HIV-1 Protease Inhibitors Based on Acyclic Carbohydrates

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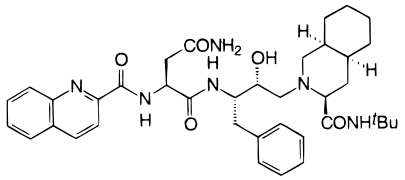
A series of acyclic C_2-symmetric HIV protease inhibitors readily accessible from D-mannitol have been developed. Several of the compounds synthesized showed significant in vitro activity against HIV-1 protease.

Introduction

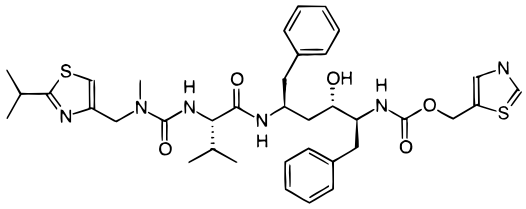
Human immunodeficiency virus (HIV), the etiologic agent of acquired immune deficiency syndrome (AIDS), is spreading at an alarming rate.[1] Progress in the treatment of AIDS leading to an effective therapy has been slow, but recent results with new AIDS drugs, notably the HIV-1 protease inhibitors, allow for cautious optimism.[2]

The HIV-1 protease (PR) is a virally encoded homodimeric aspartyl protease[3] responsible for the processing of the *gag* and *gag/pol* gene products which enables the proper organization of core structural proteins and the release of viral enzymes. Inhibition of HIV PR leads to the production of immature, noninfectious viral particles.[4] There are today four HIV-1 protease inhibitors approved by the U.S. FDA for the treatment of AIDS: Roche's saquinavir (**1**), Abbott's ritonavir (**2**), Merck's indinavir (**3**), and Agouron's nelfinavir (Chart 1).

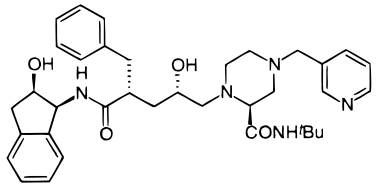
Chart 1. FDA-Approved HIV-1 Pr Inhibitors



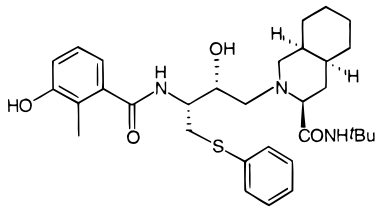
1
Saquinavir



2
Ritonavir



3
Indinavir



Nelfinavir

A number of reports on the design and synthesis of HIV PR inhibitors have been published.[5] In general in these inhibitors, the scissile bond has been replaced by a nonhydrolyzable transition-state isostere. Unfortunately, most of these peptidomimetic HIV PR inhibitors retain a substantial amount of peptide character, and as a result, their oral bioavailability is low and a short plasma half-life is observed.[6] In addition, it has been demon-

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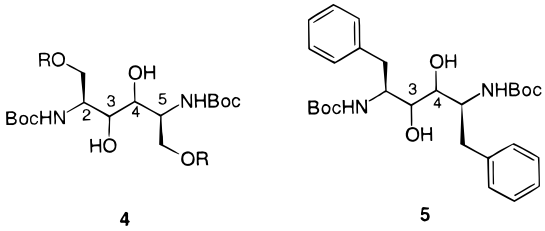
strated in clinical trials that doses in excess of 1 g daily are necessary to suppress viral replication[7] and that selection of resistance due to multiple mutations in the HIV PR genome takes place as a result of exposure to HIV PR inhibitors.[8] Results from combination therapies involving HIV PR inhibitors as one component are now beginning to emerge showing promising results.[9]

There is today a need for the development of new generations of HIV PR inhibitors with high potency, with improved oral bioavailability, and with reduced selection for resistance. The high cost of HIV-1 therapy has also emphasized the importance of chemically readily accessible inhibitors.

The carbohydrates are a diverse, chiral pool of natural compounds. They are in general inexpensive and have thus frequently been used as starting materials. In the design and synthesis of new types of peptidomimetic HIV-1 protease inhibitors, we have developed acyclic carbohydrate alditol-based transition-state mimetics as replacements for the scissile dipeptide bond of the substrate. The carbohydrate alditol serves as a structural matrix for placing the appropriate side chains in the appropriate spatial positions, with the backbone chirality selected to provide the spatial topology of the desired isostere. Several reports have described the use of commercially available and inexpensive D-mannitol for the convenient synthesis of potent acyclic HIV-1 protease inhibitors.[10] Hirschmann has earlier reported on the development of a cyclic glucose derivative as a somatostatin peptidomimetic.[11]

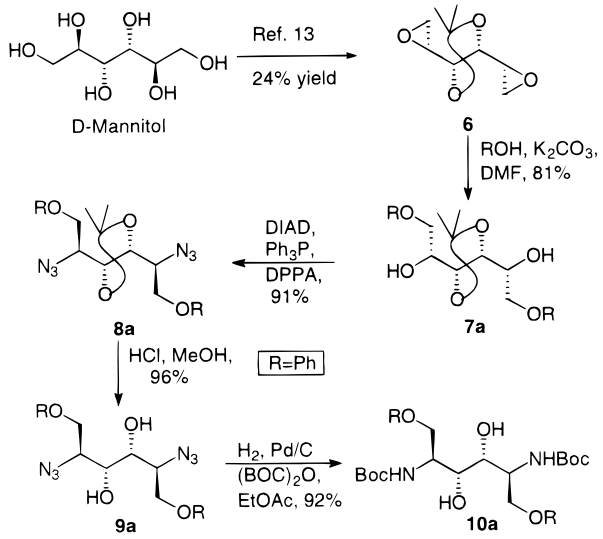
Researchers at Abbott have previously reported on the elegant design of symmetric acyclic inhibitors that capitalize on the unique C_2 symmetry of the dimeric HIV PR.[12] In this paper we have used D-mannitol to synthesize a series of compounds of the general structure **4** (Chart 2) with the 3*R*,4*R*, 3*R*,4*S* and 3*S*,4*S* chirality of the central diols that have been evaluated in antiviral assays and whose structure−activity relationships (SAR) have been compared with that of the related Abbott compound **5**. In addition, we have also synthesized the 3*S*,4-deoxy and 3*R*,4-deoxy analogues of **4** and the unsymmetrical 1-phenoxy-6-phenyl diol-related to both structures **4** and **5**. The comparative ease by which different aryl and to some extent alkyl groups corresponding to the P_1/P_1' substituents of the carbohydrate alditol HIV-1 protease inhibitor can be introduced at the 1-O and 6-O positions is also demonstrated for selected examples.

Chart 2. Structures of Compounds 4 and 5



4 **5**

Scheme 1. Synthesis of Compound 10a (R = Ph)



Results and Discussion

For the synthesis of HIV PR inhibitors, α-amino aldehydes have frequently been used as synthetic intermediates where the precursor α-amino acid side chains correspond to the selected P_1/P_1' substituents of the inhibitor. To obtain diversity for the P_1/P_1' substituents of the inhibitor, unnatural and frequently novel amino acids in isomerically pure form have been prepared and assembled in a nonconvergent synthesis to produce the compounds of interest.

The use of acyclic carbohydrates as peptidomimetic HIV PR inhibitors can allow for the facile access to sets of stereochemically diverse compounds that can be assembled in a convergent way.

Chemistry. For the synthesis of **10a**, the diepoxide **6** (Scheme 1), readily available from D-mannitol in four steps and in 23% overall yield,[13] was heated with phenol in DMF at 110 °C in the presence of potassium carbonate to give the diol **7a** in 81% yield. Compound **7a** was converted into the corresponding diazide **8a** in 91% yield,

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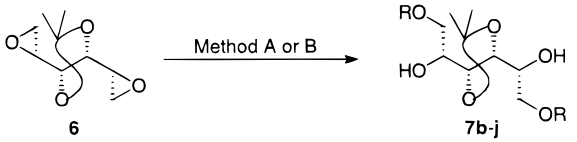
Table 1. Yields for the Synthesis of Compounds 7b−j[a]



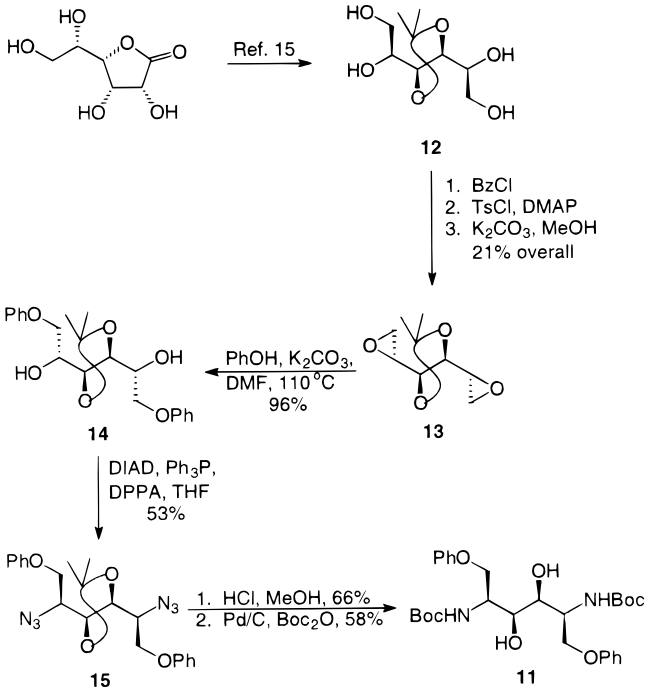
Compound	ROH	Method	Yield (%)
7b	*p*-NO_2PhOH	A	60
7c	*m*-NO_2PhOH	A	64
7d	*o*-NO_2PhOH	A	42
7e	*p*-MeOPhOH	A	56
7f	*p*-F-PhOH	A	65
7g	C_6F_5OH	A	72
7h	1-$C_{10}H_7OH$	A	73
7i	$C_6H_{11}OH$	B	25
7j	*t*BuOH	B	89

