A Facile Synthesis of 2,3-*Diepi*-phytosphingosine

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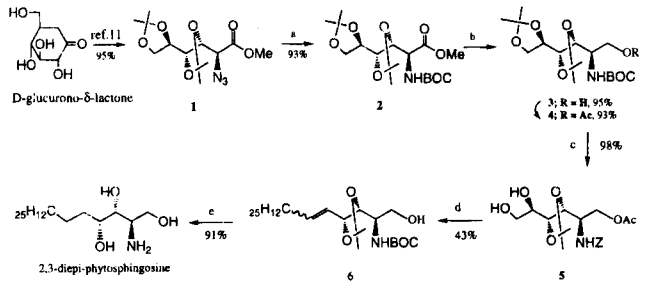
There are many biological active compounds incorporating chiral *erythro*-2-amino polyol substructures, such as sphingosine and phytosphingosine, which play important roles in the central nervous system,[1] and deoxymannojirimycin (DMM) and 2,5-dideoxy-2,5-imino-D-mannitol (DIM), which show glycosidase inhibitor activity.[2] Syntheses of optically pure natural or unnatural chiral *erythro*-2-amino poly substructure compounds have been reported in the past decade in the view of their biological importance.[3] Especially, the synthesis of unnatural chiral *erythro*-2-amino polyol substructure compounds was carried out for evaluatuing the biological activity. We also have recently reported a convenient synthesis of DMM[4] and DIM[5] using D-glucurono-δ-lactone as a chiral starting material *via* 10 and 11 reaction steps respectively.

In this paper, we wish to report a facile synthesis of 2,3-*diepi*-phytosphingosine from D-glucurono-δ-lactone as shown in Scheme 1. 2,3-*Diepi*-phytosphingosine is one of the isomers of phytosphingosine and several chemical synthetic methods were reported.[6] Biological investigations on 2,3-*diepi*-phytosphingosine and other isomers were done with skeleton muscle of rats[7] and with mesophyll cells[8]: the inhibition of protein kinase C by phytosphingosine and various sphingosine derivatives was investigated.[9]

The manno azide **1** was prepared (Scheme 1), starting from D-glucurono-δ-lactone according to known method.[10] Hydrogenation of the azide **1** was achieved through 10% palladium on charcol with H_2 under atmospheric pressure and protection with di-*tert*-butyl dicarbonate gave amino mannitol derivative **2** in 93% yield. Reduction of **2** with $LiAlH_4$ afforded corresponding alcohol **3**, which was then reacted with acetic anhydride to give acetate **4**. Selective removal of terminal isopropylidene group of acetate **4** was achieved through Dowex 50W-X8 resin (H^+-form) in 90% methanol to give diol **5** in 98% yield.[3] The diol **5** was transfered to aldehyde under the condition of $NaIO_4$ and water in CH_3CN at rt and Wittig olefination with (tridecyl) triphenylphosphonium bromide gave alkene **6** as a mixture of *cis* and *trans* in 43% yield. The ratio of *cis* and *trans* was not determined. The alkene **6** was reduced with 10% palladium on charcol with H_2 under atmospheric pressure. Finally, deprotection of acetal and BOC groups with 3 N HCl gave 2,3-*diepi*-phytosphingosine in 91% yield.



Scheme 1. (a) (i) 10% Pd/C, H_2, EtOAc, rt, (ii) $(BOC)_2$, MeOH, Et_3N, rt; (b) (i) LAH, THF, 0 °C (ii) Ac_2O, py, rt; (c) Dowex 50W-X8, 90% MeOH; (d) (i) $NaIO_4$, H_2O, CH_3CN, rt, (ii) $C_{13}H_{27}PPH_3Br$, n-BuLi, THF, rt; (e) (i) 10% Pd/C, H_2, EtOAc (ii) THF, 3 N HCl.

