A Strategy for the Solution-Phase Parallel Synthesis of *N*-(Pyrrolidinylmethyl)hydroxamic Acids

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Both five- and six-membered iminocyclitols have proven to be useful transition-state analogue inhibitors of glycosidases. They also mimic the transition-state sugar moiety of the nucleoside phosphate sugar in glycosyltransferase-catalyzed reactions. Described here is the development of a general strategy toward the parallel synthesis of a five-membered iminocyclitol linked to a hydroxamic acid group designed to mimic the transition state of GDP-fucose complexed with Mn(II) in fucosyltransferase reactions. The iminocyclitol **8** containing a protected hydroxylamine unit was prepared from D-mannitol. The hydroxamic acid moiety was introduced via the reaction of **8** with various acid chlorides. The strategy is generally applicable to the construction of libraries for identification of glycosyltransferase inhibitors.

Five- and six-membered iminocyclitols have been shown to be potent inhibitors of glycosidases as they mimic the transition state of the enzymatic reaction.[1] These heterocycles also mimic the transition state of the sugar moiety of the nucleoside phosphate derivative in glycosyltransferase-catalyzed reactions and thus have been used as core structures for development of inhibitors of glycosyltransferases.[2] Most glycosyltransferases require Mn(II) or Mg(II), which presumably form a complex with the pyrophosphate group of the nucleoside phosphate sugar substrate.[3] Incorporation of a metal chelating functionality to the iminocyclitol at the corresponding pyrophosphate position is thus considered to be a useful strategy for development of glycosyltransferase inhibitors. Here we report a new method suitable for the parallel synthesis of *N*-(pyrrolidinylmethyl)hydroxamic acids as a representative example designed to target fucosyltransferases (Figure 1), which are often associated with inflammatory diseases and cancer metastasis. We chose hydroxamic acid as it has been used successfully in the development of metalloprotease inhibitors.[4]

To begin our parallel synthesis, the fuco-type iminocyclitol, *N*-(pyrrolidinylmethyl)hydroxylamine (**8**), was first prepared for the introduction of a substituted hydroxamic acid moiety. Thus, 1-trityl-3,4-isopropylidene-D-mannitol **1** was prepared from D-mannitol as reported previously.[5] Selective tosylation of the primary hydroxy group followed by reduction with lithium aluminum hydride gave diol **2** in 84% yield (Scheme 1). Selective monomesylation on the less hindered 5-hydroxy group was conducted to give monomesylate **3** in 46% yield, which was treated with sodium azide in HMPA to afford the azide derivative **4**. Further improvement could be achieved by directly converting diol **2** into the azido alcohol **4** via a selective Mitsunobu reaction using hydrazoic acid as the azide source (Scheme 2). Compound **4** was oxidized with NMO in the presence of catalytic amounts of TPAP[6] and deprotected under acidic conditions to obtain ketotriol **5** in high yield. After selective protection on the primary hydroxy group with TBS,[7] reduction of the azide group followed by intramolecular reductive amination was performed with 5% rhodium on alumina under an atmospheric pressure (15 psi). For this reaction, rhodium on alumina is a superior catalyst[8] for the preparation of **6**, which was obtained in > 4% facial selectivity. Indeed, using 10% Pd−C gave only 80% facial selectivity even under a high hydrogen pressure (50 psi). The nitrogen group on the pyrrolidine ring was protected by the Cbz group and the two hydroxy groups were protected as benzyl ether. The TBS group on the primary hydroxy group was then removed by TBAF to give alcohol **7** in 81% yield in three steps. Subsequent oxidation of alcohol **7** with TPAP−NMO gave an aldehyde, which was reductively coupled with *O*-benzylhydroxylamine to afford

