixture was poured into sat. aq NaHCO$_3$ solution (8 mL) and extracted with CH$_2$Cl$_2$ (15 mL). The organic layer was separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (10 mL × 3). After concentration of the organic layer, the resulting residue was chromatographed on silica gel [hexane-EtOAc (3 : 1)] to give primary mesylate **20** (0.21 g, 81%) as an oil. $[\alpha]_D^{20}$ +2.8° (*c* 2.00, CHCl$_3$); IR (neat) 3425, 2941, 1640 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.26 (s, 3H), 1.35 (s, 3H), 1.43 (s, 3H), 1.44 (s, 3H), 2.58 (d, *J* = 9.0 Hz, 1H), 3.10 (s, 3H), 3.10-4.01(m, 3H), 4.05-4.09 (m, 2H), 4.15-4.32 (m, 1H), 4.34 (s, 1H), and 4.35 (s, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 25.2, 26.6, 26.8, 37.7, 68.0, 68.2, 71.2, 77.2, 79.5, 110.0, and 110.1. (Found; C, 45.86; H, 7.12. $C_{13}H_{24}O_8S$ requires C, 45.87; H, 7.11%).

1,2-Anhydro-3,4;5,6-di-*O*-isopropylidene-D-glucitol (21). To a solution of monomesylate **20** (0.50 g, 1.47 mmol) in CH$_3$OH (8 mL) was added K$_2$CO$_3$ (0.50 g, 3.67 mmol). After stirring for 2h at room temperature, the reaction mixture was quenched with excess 5% citric acid (15 mL) and extracted with EtOAc (25 mL × 2). After concentration of the combined extracts, the residue was chromatographed on silica gel [hexane-EtOAc (10 : 1)] to give epoxide **21** (0.32 g, 92%) as an oil. $[\alpha]_D^{20}$ −3.1° (*c* 0.93, CHCl$_3$); IR (neat): 3029, 2972, 2956 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.34-1.41 (m, 12H), 2.79-2.80 (m, 2H), 3.09 (dd, *J* = 3.4, 1.4 Hz, 1H), 3.83 (dd, *J* = 7.5, 4.8 Hz, 1H), 3.88 (m, 1H), 3.98 (dd, *J* = 8.6, 4.4 Hz, 1H), 4.06 (ddd, *J* = 8.3, 6.1, 4.4 Hz, 1H), and 4.14 (dd, *J* = 8.6, 6.1 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 25.6, 27.0, 27.2, 27.4, 45.1, 52.4, 68.2, 77.5, 78.9, 80.7, 110.1, and 110.6. (Found; C, 59.00; H, 8.26. $C_{12}H_{20}O_5$ requires C, 59.00; H, 8.25%).

(3*S*,4*R*)-5-Phenyl-4-[(9-phenyl-9-fluorenyl)-amino]-penten-3-ol (22). (3*S*,4*R*) allylic alcohol **22** was obtained by the same procedure as the conversion of **8** to **15**; the overall yield for this conversion was 79%. This compound was obtained as a solid. mp 51-52 °C; $[\alpha]_D^{20}$ −8.2° (*c* 2.00, CHCl$_3$); IR (KBr): 3517, 3297, 3068, 3022, 2997, 2957, 1604 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 2.37-2.43 (m, 3H), 2.57 (m, 1H), 3.13 (br, 1H), 3.33 (m, 1H), 5.04 (m, 2H), 5.63 (m, 1H), and 6.24-7.67 (m, 18H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 36.0, 59.1, 71.6, 72.3, 115.4, 119.5, 120.0, 125.0, 125.2, 125.7, 126.3, 127.2, 128.0, 128.1, 128.1, 128.4, 128.5, 128.6, 129.5, 137.1, 138.9, 139.7, 140.8, 145.0, 149.0, and 149.5 (Found; C, 86.30; H, 6.53; N, 3.34. $C_{30}H_{27}NO$ requires C, 86.30; H, 6.52; N, 3.35%).

