Electrophilic Azidation for Stereoselective Synthesis of 2-Azido-2-deoxyaldono-1,5-lactones

J. S. Dileep Kumar,† François-Yves Dupradeau,‡ M. Jane Strouse,§ Michael E. Phelps,† and Tatsushi Toyokuni*,†

Crump Institute for Molecular Imaging, Department of Molecular and Medical Pharmacology, UCLA School of Medicine, Los Angeles, California 90095-1770, and Department of Chemistry and Biochemistry, UCLA, Los Angeles, California 90095-1569

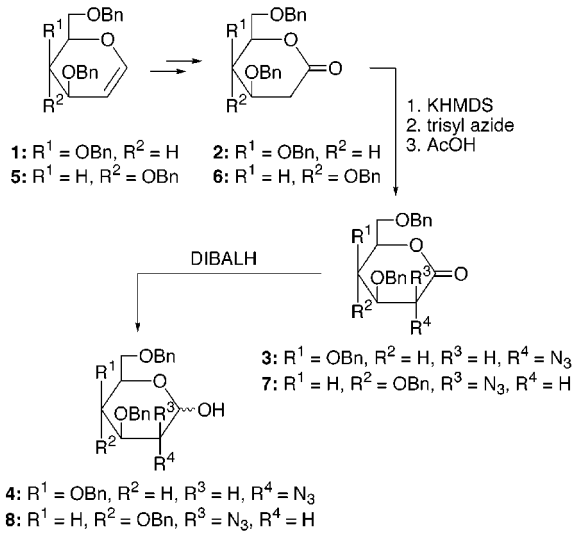
ttoyokuni@mednet.ucla.edu

Received November 8, 2000

Introduction

Aldonolactones are versatile chiral synthons for the synthesis of various natural products and their analogues.[1] Aldonolactones derived from 2-azido-2-deoxyaldoses are of particular interest for the synthesis of highly functionalized α-amino acids and nitrogen heterocycles.[2] Although being abundant in nature, 2-amino-2-deoxysugars, except for the *gluco* derivatives, are not readily available because these sugars are difficult to isolate from natural sources. Consequently, a number of methods have been developed for the practical synthesis of 2-amino-2-deoxysugars, as exemplified by azidonitration[3] and azidophenylselenylation[4] of glycals. Both methods yield 2-azido-2-deoxysugars, which are not only the precursors for 2-amino-2-deoxysugars but are also useful glycosyl donors in oligosaccharide synthesis in which α-linked 2-amino-2-deoxysugars are required.[5] The aldonolactones are in general synthesized by oxidation of the corresponding aldoses.[6] However, oxidation of 2-azido-2-deoxyaldoses is often accompanied by partial epimerization of the azido group.[6c,7] Alternatively, 2-azido-2-deoxyaldono-1,5-lactones can be prepared by the nucleophilic azide ion displacement of 2-*O*-sulfonate lactones, which also suffer a similar epimerization.[8] It is reported that oxidation of 2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-mannopyranose (i.e., **8** in Scheme 1) resulted in a complete epimerization to the *gluco* isomer.[6c] The axial azide group at C-2 tends to epimerize during oxidation.[6c,7,9] No practical route to 2-azido-2-deoxy-D-mannono-1,5-lactone (e.g., **7**) has yet been reported.

Scheme 1



Electrophilic azide transfer from arylsulfonyl azides to enolates has proven to be a practical approach to the asymmetric synthesis of α-amino acids.[10,11] Although being highly stereoselective, this enol-azidation reaction has never been exploited for the synthesis of aminosugar derivatives. Here we report that the electrophilic azidation reaction is a highly stereoselective route to 2-azido-2-deoxyaldono-1,5-lactones.[12]

Results and Discussion

2-Deoxyaldono-1,5-lactones **2**[13] and **6**[14] (Scheme 1) were prepared from the corresponding glycals (**1**[15] and **5**,[16]

* To whom correspondence should be addressesed. Tel: (310) 206-1675. Fax: (310) 206-8975.

† School of Medicine.

‡ F.-Y.D. carried out preliminary studies at the former Biomembrane Institute, Seattle WA. Current address: Biomolécules et Pathologies Dégénératives, Faculté de Pharmacie et de Médecine, UPRES EA 2629, 1-3 rue des Louvels, 80037 Amiens Cedex 1, France.

§ Department of Chemistry and Biochemistry.

(1) Some reviews: (a) Monneret, C.; Florent, J.-C. *Synlett* **1994**, 305−318. (b) De Lederkremer, R. M.; Varela, O. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 125−209. (c) Ferrier, R. J.; Blattner, R.; Clinch, K.; Furneaux, R. H.; Gardiner, J. M.; Tyler, P. C.; Wightman, R. H.; Williams, N. R. *Carbohydr. Chem.* **1996**, *28*, 199−213. (d) Varela, O. *Pure Appl. Chem.* **1997**, *69*, 621−626. (e) Lundt, I. *Top. Curr. Chem.* **1997**, *187*, 117−156. (f) Fleet, G. W. J.; Estevez, J. C.; Smith, M. D.; Bleriot, Y.; de la Fuente, C.; Krulle, T. M.; Besra, G. S.; Brennan, P. J.; Nash, R. J.; Johnson, L. N.; Oikonomakos, N. G.; Stalmans, W. *Pure Appl. Chem.* **1998**, *70*, 279−284.