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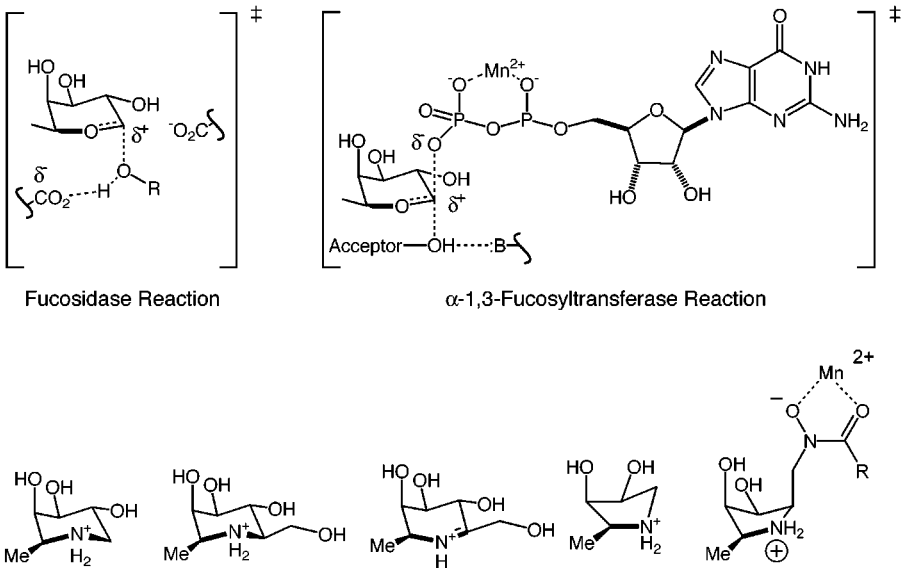
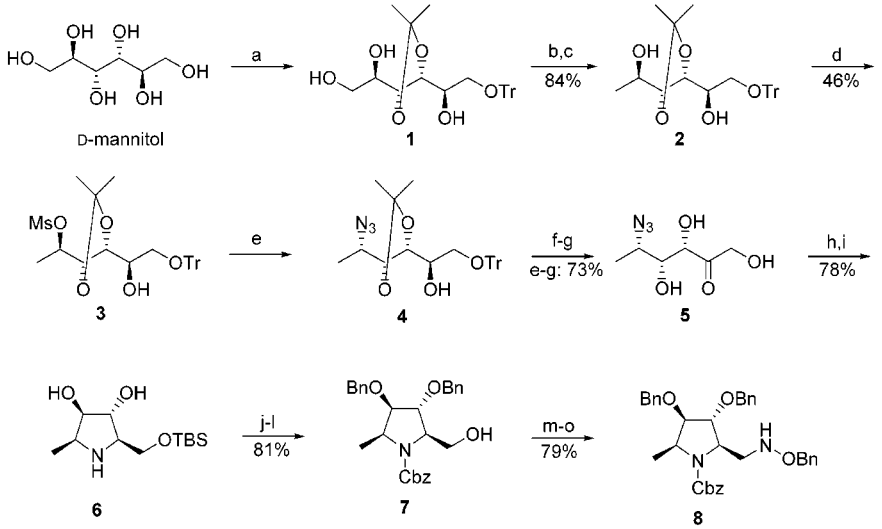


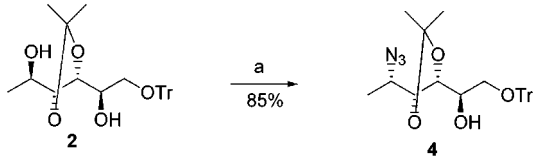
Figure 1.

Scheme 1[a]



[a] Conditions: (a) ref 5; (b) TsCl, py, 12 h; (c) LAH, THF, reflux, 10 h; (d) MsCl, Et_3N, CH_2Cl_2, 0 °C, 10 h; (e) NaN_3, HMPA, 80 °C, 8 h; (f) TPAP (cat.), NMO, 4A-MS, CH_2Cl_2, 1 h; (g) 80% TFA, 20 min; (h) TBSCl, TEA, DMAP, CH_2Cl_2, 12 h; (i) H_2, Rh−Al_2O_3, EtOH, 8 h; (j) CbzCl, K_2CO_3, THF−H_2O (4:1), 0 °C, 30 min; (k) BnBr, NaH, DMF, 10 h; (l) TBAF, THF, 0 °C, 1 h; (m) TPAP (cat.), NMO, 4Å-MS, CH_2Cl_2, 1 h; (n) H_2NOBn·HCl, py, 2 h; (o) $NaBH_3CN$, AcOH, 2 h.

Scheme 2[a]



[a] Conditions: (a) DEAD, PPh_3, HN_3 in toluene (1.3 M), THF, 3 h.

protected *N*-(pyrrolidinylmethyl)hydroxylamine **8** in 79% yield. The stereochemistry of **6** was determined by NMR on the basis of NOE between H-2 and H-5.

A substituted hydroxamic acid was then introduced to **8** in a format suitable for library construction. The solution-phase parallel synthesis of *N*-(pyrrolidinylmethyl)hydroxamic acids was performed with polymer-supported base (**11**), polyamine-type scavenger resins (**12**), and isocyanate-type scavenger resin (**13**).[9] Thus, *N*-(pyrrolidinylmethyl)hydroxylamine **8** was treated with 1.5 equiv of acid chloride in dichloromethane in the presence of polymer-supported base **11**. After the reaction was complete (1 h) as monitored by TLC, scavenger resins were added and the reaction mixtures were stirred for additional 4 h. During this period, the excess acid chloride was trapped on the polyamine-type resin (**12**) by amide formation, and trace amounts of the unreacted starting material **8** were trapped by the isocyanate-type resin (**13**) through the formation of urea. Filtration to remove the resins followed by evaporation yielded sufficiently pure products without aqueous workup or further purification. Deprotection of the Cbz and benzyl groups by hydrogenation with 10% Pd−C in acetic acid gave the desired *N*-(pyrolidinylmethyl)hydroxamic acids

