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Note

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

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Abstract—A stereoselective approach for synthesizing (2*R*,5*S*)-dihydroxymethyl-(3*R*,4*R*)-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.

Keywords: Chlorosulfonyl isocyanate; Amination; 2,5-Dideoxy-2,5-imino-D-glucitol; DGDP

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.[1] Therefore, glycosidase inhibitors have enormous therapeutic potential for the treatment of diseases as diverse as viral infections, cancer, and diabetes.[2] 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 activities[5] 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

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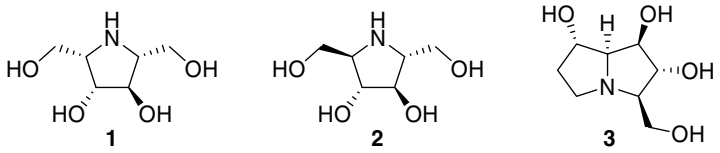
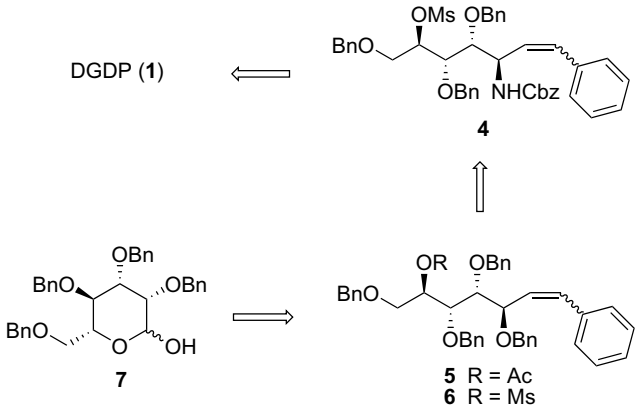


Figure 1. Structure of DGDP analogs.

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**),[13] 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^tBu, DMSO, 80 °C),[14] and oxidation of the resulting olefin with OsO_4[15] 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,[16] furnished the desired olefin **8** in low yield. Fortunately, olefination of **7** to **8** was successfully accomplished, in 91% yield, by using the dimsyl anion[17] (sodium methylsulfinylmethanide, 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%).



Scheme 1. Retrosynthetic analysis.

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,[10,12,18] 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.

