Note

Synthesis of (2R,5S)-dihydroxymethyl-(3R,4R)-dihydroxypyrrolidine (DGDP) via stereoselective amination using chlorosulfonyl isocyanate

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Abstract—A stereoselective approach for synthesizing (2R,5S)-dihydroxymethyl-(3R,4R)-dihydroxypyrrolidine 1 (2,5-dideoxy-2,5-imino-D-glucitol, DGDP) was achieved using a seven-step approach starting from 2,3,4,6-tetra-O-benzyl-D-mannose (7). Key steps for the preparation of the title compound 1 involved the regioselective and diastereoselective amination of the cinnamyl anti-1,2-polybenzyl ethers 5 and 6 using chlorosulfonyl isocyanate (CSI) and ring cyclization to form the pyrrolidine ring. The reaction between anti-1,2-polybenzyl ether 5 and CSI in toluene at 0 °C afforded the corresponding anti-1,2-amino alcohol 4 as a major product with a diastereoselectivity of 16:1 in 76% yield. The mechanism underlying these reactions may be explained by the neighboring-group effect leading to the retention of stereochemistry.

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Imino sugars (frequently termed ‘azasugars’), in which an oxygen atom is replaced by a nitrogen atom in the ring, are one of the most interesting discoveries in the natural products field. They bind specifically to the active sites of glycosidases by mimicking the corresponding natural substrates. Glycosidases are involved in a wide range of important biological processes, such as intestinal digestion, the post-translational processing of glycoproteins, and the lysosomal catabolism of glycoconjugates. Therefore, glycosidase inhibitors have enormous therapeutic potential for the treatment of diseases as diverse as viral infections, cancer, and diabetes.

In particular, 2,5-dideoxy-2,5-imino-D-glucitol (DGDP, 1), a 5-epimer of 2,5-dideoxy-2,5-imino-D-mannitol (DMDP, 2) isolated in leaves of the legume Derris elliptica in 1976,3 is known to be a selective inhibitor of α-galactosidase, and to exhibit broad-spectrum inhibition against α- and β-glucosidases and α-mannosidases.4 Moreover, DGDP (1) has the same configuration as the pyrrolidine ring of tetrahydroxylated pyrrolizidine (+)-alexine (3), which exhibits potent anti-viral and anti-retroviral activities5 and powerful glycosidase inhibitory properties (Fig. 1).6

To date, several synthetic methods to DGDP analogs have been reported. To our knowledge, the majority of these synthetic approaches have involved carbohydrate,7 enzymatic,4,8 or asymmetric syntheses.9 Carbohydrates are generally considered as attractive starting materials for the straightforward installation of four contiguous stereogenic centers in most syntheses. The synthetic potential of carbohydrate-based synthesis has been exploited by our CSI-mediated stereoselective amination of the polybenzyl ethers derived from carbohydrates.10

In connection with our previous work on the stereoselective amination of various allylic ethers using CSI,11 and on the application of this method to the total synthesis of polyhydroxylated alkaloids,10,12 we envisioned the facile stereoselective synthesis of DGDP (1) utilizing
CSI-mediated stereoselective amination as a key transformation.

Retrosynthetic analysis of DGDP (1) is illustrated in Scheme 1. It was envisaged that pyrrolidine alkaloid 1 could be prepared via the intramolecular cyclization of mesylate 4, followed by oxidation/reduction of the olefin and removal of the benzyl groups. The desired anti-1,2-amino alcohol 4 could be synthesized via the regioselective and diastereoselective installation of an NHCbz moiety into anti-1,2-polybenzyl ethers 5 and 6, which in turn could be easily derived from 2,3,4,6-tetra-O-benzyl-d-mannose (7).