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Scheme 3

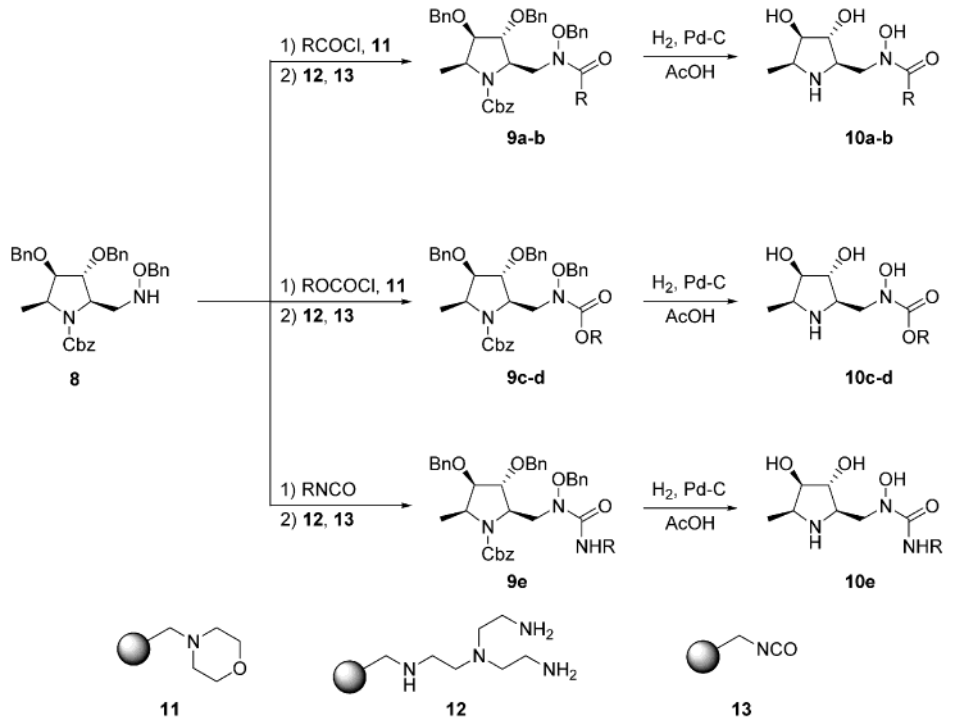
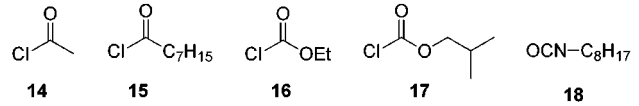


Table 1. Solution-Phase Parallel Synthesis of *N*-(Pyrrolidylmethyl)hydroxamic Acids, *N*-(Pyrrolidylmethyl)-*N*-hydroxycarbamates, and *N*-(Pyrrolidylmethyl)-*N*-hydroxyureas



entry	electrophile	product	molecular formula	obsd MS[a]	yield[b] (%)	purity[c] (%)
1	14	10a	$C_8H_{16}N_2O_4$	205.1	82	84
2	15	10b	$C_{14}H_{28}N_2O_4$	289.2	83	93
3	16	10c	$C_9H_{18}N_2O_5$	235.1	90	77
4	17	10d	$C_{11}H_{22}N_2O_5$	263.1	88	93
5	18	10e	$C_{15}H_{31}N_3O_4$	318.2	85	83

[a] Confirmed by mass spectra (ESI, MH^+). [b] Yields are based on weight of crude sample. [c] Purity was determined by HPLC analysis of crude product.

10a,**b** in good yield and purity. This method was also applied successfully using chloroformates and isocyanates as electrophiles to obtain *N*-hydroxycarbamates **10c**,**d** and *N*-hydroxyurea **10e** in good yields and purity (Scheme 3, Table 1). In the isocyanate case, it was not necessary to use the polymer-supported resin **11**.

In summary, we have described a new parallel method for the synthesis of *N*-(pyrrolidinylmethyl)hydroxamic acids. We have also described a novel method for the solution-phase parallel synthesis of hydroxamic acids using polymer-supported reagents and scavenger resins. This method is useful for the rapid construction of iminocyclitol libraries containing hydroxamic acid, *N*-hydroxycarbamate, or *N*-hydroxyurea side chains, which may have potential applications in development of glycosyltransferase inhibitors.