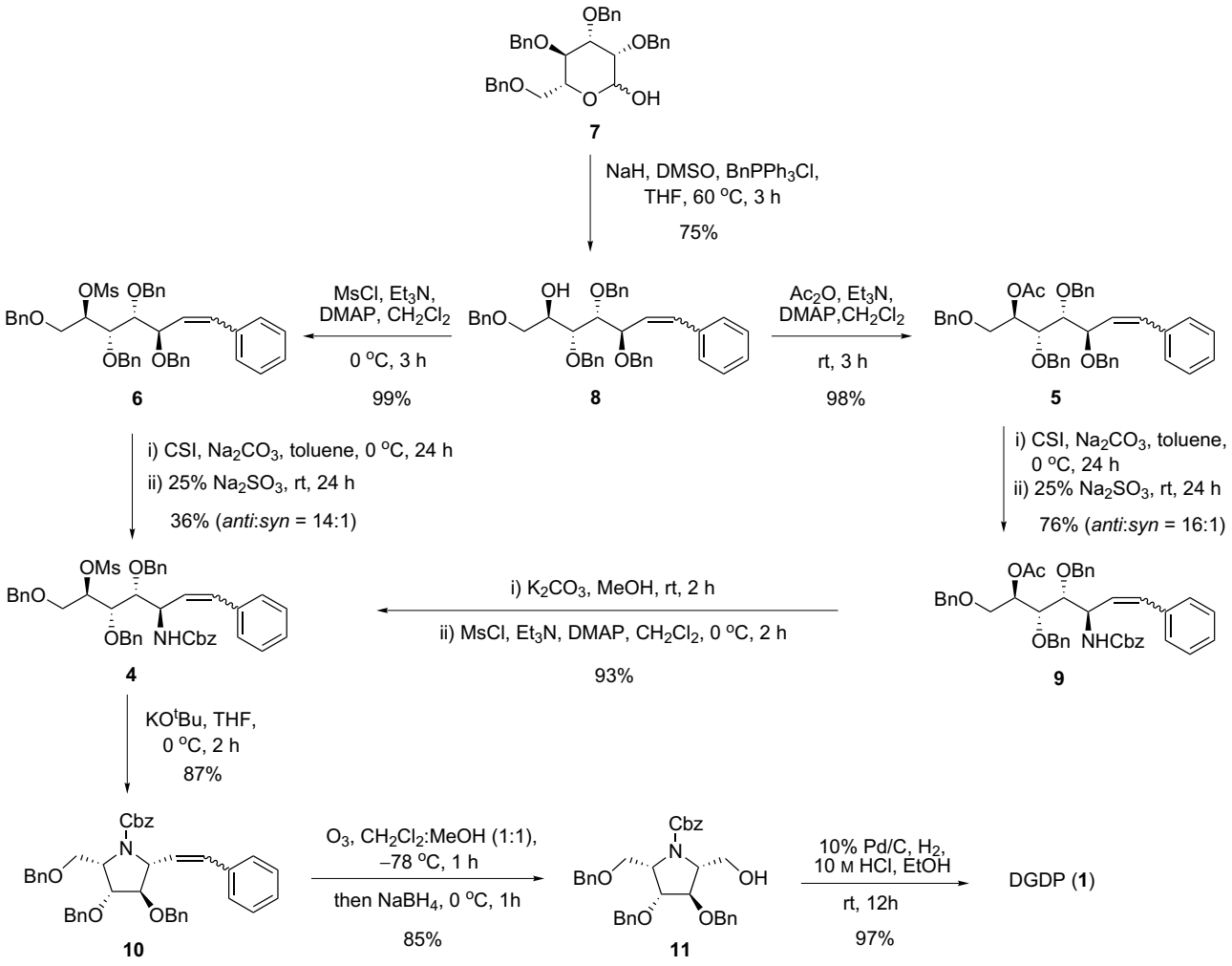
Compound **4** was treated with potassium *tert*-butoxide to provide **10** in 87% yield. Ozonolysis of **10**, followed by reduction with sodium borohydride, afforded alcohol **11** in 85% yield. Finally, catalytic hydrogenation of **11** over Pd/C in EtOH furnished DGDP (**1**) as a white solid. Spectroscopic data (^1H and ^{13}C NMR) and the optical rotation {$[\alpha]_D^{22}$ +24.1 (*c* 1.0, H_2O)} of **1** were consistent with the literature values {[lit.[7a] $[\alpha]_D^{28}$ +22.7 (*c* 0.14, H_2O)], [lit.[7c] $[\alpha]_D^{20}$ +25.1 (*c* 1.5, H_2O)]}.

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_2O_5 or Na/benzophenone prior to reaction. All reactions



Scheme 2. Total synthesis of DGDP (**1**).

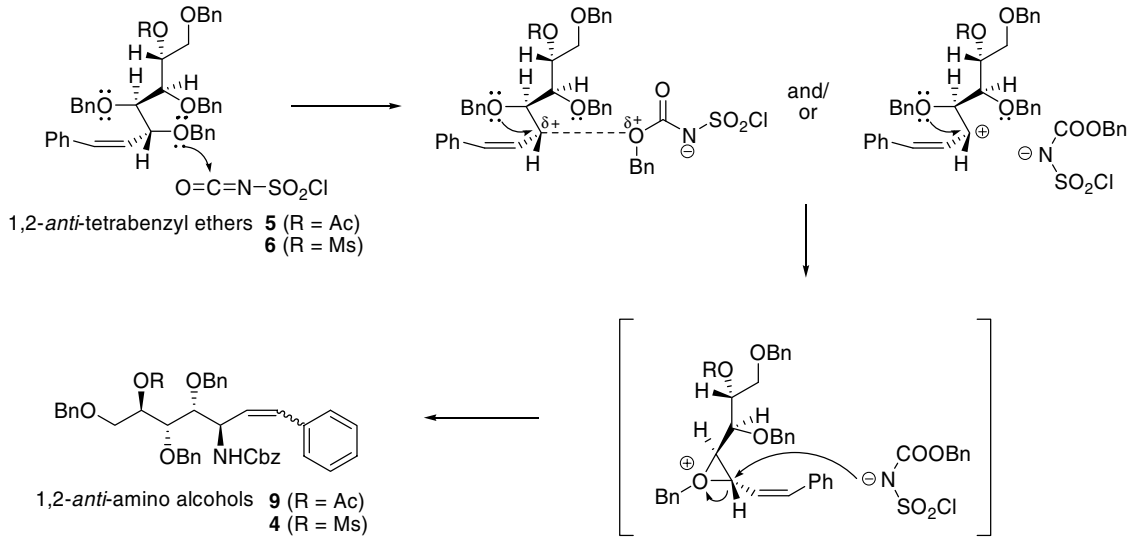


Figure 2. Mechanistic pathway of CSI-mediated stereoselective amination.