Experimental Section

Dowex 50W-X8 was purchased from Sigma Chemical Co. All non-aqueous reactions were carried out under nitrogen. THF and ether were distilled from Na/benzophenon; methanol was distilled from Mg; DMF and methylene chloride were distilled from CaH_2. Melting points were determined by using a Thomas-Hoover melting point apparatus and are uncorrected. Optical rotation was measured with a JASCO DIP-1000 digital polarimeter in a 1-dm cell. IR spectra were determined on a Hitachi 270-50 spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on either Varian 200 MHz, 400 MHz, or Bruker ARX-300 (500 MHz) spectrometer in $CDCl_3$ unless otherwise noted (value in ppm); coupling constants are reported in Hz. The elemental analyses were performed with a LECO Micro Carbon Hydrogen Determinator (CHN-800). TLC was run on Merck precoated silicagel plates. Merck silica gel 60 (230-400 mesh) was used for column chromatography.

Methyl 2-Azido-2-deoxy-3,4;5,6-di-*O*-isopropylidene-D-mannoate (1). This compound was prepared as described.[6]

Methyl 2-*tert*-Butoxycarbonylamino-2-deoxy-3,4;5,6-di-*O*-isopropylidene-D-mannoate (2). A solution of azido mannoate (**1**) (3.5 g, 11.1 mmol) in dry EtOAc (30 mL) was treated at rt with 10% palladium on charcoal (350 mg) under hydrogen at atmospheric pressure and was stirred for 1 h. The mixture was filtered, and the filterate was evaporated at reduced pressure to afford gel-like product. The crude product was used for next reaction without purification. The product was dried for 1 h with vacuum pump and dissolved in MeOH (30 mL). To this solution was added triethyl amine (2.0 mL, 14.4 mmol) and di-*tert*-butyl dicarbonate (3.12 g, 14.4 mmol) and the mixture was srirred at rt for 20 min. After addition of water (15 mL), the mixture was extracted three times with CH_2Cl_2 (50 mL), the combined organic phases were washed with brine, and dried over $MgSO_4$ and the solvent was evaporated at reduced pressure. The crude product was purified by flash chromatography (silica gel, hexane/EtOAc, 1 : 1) to afford **2** (4.02 g, 93%) as colorless oil. $[\alpha]^{20}_D$ +17.8° (c 1.03, CH_2Cl_2); IR (film) 3400, 2950, 1735, 1715, 1640, 1620 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.62 (d, 1H, *J*=7.2 Hz), 4.42 (t, 1H, *J*=6.5 Hz), 4.17 (m, 2H), 3.76 (m, 3H), 1.47 (m, 2H),

3.76 (m, 3H), 1.42 (s, OH), 1.34 (s, 9H); Anal. Calcd for $C_{18}H_{31}NO_8$: C; 55.50, H; 8.03, N; 3.60. Found: C; 55.37, H; 8.04, N; 3.55.

1-*O*-Acetyl-2-*tert*-butoxycarbonylamino-2-deoxy-3,4;5,6-di-*O*-isopropylidene-D-mannitol (4). A solution of the mannoate derivatives (**2**) (1.02 g, 2.6 mmol) in dry THF (20 mL) was treated at 0 °C with $LiAlH_4$ (0.2 g, 5.2 mmol) for 20 min, then the mixture was allowed to warm to rt and stirring was continued for 13 h. The reaction mixture was cooled down to 0 °C and hydrolyzed by addition of an aqueous solution of NaOH (15%, 0.5 mL) and water (1 mL), then the mixture was filtered, and filtrate was evaporated at reduced pressure. The crude product was purified by flash chromatography (silica gel, hexane/EtOAc, 3 : 1) to afford **3** (0.89 g, 95.0%) as colorless oil. This was used next step directly. A solution of the methyl mannoate (**3**) (1.54 g, 4.3 mmol) in dry pyridine (25 mL) was treated with acetic anhydride (0.06 mL, 6.3 mmol) and stirring was continued for 15 h at rt. The solution was then hydrolyzed by addition of water (30 mL), extracted three times with EtOAc (30 mL), the combined organic phases were washed with saturated $CuSO_4$, brine and dried over $MgSO_4$ and the solvent was evaporated at reduced pressure. The crude product was purified by flash chromatography (silica gel, hexane/EtOAc, 2 : 1) to afford **4** (1.60 g, 93.0%) as white solid. $[\alpha]^{20}_D$ +4.6° (c 1.2, CH_2Cl_2); IR (film), 3425, 2900, 1770, 1710 1510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.07 (1H, *J*=7.47 Hz), 4.37 (dd, 1H, *J*=3.13, 3.30 Hz), 4.09-4.15 (m, 2H), 4.04-4.00 (m, 3H), 3.96-3.94 (m, 1H), 3.91-3.87 (m, 2H), 2.08 (s, 3H), 1.45 (s, 3H), 1.44 (s, 9H), 1.39 (s, 3H), 1.37 (d, 6H, *J*=2.56 Hz); Anal. Calcd for $C_{19}H_{33}NO_8$: C; 56.54, H; 8.25, N; 3.47. Found: C; 55.51, H; 8.18, N; 3.43.