Experimental Section

General Methods. The reagents and solvents used were reagent grade and used as supplied except for THF, which was distilled before use. Solvent evaporation was performed under reduced pressure below 30 °C using a rotary evaporator, followed by evacuation (<0.1 mmHg) to constant sample weight. High-resolution mass spectra (HRMS) were recorded. ^{1}H NMR spectra were obtained at 400, 500, or 600 MHz and ^{13}C NMR at 125 or 150 MHz. Silica gel 60 (230−240 mesh) was used in chromatography.

6-Deoxy-3,4-*O*-isopropylidene-1-*O*-trityl-D-mannitol (2). To a solution of 3,4-*O*-isopropylidene-1-*O*-trityl-D-mannitol (**1**) (35.1 g, 75.6 mmol) in dry pyridine (200 mL) was added *p*-tolenesulfonyl chloride (17.3 g, 90.7 mmol) at room temperature under argon. The reaction mixture was stirred for 12 h at room temperature and quenched by addition of saturated aqueous $NaHCO_3$ solution. The aqueous layer was then extracted with EtOAc three times. The combined organic extracts were washed with saturated aqueous $CuSO_4$ solution (to remove pyridine), saturated aqueous $NaHCO_3$ solution, water, and brine successively and dried over Na_2SO_4. Removal of solvent gave 3,4-*O*-isopropylidene-6-*O*-*p*-tolenesunfonyl-1-*O*-trityl-D-mannitol as a crude compound. To a solution of crude 3,4-*O*-isopropylidene-6-*O*-*p*-toluenesulfonyl-1-*O*-trityl-D-mannitol in dry THF (500 mL) was added LAH (11.5 g, 302.4 mmol) at 0 °C under argon. The reaction mixture was refluxed for 10 h and quenched by addition of 10% aqueous $KHSO_4$ solution. Then the aqueous layer was extracted with ethyl acetate three times. The combined organic extracts were washed with 10% aqueous $KHSO_4$ solution, saturated aqueous NH_4Cl solution, water, and brine successively and dried over Na_2SO_4. Removal of the solvent followed by silica gel column chromatography (EtOAC/toluene = 1:5) gave **2** (28.5 g, 84% in two steps): ^{1}H NMR (500 MHz, acetone-d_6) δ 1.21 (d, 3 H, J = 5.9 Hz), 1.25 (s, 3 H), 1.28 (s, 3 H), 3.22 (dd, 1 H, J = 5.9, 9.5 Hz), 3.35 (dd, 1 H, J = 2.6, 9.5 Hz), 3.68 (t, 1 H, J = 7.2 Hz), 3.73 (m, 1 H), 3.84 (m, 1 H), 3.89 (dd, 1 H, J = 7.2, 8.3 Hz), 4.53 (d, 1 H, J = 3.3 Hz), 4.97 (d, 1 H, J = 3.7 Hz), 7.22−7.26 (m, 3 H), 7.29−7.33 (m, 6 H), 7.51−7.54 (m, 6 H); ^{13}C NMR (125 MHz, acetone-d_6) δ 20.73, 27.24, 27.30, 66.90, 69.53, 73.32, 81.13, 85.42, 87.25, 109.27, 127.74 (3 C), 128.49 (6 C), 129.65 (6 C), 145.27 (3 C); $[\alpha]^{20}_D$ 8.1 (*c* 1.27, EtOAc); HRMS (MALDI-FTMS) calcd for $C_{28}H_{32}O_5 + Na^+$ 471.2147, found 471.2149.

6-Deoxy-3,4-*O*-isopropylidene-5-*O*-methanesulfonyl-1-*O*-trityl-D-mannitol (3). To a mixture of **2** (14.4 g, 32.0 mmol) and triethylamine (8.9 mL, 64.0 mmol) in dry CH_2Cl_2 (320 mL)

was added methanesulfonyl chloride (3.0 mL, 38.4 mmol) at 0 °C under argon. The reaction mixture was stirred for 10 h at 0 °C and quenched by addition of saturated aqueous $NaHCO_3$ solution. The aqueous layer was then extracted with EtOAc three times. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution, water, and brine successively and dried over Na_2SO_4. Removal of the solvent followed by silica gel column chromatography (EtOAC/toluene = 1:5) gave **3** (7.75 g, 46%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.29 (s, 3 H), 1.36 (s, 3 H), 1.44 (d, 3 H, J = 6.6 Hz), 2.60 (d, 1 H, J = 4.4 Hz), 2.96 (s, 3 H), 3.27 (dd, 1 H, J = 6.6, 9.7 Hz), 3.43 (dd, 1 H, J = 3.5, 9.7 Hz), 3.73 (m, 1 H), 3.79 (t, 1 H, J = 7.0 Hz), 4.19 (dd, 1 H, J = 3.5, 7.0 Hz), 4.95 (dq, 1 H, J = 3.5, 6.6 Hz), 7.22−7.47 (m, 15 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.96, 26.98, 27.11, 38.45, 65.08, 72.48, 77.35, 78.33, 81.53, 87.02, 110.33, 127.12 (3 C), 127.86 (6 C), 128.52 (6 C), 143.59 (3 C); $[\alpha]^{20}_D$ 9.4 (*c* 1.57, EtOAc); HRMS (MALDI-FTMS) calcd for $C_{29}H_{34}O_7S + Na^+$ 549.1917, found 549.1929.