[a] Method A: ROH, K_2CO_3, DMF, 110 °C, 16 h. Method B: ROH, $Mg(ClO_4)_2$, CH_3CN, 82 °C, 16 h.

using Mitsunobu conditions with DIAD, triphenylphosphine, and diphenyl phosphorazidate.[14] Hydrolysis of the isopropylidene group in **8a** by 3 N HCl in methanol gave diazido diol **9a** in 96% yield from which the final product **10a** was obtained in 92% yield by reduction of the azide groups and simultaneous protection of the resulting diamine using catalytic hydrogenation over 10% palladium on carbon in the presence of di-*tert*-butyl dicarbonate (Boc_2O).[15]

The synthesis of compound **10a** provides ready access to variations of the P_1/P_1' groups starting from diepoxide **6** (Scheme 1). Heating various substituted phenols with diepoxide **6** at 110 °C in DMF in the presence of potassium carbonate gave diols **7b−h** in yields ranging from moderate to good (Table 1). However, when alcohols were used to effect this epoxide opening the reaction failed. Varying the base (KO*t*Bu, NaH), solvent (toluene, DMSO, THF), or temperature (−10 → 110 °C) did not lead to improvements either giving unreacted starting material or resulting in the decomposition of the diepoxide. When Lewis acids such as boron trifluoride diethyl etherate,[16] cerium ammonium nitrate,[17] magnesium triflate, or calcium chloride were used in the reaction, low and variable yields (<20%) of the desired diepoxide-opened products were obtained. However, with magnesium perchlorate (potentially explosive)[18] in refluxing acetonitrile, diols **7i,j** were obtained in reproducible yields (25% and 89%, respectively). Diols **7b−j** were readily converted to the corresponding diazides **8b−j** in fair to excellent yields (32−100%), using Mitsunobu conditions. Hydrolysis of the isopropylidene group either in 90% aqueous trifluoroacetic acid or with 3 N HCl in methanol afforded the diazido diols **9b−j** in good to excellent yields (46−85%). Compounds **10f−j** were obtained from catalytic hydrogenation of the corresponding diazido diols over 10% palladium on carbon in the presence of di-*tert*-butyl dicarbonate. A two-step procedure was used to prepare **10b−e** utilizing triphenylphosphine in tetrahydrofuran/water for the azide reduction followed by reacting the resulting diamine with di-*tert*-butyl dicarbonate.

Scheme 2. Synthesis of the C-3 and C-4 Diastereoisomers of 10a



Many reports have shown that the stereochemistry at the core of the HIV protease inhibitor has a major effect on the potency of the inhibitors. The P_1/P_1' groups usually have the chirality corresponding to that of the L-amino acids, whereas the stereochemistry of the central diols can vary.

Compound **11**, corresponding to compound **10a** but having the hydroxyls of the central diol inverted, was prepared starting from L-mannonic 1,4-lactone (Scheme 2). The monoisopropylidene intermediate **12**, prepared from L-mannonio-1,4-lactone,[19] was selectively benzoylated at the primary hydroxyls, using benzoyl chloride, tosylated at the secondary hydroxyls, and subsequently treated with potassium carbonate in methanol to give epoxide **13**[20] in 21% yield from **12**.[13] Compound **13** was heated with phenol in DMF at 110 °C in the presence of potassium carbonate to give the diol **14**[20] in 96% yield, which was converted into the corresponding diazide **15**[20] in 53% yield, using Mitsunobu conditions. The isopropylidene group in **15** was hydrolyzed using 3 N HCl in methanol to give the corresponding diazido diol in 66% yield. In situ reduction of the azide groups by hydrogenation over 10% palladium on carbon followed by protection of the resulting diamino groups with di-*tert*-butyl dicarbonate gave the desired product **11** in 58% yield.

Preparation of compound **16**, corresponding to compound **10a** having one of the hydroxyls of the central diol

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(15) Saito, S.; Nakajima, H.; Inaba, M.; Moriwake, T. *Tetrahedron Lett.* **1989**, *30*, 837−838.
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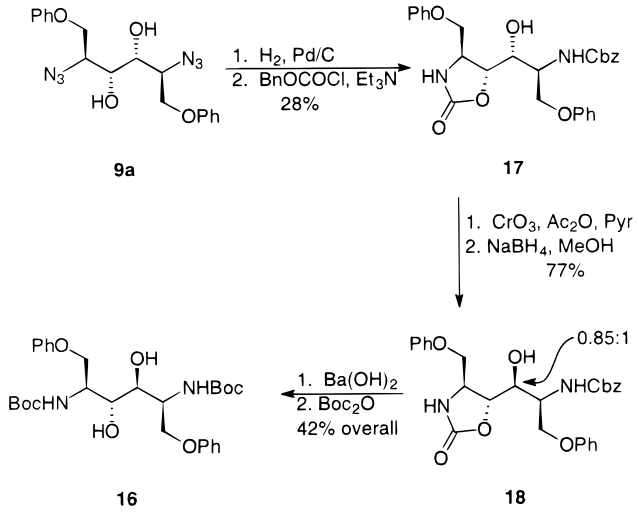
Scheme 3. Inversion of the C-4 Hydroxyl of 10a

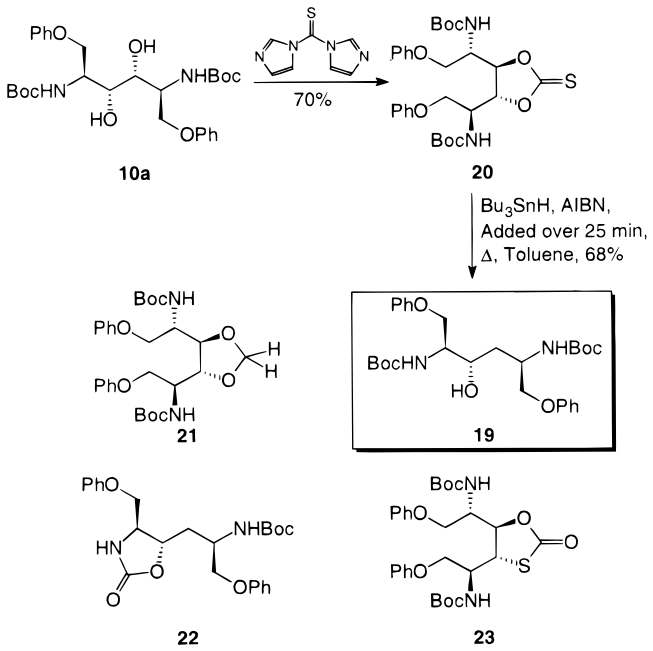


inverted, was attempted from the monoacetylated diol **9a.** The mono-*O*-acetate or mono-*O*-benzoate having a single unprotected hydroxyl group was then subjected to standard Mitsunobu inversion conditions or exposed to chromium(VI)-based oxidants. Surprisingly this hydroxyl group was inert to these reaction conditions, probably due to steric shielding.

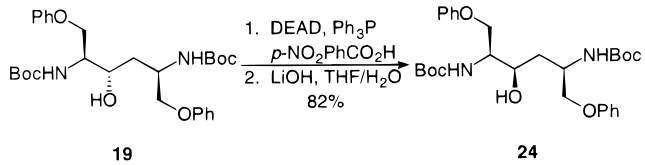
Instead, compound **9a** was hydrogenated using palladium on carbon (10%) to give the corresponding diamine which was reacted with benzyl chloroformate in the presence of excess triethylamine to give the cyclic carbamate **17**, in 28% yield, having one unprotected hydroxyl group (Scheme 3). Oxidation of the hydroxyl group to the corresponding ketone using chromium(VI) oxide−acetic anhydride−pyridine[21] followed by reduction with sodium borohydride in methanol gave the desired epimer **18** along with **17** in 77% total yield (0.85:1 ratio). Hydrolysis of the carbamate in **18** using barium hydroxide and Boc protection of the amino groups using di-*tert*-butyl dicarbonate gave the desired compound **16** in 42% yield from **18**.

For the synthesis of compound **19**, compound **10a** was reacted with thiocarbonyldiimidazole to give the cyclic thiocarbonate **20** in 70% yield, which was subjected to radical deoxygenation conditions (Scheme 4). Addition of tributyltin hydride and 2,2′-azobis(isobutyronitrile) to the cyclic thiocarbonate **20** over 20 min gave the desired deoxygenation product **19** in 68% yield along with minor amounts of compounds **21**−**23**. Yields were comparable when benzyloxycarbonyl was used instead of *tert*-butoxycarbonyl as amino protecting group in **20.** Addition of tributyltin hydride and 2,2′-azobis(isobutyronitrile) to the cyclic thiocarbonate **20** over a short time (15 min) gave as the main products the desulfurization compound **21** (22% yield) and the cyclic carbamate **22** (17% yield). Compound **22** could be converted to the desired product **19** in 56% overall yield by hydrolysis with barium hydroxide followed by reaction of the resulting diamine with di-*tert*-butyl dicarbonate. Applying longer addition times (50 min) or high dilution conditions (7 mM) in the radical deoxygenation reaction led to the rearranged product **23**[22] (15% yield). The trans stereochemistry of

Scheme 4. Monodeoxygenation of Diol 10a



Scheme 5. Inversion of the Hydroxyl Stereochemistry of 19



the oxathiolone ring in **23** was determined by the large coupling between the ring hydrogens (J = 8.5 Hz).