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. (3*S*,4*S*,5*R*,6*R*)-6-(Benzyloxymethyl)-3,4,5-tribenzyloxytetrahydro-2*H*-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 D-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 $NaHCO_3$, filtered over a Celite bed, and concentrated in vacuo. Repeated co-evaporation of the residue with toluene gave 25.0 g of crude allyl α-D-mannoside as brownish syrup. Crude allyl α-D-mannoside (25.0 g) was dissolved in 33% aq NaOH solution (300 mL). Tetrabutylammonium bromide (32.0 g, 0.099 mol) was added, and benzyl chloride (77.0 mL, 0.669 mol) was 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 $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (8:1 hexane–EtOAc) to give 39.0 g (81%) of (3*S*,4*S*,5*R*,6*R*)-2-(allyloxy)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2*H*-pyran as a colorless syrup. R_f 0.27 (8:1 hexane–EtOAc); $[\alpha]_D^{16}$ +33.4 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 3.75–3.85 (m, 4H), 3.95–4.05 (m, 3H), 4.19 (dd, 1H, *J* 13.0, 5.0 Hz), 4.54 (d, 1H, *J* 11.0 Hz), 4.57 (d, 1H, *J* 12.0 Hz), 4.66 (s, 2H), 4.69 (d, 1H, *J* 12.0 Hz), 4.74 (d, 1H, *J* 12.5 Hz), 4.78 (d, 1H, *J* 12.5 Hz), 4.91 (d, 1H, *J* 11.0 Hz), 4.95 (d, 1H, *J* 2.0 Hz), 5.17 (dd, 1H, *J* 10.5, 1.5 Hz), 5.26 (dd, 1H, *J* 17.0, 1.5 Hz), 5.88 (ddd, 1H, *J* 17.0, 10.5, 5.0 Hz), 7.19–7.41 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 68.05, 69.59, 72.19, 72.43, 72.86, 73.60, 75.03, 75.27, 75.37, 80.53, 97.38, 117.42, 127.67, 127.79, 127.91, 128.05, 128.23, 128.26, 128.32, 128.36, 128.42, 128.47, 128.54, 128.63, 134.07, 138.65, 138.72, 138.77, 138.83; HRFABMS: $[M+H^+]$ calcd for $C_{37}H_{41}O_6$, 579.2747; found, 579.2745. To a solution of the above syrup (39.0 g, 0.067 mol) in distilled dimethyl sulfoxide (114 mL) was added potassium *tert*-butoxide (45.2 g, 0.403 mol) at 0 °C. The reaction mixture was stirred for 3 h at 80 °C. The mixture was cooled to room temperature and quenched with H_2O (25 mL). The aq layer was extracted with Et_2O (200 mL), and the organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo to give 36.0 g of crude brownish syrup. To a solution of the crude syrup (36.0 g, 0.062 mol) in 80% aq acetone (33 mL) was added *N*-methylmorpholine N-oxide (32.1 mL, 0.155 mol, 50% in H_2O) and OsO_4 (16.0 mL, 0.319 mmol, 0.02 M solution in *tert*-BuOH). The mixture was stirred for 1 h at room temperature and quenched with satd $NaHSO_3$ solution (5 mL). The aq layer was extracted with EtOAc (50 mL), and the organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo and extracted with EtOAc. The extract was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (2:1 hexane–EtOAc) to afford 33.0 g (91%, $\alpha:\beta = 4.6:1$) of lactol **7** as a colorless syrup. R_f 0.20 (2:1 hexane–EtOAc); $[\alpha]_D^{16}$ +6.0 (*c* 1.0, $CHCl_3$); IR (neat) 3400, 1600, 1453, 1097 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.91 (d, 1H, *J* 3.5 Hz), 3.47–4.07 (m, 6H), 4.50–5.16 (m, 8H), 5.28 (d, 1H, *J* 1.5 Hz), 7.18–7.38 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) 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, 75.28, 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, 128.55, 128.57, 138.37, 138.41, 138.48, 138.57, 138.63, 138.65, 138.67, 138.76; HRFABMS: $[M+H^+]$ calcd for $C_{34}H_{37}O_6$, 539.2434; found, 539.2426.