The total synthesis of DGDP (1) began with 2,3,4,6-tetra-O-benzyl-d-mannose (7), which was prepared from commercially available d-mannose, as reported (Scheme 2). Fischer glycosylation of d-mannose, followed by protection of the hydroxyl groups, isomerization of the allyl group (KO$_2$Bu, DMSO, 80°F), and oxidation of the resulting olefin with OsO$_4$, afforded lactol 7, which was subjected to a Wittig reaction to give the olefin 8. Several other attempts to introduce a cinnamyl moiety under various basic conditions, for example, using BuLi, NaH, NaNH$_2$, NaHMDS, and others, furnished the desired olefin 8 in low yield. Fortunately, olefination of 7 to 8 was successfully accomplished, in 91% yield, by using the dimysl anion ($\text{OMs}^-$) (sodium methysulfinylmethanide, 3 equiv of NaH, and 5 equiv of DMSO) in THF at 60°C. In an initial approach, the secondary alcohol 8 was converted to anti-1,2-polybenzyl ether 6 using methanesulfonyl chloride in 98% yield. Treatment of 6 with CSI in toluene at 0°C provided anti-1,2-amino alcohol 4 with a high diastereoselectivity (14:1) in low yields (35–40%).

In order to improve the chemical yield and purity of the CSI reaction, we decided to slightly modify our strategy to that of the CSI reaction with acetate 5. After acetylation of 8, the reaction between anti-1,2-polybenzyl ether 5 and CSI was carried out in toluene at 0°C, and this was followed by an aqueous workup using 25% sodium sulfite solution to furnish 9 with a diastereoselectivity of 16:1 in 76% yield. Compound 9 was then hydrolyzed, and without purification, transformed into the desired anti-1,2-amino alcohol 4 in 93% yield.

The diastereoselectivity of the reactions of the anti-1,2-polybenzyl ethers 5 and 6 with CSI may be explained by the neighboring-group effect, in which the orientation of the NHCbz group retains the original configuration of the benzyl ether via a double inversion of the configuration, as shown in Figure 2.

Compound 4 was treated with potassium tert-butoxide to provide 10 in 87% yield. Ozonolysis of 10, followed by reduction with sodium borohydride, afforded alcohol 11 in 85% yield. Finally, catalytic hydrogenation of 11 over Pd/C in EtOH furnished DGDP (1) as a white solid. Spectroscopic data ($^1$H and $^{13}$C NMR) and the optical rotation ([$^a$$^2$$^5$$^c$]$_D$ +24.1 (c 1.0, H$_2$O)) of 1 were consistent with the literature values ([lit.$^a$$^2$$^5$$^c$]$_D$ +22.7 (c 0.14, H$_2$O), [lit.$^a$$^2$$^5$$^c$]$_D$ +25.1 (c 1.5, H$_2$O)]).

In conclusion, we demonstrated a short synthetic route to 2,5-dideoxy-2,5-imino- d-glucitol (DGDP) as a potent glycosidase inhibitor, using the readily available 2,3,4,6-tetra-O-benzyl-d-mannose. Key features of the synthesis involve the CSI-mediated stereoselective amination of anti-1,2-polybenzyl ethers and intramolecular cyclization to form the pyrrolidine framework. We believe that our synthetic strategy can be easily applied to the preparation of various polyhydroxylated alkaloids or other natural products containing a nitrogen atom.

1. Experimental

1.1. General methods

Commercially available reagents were used without additional purification, unless otherwise stated. All anhydrous solvents were distilled over CaH$_2$ or P$_2$O$_5$ or Na/benzophenone prior to reaction. All reactions

![Scheme 1. Retrosynthetic analysis.](image-url)
were performed under an inert atmosphere of nitrogen or argon. Nuclear magnetic resonance spectra ($^1$H and $^{13}$C NMR) were recorded on a Varian Unity Inova 500 and 300 MHz spectrometer and chemical shifts are
reported as parts per million (ppm). Resonance patterns are reported with the notations s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). In addition, the notation br is used to indicate a broad signal. Coupling constants (J) are reported in hertz (Hz). IR spectra were recorded on a Nicolet 205 infrared spectrophotometer or Bruker Vector 22 infrared spectrophotometer and are reported as cm⁻¹. Optical rotations were measured with a Jasco P1020 polarimeter. Thin-layer chromatography was carried out using plates coated with Kieselgel 60F 254 (E. Merck). Flash column chromatography was performed using Kieselgel 60 (230–400 mesh, E. Merck). High-resolution mass spectra (HRMS) were recorded on a JEOL, JMS-505 or JMS-600 spectrometer.