The hydroxyl epimer of **19** was synthesized using 4-nitrobenzoic acid[23] in the Mitsunobu reaction followed by hydrolysis of the 4-nitrobenzoate with lithium hydroxide to give **24** in 82% yield (Scheme 5).

The unsymmetrical inhibitor **25**, which has structural similarity to both compounds **5** and **10a**, was also synthesized (Scheme 6). Diepoxide **6** was heated with 2 equiv of phenol at 90 °C in dimethylformamide in the presence of potassium carbonate. The monoaddition product **26** was isolated in 31% yield (45% based on recovered starting material) along with **7a.** Reacting the monoepoxide **26** with phenyllithium and CuBr·SMe_2 afforded the unsymmetrical diol **27**, in 86% yield. Conversion of **27** to the corresponding diazide using the Mitsunobu reaction was accompanied by elimination.[10] The isopropylidene group of the diazide was hydrolyzed using HCl in methanol, and **28** was isolated in 18% yield from **27**. Catalytic hydrogenation over 10% palladium on carbon in the presence of di-*tert*-butyl dicarbonate gave the unsymmetrical inhibitor **25**, in 85% yield.

HIV-1 Protease Inhibition. The inhibitory effect of the synthesized compounds was determined with purified HIV-1 protease in a standardized assay. The results are presented as IC_{50} values, i.e., the concentration of inhibitor resulting in 50% inhibition in this assay.[24]

Structure−Activity Relationship. The enzyme inhibitory activity (Table 2) of compound **10a** is 5−8 times

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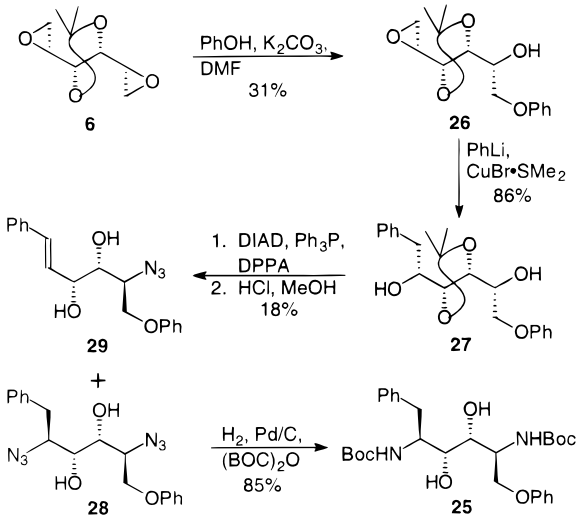
Scheme 6. Synthesis of the Unsymmetrical Inhibitor 25



less active than that of the Abbott compound **5,** whereas the unsymmetrical inhibitor **25** is equipotent with **5**. Inversion of both the hydroxyls in **10a** gives, in contrast to that observed for the isomers of compound **5**, the inactive compound **11**,[12a,c] whereas inversion of one hydroxyl gives inhibitor **16**, which is equipotent with inhibitor **10a**. Notably however, when one of the hydroxyls in diol **10a** is deoxygenated, giving inhibitor **19**, an increase in activity is observed as previously described,[12c] resulting in an inhibitor equipotent with Abbott compound **5**. The hydroxyl epimer of inhibitor **19**, compound **24**, is inactive which demonstrates the importance of the interaction of the hydroxyl group with the catalytic aspartic acids in the active site of the HIV-1 protease. Modification of the P_1/P_1' substituent of **10a** did not improve on the antiviral activity compared to **10a** (unpublished data).

Conclusion

It has been demonstrated that potent HIV-1 protease inhibitors can be obtained by employing carbohydrate alditols as templates. Work is in progress to optimize this new class of inhibitors using X-ray crystal structures of protease−inhibitor complexes and molecular modeling.

Experimental Section

3,4-*O*-Isopropylidene-1,6-di-*O*-phenyl-D-mannitol, 7a. To 1,2:5,6-dianhydro-3,4-*O*-isopropylidene-D-mannitol, **6** (5.0 g, 26.9 mmol), and phenol (10.3 g, 110 mmol) in DMF (100 mL) was added K_2CO_3 (1.8 g, 13.4 mmol). The reaction mixture was heated at 110 °C for 7 h. After cooling, it was added to saturated aqueous NH_4Cl (200 mL) and extracted with Et_2O (200 mL). The organic phase was washed with H_2O (2 × 100 mL), dried ($MgSO_4$), and concentrated to give a solid. Purification by flash column chromatography (4:1 $PhCH_3$/EtOAc) gave **7a** as a white solid (8.18 g, 81% yield): mp 116−117 °C; $[\alpha]_D$ +44.9 (*c* = 1.52, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.27 (t, *J* = 8.0 Hz, 4H), 6.96 (t, *J* = 7.2 Hz, 2H), 6.94 (d, *J* = 8.2 Hz, 4H), 4.23 (d, *J* = 8.3 Hz, 2H), 4.09−4.04 (m, 6H), 3.81 (s, 2H), 1.38 (s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 158.6 (s), 129.4 (d), 121.1 (d), 114.7 (d), 109.8 (s), 79.7 (d), 71.7 (d), 69.5 (t), 26.9 (q). Anal. Calcd for $C_{21}O_6$ H_{26}: C, 67.36; H, 7.00. Found: C, 67.17; H, 7.18.

1,6-Di-*O*-cyclohexyl-3,4-*O*-isopropylidene-D-mannitol, 7i. To a solution of **6** (0.206 g, 1.11 mmol) and cyclohexanol (2.30 mL, 22.1 mmol) in acetonitrile (2.2 mL) was added $Mg(ClO_4)_2$ (0.50 g, 2.24 mmol). The reaction mixture was heated to reflux for 7.5 h and then added to Et_2O (50 mL) and saturated aqueous $NaHCO_3$ (30 mL). The organic phase was washed with H_2O (30 mL) and saturated aqueous NaCl (30 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography (9:1 → 2:1 $PhCH_3$/EtOAc) to give **7i** (0.104 g, 24% yield) as a colorless liquid along with the monoaddition product (39% yield) as a colorless liquid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.91 (m, 2H), 3.79 (m, 2H), 3.74 (dd, *J* = 10.6, 2.8 Hz, 2H), 3.52 (dd, *J* = 10.2, 7.0 Hz, 2H), 3.46 (d, *J* = 3.0 Hz, 2H), 3.30 (tt, *J* = 8.9, 3.8 Hz, 2H), 1.92 (m, 4H), 1.75 (m, 4H), 1.52 (m, 2H), 1.37 (s, 6H), 1.34−1.20 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 109.2 (s), 79.9 (d), 78.3 (d), 71.9 (d), 69.1 (t), 32.3 (t), 32.1 (t), 27.0 (q), 25.8 (t), 24.1 (t).

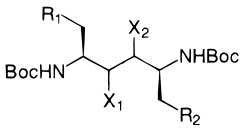
Monoaddition Product: ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.05 (dd, *J* = 6.7, 4.2 Hz, 1H), 3.89 (t, *J* = 7.0 Hz, 1H), 3.79 (ddd, *J* = 10.3, 6.9, 3.6 Hz, 1H), 3.68 (dd, *J* = 9.6, 3.4 Hz, 1H), 3.50 (dd, *J* = 9.6, 6.4 Hz, 1H), 3.31 (tt, *J* = 8.8, 3.8 Hz, 1H), 3.19 (q, *J* = 3.6 Hz, 1H), 2.84 (s, 1H), 2.84 (d, *J* = 3.5 Hz, 1H), 2.73 (d, *J* = 3.9 Hz, 1H), 1.89 (m, 2H), 1.73 (m, 2H), 1.52 (m, 1H), 1.38−1.20 (m, 5H), 1.42 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 109.8 (s), 78.5 (d), 78.3 (d), 78.2 (d), 71.5 (d), 68.7 (t), 52.2 (d), 44.9 (t), 32.2 (t), 32.0 (t), 27.0 (q), 26.7 (q), 25.8 (t), 24.1 (t), 24.0 (t).

1,6-Di-*O*-isobutyl-3,4-*O*-isopropylidene-D-mannitol, 7j. Synthesized by the same method as for **7i** in 89% yield: ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.91 (dd, *J* = 5.9, 1.9 Hz, 2H), 3.78 (m, 2H), 3.69 (dd, *J* = 9.8, 2.8 Hz, 2H), 3.58 (d, *J* = 3.1 Hz, 2H), 3.51 (dd, *J* = 9.8, 6.3 Hz, 2H), 3.28 (dd, *J* = 10.1, 7.6 Hz, 2H), 3.25 (dd, *J* = 10.1, 7.6 Hz, 2H), 1.90 (nonet, *J* = 6.7 Hz, 2H), 1.37 (s, 6H), 0.91 (d, *J* = 6.7 Hz, 12H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 109.3 (s), 79.9 (d), 78.5 (t), 72.0 (d), 71.9 (t), 28.3 (d), 26.9 (q), 19.3 (q).