1.3. (2*R*,3*R*,4*R*,5*R*)-7-Phenyl-1,3,4,5-tetrabenzyloxyhept-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 N_2. 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 NH_4Cl (30 mL). The aq layer was extracted with EtOAc (100 mL), and the organic layer was washed with H_2O and brine, dried over $MgSO_4$, 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. R_f 0.30 (4:1 hexane–EtOAc);

$[\alpha]_D^{24}$ −24.4 (*c* 1.0, $CHCl_3$); IR (neat) 3429, 1599, 1453, 1092 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.56 (d, 0.77H, *J* 6.5 Hz), 2.68 (d, 0.23H, *J* 6.5 Hz), 3.60–3.71 (m, 2H), 3.91–3.99 (m, 3H), 4.02–4.10 (br, 1H), 4.28 (d, 0.77H, *J* 11.0 Hz), 4.30 (d, 0.23H, *J* 11.0 Hz), 4.31 (d, 0.23H, *J* 11.0 Hz), 4.38 (d, 0.77H, *J* 11.0 Hz), 4.46 (d, 0.77H, *J* 11.5 Hz), 4.47 (d, 0.23H, *J* 11.5 Hz), 4.49 (d, 0.23H, *J* 11.5 Hz), 4.52 (d, 0.77H, *J* 11.5 Hz), 4.55 (d, 0.77H, *J* 11.0 Hz), 4.58 (d, 0.23H, *J* 11.0 Hz), 4.65 (d, 0.77H, *J* 11.0 Hz), 4.66 (d, 0.77H, *J* 11.0 Hz), 4.67 (d, 0.23H, *J* 10.0 Hz), 4.70 (d, 0.23H, *J* 11.0 Hz), 4.83 (d, 0.77H, *J* 11.0 Hz), 4.87 (d, 0.23H, *J* 10.0 Hz), 5.77 (dd, 0.77H, *J* 11.5, 10.0 Hz), 6.26 (dd, 0.23H, *J* 16.0, 7.5 Hz), 6.78 (d, 0.23H, *J* 16.0 Hz), 6.95 (d, 0.77H, *J* 11.5 Hz), 7.03–7.52 (m, 25H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 69.75, 70.13, 71.55, 73.01, 73.54, 74.27, 75.20, 78.50, 80.46, 126.88, 127.46, 127.66, 127.71, 127.76, 127.80, 128.00, 128.06, 128.09, 128.15, 128.25, 128.38, 128.47, 128.54, 128.62, 128.87, 131.07, 135.56, 136.77, 138.28, 138.49, 138.54; HRCIMS: $[M+H^+]$ calcd for $C_{41}H_{43}O_5$, 615.3114; found, 615.3110.

1.4. (2*R*,3*S*,4*R*,5*R*)-7-Phenyl-1,3,4,5-tetrabenzyloxy-hept-6-en-2-yl methanesulfonate (6)

To a stirred solution of the secondary alcohol **8** (3.00 g, 4.88 mmol) in anhyd CH_2Cl_2 (25 mL) was added Et_3N (1.36 mL, 9.76 mmol), 4-(dimethylamino)pyridine (DMAP, 60 mg, 0.49 mmol) and methanesulfonyl chloride (0.57 mL, 7.3 mmol) at 0 °C under N_2. The reaction mixture was stirred for 3 h at 0 °C and quenched with a solution of satd aq NH_4Cl (3 mL). The aq layer was extracted with CH_2Cl_2 (30 mL), and the organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (5:1 hexane–EtOAc) to afford 3.35 g (99%, cis:trans = 3.9:1) of mesylate **6** as a colorless syrup. R_f 0.30 (5:1 hexane–EtOAc); $[\alpha]_D^{24}$ −59.6 (*c* 0.5, $CHCl_3$); IR (neat) 1494, 1453, 1351, 1213, 1174, 1089, 1049, 1026 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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, 128.40, 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 $C_{42}H_{45}O_7S$, 691.2730; found, 691.2735.