1.2. (3S,4S,5R,6R)-6-(Benzyloxyethyl)-3,4,5-tribenzyl-oxytetrahydro-2H-pyran-2-ol (7)

Portions of acetyl chloride (15.0 mL, 0.211 mol) were slowly added to allyl alcohol (190 mL) at 0 °C, then α-mannose (15.0 g, 0.083 mol) was added and the reaction mixture was stirred for 2.5 h at 70 °C and for overnight at 40 °C. The mixture was neutralized with solid NaHCO₃, filtered over a Celite bed, and concentrated in vacuo. The organic layer was dried over MgSO₄ and concentrated in vacuo to give 36.0 g of crude brownish syrup. To a solution of the crude syrup (39.0 g, 0.067 mol) in distilled dimethyl sulfoxide (114 mL) was added potassium tert-butoxide (32.0 g, 0.099 mol) and the reaction mixture was slow added dropwise over 1 h. The reaction mixture was stirred for 4.5 h at 55 °C and for overnight at room temperature. The mixture was extracted with toluene (200 mL), and the organic layer was washed with water until it was neutral. The organic layer was dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash chromatography (2:1 hexane–EtOAc) to afford 39.0 g (81%) of (3S,4S,5R,6R)-2-(allyloxy)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2H-pyran-2-ol (7).

To a stirred solution of dimethyl sulfoxide (5.3 mL, 0.075 mol) in anhyd THF (45 mL) was added NaH (1.8 g, 0.045 mol, 60% in mineral oil) at 0 °C under N₂. The reaction mixture was stirred for 1 h at room temperature and cooled to 0 °C. Benzyltriphenylphosphonium chloride (17.3 g, 0.045 mol) was added in one portion, and the reaction mixture was stirred for 2 h at room temperature, then cooled to 0 °C. A solution of 7 (8.0 g, 0.015 mol) in anhyd THF (14.0 mL) was slowly added, and the reaction mixture was stirred for 3 h at 60 °C. After cooling, the reaction mixture was quenched with a solution of satd aq NH₄Cl (30 mL). The aq layer was extracted with EtOAc (100 mL), and the organic layer was washed with H₂O and brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified by column chromatography (4:1 hexane–EtOAc) to afford 6.8 g (75%, cis:trans = 3.3:1) of olefin 8 as a colorless syrup. Rₐ 0.20 (2:1 hexane–EtOAc); [α]D +6.0 (c 1.0, CHC₁₃); IR (neat) 3400, 1600, 1453, 1097 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 2.91 (d, 1H, J 12.0 Hz), 4.66 (s, 2H), 4.79 (d, 1H, J 12.5 Hz), 7.18–7.38 (m, 20H); 13C NMR (125 MHz, CDCl₃) δ 69.39, 69.93, 71.94, 72.46, 72.97, 73.11, 73.61, 73.80, 74.86, 74.90, 75.16, 75.26, 75.48, 75.52, 76.43, 79.98, 83.33, 93.06, 93.97, 127.67, 127.79, 127.80, 127.83, 127.84, 127.89, 127.90, 127.91, 127.93, 128.05, 128.08, 128.17, 128.20, 128.21, 128.22, 128.23, 128.26, 128.32, 128.36, 128.37, 128.42, 128.47, 128.48, 128.57, 128.55, 138.37, 138.41, 138.48, 138.57, 138.63, 138.65, 138.76; HRFABMS: [M+H⁺] calcd for C₃₄H₃₅O₆, 539.2434; found, 539.2426.