6-Deoxy-3,4-*O*-isopropylidene-5-azido-1-*O*-trityl-D-mannitol (4). (A) To a solution of **3** (7.75 g, 14.7 mmol) in dry HMPA (150 mL) was added sodium azide (9.57 g, 147 mmol) at room temperature under argon. The reaction mixture was stirred for 8 h at 80 °C and quenched by addition of saturated aqueous NH_4Cl solution. The aqueous layer was then extracted with EtOAc three times. The combined organic extracts were washed with saturated aqueous NH_4Cl solution, saturated aqueous $NaHCO_3$ solution, water, and brine successively and dried over Na_2SO_4. Removal of solvent gave 5-azide-5,6-dideoxy-3,4-*O*-isopropylidene-1-*O*-trityl-L-gulitol as a crude compound. The yield was determined when compound **5** was purified.

(B) To an ice-cold solution of **2** (2.0 g, 4.46 mmol) and triphenylphoshine (1.64 g, 6.24 mmol) in 20 mL of THF were added diethylazodicarboxylate (983 μL, 6.24 mmol) and a 1.3 M solution of hydrazoic acid in toluene (11 mL). After 3 h at room temperature, water and Et_2O were added. The aqueous layer was extracted with Et_2O, and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent the crude material was purified on silica gel (EtOAc/hexanes 1/15, then 1/10) to give **4** (1.79 g, 85%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (s, 3 H), 1.37 (d, 3 H, J = 7.0 Hz), 1.45 (s, 3 H), 3.32 (m, 2 H), 3.38 (dq, 1 H, J = 2.4, 6.8 Hz), 3.74 (m, 1 H), 3.93 (dd, 1 H, J = 7.3, 2.4 Hz), 4.04 (dd, 1 H, J = 7.3, 7.3 Hz), 7.22−7.44 (m, 15 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 16.22, 26.79, 27.24, 56.49, 64.71, 72.05, 77.15, 82.56, 87.01, 109.81, 127.18 (3 C), 127.92 (6 C), 128.57 (6 C), 143.55 (3 C); HRMS (MALDI-FTMS) calcd for $C_{28}H_{31}N_3O_4 + Na^+$ 496.2212, found 496.2202.

5-Azide-5,6-dideoxy-L-*xylo*-hexo-2-ulose (5). To a suspension of cude 5-azide-5,6-dideoxy-3,4-*O*-isopropylidene-1-*O*-trityl-L-gulitol and predried 4 Å molecular sieves (2.5 g) in dry CH_2Cl_2 (150 mL) was added *N*-methylmorpholine *N*-oxide (2.58 g, 22.1 mmol) at room temperature under argon. The reaction mixture was stirred for 10 min at room temperature, before TPAP (258 mg, 0.74 mmol) was added. The reaction mixture was stirred for 1 h at room temperature and filtered through a pad of silica gel, eluting with CH_2Cl_2. Evaporation of the filtrate gave 5-azide-5,6-deoxy-3,4-*O*-isopropylidene-1-*O*-trityl-L-*xylo*-hexo-2-ulose as a crude compound. The solution of crude 5-azide-5,6-deoxy-3,4-*O*-isopropylidene-1-*O*-trityl-L-*xylo*-hexo-2-ulose in 80% TFA (50 mL) was stirred for 1 h at 0 °C. Removal of the solvent followed by silica gel column chromatography (MeOH/CH_2Cl_2 = 5:95) gave **5** (2.03 g, 73%): ^{1}H NMR (600 MHz, MeOH-d_4) δ 1.23 (d, 3 H, J = 7.0 Hz), 3.66 (dq, 1 H, J = 7.0, 7.0 Hz), 3.76 (dd, 1 H, J = 2.6, 7.0 Hz), 4.29 (d, 1 H, J = 2.6 Hz), 4.46 (d, 1 H, J = 19.3 Hz), 4.54 (d, 1 H, J = 19.3 Hz); ^{13}C NMR (150 MHz, MeOH-d_4) δ 16.29, 60.89, 67.68, 77.06 (3 C), 212.99; $[\alpha]^{20}_D$ −20.5 (*c* 0.79, MeOH); HRMS (FAB) calcd for $C_6H_{11}N_3O_4 + Na^+$ 212.0647, found 212.0639.