1.5. (2*R*,3*S*,4*R*,5*R*)-5-Benzyloxycarbonylamino-7-phenyl-1,3,4-tribenzyloxy-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 Na_2CO_3 (4.13 g, 0.039 mol) and chlorosulfonyl isocyanate (2.26 mL, 0.026 mol) at 0 °C under N_2. The reaction mixture was stirred for 24 h at 0 °C and quenched with H_2O (10 mL). The aq layer was extracted with EtOAc (30 mL × 2). The organic layer was added to a solution of 25% aq Na_2SO_3 (25 mL), and the reaction mixture was stirred for 24 h at room temperature. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, 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, *anti*:*syn* = 14:1) of *anti*-1,2-amino alcohol **4** as pale yellow syrup. R_f 0.30 (3:1 hexane–EtOAc); $[\alpha]_D^{24}$ +47.2 (*c* 0.2, $CHCl_3$); IR (neat) 1715, 1496, 1454, 1350, 1217, 1174, 1092, 912 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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, 128.69, 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 $C_{43}H_{46}NO_4S$, 736.2944; found, 736.2932.

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

To a stirred solution of **8** (4.0 g, 6.5 mmol) in anhyd CH_2Cl_2 (28 mL) was added Et_3N (1.8 mL, 0.013 mol), 4-(dimethylamino)pyridine (DMAP, 80 mg, 0.651 mmol) and Ac_2O (0.92 mL, 9.76 mmol) at 0 °C under N_2. The reaction mixture was stirred for 3 h at room temperature and quenched with a solution of satd aq NH_4Cl (5 mL). The aq layer was extracted with CH_2Cl_2 (40 mL), and the organic layer was washed with H_2O and brine, dried over $MgSO_4$, 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. R_f 0.32 (5:1 hexane–EtOAc); $[\alpha]_D^{22}$ −80.5 (*c* 1.0, $CHCl_3$); IR (neat) 1737, 1603, 1495, 1453, 1238 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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, 129.54, 130.84, 135.85, 136.61, 138.45, 170.43; HRCIMS: $[M+H^+]$ calcd for $C_{43}H_{45}O_6$, 655.3060; found, 655.3066.

1.7. (2*R*,3*S*,4*R*,5*R*)-5-(Benzyloxycarbonylamino)-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 Na_2CO_3 (4.9 g, 0.047 mol) and chlorosulfonyl isocyanate (2.7 mL, 0.031 mol) at 0 °C under N_2. The reaction mixture was stirred for 24 h at 0 °C and quenched with H_2O (12 mL). The aq layer was extracted with EtOAc (35 mL × 2). The organic layer was added to a solution of 25% aq Na_2SO_3 (30 mL), and the reaction mixture was stirred for 24 h at room temperature. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (4:1 hexane–EtOAc) to afford 2.76 g (76%, cis:trans = 3.7:1, *anti*:*syn* = 16:1) of *anti*-1,2-amino alcohol **9** as pale yellow syrup. R_f 0.28 (4:1 hexane–EtOAc); $[\alpha]_D^{23}$ +43.1 (*c* 1.0, $CHCl_3$); IR (neat) 1723, 1497, 1453, 1235, 1061 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.94 (s, 2.37H), 2.03 (s, 0.63H), 3.59 (dd, 0.79H, *J* 5.0, 4.0 Hz), 3.69–3.83 (m, 1.94H), 3.91–3.98 (m, 1H), 4.33–4.75 (m, 6H), 4.86–4.91 (m, 0.21H), 5.05–5.19 (m, 3.58H), 5.30–5.33 (br, 0.21H), 5.55 (dd, 0.79H, *J* 11.5, 9.0 Hz), 5.82 (d, 0.79H, *J* 7.0 Hz), 5.88 (d, 0.21H, *J* 8.0 Hz), 6.10 (dd, 0.21H, *J* 15.5, 6.0 Hz), 6.60 (d, 0.21H, *J* 15.5 Hz), 6.65 (d, 0.79H, *J* 11.5 Hz), 7.12–7.44 (m, 25H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.32, 49.47, 66.66, 68.40, 72.52, 73.25, 73.40, 73.47, 74.30, 76.68, 78.08, 78.29, 126.88, 127.58, 127.89, 127.98, 128.02, 128.08, 128.15, 128.29, 128.43, 128.51, 128.59, 128.60, 128.66, 128.74, 129.02, 129.08, 133.12, 136.58, 136.97, 137.52, 137.58, 138.23, 156.21, 170.30; HRFABMS: $[M+H^+]$ calcd for $C_{44}H_{46}NO_7$, 700.3274; found, 700.3264.