(2) For example: (a) Baird, P. D.; Dho, J. C.; Fleet, G. W.; Peach, J. M.; Prout, K.; Smith, P. W. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1785−1791. (b) Fairbanks, A. J.; Elliott, R. P.; Smith, C.; Hui, A.; Way, G.; Storer, R.; Taylor, H.; Watkin, D. J.; Winchester, B. G.; Fleet, G. W. J. *Tetrahedron Lett.* **1993**, *34*, 7953−7956. (c) Dodd, R. H. *Molecules* **2000**, *5*, 293−298.

(3) Lemieux, R. U.; Ratcliffe, R. M. *Can. J. Chem.* **1979**, *57*, 1244−1251.

(4) (a) Santoyo-González, F.; Calvo-Flores, F. G.; García-Mendoza, P.; Hernández-Mateo, F.; Isac-García, J.; Robles-Díaz, R. *J. Org. Chem.* **1993**, *58*, 6122−6125. (b) Czernecki, S.; Ayadi, E.; Randriamandimby, D. *J. Org. Chem.* **1994**, *59*, 8256−8260.

(5) Banoub, J.; Boullanger, P.; Lafont, D. *Chem. Rev.* **1992**, *92*, 1167−1195.

(6) (a) Pravdic, N.; Danilov, B.; Fletcher, H. G., Jr. *Carbohydr. Res.* **1974**, *36*, 168−180. (b) Benhaddou, R.; Czernecki, S.; Farid, W.; Ville, G.; Xie, J.; Zegar, A. *Carbohydr. Res.* **1994**, *260*, 243−250. (c) Ayadi, E.; Czernecki, S.; Xie, J. *J. Carbohydr. Chem.* **1996**, *15*, 191−199.

(7) (a) Kuzuhara, H.; Oguchi, N.; Ohrui, H.; Emoto, S. *Carbohydr. Res.* **1972**, *23*, 217−222. (b) Oxidation of 2-acetamido-2-deoxyaldoses is also reported to yield their 2-epimers, see: Pravdic, N. *Carbohydr. Res.* **1971**, *19*, 353−364.

(8) (a) Bruce, I.; Fleet, G. W. J.; Girdhar, A.; Haraldsson, M.; Peach, J. M.; Watkin, D. J. *Tetrahedron* **1990**, *46*, 19−32. (b) Fairbanks, A. J.; Ford, P. S.; Watkins, D. J.; Fleet, G. W. J. *Tetrahedron Lett.* **1993**, *34*, 3327−3330.

(9) Ali, Y.; Richardson, A. C. *Carbohydr. Res.* **1967**, *5*, 441−448.

(10) (a) Evans, D. A.; Britton, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 6881−6883. (b) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011−4030.

(11) See also a review on the electrophilic amination of carbanions: Dembech, P.; Seconi, G.; Ricci, A. *Chem. Eur. J.* **2000**, *6*, 1281−1286.

(12) A preliminary account has been published: Dupradeau, F.-Y.; Hakomori, S.; Toyokuni, T. *J. Chem. Soc., Chem. Commun.* **1995**, 221−222.

(13) Rollin, P.; Sinaÿ, P. *Carbohydr. Res.* **1981**, *98*, 139−142. This paper reported the direct oxidation of glycals to lactones. However, in our hands, this procedure yielded **2** and **6** with various amounts of α,β-unsaturated lactones (see also ref 6b).

10.1021/jo005728c CCC: $20.00
Published on Web 03/29/2001

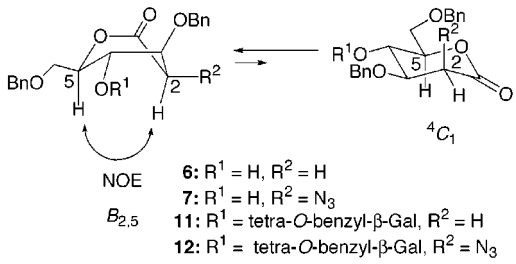
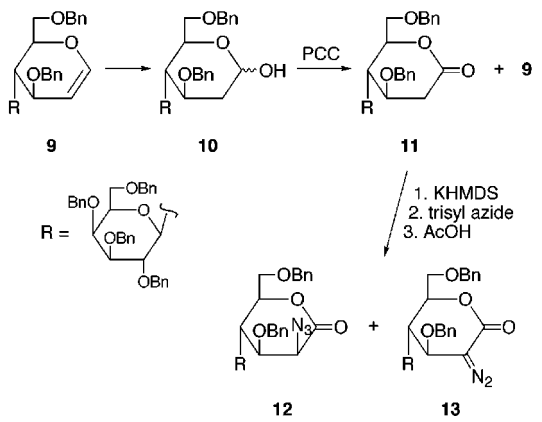