1-*O*-(*tert*-Butyldimethylsilyl)-2,5-imino-2,5,6-trideoxy-L-iditol (6). To a mixture of **5** (1.00 g, 5.31 mmol), triethylamine (1.48 mL, 10.6 mmol), and 4-(*N*,*N*-dimethylamino)-pyridine (6.5 mg, 0.05 mmol) in dry CH_2Cl_2 (50 mL) was added *tert*-butyldimethylsilyl chloride (1.20 g, 7.97 mmol) at room temperature under argon. The reaction mixture was stirred for 12 h at room temperature and quenched by addition of saturated aqueous $NaHCO_3$ solution. Then the aqueous layer was extracted with EtOAc three times. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution, water, and brine successively and dried over Na_2SO_4. Removal of solvent gave 5-azido-1-*O*-(*tert*-butyldimethylsilyl)-5,6-deoxy-L-*xylo*-hex-2-ulose as a crude compound. A mixture of crude 5-azide-1-*O*-(*tert*-butyldimethylsilyl)-5,6-deoxy-L-*xylo*-hex-2-ulose and 5% rhodium−alumina (100 mg) in ethanol (50 mL) was hydrogenated under an atmospheric pressure of hydrogen using a balloon with vigorous stirring for 3 h. The mixture was filtered through Celite, and the solvent was evaporated. Purification by silica gel column chromatography (MeOH/CH_2Cl_2 = 5:95) gave **6** (1.08 g, 78% in two steps): ^{1}H NMR (500 MHz, MeOH-d_4) δ 0.11 (s, 6 H), 0.93 (s, 9 H), 1.20 (d, 3 H, J = 6.6 Hz), 2.99 (q, 1 H, J = 4.6 Hz), 3.31 (dq, 1 H, J = 6.6, 4.1 Hz), 3.77 (dd, 1 H, J = 4.6, 10.3 Hz), 3.79 (dd, 1 H, J = 2.0, 4.6 Hz), 3.82 (dd, 1 H, J = 4.6, 10.3 Hz), 3.84 (dd, 1 H, J = 2.0, 4.1 Hz); ^{13}C NMR (125 MHz, MeOH-d_4) δ −5.39, −5.33, 13.27, 19.19, 26.37 (3 C), 58.20, 63.80, 68.80, 80.13, 80.51; $[\alpha]^{20}_D$ 20.9 (*c* 0.54, MeOH); HRMS (MALDI-FTMS) calcd for $C_{12}H_{27}NO_3Si + H^+$ 262.1833, found 262.1834.

5-*N*-Benzyloxycarbonyl-3,4-di-*O*-benzyl-2,5-imino-2,5,6-trideoxy-L-iditol (7). To a mixture of **5** (439 mg, 1.68 mmol) and K_2CO_3 (423 mg, 5.04 mmol) in a 2:1 mixture of THF and water (8 mL) was added benzyl chloroformate (360 μL, 2.52 mmol) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and quenched by addition of saturated aqueous $NaHCO_3$ solution. Then the aqueous layer was extracted with EtOAc three times. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution, water, and brine successively and dried over Na_2SO_4. Removal of solvent gave 5-*N*-benzyloxycarbonyl-1-*O*-(*tert*-butyldimethylsilyl)-2,5-imino-2,5,6-trideoxy-L-iditol as a crude compound. To a mixture of crude 5-*N*-benzyloxycarbonyl-1-*O*-(*tert*-butyldimethylsilyl)-2,5-imino-2,5,6-trideoxy-L-iditol and benzylbromide (799 μL g, 6.72 mmol) in dry DMF (17 mL) was added 95% sodium hydride (170 mg, 6.72 mmol) at room temperature under argon. The reaction mixture was stirred for 10 h at room temperature and quenched by addition of saturated aqueous NH_4Cl solution. Then the aqueous layer was extracted with ether three times. The combined organic extracts were washed with saturated aqueous NH_4Cl solution, water, and brine successively and dried over Na_2SO_4. Removal of solvent gave 3,4-di-*O*-benzyl-5-*N*-benzyloxycarbonyl-1-*O*-(*tert*-butyldimethylsilyl)-2,5-imino-2,5,6-trideoxy-L-iditol as a crude compound. To a solution of crude 3,4-di-*O*-benzyl-5-*N*-benzyloxycarbonyl-1-*O*-(*tert*-butyldimethylsilyl)-2,5-imino-2,5,6-trideoxy-L-iditol in THF (17 mL) was added 1.0 M THF solution of tetrabutylammonium fluoride (20.2 mL, 2.02 mmol) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and quenched by addition of saturated aqueous NH_4Cl solution. Then the aqueous layer was extracted with EtOAc three times. The combined organic extracts were washed with saturated aqueous NH_4Cl solution, water, and brine successively and dried over Na_2SO_4. Removal of the solvent followed by silica gel column chromatography (EtOAc/hexane = 1:2) gave **7** (628 mg, 81% in three steps): ^{1}H NMR (500 MHz, C_6D_6, 340 K) δ 1.21 (d, 3 H, J = 6.6 Hz), 3.72 (t, 2 H, J = 6.3 Hz), 3.88 (m, 1 H), 3.95 (t, 1 H, J = 5.5 Hz), 4.00 (m, 1 H), 4.17 (m, 1 H), 4.19 (d, 1 H, J = 12.5 Hz), 4.21 (d, 1 H, J = 12.5 Hz), 4.46 (d, 1 H, J = 12.1 Hz), 4.50 (d, 1 H, J = 12.1 Hz), 5.08 (s, 2 H), 6.98−7.24 (m, 15 H); $[\alpha]^{20}_D$ 12.5 (*c* 1.03, EtOAc); HRMS (MALDI-FTMS) calcd for $C_{28}H_{31}NO_5 + Na^+$ 484.2100, found 484.2081.