2,5-Diazido-2,5-dideoxy-3,4-*O*-isopropylidene-1,6-di-*O*-phenyl-L-iditol, 8a. To a cooled (−5 °C) solution of diisopropoxy azodicarboxylate, DIAD (7.9 g, 93 mmol) in THF (5 mL) were added **7a** (7.06 g, 18.7 mmol) in THF (50 mL) and Ph_3P (10.3 g, 39.1 mmol). After 15 min, diphenyl phosphorazidate (DPPA; 12.86 g, 46.77 mmol) was added and the reaction mixture allowed to warm to room temperature. After stirring overnight, the solvent was removed in vacuo to give a yellow oil. The crude material was purified by flash column chromatography (2:1 petroleum ether/$PhCH_3$ → 9:1 $PhCH_3$/EtOAc) to give **8a** (7.28 g, 91% yield) as a colorless oil: $[\alpha]_D$ +40.4 (*c* = 1.35, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 8.2, 7.6 Hz, 4H), 6.98 (t, *J* = 7.4 Hz, 2H), 6.91 (d, *J* = 8.2 Hz, 4H), 4,33 (s, 2H), 4.25−4.20 (m, 4H), 3.73 (dd, *J* = 6.4, 5.9 Hz, 2H), 1.47 (s, 6H); ^{13}C NMR (62 MHz, $CDCl_3$) δ 157.9 (s), 129.6 (d), 121.7 (d), 114.7 (d), 110.9 (s), 76.9 (d), 67.8 (t), 59.6(d), 26.9 (q). Anal. Calcd for $C_{21}O_4$ $H_{24}N_6$: C, 59.42; H, 5.70; N, 19.80. Found: C, 59.64; H, 5.57; N, 19.76.

2,5-Diazido-2,5-dideoxy-1,6-di-*O*-phenyl-L-iditol, 9a. To **8a** (0.896 g, 2.11 mmol) was added a cold (0 °C) solution of acetyl chloride (3.5 mL, 49.2 mmol) in MeOH (75 mL) which

Table 2. Values for the Inhibition of HIV-1 Pr



Compound	R_1	R_2	X_1	X_2	K_i (nM)
5	Ph	Ph	···OH	···OH	38 (0.040)[a]
	Ph	Ph	···OH	—OH	(0.012)[a]
	Ph	Ph	—OH	—OH	(0.280)[a]
10a	PhO	PhO	···OH	···OH	300
11	PhO	PhO	—OH	—OH	Inactive
16	PhO	PhO	···OH	—OH	232
19	PhO	PhO	···OH	H	52
24	PhO	PhO	—OH	H	Inactive
25	Ph	PhO	···OH	···OH	73

[a] Values from ref 12a.

had been stirring for 10 min. After stirring for 24 h at room temperature, the reaction mixture was concentrated in vacuo to give an oil. The crude product was purified by flash column chromatography (4:1 $PhCH_3$/EtOAc) to give **9a** (0.79 g, 96% yield) as a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.28 (dd, J = 8.3, 7.6 Hz, 4H), 6.98 (t, J = 7.3 Hz, 2H), 6.90 (d, J = 8.1 Hz, 6H), 4.25 (m, 4H), 3.93 (br s, 4H), 3.03 (d, J = 2.6 Hz, 2H); ^{13}C NMR (62 MHz, $CDCl_3$) δ 157.9 (s), 129.6 (d), 121.7 (d), 114.6 (d), 70.9 (d), 68.0 (t), 62.4 (d).

2,5-Bis[*N*-(*tert*-butoxycarbonyl)amino]-2,5-dideoxy-1,6-di-*O*-phenyl-L-iditol, 10a. To **9a** (0.77 g, 2.00 mmol) and *tert*-butoxycarbonyl anhydride (Boc_2O; 0.80 g, 3.6 mmol) in EtOAc (15 mL) was added Pd/C (10%, 0.12 g). Hydrogen was added (with flushing) at atmospheric pressure to the system and the reaction mixture stirred for 3 h. The suspension was then filtered through Celite and concentrated in vacuo to give a colorless solid. This was purified by flash column chromatography (4:1 $PhCH_3$/EtOAc) to give **10a** (0.98 g, 92% yield) as a colorless oil: mp 115−116 °C; $[\alpha]_D$ −26.4 (c = 1.42, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.27 (ddd, J = 8.2, 7.3, 2.2 Hz, 6H), 6.96 (t, J = 7.3 Hz, 2H), 6.88 (d, J = 8.0 Hz, 4H), 5.17 (d, J = 7.7 Hz, 2H), 4.15 (m, 6H), 3.91 (s, 2H), 3.53 (br s, 2H), 1.43 (s, 18H); ^{13}C NMR (62 MHz, $CDCl_3$) δ 158.3 (s), 156.3 (s), 129.5 (d), 121.3 (d), 114.7 (d), 80.1 (s), 71.5 (d), 68.2 (t), 51.0 (d), 28.3 (q). Anal. Calcd for $C_{28}O_8H_{40}N_2$: C, 63.14; H, 7.57; N, 5.26. Found: C, 63.25; H, 7.47; N, 5.08.

2,5-Bis[*N*-(*tert*-butoxycarbonyl)amino]-2,5-dideoxy-1,6-bis-*O*-(4′-nitrophenyl)-L-iditol, 10b. To **9b** (0.462 g, 0.97 mmol) in MeOH (25 mL) was added Ph_3P (0.639 g, 2.43 mmol). After stirring overnight, the solvent was removed in vacuo. The residue was dissolved in EtOAc (40 mL) and Boc_2O (0.491 g, 2.26 mmol) added. After stirring for 3 days at room temperature, the reaction mixture was concentrated. The reaction mixture was purified by crystallization (petroleum ether/acetone) to give **10b** (0.422 g, 70% yield): $[\alpha]_D$ +37.0 (c = 0.40, $CHCl_3$); ^{1}H NMR (100 MHz, $CDCl_3$) δ 8.17 (d, J = 9.2 Hz, 4H), 7.00 (d, J = 9.3 Hz, 4H), 5.43 (d, J = 8.7 Hz, 2H), 4.52−3.88 (m, 10H), 1.44 (s, 18H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 163.1 (s), 155.9 (s), 141.2 (s), 125.5 (d), 114.3 (d), 80.0 (s), 70.2 (d), 68.0 (t), 50.1 (d), 28.2 (q). Anal. Calcd for $C_{28}O_{12}H_{38}N_4$: C, 54.01; H, 6.15; N, 9.00. Found: C, 53.70; H, 5.77; N, 8.08.

2,5-Bis[*N*-(*tert*-butoxycarbonyl)amino]-2,5-dideoxy-1,6-bis-*O*-(3′-nitrophenyl)-L-iditol, 10c. Synthesized by the same method as for **10b** in 62% yield: $[\alpha]_D$ +42.7 (c = 0.89, $CHCl_3$); ^{1}H NMR (100 MHz, $CDCl_3$) δ 7.86 (ddd, J = 7.9, 1.8, 1.3 Hz, 2H), 7.73 (t, J = 2.2 Hz, 2H), 7.45 (t, J = 7.9 Hz, 2H), 7.23 (ddd, J = 8.2, 2.3, 1.3 Hz, 2H), 5.02 (d, J = 7.3 Hz, 2H), 4.97 (br s, 2H), 4.53−4.23 (m, 2H), 4.11−4.19 (m, 4H), 1.47 (s, 18H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 157.9 (s), 155.3 (s), 148.8 (s), 129.9 (d), 121.1 (d), 116.5 (d), 108.9 (d), 81.2 (s), 77.4 (d), 66.9 (t), 50.0 (d), 28.1 (q). Anal. Calcd for $C_{28}O_{12}H_{38}N_4$: C, 54.01; H, 6.15; N, 9.00. Found: C, 54.21; H, 5.99; N, 7.80.

2,5-Bis[*N*-(*tert*-butoxycarbonyl)amino]-2,5-dideoxy-1,6-bis-*O*-(2′-nitrophenyl)-L-iditol, 10d. Synthesized by the same method as for **10b** in 45% yield: $[\alpha]_D$ +22.76 (c = 1.16, $CHCl_3$); ^{1}H NMR (100 MHz, $CDCl_3$) δ 7.90 (dd, J = 8.3, 1.9 Hz, 2H), 7.53 (ddd, J = 9.1, 6.7, 1.8 Hz, 2H), 7.14−6.98 (m, 4H), 5.18−5.02 (4H), 4.65−4.19 (m, 6H), 1.45 (s, 18H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 154.9 (s), 151.0 (s), 139.0 (d), 134.4 (s), 125.9 (d), 121.1 (d), 114.2 (d), 80.8 (s), 77.5 (d), 67.3 (t), 50.6 (d), 28.0 (q). Anal. Calcd for $C_{28}O_{12}H_{38}N_4 \cdot 0.25C_7H_8$: C, 55.34; H, 6.24; N, 8.68. Found: C, 55.17; H, 6.26; N, 8.50.

2,5-Bis[*N*-(*tert*-butoxycarbonyl)amino]-2,5-dideoxy-1,6-bis-*O*-(4′-methoxyphenyl)-L-iditol, 10e. Synthesized by the same method as for **10a** in 81% yield: $[\alpha]_D$ +14.89 (c = 1.90, $CHCl_3$); ^{1}H NMR (100 MHz, $CDCl_3$) δ 7.16 (s, 8H), 5.54 (d, J = 8 Hz, 2H), 4.48−4.06 (m, 10H), 3.95 (s, 6H), 1.50 (s, 18H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 156.0 (s), 153.6 (s), 152.2 (s), 115.4 (d), 114.3 (d), 79.7 (s), 71.1 (d), 68.5 (t), 55.5 (q), 50.7 (d), 28.2 (q). Anal. Calcd for $C_{30}O_{10}H_{44}N_2$: C, 60.79; H, 7.48; N, 4.73. Found: C, 60.56; H, 7.52; N, 4.60.