1.3. (2R,3R,4R,5R)-7-Phenyl-1,3,4,5-tetramethoxy-hept-6-en-2-ol (8)

To a stirred solution of dimethyl sulfoxide (5.3 mL, 0.075 mol) in anhyd THF (45 mL) was added NaH (1.8 g, 0.045 mol, 60% in mineral oil) at 0 °C under N₂. The reaction mixture was stirred for 1 h at room temperature and cooled to 0 °C. Benzyltriphenylphosphonium chloride (17.3 g, 0.045 mol) was added in one portion, and the reaction mixture was stirred for 2 h at room temperature, then cooled to 0 °C. A solution of 7 (8.0 g, 0.015 mol) in anhyd THF (14.0 mL) was slowly added, and the reaction mixture was stirred for 3 h at 60 °C. After cooling, the reaction mixture was quenched with a solution of satd aq NH₄Cl (30 mL). The aq layer was extracted with EtOAc (100 mL), and the organic layer was washed with H₂O and brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified by column chromatography (4:1 hexane–EtOAc) to afford 6.8 g (75%, cis:trans = 3.3:1) of olefin 8 as a colorless syrup. Rₐ 0.30 (4:1 hexane–EtOAc);
1.4. (2R,3S,4R,5R)-7-Phenyl-1,3,4,5-tetabenzyloxy-hept-6-en-2-yl methanesulfonate (6)

To a stirred solution of the secondary alcohol 8 (3.00 g, 4.88 mmol) in anhyd CH₂Cl₂ (25 mL) was added Et₃N (1.36 mL), pyridine (DMAP, 60 mg, 0.49 mmol) and methanesulfonyl chloride (0.57 mL, 7.3 mmol) at 0 °C under N₂. The reaction mixture was stirred for 3 h at 0 °C and quenched with a solution of satd aq NH₄Cl (3 mL). The aq layer was extracted with CH₂Cl₂ (30 mL), and the organic layer was washed with H₂O and brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified by flash column chromatography (3:1 hexane–EtOAc) to afford 1.15 g (36%, cis:trans = 3.6:1, antisy = 14:1) of colorless syrup. Rf 0.30 (3:1 hexane–EtOAc); [α]D° 59.6 (c 0.5, CHCl₃); IR (neat) 1494, 1453, 1351, 1213, 1174, 1089, 1049, 1026 cm⁻¹; ³¹P NMR (500 MHz, CDCl₃) δ 2.90 (s, 0.6H), 2.91 (s, 2.4H), 3.75-3.98 (m, 3H), 4.16 (t, 0.8H, J 7.0 Hz), 4.25 (d, 0.8H, J 11.5 Hz), 4.29 (d, 0.2H, J 11.5 Hz), 4.41 (d, 0.2H, J 10.5 Hz), 4.42 (d, 0.8H, J 10.5 Hz), 4.44 (d, 0.8H, J 10.5 Hz), 4.45 (d, 0.2H, J 10.5 Hz), 4.47 (d, 0.8H, J 11.0 Hz), 4.52 (d, 0.2H, J 11.0 Hz), 4.54 (d, 0.8H, J 11.0 Hz), 4.58 (d, 0.8H, J 10.5 Hz), 4.59 (d, 0.2H, J 10.5 Hz), 4.66 (d, 0.2H, J 10.5 Hz), 4.78 (t, 1H, J 9.5 Hz), 4.84 (d, 0.8H, J 10.5 Hz), 5.10 (t, 1H, J 7.0 Hz), 5.78 (dd, 0.8H, J 11.5, 10.0 Hz), 6.26 (dd, 0.2H, J 16.0, 8.5 Hz), 6.73 (d, 0.2H, J 16.0 Hz). 6.98 (d, 0.8H, J 11.5 Hz), 7.07-7.49 (m, 25H); ¹³C NMR (125 MHz, CDCl₃) δ 39.00, 69.47, 69.86, 73.16, 73.50, 74.72, 75.29, 79.15, 80.76, 82.88, 126.90, 127.61, 127.79, 127.82, 127.88, 127.98, 128.18, 128.25, 128.44, 128.46, 128.51, 128.62, 128.67, 128.86, 129.52, 130.48, 135.99, 136.55, 137.89, 138.02, 138.10; HRFABMS: [M+H⁺] calcd for C₄₂H₄₅O₇S, 691.2730; found, 691.2735.