1-*O*-Acetyl-2-*tert*-butoxycarbonylamino-2-deoxy-3,4-O-isopropylidene-D-mannitol (5). A solution of the acetate (**4**) (3.87 g, 9.6 mmol) in 90% MeOH (30 mL) was treated with Dowex 50W-X8 (0.5 g) and stirring was continued for 18 h at rt. The reaction mixture was filtered through a pad of Celite to remove the Dowex 50W-X8 resin and the solvent was removed at reduced pressure. The crude product was purified by the flash chromatography (silica gel, hexane/EtOAc, 1 : 1) to afford **5** (3.57 g, 97.0%) as white solid. $[\alpha]^{20}_D$ +7.2° (c 1.0, CH_2Cl_2); mp 94 °C; IR (film), 3500, 3400, 3000, 1750 1720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.41 (d, 1H, *J*=7.66 Hz), 4.33 (d, 1H, *J*= 9.79 Hz), 4.20 (t, 1H, *J*=10.5 Hz), 4.12 (t, 2H, *J*=6.12 Hz), 3.97-3.94 (m, 2H), 3.82 (d, 2H, *J*=9.04 Hz), 3.68 (s, 2H), 3.55 (s, 1H), 2.08 (s, 3H), 1.45 (s, 9H), 1.39 (d, 6H, *J*=8.47 Hz); Anal. Calcd for $C_{16}H_{29}NO_8$: C; 52.86, H; 8.05, N; 3.86. Found: C; 52.81, H; 8.01, N; 3.83.

Synthesis of olefin compound (6). To a solution of **5** (0.74 g, 1.9 mmol) in actonitrile (6 mL) at rt was added $NaIO_4$ (0.45 g, 1.1 eq) and water (10 mL). After 5 min, the reaction mixture diluted with water (20 mL) and extracted three times with EtOAc (20 mL×3) and the combined organic layers were washed brine (40 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford aldehyde (0.61 g, 98.0%) as colorless oil. The aldehyde was dried under vaccum pump (1 torr) for 2 h and kept in 25 mL of one neck flask for next step without purification. By the way, a suspension of (tridecyl)triphenylphosphonium bromide (2.26 g 4.3 mmol) in THF (30 mL) was treated with *n*-Buli (1.6 M in hexane, 4.1 mL, 3 eq) and stirring was continued for 15 min at rt. This reaction mixture, cooled to −40 °C was treated with aldehyde in THF (3 mL) for 10 min and stirring was continued for 1 h, then quenched by adding sat. NH_4Cl solution (10 mL) and water (40 mL). The aqueous layer was extracted with EtOAc (50 mL×3) and the combined organic layers were washed with brine (50 mL×2), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was flash chromatographed to afford **6** (4.3 g, 43%) as colorless oil. $[\alpha]^{20}_D$ −8.3° (c 1.3, CH_2Cl_2); IR (film), 3300, 2950, 2710, 1770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.71-5.95 (m, 1H), 5.30-5.55 (m, 1H), 4.54 (t, 1H, *J*=8.60 Hz), 4.47 (t, 1H, *J*=8.90 Hz), 4.33 (t, 1H, *J*=7.20 Hz), 4.03 (m, 1H), 3.71 (t, 1H, *J*=7.10 Hz), 2.15 (m, 1H), 2.09 (m, 1H), 1.42 (s, 9H), 1.40 (s, 3H), 1.26 (s, 25H) 0.88 (t, 3H, *J*=4.80 Hz).