2,5-Bis[*N*-(*tert*-butoxycarbonyl)amino]-2,5-dideoxy-1,6-bis-*O*-(4′-fluorophenyl)-L-iditol, 10f. Synthesized by the same method as for **10a** in 86% yield: $[\alpha]_D$ +9.90 (c = 1.77, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.93 (dd, J_{HH} = 9.2 Hz, J_{HF} = 7.7 Hz, 4H), 6.78 (dd, J_{HH} = 9.2 Hz, J_{HF} = 4.6 Hz, 4H), 5.29 (d, J = 8.0 Hz, 2H), 4.24−3.68 (m, 10H), 1.40 (s, 18H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 157.4 (d, J_{CF} = 238.7 Hz), 156.3 (s), 154.4 (s), 115.8 (dd, J_{CF} = 24.5 Hz), 115.6 (dd, J_{CF} = 6.8 Hz), 80.2 (s), 71.2 (d), 68.6 (t), 50.9 (d), 28.2 (q). Anal. Calcd for $C_{28}O_8H_{38}N_2F_2$: C, 59.14; H, 6.74; N, 4.93. Found: C, 59.35; H, 6.84; N, 4.85.

2,5-Bis[*N*-(*tert*-butoxycarbonyl)amino]-2,5-dideoxy-1,6-bis-*O*-(pentafluorophenyl)-L-iditol, 10g. Synthesized by the same method as for **10a** in 70% yield: mp 190−192 °C; $[\alpha]_D$ +13.90 (c = 0.41, $CHCl_3$); ^{1}H NMR (250 MHz, DMSO-d_6) δ 6.63 (d, J = 8.8 Hz, 2H), 4.60 (s, 2H), 4.26−3.97 (m, 6H), 3.16 (s, 2H), 1.34 (s, 18H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 156.3 (s), 144.6 (s), 140.9 (s), 136.4 (s), 133.6 (s), 78.7 (s), 76.6 (d), 71.4 (t), 51.7 (d), 29.1 (q). Anal. Calcd for $C_{28}O_8H_{30}N_2F_{10}$: C, 47.19; H, 4.24; N, 3.93. Found: C, 47.22; H, 4.30; N, 3.82.

2,5-Bis[*N*-(*tert*-butoxycarbonyl)amino]-2,5-dideoxy-1,6-di-*O*-(1′-naphthyl)-L-iditol, 10 h. Synthesized by the same method as for **10a** in 45% yield: $[\alpha]_D$ −6.61 (c = 1.18, $CHCl_3$); ^{1}H NMR (100 MHz, $CDCl_3$) δ 8.06 (m, 2H), 7.79 (m, 2H), 7.50−7.15 (m, 8H), 6.76 (m, 2H), 5.40 (d, J = 7.2 Hz, 2H), 4.52−4.04 (m, 8H), 1.41 (s, 18H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 160.0 (s), 157.3 (s), 134.1 (s), 127.0 (d), 126.6 (d), 125.8 (d), 125.4 (s), 125.0 (d), 121.4 (d), 120.1 (d), 105.0 (d), 80.0 (s), 74.5 (d), 70.3 (t), 48.2 (d), 28.3 (q). Anal. Calcd for $C_{36}O_8H_{44}N_2$: C, 68.33; H, 7.01; N, 4.43. Found: C, 68.56; H, 7.09; N, 4.31.

2,5-Bis[*N*-(*tert*-butoxycarbonyl)amino]-1,6-di-*O*-cyclohexyl-2,5-dideoxy-L-iditol, 10i. Synthesized by the same method as for **10a** in 36% yield: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.13 (d, J = 7.7 Hz, 2H), 3.98 (m, 2H), 3.80 (s, 2H), 3.64 (m, 6H), 3.27 (m, 2H), 1.88 (m, 4H), 1.71 (m, 4H), 1.44 (br s, 20H), 1.23 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 156.0 (s), 79.4 (s), 78.0 (d), 72.0 (d), 69.0 (t), 50.7 (d), 31.9 (t), 28.4 (q), 25.7 (t), 23.8 (t).

2,5-Bis[*N*-(*tert*-butoxycarbonyl)amino]-2,5-dideoxy-1,6-di-*O*-isobutyl-L-iditol, 10j. Synthesized by the same method as for **10a** in 36% yield: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.12 (d, J = 8.9 Hz, 2H), 3.99 (br s, 2H), 3.77 (s, 2H), 3.64−3.49 (m, 6H), 3.21 (d, J = 6.7 Hz, 4H), 1.85 (nonet, J = 6.7 Hz, 2H), 1.44 (s, 18H), 0.89 (d, J = 6.7 Hz, 12H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 156.0 (s), 79.5 (s), 78.3 (d), 72.0 (t), 50.5 (d), 28.3 (q, d), 19.3 (q).

1,2:5,6-Dianhydro-3,4-*O*-isopropylidene-D-iditol, 13. To a cooled (−80 °C) solution of 3,4-*O*-isopropylidene-L-mannitol, **12** (20.0 g, 90 mmol), in pyridine/CH_2Cl_2 (1:1, 1.0 L) was added benzoyl chloride (20 mL, 172 mmol) in CH_2Cl_2 (20 mL) dropwise. After stirring for 1.5 h, the reaction mixture was allowed to slowly warm to 0 °C. The reaction mixture was then added to cold (0 °C) 6 N HCl (500 mL) and the aqueous layer extracted with CH_2Cl_2 (150 mL). The combined organic layers were washed with 3% aqueous Na_2CO_3 (100 mL), dried ($MgSO_4$), and concentrated in vacuo to give a syrup that was used without further purification.

To a cooled (0 °C) solution containing the crude dibenzoate, triethylamine (25 mL, 180 mmol), and *N*,*N*-dimethyl-4-aminopyridine (2.2 g, 18 mmol) in dichloromethane (150 mL) was added tosyl chloride (34.3 g, 180 mmol) portionwise. The reaction mixture was stirred at 0 °C for 1 h and then allowed to warm to room temperature and stirred for 16 h. It was then added to cold (0 °C) 3 N HCl (50 mL) and the aqueous layer extracted with CH_2Cl_2 (50 mL). The combined organic layers were washed with saturated aqueous NaCl (50 mL), dried ($MgSO_4$), and concentrated in vacuo to give a syrup that was used without further purification.

The syrup was dissolved in CH_2Cl_2/MeOH (5:6, 550 mL) and K_2CO_3 (62 g, 449 mmol) added. After 2.5 h, H_2O (300 mL) was added and the aqueous layer extracted with CH_2Cl_2 (150 mL). The combined organic layers were washed with saturated aqueous NH_4Cl (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The syrup was purified by flash column chromatography (4:1 $PhCH_3$/EtOAc) to give 3.50 g of **13** (21% yield): ^{1}H NMR (100 MHz, $CDCl_3$) δ 3.83 (dd, J = 3.3, 1.5 Hz, 2H), 3.08 (m, 2H), 2.84 (dd, J = 5.1, 4.1 Hz, 1H), 2.63 (ddd, J

= 5.2, 2.6, 0.8 Hz, 1H), 1.41 (s, 6H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 110.2 (s), 77.8 (d), 50.8 (d), 43.5 (t), 26.5 (q).

3,4-*O*-Isopropylidene-1,6-di-*O*-phenyl-D-iditol, 14. To 1,2:5,6-dianhydro-3,4-*O*-isopropylidene-D-iditol, **13** (0.50 g, 2.69 mmol), and phenol (1.03 g, 10.9 mmol) in DMF (20 mL) was added K_2CO_3 (0.18 g, 1.4 mmol). The reaction mixture was heated to 110 °C for 16 h. The reaction mixture was then diluted with Et_2O (120 mL), washed with saturated aqueous NH_4Cl (30 mL) and H_2O (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (4:1 $PhCH_3$/EtOAc) to give 0.96 g of the product (96% yield): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.25 (t, J = 7.6 Hz, 4H), 6.94 (t, J = 7.3 Hz, 2H), 6.89 (d, J = 8.5 Hz, 4H), 4.33 (s, 2H), 4.08−4.00 (m, 6H), 2.66 (d, J = 5.5 Hz, 2H), 1.46 (s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 158.4 (s), 129.6 (d), 121.3 (d), 114.6 (d), 110.1 (s), 77.1 (d), 69.4 (d), 68.6 (t), 27.2 (q).

2,5-Diazido-2,5-dideoxy-3,4-*O*-isopropylidene-1,6-di-*O*-phenyl-L-mannitol, 15. To a cooled (−5 °C) solution of DIAD (0.54 mL, 2.7 mmol) in THF (0.5 mL) were added 3,4-*O*-isopropylidene-1,6-di-*O*-phenyl-L-iditol (0.50 g, 1.34 mmol) in THF (5 mL) and Ph_3P (0.70 g, 2.67 mmol). After 15 min, DPPA (0.67 mL, 3.11 mmol) was added and the reaction mixture allowed to warm to room temperature. After stirring overnight, the solvent was removed in vacuo to give a yellow oil. The crude material was purified by flash column chromatography ($PhCH_3$) to give 0.30 g of the diazide (53% yield) as a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.30 (t, J = 7.8 Hz, 4H), 6.98 (t, J = 7.2 Hz, 2H), 6.93 (d, J = 8.4 Hz, 4H), 4.36 (dd, J = 3.6, 10.2 Hz, 2H), 4.20 (dd, J = 1.8, 5.4 Hz, 2H), 4.11 (dd, J = 7.2, 9.6 Hz, 2H), 3.97 (m, 2H), 1.44 (s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 158.0 (s), 129.6 (d), 121.5 (d), 114.6 (d), 111.2 (s), 78.0 (d), 68.1 (t), 62.6 (d), 27.4 (q).