1.5. (2R,3S,4R,5R)-5-Benzoylcarbonylamino-7-phenyl-1,3,4,5-tetabenzyloxy-hept-6-en-2-yl methanesulfonate (4)

To a stirred solution of 6 (3.0 g, 4.3 mmol) in anhyd toluene (22 mL) was added Na₂CO₃ (4.13 g, 0.039 mol) and chlorosulfonyl isocyanate (2.26 mL, 0.026 mol) at 0 °C under N₂. The reaction mixture was stirred for 24 h at 0 °C and quenched with H₂O (10 mL). The aq layer was extracted with EtOAc (30 mL × 2). The organic layer was added to a solution of 25% aq Na₂SO₄ (25 mL) and the reaction mixture was stirred for 24 h at room temperature. The organic layer was washed with H₂O and brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified by flash column chromatography (3:1 hexane–EtOAc) to afford 1.15 g (36%, cis:trans = 3.6:1, antisy = 14:1) of anti-1,2-aminoo alcohol 4 as pale yellow syrup. Rf 0.30 (3:1 hexane–EtOAc); [α]D° 59.6 (c 0.2, CHCl₃); IR (neat) 1715, 1496, 1454, 1350, 1217, 1174, 1092, 912 cm⁻¹; ¹³C NMR (500 MHz, CDCl₃) δ 1.28 (s, 2.34H), 2.96 (s, 0.66H), 3.59 (br, 0.78H), 3.74 (t, 0.78H, J 8.0 Hz), 3.75-3.85 (m, 0.44H), 3.92-3.96 (m, 1H), 4.10 (br, m, 1H), 4.34 (d, 0.78H, J 11.5 Hz), 4.39 (d, 0.78H, J 11.5 Hz), 4.42 (d, 0.78H, J 11.5 Hz), 4.44-4.65 (m, 3.22H), 4.72 (d, 0.22H, J 11.5 Hz), 4.73 (d, 0.22H, J 11.5 Hz), 4.79 (d, 0.78H, J 11.0 Hz), 4.95-4.99 (br, 0.22H), 5.06-5.16 (m, 2.78H), 5.44 (dd, 0.78H, J 10.5, 9.5 Hz), 5.74 (d, 0.78H, J 7.5 Hz), 5.82 (d, 0.22H, J 8.0 Hz), 6.03 (dd, 0.22H, J 16.0, 6.0 Hz), 6.57 (d, 0.22H, J 16.0 Hz), 6.65 (d, 0.78H, J 11.5 Hz), 7.11-7.39 (m, 25H); ¹³C NMR (125 MHz, CDCl₃) δ 38.33, 38.66, 49.35, 53.41, 66.75, 67.45, 69.29, 69.36, 72.87, 73.53, 73.70, 74.65, 75.56, 78.84, 79.44, 80.45, 80.80, 83.82, 84.13, 116.53, 125.39, 126.77, 126.91, 127.72, 127.95, 128.03, 128.09, 128.17, 128.23, 128.30, 128.46, 128.51, 128.66, 128.76, 128.78, 128.81, 128.86, 131.35, 132.79, 133.66, 136.43, 136.53, 136.94, 137.18, 137.50, 137.58, 137.75, 137.86, 156.18, 156.42; HRFABMS: [M+H⁺] calcd for C₄₃H₄₆NO₇S, 736.2944; found, 736.2932.

1.6. (2R,3S,4R,5R)-7-Phenyl-1,3,4,5-tetabenzyloxy-hept-6-en-2-yl acetate (5)