2,3-*Diepi*-phytosphingosine (7). A solution of the olefin (**6**) (0.06 g, 0.13 mmol) in THF (15 mL) was treated with 3 N HCl solution (0.24 mL, 5 eq). The reaction mixture was refluxed for 5 h and cooled down to rt. The reaction mixture was neutralized by addition of an aqueous solution of NH3 (3 N, 0.24 mL). The aqueous layer was extracted with EtOAc (20 mL×3) and the combined organic layers were washed with brine (20 mL×2), dried over $MgSO_4$ and concentrated in vacuo. The residue was flash chromatographed to afford 7 (0.045 g, 90.0%) as white solid. $[\alpha]^{20}_D$ +27.2° (c 1.2, MeOH). Spectral data of **7** are identical with those reported.[11]

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Synthesis of Novel C_2 Symmetric Receptors Containing a Diaza-Crown Macrocycle

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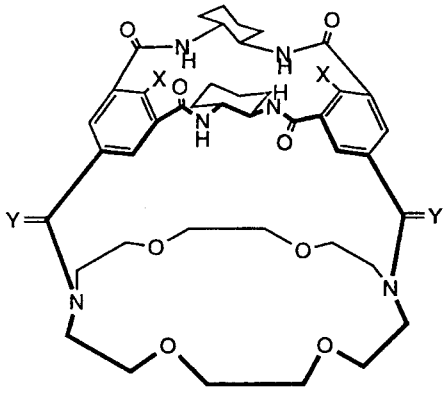
Recently, the cation-π interaction has been recognized as an important noncovalent intermolecular force.[1] The scope and importance of this interaction have been established by theoretical calculations[2] and by studies of organic model systems[3] and biological recognition systems.[1b,1c,2d,4] Dougherty et al proposed that in most aromatic systems, electrostatic interactions between the positive charge and the permanent quadrupole moment of an aromatic make major contributions to the cation-π interaction.[2a] However, there remains much need to experimentally verify the origin and magnitude of the cation-π interaction.

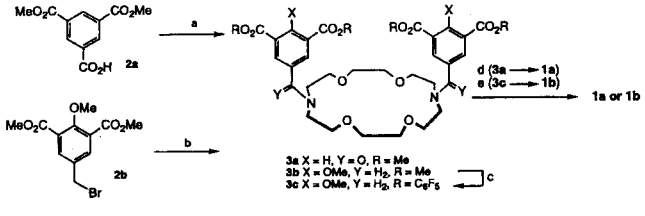
In the present work, we describe design and synthesis of chiral model receptors (**1a** and **1b**) which might provide a quantitative measurement for the cation-π interaction in a nonpolar organic solvent.



1a X = H, Y = O
1b X = OMe, Y = H_2

Since the cation-π interaction is relatively weak binding force in a nonpolar organic solvent compared to the other noncovalent interactions such as hydrogen bonding, ion-dipole interaction, and electrostatic interaction, the azacrown ether was used as a primary binding site for cations. Our strategy is to compare an azacrown ether derived acyclic precursor (**3a** or **3b**) with an azacrown ether based receptor (**1a** or **1b**)[5] for the cation binding which might show enhanced binding by an additional cation-π interaction. In order to provide a potent binding site for cations in a nonpolar organic solvent, we designed chiral, C_2 symmetric, and macrocyclic host molecules (**1a** and **1b**)[6] possessing a rigidly defined cavity consisting of an azacrown ether moiety, amide functionalities, and aromatic rings used to define the "walls" of the host. CPK models of the designed receptors indicated that alkali metal cations can be embedded within the cavity through the combination of the ion-dipole interaction between the cation and azacrown ether moiety, the hydrogen bonding interaction between the cation and amide carbonyls, and the cation-π interaction between the cation and the aromatic rings. The binding cavity of **1a** and **1b** with a rigid framework is expected to show size-selectivities in the binding of alkali metal cations and an ammonium ion.

The synthesis of the receptor **1a** starts from the amide bond formation between the pentafluorophenyl active ester



Scheme 1. (a) C_6F_5OH, EDC, THF; 4,13-diaza-18-crown-6, THF (b) 4,13-diaza-18-crown-6, Cs_2CO_3, CH_3CN, reflux (c) LiOH, THF-MeOH-H_2O; C_6F_5OH, EDC, THF (d) LiOH, THF-MeOH-H_2O; C_6F_5OH, EDC, THF; (1*R*,2*R*)-1,2-diaminocyclohexane, THF. (e) (1*R*,2*R*)-1,2-diaminocyclohexane, THF.