1-Amino-1-*N*-benzyloxy-5-*N*-benzyloxycarbonyl-3,4-di-*O*-benzyl-2,5-imino-1,2,5,6-tetradeoxy-L-iditol (8). To a suspension of **7** (558 mg, 1.21 mmol) and predried 4 Å molecular sieves (210 mg) in dry CH_2Cl_2 (12 mL) was added *N*-methylmorpholine *N*-oxide (213 mg, 1.82 mmol) at room temperature under argon. The reaction mixture was stirred for 10 min at room temperature, and TPAP (21.3 mg, 0.061 mmol) was then added. The reaction mixture was stirred for 1 h at room temperature and filtered through a pad of silica gel, eluting with a 1:1 mixture of EtOAc and CH_2Cl_2. Evaporation of the filtrate gave 3,4-di-*O*-benzyl-5-*N*-benzyloxycarbonyl-

2,5-imino-2,5,6-trideoxy-L-idose as a crude compound. The mixture of crude 3,4-di-*O*-benzyl-5-*N*-benzyloxycarbonyl-2,5-imino-2,5,6-trideoxy-L-idose and *O*-benzylhydroxylamine hydrochloride (251 mg, 1.57 mmol) in dry pyridine (12 mL) was stirred for 2 h at room temperature. Removal of solvent gave oxime as a crude compound. To a solution of oxime in glacial AcOH (12 mL) was added sodium cyanoborohydride (129 mg, 2.06 mmol) at room temperature under argon. The reaction mixture was stirred for 2 h at room temperature and quenched by addition of water. Then the aqueous layer was extracted with EtOAc three times. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution, water ,and brine successively and dried over Na_2SO_4. Removal of the solvent followed by silica gel column chromatography (EtOAc/hexane = 1:4) gave **8** (542 mg, 79% in three steps): ^{1}H NMR (500 MHz, C_6D_6, 340 K) δ 1.32 (d, 3 H, J = 6.6 Hz), 3.28 (dd, 1H, J = 7.1, 13.0 Hz), 3.39 (dd, 1 H, J = 4.6, 13.0 Hz), 3.75 (dd, 1 H, J = 4.4, 6.6 Hz), 4.12 (t, 1 H, J = 4.4 Hz), 4.20 (d, 1 H, J = 11.7 Hz), 4.25 (d, 1 H, J = 11.7 Hz), 4.27 (m, 2 H), 4.48 (d, 1 H, J = 12.5 Hz), 4.51 (d, 1 H, J = 12.5 Hz), 4.61 (d, 1 H, J = 12.2 Hz), 4.64 (d, 1 H, J = 12.2 Hz), 5.11 (s, 2 H), 5.69 (br s, 1 H), 7.00−7.35 (m, 20 H); ^{13}C NMR (125 MHz, C_6D_6, 340 K) δ 15.96, 55.18, 56.31, 61.88, 67.49, 72.29, 72.89, 76.51, 83.71, 84.16, 128.10, 128.25, 128.68, 128.85, 128.93, 128.98, 129.03, 138.07, 138.99, 139.41, 139.48, 154.14; $[\alpha]^{20}_D$ 10.2 (*c* 1.23, EtOAc); HRMS (MALDI-FTMS) calcd for $C_{35}H_{38}N_2O_5$ + H^+ 567.2853, found 567.2851.

General Procedure for Solution-Phase Parallel Synthesis. To a suspension of morpholinomethyl polystyrene resin (0.3 mmol) in dry CH_2Cl_2 (1 mL) was added **8** (0.1 mmol) and the electrophile (0.3 mmol) at room temperature under argon. The reaction mixture was stirred for 1 h at room temperature, and then methylisocyanate polystyrene resin (0.1 mmol) and Tris-(2-aminoethyl)amine polystyrene resin (0.6 mmol) were added. The reaction mixture was stirred for additional 4 h at room temperature and filtered. Evaporation of the filtrate gave **9**. A mixture of **9** and 10% Pd−C (10 mg) in AcOH (1 mL) was hydrogenated under 1 atm pressure of hydrogen using a balloon with vigorous stirring for 3 h. The mixture was filtered through Celite, and the solvent was evaporated to afford **10**.