To a stirred solution of 8 (4.0 g, 6.5 mmol) in anhyd CH₂Cl₂ (28 mL) was added Et₃N (1.8 mL, 0.013 mol), pyridine (DMAP, 80 mg, 0.651 mmol) and Ac₂O (0.92 mL, 9.76 mmol) at 0 °C under N₂. The reaction mixture was stirred for 3 h at room temperature and quenched with a solution of satd aq NH₄Cl (5 mL). The aq layer was extracted with CH₂Cl₂ (40 mL), and the organic layer was washed with H₂O and brine, dried over MgSO₄, and concentrated in vacuo.
The residue was purified by flash column chromatography (5:1 hexane–EtOAc) to afford 4.2 g (98%, cis:trans = 3:6:1) of acetate 5 as a colorless syrup. Rf 0.32 (5:1 hexane–EtOAc); [α]D 22 −80.5 (c 1.0, CHCl3); IR (neat) 1737, 1603, 1495, 1453, 1238 cm−1. 1H NMR (300 MHz, CDCl3) δ 2.07 (s, 0.66H), 2.13 (s, 2.34H), 3.25–3.95 (m, 3.78H), 4.01 (d, 0.78H, J 11.4 Hz), 4.09–4.76 (m, 6.66H), 4.84 (d, 0.78H, J 10.2 Hz), 4.91 (d, 0.78H, J 9.0 Hz), 5.35–5.43 (m, 1H), 5.85 (t, 0.78H, J 11.7 Hz), 6.39 (dd, 0.22H, J 15.9, 8.1 Hz), 6.79 (d, 0.22H, J 15.9 Hz), 7.04 (d, 0.78H, J 11.7 Hz), 7.11–7.55 (m, 25H); 13C NMR (125 MHz, CDCl3) δ 21.58, 68.79, 69.78, 72.90, 73.13, 73.27, 74.65, 75.40, 80.64, 127.53, 127.62, 127.75, 127.80, 127.83, 127.85, 128.13, 128.34, 128.35, 128.38, 128.43, 128.48, 128.57, 128.93, 130.54, 130.84, 135.85, 136.61, 138.45, 170.43; HRFICMS: [M+H]+ calcd for C43H45O6 655.3060; found, 655.3066.

1.7. (2R,3S,4R,5R)-5-(Benzyloxy)carbonylaminono)-7-phenyl-1,3,4-tribenzyloxy-hept-6-en-2-yl acetate (9)

To a stirred solution of 5 (3.4 g, 5.18 mmol) in anhyd toluene (26 mL) was added Na2CO3 (4.9 g, 0.047 mol) and chlorosulfonyl isocyanate (2.7 mL, 0.031 mol) at 0 °C under N2. The reaction mixture was stirred for 24 h at 0 °C and quenched with H2O (12 mL). The aq layer was extracted with EtOAc (35 mL × 2). The organic layer was added to a solution of 25% aq Na2SO3 (30 mL), and the reaction mixture was stirred for 24 h at room temperature. The organic layer was washed with H2O and brine, dried over MgSO4, and concentrated in vacuo. The residue was purified by flash column chromatography (3:1 hexane–EtOAc to afford 0.76 g (87%, cis:trans = 3:9:1) of 10 as a colorless syrup. Rf 0.28 (5:1 hexane–EtOAc); [α]D 22 −1.0 (c 0.3, CHCl3); IR (neat) 1700, 1455, 1405, 1101 cm−1. 1H NMR (500 MHz, CDCl3) δ 3.74–3.77 (br, 1.59H, cis-H-2’a, 2’b), 3.74–3.77 (br, 0.41H, trans-H-2’a, 2’b), 4.17–5.12 (m, 10H, 3CH2Ph and H-2, 3, 4, 5), 4.82 (s, 2H, Cbz), 5.72 (dd, 0.79H, J 11.5, 10.0 Hz), 6.11 (dd, 0.21H, J 16.0, 6.0 Hz), 6.39 (d, 0.21H, J 16.0 Hz), 6.45 (d, 0.79H, J 11.5 Hz), 7.10–7.41 (m, 25H); 13C NMR (125 MHz, CDCl3) δ 59.01 (two carbons), 66.95, 72.21, 72.82, 73.30, 73.68, 81.63, 85.70, 126.82, 127.42, 127.72, 127.79, 127.85, 127.93, 128.09, 128.19, 128.27, 128.42, 128.46, 128.74, 128.82, 130.29, 130.76, 131.90, 133.25, 136.58, 137.05, 138.11, 138.22, 138.48, 155.82; HRFABMS: [M+H]+ calcd for C42H39NO7, 640.3063; found, 640.3068.