2,5-Diazido-2,5-dideoxy-1,6-di-*O*-phenyl-L-mannitol. To 2,5-diazido-2,5-dideoxy-3,4-*O*-isopropylidene-1,6-di-*O*-phenyl-D-mannitol (0.10 g, 0.24 mmol) was added a cold (0 °C) solution of acetyl chloride (0.142 mL, 2.00 mmol) in MeOH (5 mL) which had been stirring for 10 min. After stirring for 24 h at room temperature, the reaction mixture was diluted with H_2O (10 mL), extracted with Et_2O (20 mL), dried ($MgSO_4$), and concentrated in vacuo to give an oil. The crude product was purified by flash column chromatography (4:1 $PhCH_3$/EtOAc) to give 0.060 g of the diazide diol (66% yield) as a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.31 (dd, J = 8.1, 7.6 Hz, 4H), 7.00 (t, J = 7.2 Hz, 2H), 6.95 (d, J = 8.7 Hz, 4H), 4.41 (dd, J = 9.8, 2.8 Hz, 2H), 4.23 (dd, J = 9.9, 5.9 Hz, 2H), 3.95 (m, 4H), 2.82 (d, J = 5.8 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 158.0 (s), 129.7 (d), 121.7 (d), 114.7 (d), 69.3 (d), 68.3 (t), 61.7 (d).

2,5-Bis[*N*-(*tert*-butoxycarbonyl)amino]-2,5-dideoxy-1,6-di-*O*-phenyl-L-mannitol, 11. To 2,5-diazido-2,5-dideoxy-1,6-di-*O*-phenyl-D-mannitol (0.10 g, 0.26 mmol) and Boc_2O (0.1154 g, 0.529 mmol) in EtOAc (4 mL) was added Pd/C (10%, 0.0612 g). Hydrogen was added (with flushing) at atmospheric pressure to the system and the reaction mixture stirred for 4 h. The suspension was then filtered through Celite and concentrated in vacuo to give a colorless solid. This was purified by flash column chromatography (4:1 $PhCH_3$/EtOAc) to give 0.078 g of **11** (58% yield) as a solid: mp 125 °C; $[\alpha]_D$ +48.20 (c = 0.4, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.26 (dd, J = 8.2, 7.2 Hz, 4H), 6.96 (t, J = 7.2 Hz, 2H), 6.89 (d, J = 8.2 Hz, 4H), 5.32 (d, J = 8.7 Hz, 2H), 4.60 (d, J = 7.7 Hz, 2H), 4.31 (d, J = 4.6 Hz, 2H), 4.09−3.92 (m, 4H), 3.76 (dd, J = 10.3, 4.9 Hz, 2H), 1.43 (s, 18H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 158.6 (s), 157.2 (s), 129.5 (d), 121.1 (d), 114.5 (d), 80.7 (s), 68.3 (t), 66.8 (d), 50.7 (d), 28.3 (q). Anal. Calcd for $C_{28}O_8H_{40}N_2$: C, 63.14; H, 7.57; N, 5.26. Found: C, 63.32; H, 7.49; N, 5.13.

5-*N*-(Benzyloxycarbonyl)-2,3-*N*,*O*-carbonyl-2,5-diamino-2,5-dideoxy-1,6-di-*O*-phenyl-L-iditol, 17. To **9a** (0.303 g, 0.79 mmol) in EtOAc (20 mL) was added Pd/C (10%, 0.087 g). Hydrogen was added (with flushing) at atmospheric pressure to the system and the reaction mixture stirred for 16 h. The suspension was then filtered through Celite and concentrated in vacuo to give a colorless solid. This was dissolved in CH_2Cl_2 (10 mL), and benzyl chloroformate (3.0 g, 17.5 mmol) and triethylamine (1.1 g, 10.8 mmol) were added. The reaction mixture was stirred overnight at room temperature, and the solution was washed with water (10 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash column chromatography (1:1 $PhCH_3$/EtOAc) gave 0.110 g of the product (28% yield): $[\alpha]_D$ −33.51 (c = 0.57, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.25−7.12 (m, 9H), 6.92 (t, J = 7.3 Hz, 1H), 6.91 (t, J = 7.4 Hz, 1H), 6.84 (d, J = 9.6 Hz, 2H), 6.80 (d, J = 9.2 Hz, 2H), 6.46 (s, 1H), 5.71 (d, J = 8.9 Hz, 1H), 5.05 (d, J = 12.1 Hz, 1H), 4.99 (d, J = 12.5 Hz, 1H), 4.40 (t, J = 5.2 Hz, 1H), 4.33 (d, J = 5.3 Hz, 1H), 4.17 (m, 1H), 4.03 (m, 4H), 3.85 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 159.1 (s), 158.2 (s), 158.0 (s), 156.6 (s), 136.2 (s), 129.5 (d), 128.5 (d), 128.2 (d), 128.0 (d), 121.5 (d), 121.3 (d) 114.7 (d), 79.5 (d), 70.6 (d), 68.7 (t), 67.1 (t), 66.8 (t), 53.7 (d), 51.2 (d). Anal. Calcd for $C_{27}O_7H_{28}N_2$: C, 65.84; H, 5.73; N, 5.69. Found: C, 66.09; H, 5.89; N, 5.83.

5-*N*-(Benzyloxycarbonyl)-2,3-*N*,*O*-carbonyl-2,5-diamino-2,5-dideoxy-1,6-di-*O*-phenyl-L-altritol, 18. To CrO_3 (0.0195 g, 0.195 mmol) and acetic anhydride (0.02 g, 0.20 mmol) in CH_2Cl_2 (5 mL) was added pyridine (0.031 g, 0.39 mmol). After 5 min, the alcohol (0.044 g, 0.089 mmol) in CH_2Cl_2 (10 mL) was added. The reaction mixture was stirred for 3 h and the solvent removed in vacuo. The residue was filtered through a SiO_2 column (EtOAc) to give 0.050 g of the crude ketone.

This crude product was dissolved in MeOH (5 mL) and $NaBH_4$ (0.0152 g, 0.40 mmol) added. After 1 h, the reaction mixture was partitioned between H_2O (20 mL) and EtOAc (30 mL). The organic layer was washed with H_2O (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (1:1 $PhCH_3$/EtOAc) to give 0.034 g of an inseparable mixture of **18** and **17** (∼0.85:1 by NMR, 77% yield): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.25−7.12 (m, 9H), 6.92 (t, J = 7.3 Hz, 1H), 6.91 (t, J = 7.4 Hz, 1H), 6.84 (d, J = 9.6 Hz, 2H), 6.80 (d, J = 9.2 Hz, 2H), 6.15 (s, 1H), 5.58 (d, J = 9.9 Hz, 1H), 5.04 (s, 1H), 4.99 (s, 1H), 4.50 (t, J = 4.3 Hz, 1H), 4.33 (m, 1H), 4.17 (m, 1H), 4.03 (m, 4H), 3.85 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 158.7 (s), 158.2 (s), 158.0 (s), 156.6 (s), 136.0 (s), 129.5 (d), 128.5 (d), 128.2 (d), 128.0 (d), 121.5 (d), 121.3 (d) 114.7 (d), 78.5 (d), 71.3 (d), 69.3 (t), 67.3 (t), 66.8 (t), 52.7 (d), 51.1 (d). Anal. Calcd for $C_{27}O_7H_{28}N_2\cdot 0.5H_2O$: C, 64.65; H, 5.83; N, 5.59. Found: C, 64.43; H, 5.73; N, 5.35.

2,5-Bis[*N*-(*tert*-butoxycarbonyl)amino]-2,5-dideoxy-1,6-di-*O*-phenyl-L-altritol, 16. To the mixture of alcohols (0.034 g, 0.069 mmol) in dioxane (2.0 mL) was added $Ba(OH)_2\cdot 8H_2O$ (0.107 g, 0.34 mmol) in water (1.3 mL). The reaction mixture was heated to 80 °C for 24 h. The suspension was then filtered, and the solids were washed with acetone (20 mL). The organic solvents were removed in vacuo and the aqueous remainder was diluted with H_2O (20 mL) and extracted with EtOAc (2 × 30 mL) and CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried (K_2CO_3) and concentrated in vacuo. The residue was dissolved in EtOAc (3.5 mL) and Boc_2O (0.079 g, 0.036 mmol) added. After 4 h, the solvent was removed in vacuo. The residue was purified by flash column chromatography (2:1 $PhCH_3$/EtOAc) to give 0.015 g of **16** (91% yield) along with 0.012 g of the **10a**: $[\alpha]_D$ +32.60 (c = 0.8, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.28 (t, J = 7.9 Hz, 4H), 6.97 (t, J = 7.3 Hz, 1H), 6.97 (t, J = 7.5 Hz, 1H), 6.90 (d, J = 7.6 Hz, 2H), 6.87 (d, J = 7.6 Hz, 2H), 5.32 (d, J = 8.9 Hz, 1H), 5.15 (d, J = 9.2 Hz, 1H), 4.32 (m, 2H), 4.24 (m, 4H), 4.10 (s, 2H), 4.00 (m, 1H), 3.70 (m, 1H), 1.46 (s, 9H), 1.45 (s, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 158.2 (s), 157.5 (s), 155.8 (s), 129.6 (d), 121.5 (d), 121.4 (d) 114.7 (d), 80.7 (s), 79.9 (s), 72.7 (d), 71.6 (d), 69.0 (t), 67.0 (t), 51.2 (d), 50.3 (d), 28.3 (q), 27.4 (q). Anal. Calcd for $C_{28}O_8H_{40}N_2$: C, 63.14; H, 7.57; N, 5.26. Found: C, 63.22; H, 7.62; N, 5.27.