1-*N*-Acetyl-1-amino-1-*N*-hydroxy-2,5-imino-1,2,5,6-tetradeoxy-L-iditol (10a): ^{1}H NMR (600 MHz, MeOH-d_4) δ 1.39 (d, 3 H, J = 6.5 Hz), 2.14 (s, 3 H), 3.63 (m, 1 H), 3.75 (dt, 1 H, J = 3.1, 6.6 Hz), 3.91 (br s, 1 H), 3.98 (dd, 1 H, J = 6.6, 12.5 Hz), 4.02 (dd, 1 H, J = 6.6, 12.5 Hz), 4.06 (br s, 1 H); HRMS (MALDI-FTMS) calcd for $C_8H_{16}N_2O_4$ + H^+ 205.1183, found 205.1178.

1-Amino-1-*N*-hydroxy-2,5-imino-1-*N*-septylcarbonyl-1,2,5,6-tetradeoxy-L-iditol (10b): ^{1}H NMR (500 MHz, MeOH-d_4, 330 K) δ 0.89 (t, 3 H, J = 7.0 Hz), 1.26 (d, 3 H, J = 7.0 Hz), 1.28−1.36 (m, 8 H), 1.61 (m, 2 H), 2.48 (dt, 2 H, J = 4.9, 7.6 Hz), 3.38 (ddd, 1 H, J = 3.3, 4.8, 8.1 Hz), 3.46 (dq, 1 H, J = 3.7, 7.0 Hz), 3.84 (dd, 1 H, J = 1.8, 3.7 Hz), 3.85 (dd, 1 H, J = 4.8, 14.7 Hz), 3.93 (dd, 1 H, J = 1.8, 3.3 Hz), 3.97 (dd, 1 H, J = 8.1, 14.7 Hz); HRMS (MALDI-FTMS) calcd for $C_{14}H_{28}N_2O_4$ + H^+ 289.2122, found 289.2120.

1-Amino-1-*N*-ethoxycarbonyl-1-*N*-hydroxy-2,5-imino-1,2,5,6-tetradeoxy-L-iditol (10c): ^{1}H NMR (500 MHz, MeOH-d_4, 330 K), δ 1.24 (t, 3 H, J = 7.2 Hz), 1.27 (d, 3 H, J = 7.0 Hz), 3.82 (m, 2 H), 3.86 (br s, 1 H), 3.94 (br s, 1 H), 4.13 (q, 2 H, J = 7.2 Hz), 4.17 (d, 1 H, J = 7.0 Hz), 4.20 (d, 1 H, J = 7.0 Hz); HRMS (MALDI−FTMS) calcd for $C_9H_{18}N_2O_5$ + H^+ 235.1288, found 235.1288.

1-Amino-1-*N*-hydroxy-2,5-imino-1-*N*-isobutoxycarbonyl-1,2,5,6-tetradeoxy-L-iditol (10d): ^{1}H NMR (500 MHz, MeOH-d_4, 330 K), δ 0.93 (d, 6 H, J = 7.0 Hz), 1.24 (d, 3 H, J = 6.6 Hz), 1.28 (m, 1 H), 3.44 (t, 1 H, J = 4.4 Hz), 3.62 (t, 1 H, J = 4.4 Hz), 3.72−3.78 (m, 2 H), 3.84−3.92 (m, 4 H); HRMS (MALDI-FTMS) calcd for $C_{11}H_{22}N_2O_5$ + H^+ 263.1601, found 263.1608.

1-Amino-1-*N*-hydroxy-2,5-imino-1-*N*-octylaminocarbonyl-1,2,5,6-tetradeoxy-L-iditol (10e): ^{1}H NMR (500 MHz, MeOH-d_4, 330 K), δ 0.88 (t, 3 H, J = 7.0 Hz), 1.25 (d, 3 H, J = 6.6 Hz), 1.28−1.33 (m, 12 H), 3.00 (t, 2 H, J = 6.8 Hz), 3.20−3.36 (m, 3 H), 3.55 (dq, 1 H, J = 4.0, 6.6 Hz), 3.81 (dd, 1 H, J = 2.5, 4.0 Hz), 3.86 (dd, 1 H, J = 2.5, 4.0 Hz).

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Supporting Information Available: ^{1}H NMR spectra for the compounds **2**−**8** and **10** and ^{13}C NMR spectra for the compounds **2**−**6** and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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