1.9. (2S,3R,4R,5R)-Benzy1 2-(benzyloxyethyl)-3,4-bis(benzyloxy)-5-(hydroxymethyl)pyrrolidine-1-carboxylate (10)

To a stirred solution of carbamate 4 (1.0 g, 1.4 mmol) in THF (6.8 mL) was added KOtBu (0.23 g, 2.04 mol) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C. The reaction mixture was quenched with H2O (5 mL) and extracted with EtOAc (30 mL). The organic layer was washed with H2O and brine, dried over MgSO4, and concentrated in vacuo. The residue was purified by flash column chromatography (5:1 hexane–EtOAc) to afford 0.76 g (87%, cis:trans = 3:9:1) of 10 as a colorless syrup. Rf 0.28 (5:1 hexane–EtOAc); [α]D 22 −1.0 (c 0.3, CHCl3); IR (neat) 1700, 1455, 1405, 1101 cm−1. 1H NMR (500 MHz, CDCl3) δ 3.74–3.77 (br, 1.59H, cis-H-2’a, 2’b), 3.74–3.77 (br, 0.41H, trans-H-2’a, 2’b), 4.17–5.12 (m, 10H, 3CH2Ph and H-2, 3, 4, 5), 4.82 (s, 2H, Cbz), 5.72 (dd, 0.79H, J 11.5, 10.0 Hz), 6.11 (dd, 0.21H, J 16.0, 6.0 Hz), 6.39 (d, 0.21H, J 16.0 Hz), 6.45 (d, 0.79H, J 11.5 Hz), 7.10–7.41 (m, 25H); 13C NMR (125 MHz, CDCl3) δ 59.01 (two carbons), 66.95, 72.21, 72.82, 73.30, 73.68, 81.63, 85.70, 126.82, 127.42, 127.72, 127.79, 127.85, 127.93, 128.09, 128.19, 128.27, 128.42, 128.46, 128.74, 128.82, 130.29, 130.76, 131.90, 133.25, 136.58, 137.05, 138.11, 138.22, 138.48, 155.82; HRFABMS: [M+H]+ calcd for C42H39NO7, 640.3063; found, 640.3068.

1.10. (2S,3R,4R,5R)-Benzy1 2-(benzyloxyethyl)-3,4-bis(benzyloxy)-5-(hydroxymethyl)pyrrolidine-1-carboxylate (11)

A solution of pyrrolidine 10 (0.50 g, 0.78 mmol) in anhyd CH2Cl2 (35 mL) and MeOH (35 mL) was cooled to −78 °C. Ozone was bubbled (15 mL/min) through the solution for 1 h at −78 °C and the excess ozone was then removed by purging with nitrogen until the solution was clear. The reaction mixture was cooled to 0 °C, and sodium borohydride (0.23 g, 7.8 mmol) was
added in portions. The reaction mixture was stirred for 1 h at 0 °C and concentrated in vacuo. The resulting mixture was quenched with H2O (10 mL) and extracted with EtOAc (45 mL). The organic layer was washed with brine, dried over MgSO4, and concentrated in vacuo. The residue was purified by flash column chromatography: to afford 49.5 mg (97%) of DGDP (1)

To a solution of pyrrolidine (1) 7.17–7.28 (m, 20H); 13C NMR (125 MHz, CDCl3) δ 112.64, 112.74, 112.97, 113.00, 113.10, 113.33, 113.41, 113.87, 113.88, 113.25, 156.85; HRCIMS: [M+H]+ calcd for C35H39NO6, 568.2699; found, 568.2710.

11. 11.1. (2R,5S)-Dihydroxymethyl-(3R,4R)-dihydroxy-pyrrylidone (1)

To a solution of 11 (177 mg, 0.312 mmol) in EtOH (5 mL) was added a solution of aq 6 N HCl (2 mL) and 10% Pd/C (0.18 g). The reaction mixture was shaken on a Parr apparatus under H2 gas (60 psi) for 24 h. The reaction mixture was filtered through a Celite pad and concentrated in vacuo. The residue was purified by column chromatography: 5.1 CH2Cl2-MeOH–30%H2O (5%) to afford 49.5 mg (97%) of DGDP (1) as a white solid.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.carres.2007.04.021.

References