(2*R*,3*R*)-3-Amino-2-hydroxy-4-phenylbutanoic acid hydrochloride (3·HCl). This compound was prepared according to the **1·HCl** compound method and obtained as a solid; mp 225-228 °C; $[\alpha]_D^{20}$ +4.8° (*c* 0.70, 1 N HCl); IR (KBr) 3400, 3032, 2909, 2851, 1606 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) δ 2.90 (dd, *J* = 15.0, 9.5 Hz, 1H), 2.99 (dd, *J* = 14.5, 5.5 Hz, 1H), 3.98 (m, 1H), 4.51 (d, *J* = 3.5 Hz, 1H), and 7.28-7.37 (m, 5H); ^{13}C NMR (125 MHz, D_2O) δ 33.2, 55.1, 70.0, 128.0, 129.3, 129.8, 135.2, and 174.3; MS m/z: 134, 120, 104, 91 (M^+); (Found; C, 51.82; H, 6.09; N, 6.07. $C_{10}H_{14}ClNO_3$ requires C, 51.84; H, 6.09; N, 6.05%).

Methyl *N*-[(2*R*,3*R*)-2-*O*-benzyl-4-phenyl-3-{(9-phenyl-9-fluorenyl)-amino}-butano-yl]-L-leucinate (23). This compound **23** was prepared according to the same method to obtain **18** to provide a solid; the yield for this conversion was 90%; mp 41-43 °C; $[\alpha]_D^{20}$ +47.3° (*c* 3.00, $CHCl_3$); IR (KBr) 3412, 3335, 3063, 3017, 2957, 1743, 1674, 1602 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (d, *J* = 4.7 Hz, 3H), 0.96 (d, *J* = 4.7 Hz, 3H), 1.51-1.69 (m, 3H), 2.50 (br, 1H), 2.55 (dd, *J* = 12.5, 6.9 Hz, 1H), 2.84 (m, 2H), 3.43 (dd, *J* = 1.9 Hz, 1H), 3.73 (s, 3H), 4.10 (d, *J* = 11.7 Hz, 1H), 4.20 (d, *J* = 11.7 Hz, 1H), 4.58 (m, 1H), and 6.70-7.79 (m, 23H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.3, 23.2, 25.3, 38.7, 41.7, 50.6, 52.6, 58.1, 72.6, 73.1, 81.4, 120.2, 120.4, 126.1, 126.2, 126.4, 126.7, 127.4, 128.0, 128.1, 128.3, 128.4, 128.5, 128.7, 128.9, 130.3, 137.9, 140.2, 140.6, 141.0, 146.0, 149.8, 150.8, 171.5, and 173.4 (Found; C, 79.09; H, 6.81; N, 4.29. $C_{43}H_{44}N_2O_4$ requires C, 79.11; H, 6.79; N, 4.29%).

***N*-[(2*R*,3*R*)-3-amino-2-hydroxy-4-phenylbutanoyl]-L-leucine (4).** This compound **4** was prepared according to the same method to obtain **2** and provided a solid; the yield for this conversion was 85%; mp 220-221 °C; $[\alpha]_D^{20}$ +30.3° (*c* 0.85, AcOH); IR (KBr) 3497, 3380, 3277, 2957, 2870, 1656, 1627 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) δ 0.95 (m, 6H), 1.61-1.75 (m, 3H), 2.89 (dd, *J* = 14.1, 8.2 Hz, 1H), 3.06 (dd, *J* = 14.1, 6.8 Hz, 1H), 3.73 (m, 1H), 4.29 (m, 2H), and 7.22-7.31 (m, 5H); ^{13}C NMR (125 MHz, D_2O) δ 21.0, 22.8, 25.4, 34.4, 41.4, 53.9, 57.1, 70.6, 127.3, 128.9, 129.6, 136.4, 171.4, and 178.7 (Found; C, 62.30; H, 7.84; N, 9.07. $C_{16}H_{24}N_2O_4$ requires C, 62.32; H, 7.84; N, 9.08%).

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR of compounds **1-4** and EIMS of compounds **1** and **3**. This material is available *via* the Internet at *http://www.kcsnet.or.kr.*

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