2,5-Bis[*N*-(*tert*-butoxycarbonyl)amino]-2,5-dideoxy-1,6-di-*O*-phenyl-3,4-*O*-thiocarbonyl-L-iditol, 20. To a stirred solution of **10a** (0.572 g, 1.10 mmol) in THF (10 mL) was added *N*,*N*′-thiocarbonyldiimidazole (0.317 g, 1.78 mmol). The reaction mixture was stirred at 55 °C for 22 h and then concentrated in vacuo. The residue was purified by flash column chromatography (19:1 $PhCH_3$/EtOAc) to give 0.433 g of **20** (70%

yield) along with 0.075 g of the corresponding carbonate (12% yield): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.27 (dd, J = 8.2, 7.6 Hz, 4H), 6.97 (t, J = 7.3 Hz, 2H), 6.88 (d, J = 8.1 Hz, 4H), 5.18 (s, 2H), 4.88 (d, J = 9.5 Hz, 2H), 4.39 (m, 2H), 4.07 (m, 4H), 1.46 (s, 18H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 190.7 (s), 157.7 (s), 155.6 (s), 129.6 (d), 121.7 (d), 114.7 (d), 82.8 (d), 81.0 (s), 66.3 (t), 50.4 (d), 28.2 (q). Anal. Calcd for $C_{29}O_8H_{38}N_2S$: C, 60.61; H, 6.66; N, 4.88; S, 5.58. Found: C, 60.83; H, 6.50; N, 4.87; S, 5.34.

2,5-Bis[*N*-(*tert*-butoxycarbonyl)amino]-3,4-*O*-carbonyl-2,5-dideoxy-1,6-di-*O*-phenyl-L-iditol. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.28 (t, J = 7.8 Hz, 4H), 6.98 (t, J = 7.4 Hz, 2H), 6.89 (d, J = 7.8 Hz, 4H), 4.95 (s, 2H), 4.86 (d, J = 9.4 Hz, 2H), 4.34 (m, 2H), 4.11 (td, J = 9.4, 7.2 Hz, 2H), 4.04 (td, J = 9.6, 7.8 Hz, 2H), 1.46 (s, 18H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 157 0.8 (s), 155.6 (s), 153.9 (s), 129.6 (d), 121.7 (d), 114.7 (d), 80.9 (s), 77.9 (d), 66.6 (t), 50.5 (d), 28.2 (q).

2,5-Bis[*N*-(*tert*-butoxycarbonyl)amino]-2,4,5-trideoxy-1,6-di-*O*-phenyl-L-iditol, 19. A solution of **20** (0.176 g, 0.314 mmol), tributyltin hydride (0.20 mL, 0.74 mmol), and AIBN (0.011 g, 0.067 mmol) in dry toluene (5 mL) was added dropwise to refluxing toluene (6.5 mL) over 25 min. After an additional 45 min, the reaction mixture was allowed to cool, and the solution was concentrated in vacuo. The residue was dissolved in acetonitrile (20 mL) and washed with hexane (4 × 10 mL). The acetonitrile layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash column chromatography (4:1 $PhCH_3$/EtOAc) to give 0.093 g of **19** (59% yield) along with small amounts of **21**−**23**: $[\alpha]_D$ +21.59 (c = 0.91, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.31−7.24 (m, 4H), 6.95 (t, J = 7.5 Hz, 2H), 6.91−6.85 (m, 4H), 5.40 (d, J = 7.7 Hz, 1H), 5.23 (d, J = 9.2 Hz, 1H), 4.25 (dd, J = 9.5, 3.4 Hz, 1H), 4.16−3.96 (m, 5H), 3.84 (m, 1H), 3.11 (dd, J = 9.1, 6.3 Hz, 1H), 1.98 (m, 2H), 1.44 (s, 18H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 158.0 (s), 155.8 (s), 155.5 (s), 129.3 (d), 121.0 (d), 114.4 (d), 79.7 (s), 79.6 (s), 69.5 (d), 69.2 (t), 68.7 (t), 53.1 (d), 48.3 (d), 36.6 (t), 28.4 (q). Anal. Calcd for $C_{28}O_7H_{40}N_2$: C, 65.09; H, 7.80; N, 5.42. Found: C, 65.26; H, 7.82; N, 5.60.

2,5-Bis[*N*-(*tert*-butoxycarbonyl)amino]-2,5-dideoxy-3,4-*O*-methylene-1,6-di-*O*-phenyl-L-iditol, 21: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.28 (t, J = 7.9 Hz, 4H, *H*2′, *H*6′), 6.98 (t, J = 7.3 Hz, 2H, *H*4′), 6.93 (d, J = 8.2 Hz, 4H, *H*3′, *H*5′), 5.04 (s, 2H, OCH_2O), 4.99 (d, J = 8.8 Hz, 2H, N*H*), 4.37 (d, J = 7.3 Hz, 2H, OC*H*), 4.24 (m, 2H, OC*H*aHb), 4.07 (m, 4H, OCHa*H*b, NC*H*), 1.48 (s, 18H, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$) δ 158.4 (s), 155.4 (s), 129.5 (d), 121.2 (d), 114.5 (d), 94.5 (t), 80.0 (s), 77.2 (d), 66.9 (t), 51.3 (d), 28.4 (q).

2-Amino-5-[*N*-(*tert*-butoxycarbonyl)amino]-2,3-*N*,*O*-carbonyl-2,4,5-trideoxy-1,6-di-*O*-phenyl-L-iditol, 22: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.29 (t, J = 7.7 Hz, 2H, *H*3′), 7.27 (t, J = 7.9 Hz, 2H, *H*3″), 6.97 (t, J = 7.3 Hz, 2H, *H*4′, *H*4″), 6.89 (d, J = 7.7 Hz, 2H, *H*2′), 6.87 (d, J = 7.5 Hz, 2H, *H*2″), 5.94 (s, 1H, C2*NH*), 5.04 (d, J = 8.9 Hz, 1H, C5N*H*), 4.52 (td, J = 6.5, 4.0 Hz, 1H, COOC*H*), 4.15 (td, J = 8.5, 4.0 Hz, 1H, NC5*H*), 4.07−3.92 (m, 5H, OCH_2, NC2*H*), 2.10−2.30 (m, 2H, CH_2), 1.45 (s, 9H, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$) δ 158.5 (s, C2NH*C*O), 158.3 (s, *C*1′), 158.0 (s, *C*1″), 155,5 (s, $(CH_3)_3COCO$), 129.6 (d, *C*3′, *C*3″), 121.6 (d, *C*4′), 121.4 (d, *C*4″), 114.6 (d, *C*2′, *C*2″), 80.1 (s, $(CH_3)_3CO$), 76.8 (d, *C*3), 69.5 (t, *C*2), 69.2 (t, *C*5), 56.9 (d, *C*5), 46.9 (d, *C*2), 37.1 (t, *C*4), 28.3 (q, CH_3).

2,5-Bis[*N*-(*tert*-butoxycarbonyl)amino]-3,4-*O*,*S*-carbonyl-2,4,5-trideoxy-1,6-di-*O*-phenyl-4-thio-L-iditol, 23: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.31 (t, J = 8.4 Hz, 2H, *H*3″), 7.26 (t, J = 8.2 Hz, 2H, *H*3′), 6.99 (t, J = 7.2 Hz, 1H, *H*4″), 6.97 (t, J = 7.4 Hz, 1H, *H*4′), 6.90 (d, J = 8.1 Hz, 2H, *H*2″), 6.87 (d, J = 8.3 Hz, 2H, *H*2′), 5.29 (dd, J = 8.9, 1.3 Hz, 1H, C5N*H*), 4.88 (d, J = 9.5 Hz, 1H, C2N*H*), 4.76 (d, J = 8.6 Hz, 1H, COOC*H*), 4.62−4.49 (m, 2H, NC*H*), 4.32 (dd, J = 8.4, 1.6 Hz, 1H, SC*H*), 4.07 (m, 3H, OCH_2), 3.98 (dd, J = 9.5, 2.8 Hz, 1H, OC1*H*aHb), 1.48 (s, 9H, CH_3), 1.45 (s, 9H, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$) δ 172.2 (s, S*C*OO), 158.1 (s, *C*1″), 157.7 (s, *C*1′), 155.9 (s, O*C*OO), 155.4 (s, O*C*OO), 129.7 (d, *C*3″), 129.5 (d, *C*3′), 121.8 (d, *C*4″), 121.5 (d, *C*4′), 114.8 (d, *C*2″), 114.4 (d, *C*2′), 82.1 (d, *C*3), 80.7 (s, *C*$(CH_3)_3$), 69.7 (t, *C*1), 67.4 (t, *C*6), 53.0 (d, *C*4), 50.2 (d, *C*5), 49.0 (d, *C*2), 28.3 (q, CH_3). Anal. Calcd for $C_{29}O_8H_{38}N_2S$: C, 60.61; H, 6.66; N, 4.88; S, 5.58. Found: C, 60.76; H, 6.57; N, 4.75; S, 5.43.