1.8. Deacetylation of 9 and mesylation

To a stirred solution of acetate **9** (2.6 g, 3.7 mmol) in MeOH (19 mL) was added K_2CO_3 (0.77 g, 5.6 mmol) at 0 °C. The mixture was stirred for 2 h at room temperature and quenched with H_2O (3 mL). The aq layer was extracted with EtOAc (30 mL × 2), and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residual oil was subjected to the next step without purification. The secondary alcohol was stirred for 2 h with Et_3N (1.0 mL, 7.4 mmol), 4-(dimethylamino)pyridine (DMAP, 45 mg, 0.37 mmol) and methanesulfonyl chloride (0.43 mL, 5.6 mmol) in the presence of CH_2Cl_2 (15 mL) at 0 °C under N_2. The reaction mixture was quenched with H_2O (3 mL) and extracted with CH_2Cl_2 (20 mL × 2). The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (3:1 hexane–EtOAc) to afford 2.55 g (93%) of mesylate **4** as a colorless syrup.

1.9. (2*S*,3*R*,4*R*,5*R*)-Benzyl 2-(benzyloxymethyl)-3,4-bis(benzyloxy)-5-styrylpyrrolidine-1-carboxylate (10)

To a stirred solution of carbamate **4** (1.0 g, 1.4 mmol) in THF (6.8 mL) was added KO^{t}Bu (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 H_2O (5 mL) and extracted with EtOAc (30 mL). The organic layer was washed with H_2O and brine, dried over $MgSO_4$, 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. R_f 0.28 (5:1 hexane–EtOAc); $[\alpha]_D^{22}$ −1.0 (*c* 0.3, $CHCl_3$); IR (neat) 1700, 1455, 1405, 1101 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) 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, $3CH_2Ph$ 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); ^{13}C NMR (125 MHz, CD_3OD) 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 $C_{42}H_{42}NO_5$, 640.3063; found, 640.3068.

1.10. (2*S*,3*R*,4*R*,5*R*)-Benzyl 2-(benzyloxymethyl)-3,4-bis(benzyloxy)-5-(hydroxymethyl)pyrrolidine-1-carboxylate (11)

A solution of pyrrollidine **10** (0.50 g, 0.78 mmol) in anhyd CH_2Cl_2 (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 H_2O (10 mL) and extracted with EtOAc (45 mL). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (3:1 hexane–EtOAc) to give 377 mg (85%) of **11** as a colorless syrup. R_f 0.24 (3:1 hexane–EtOAc); $[\alpha]_D^{22}$ −7.7 (*c* 0.1, $CHCl_3$); IR (neat) 3371, 1703, 1601, 1452, 1411, 1355, 1101 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_3) δ 3.58 (dd, 1H, *J* 11.5, 5.5 Hz, H-5′a), 3.61 (dd, 1H, *J* 11.5, 7.5 Hz, H-5′b), 3.62-3.80 (br, 2H, H-2′a, 2′b), 4.05–4.60 (m, 10H, $3CH_2Ph$ and H-2, 3, 4, 5), 5.04 (s, 2H, Cbz), 7.17–7.28 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 58.40, 63.98, 64.31, 64.69, 67.73, 67.86, 72.95, 73.29, 73.70, 82.23, 127.23, 127.87, 127.96, 128.00, 128.02, 128.06, 128.14, 128.26, 128.32, 128.37, 128.41, 128.45, 128.54, 128.62, 128.66, 128.73, 128.81, 128.87, 128.91, 129.05, 129.97, 130.06, 131.10, 136.33, 137.41, 137.88, 138.25, 156.85; HRCIMS: [M+H$^+$] calcd for $C_{35}H_{38}NO_6$, 568.2699; found, 568.2710.

1.11. (2*R*,5*S*)-Dihydroxymethyl-(3*R*,4*R*)-dihydroxypyrrolidine (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 H_2 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 (5:5:1 CH_2Cl_2–MeOH–30%NH_4OH) to afford 49.5 mg (97%) of DGDP (**1**) as a white solid. R_f 0.22 (5:5:1 CH_2Cl_2–MeOH–30%NH_4OH); $[\alpha]_D^{22}$ +24.1 (*c* 1.0, H_2O); IR (neat) 3426, 1641 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 3.35–3.40 (m, 1H), 3.65–3.90 (m, 5H), 3.96 (br dd, 1H, *J* 4.0, 2.5 Hz), 4.16 (br dd, 1H, *J* 4.0, 2.0 Hz); ^{13}C NMR (125 MHz, D_2O) δ 57.21, 59.56, 63.30, 66.98, 74.86, 76.35; HRCIMS: [M+H$^+$] calcd for $C_6H_{14}NO_4$, 164.0923; found, 164.0926.

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Supplementary data

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