2,5-Bis[*N*-(*tert*-butoxycarbonyl)amino]-2,4,5-trideoxy-3-*O*-(4-nitrobenzoyl)-1,6-di-*O*-phenyl-L-mannitol. To a solution of **19** (0.029 g, 0.058 mmol), Ph_3P (0.067 g, 0.26 mmol), and *p*-nitrobenzoic acid (0.0415 g, 0.248 mmol) in THF (1 mL) was added DEAD (0.040 mL, 0.254 mmol). After stirring overnight, the solvent was removed in vacuo to give a yellow oil. The crude material was purified by flash column chromatography (9:1 $PhCH_3$/EtOAc) to give 0.052 g of the crude *p*-nitrobenzoate ester which was used in the next step: ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.21 (d, J = 8.7 Hz, 2H), 8.12 (d, J = 8.6 Hz, 2H), 7.26 (t, J = 7.7 Hz, 4H), 6.97 (t, J = 7.3 Hz, 1H), 6.95, J = 7.3 Hz, 1H), 6.86 (d, J = 8.6 Hz, 4H), 5.50 (m, 1H), 5.25 (d, J = 9.2 Hz, 1H), 4.89 (d, J = 9.6 Hz, 1H), 4.46 (m, 1H), 4.25−4.00 (m, 5H), 2.25 (m, 2H), 1.42 (s, 9H), 1.36 (s, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.3 (s), 158.5 (s), 158.1 (s), 155.4 (s), 155.2 (s), 150.4 (s), 135.8 (s), 130.8 (d), 129.6 (d), 128.9 (d), 121.5 (d), 121.2 (d), 114.5 (d), 114.4 (d), 80.1 (s), 79.7 (s), 73.2 (d), 70.2 (t), 67.0 (t), 52.0 (d), 46.6 (d), 33.0 (t), 28.3 (q).

2,5-Bis[*N*-(*tert*-butoxycarbonyl)amino]-2,4,5-trideoxy-1,6-di-*O*-phenyl-L-mannitol, 24. To a solution of the crude ester (0.038 g theoretical, 0.058 mmol) in a mixture of EtOH/H_2O/THF (5 mL, 2:1:2) was added LiOH (0.0086 g, 0.36 mmol). After 1 h, the reaction mixture had turned yellow, and it was added to Et_2O (20 mL) and saturated aqueous NH_4Cl (10 mL). The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (9:14:1 $PhCH_3$/EtOAc) to give 0.024 g of **24** (82% yield): $[\alpha]_D$ +2.63 (c = 0.99, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.26 (m, 4H), 6.96 (t, J = 6.6 Hz, 2H), 6.88 (d, J = 7.7 Hz, 2H), 6.86 (d, J = 7.7 Hz, 2H), 5.17 (d, J = 8.8 Hz, 1H), 5.15 (d, J = 7.3 Hz, 1H), 4.35 (dd, J = 9.2, 3.0 Hz, 1H), 4.29 (m, 1H), 4.22 (m, 1H), 4.05 (dd, J = 9.0, 3.0 Hz, 1H), 3.96 (dd, J = 9.1, 3.0 Hz, 1H), 3.86 (m, 2H), 1.70 (m, 2H), 1.43 (s, 9H), 1.43 (s, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 158.7 (s), 158.4 (s), 157.3 (s), 155.6 (s), 129.5 (d), 129.5 (d), 121.3 (d), 121.0 (d), 114.5 (d), 114.4 (d), 80.3 (s), 79.6 (s), 70.3 (d), 67.8 (t), 66.9 (t), 53.9 (d), 47.1 (d), 37.4 (t), 28.4 (q), 28.3 (q). Anal. Calcd for $C_{28}O_7H_{40}N_2$: C, 65.09; H, 7.80; N, 5.42. Found: C, 65.21; H, 7.95; N, 5.39.

1,2-Anhydro-3,4-*O*-isopropylidene-6-*O*-phenyl-D-mannitol, 26. To **6** (0.50 g, 2.7 mmol) and phenol (0.58 g, 6.2 mmol) in DMF (20 mL) was added K_2CO_3 (0.13 g, 1.3 mmol). The reaction mixture was heated to 90 °C and stirred overnight. After cooling, the reaction mixture was added to saturated aqueous NH_4Cl (20 mL) and extracted with Et_2O (20 mL). The organic phase washed with H_2O (2 × 10 mL), dried ($MgSO_4$), and concentrated to give a solid. Purification by flash column chromatography (4:1 $PhCH_3$/EtOAc) gave **26** (0.23 g, 31% yield, 45% yield based on recovered starting material) along with **7a** (0.23 g, 23% yield) and **6** (0.16 g, 31% yield): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.29 (t, J = 8.0 Hz, 2H), 6.97 (m, 3H), 4.29 (d, J = 8.0, 1H), 4.11−4.00 (m, 4H), 3.20 (m, 1H), 2.89 (m, 1H), 2.83 (dd, J = 4.9, 2.7 Hz, 1H), 1.45 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 158.5 (s), 129.5 (d), 121.2 (d), 114.7 (d), 110.2 (s), 79.0 (d), 78.3 (d), 71.1 (t), 69.0 (d), 52.1 (d), 45.6 (t), 27.0 (q), 26.7 (q). Anal. Calcd for $C_{15}O_5H_{20}$·0.15 C_7H_8: C, 65.54; H, 7.26. Found: C, 67.20; H, 6.11.

1-Deoxy-3,4-*O*-isopropylidene-1-phenyl-6-*O*-phenyl-D-mannitol 27. To a cold (−78 °C) suspension of **26** (0.50 g, 1.8 mmol) and CuBr·SMe_2 (0.18 g, 0.9 mmol) in THF (10 mL), was added dropwise PhLi (1.0 M in benzene, 7.1 mmol). After stirring for 1 h at −78 °C, the reaction mixture was allowed to warm to room temperature. After an additional hour, saturated aqueous NH_4Cl (10 mL) was added. The organic layer was washed with H_2O (2 × 10 mL), and the aqueous layers were back-extracted with Et_2O (30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (9:1 → 4:1 $PhCH_3$/EtOAc) to give **27** (0.55 g, 86% yield): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.32−7.24 (m, 7H), 6.98−6.91 (m, 3H), 4.26 (d, J = 8.3 Hz, 1H), 4.02 (dd, J = 9.4, 2.3 Hz, 1H), 3.97 (m,

2H), 3.85 (m, 2H), 3.55 (s, 1H), 3.18 (dd, J = 14.4, 2.4 Hz, 1H), 3.11 (s, 1H), 2.74 (dd, J = 13.8, 8.2 Hz, 1H), 1.43 (s, 3H), 1.41 (s, 3H).

2,5-Diazido-1,2,5-trideoxy-3,4-*O*-isopropylidene-1-phenyl-6-*O*-phenyl-L-iditol. To a cooled (−5 °C) solution of DIAD (0.43 g, 2.5 mmol) in THF (1 mL) was added **27** (0.40 g, 1.1 mmol) in THF (5 mL) and Ph_3P (0.64 g, 2.5 mmol). After 15 min, DPPA (0.77 g, 2.8 mmol) was added and the reaction mixture allowed to warm to room temperature. After stirring overnight, the solvent was removed in vacuo to give a yellow oil. The crude material was purified by flash column chromatography (2:1 petroleum ether/$PhCH_3$ → 9:1 $PhCH_3$/EtOAc) to give a mixture of the product and the elimination product (0.297 g, ∼2:3 by ^{1}H NMR) which was used in the next step.

2,5-Diazido-1,2,5-trideoxy-1-phenyl-6-*O*-phenyl-L-iditol, 28. To cold (0 °C) methanol (10 mL) was added acetyl chloride (0.52 g, 6.6 mmol). After stirring for 10 min, the solution was added to the crude diazide (0.297 g, ∼0.29 mmol) and stirred overnight at room temperature. The reaction mixture was concentrated, diluted with H_2O (20 mL), and extracted with Et_2O (20 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo to give an oil. This oil was purified by flash column chromatography (4:1 $PhCH_3$/EtOAc) to give **28** (0.075 g, 18% yield for two steps): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.32−7.22 (m, 7H), 6.99 (td, J = 7.3, 0.7 Hz, 1H), 6.89 (dd, J = 7.9, 0.8 Hz, 2H), 4.24 (m, 2H), 3.94−3.82 (m, 2H), 3.65 (m, 2H), 3.10 (dd, J = 5.6, 13.6 Hz, 1H), 3.01−2.93 (m, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 157.9 (s), 136.7 (s), 129.6 (d), 129.3 (d), 128.8 (d), 127.1 (d), 121.7 (d), 114.6 (d), 72.1 (d), 71.4 (d), 68.0 (t), 64.8 (d), 62.3 (d), 36.7 (t).

2,5-Bis[*N*-(*tert*-butoxycarbonyl)amino]-1,2,5-trideoxy-1-phenyl-6-*O*-phenyl-L-iditol, 25. To **28** (0.21 g, 0.57 mmol) and Boc_2O (0.28 g, 1.3 mmol) in EtOAc (6 mL) was added Pd/C (10%, 0.062 g). Hydrogen was added (with flushing) at atmospheric pressure to the system and the reaction mixture stirred for 3 h. The suspension was then filtered through Celite and concentrated. The crude product was purified by flash column chromatography (6:1 $PhCH_3$/EtOAc) to give **25** (0.245 g, 85% yield) as an oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.29−7.16 (m, 7H), 6.94 (t, J = 7.4 Hz, 1H), 6.87 (d, J = 8.0 Hz, 2H), 5.09 (d, J = 8.0 Hz, 1H), 4.91 (d, J = 8.5 Hz, 1H), 4.01 (br s, 3H), 3.93−3.83 (m, 3H), 3.66 (br s, 1H), 3.51 (br s, 1H), 3.04−2.87 (m, 2H), 1.38 (s, 18H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 158.3 (s), 156.1 (s), 138.5 (s), 129.5 (d), 129.3 (d), 128.4 (d), 126.3 (d), 121.2 (d), 114.6 (d), 79.9 (s), 72.2 (d), 68.5 (t), 53.1 (d), 50.5 (d), 38.1 (t), 28.3 (q). Anal. Calcd for: $C_{28}O_7H_{40}N_2 \cdot 0.5\ H_2O$: 63.98; H, 7.86; N, 5.33. Found: C, 63.68; H, 7.20; N, 6.02.

Supporting Information Available: Experimental procedures for compounds **7b**−**h**, **8b**−**j** and **9b**−**j** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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