Figure 1. NOE between H-2ax and H-5 observed in **6**, **7**, **11**, and **12** implies their $B_{2,5}$ conformations.

respectively) by nucleophilic hydroxylation[17] and subsequent oxidation[6] in the overall yields of 73% and 79%, respectively. It is reported that aldono-1,5-lactones favor half-chair and boat conformations to compromise the constraints caused by the planarity of the lactone moiety.[18] Conformations of **2** and **6** were therefore established based on their ^{1}H NMR investigation.[19] The J values found for **2** were almost identical to those of tri-*O*-benzyl-2-deoxy-D-galactose[17e] except for the somewhat larger $J_{2eq,3}$ (6.5 Hz), indicating its $^4C_1$ conformation[20] with some degree of flexibility at C-2. On the other hand, **6** had $J_{2ax,3} = J_{2eq,3} = J_{3,4} = 4.5$ Hz and $J_{4,5} = 7.5$ Hz, suggesting a slightly distorted $B_{2,5}$ conformation, which was further substantiated by NOE between H-2ax and H-5 (Figure 1). Interestingly, **6** favors the $B_{2,5}$ conformation similarly to D-mannono-1,5-lactone[18c] rather than the flattened $^4C_1$ conformation of D-glucono-1,5-lactone.[18] This explains the fact that the 2-deoxy-glucono-1,5-lactone is more prone to the β-elimination reaction than the 2-deoxy-galactono-1,5-lactone.[13,21] For example, the $B_{2,5}$ conformation of **6** orients the H-2ax and the oxygen group at C-3 anticoplanar, a required configuration for the E2 reaction.

Electrophilic azidation of **2** and **6** was then carried out according to the procedure reported by Evans et al.[10] Thus, the potassium enolates derived from **2** and **6**, generated with 1.1 equiv of potassium bis(trimethylsilyl)-amide (potassium hexamethyldisilylamide, KHMDS) in THF (−90 °C, 15 min), were treated with 1.2 equiv of 2,4,6-triisopropylbenzenesulfonyl azide (trisyl azide)[22] at −90 °C for 2 min. After addition of 1.2 equiv of AcOH, the triazine intermediates were fragmented to the corresponding azides by slowly warming to room temperature (overnight). The 2-azido-2-deoxyaldono-1,5-lactones **3**[23] (from **2**) and **7** (from **6**) were isolated in 70% and 50% yields, respectively, after flash column chromatography on silica gel. In either case no corresponding 2-epimers were detected. The ^{1}H NMR data accorded with a $^4C_1$ for **3** ($J_{2,3} = 10.5$ Hz, $J_{3,4} = 2.0$ Hz, $J_{4,5} = \sim 0.5$ Hz) and a $B_{2,5}$ for **7** ($J_{2,3} = 3.5$ Hz, $J_{3,4} = 1.5$ Hz, $J_{4,5} = 6.0$ Hz, and NOE between H-2 and H-5). The azide transfer took place exclusively at more accessible equatorial positions. Electrophilic azidation of **2** thus allowed the first practical synthesis of the 2-azido-2-deoxy-D-mannono-1,5-lactone **7**. Selective reduction of **3** and **7** with DIBALH furnished the 2-azido-2-deoxyaldoses **4**[24] and **8**, respectively, without any epimerization at C-2. Electrophilic azidation and subsequent DIBALH reduction can be carried out in the same pot[25] without isolation of **3** and **7**.

Scheme 2



Next, the electrophilic azidation of a disaccharide enolate was investigated. The 2-deoxy-D-lactose **10**[26] (Scheme 2) was prepared from hexa-*O*-benzyl-D-lactal[17e] (**9**) using the mercuration−reductive demercuration sequence as reported[17e] in 80% yield. The subsequent oxidation of **10** with PCC gave the 2-deoxy-1,5-lactone **11** in 75% yield together with the lactal **9** in 15% yield. It is conceivable that **9** was formed from the α-chromate ester intermediate by competing elimination. The ^{1}H NMR data of the 2-deoxy-D-glucono-1,5-lactone moiety of **11** ($J_{2ax,3} = J_{2eq,3} = 3.0$ Hz, $J_{3,4} = 2.5$ Hz, $J_{4,5} = 6.0$ Hz, and NOE between H-2aq and H-5) were in good agreement with a slightly distorted $B_{2,5}$ conformation. Electrophilic azidation of the potassium enolate derived from **11** with trisyl azide, followed by workup similar to those described above, resulted in a stereoselective azide transfer yielding the equatorial azide derivative **12** in 60% yield, whose 1,5-lactone moiety was found to adopt a $B_{2,5}$ conformation on the basis of its ^{1}H NMR data ($J_{2,3} = 3.0$ Hz, $J_{3,4} = 1.5$ Hz, $J_{4,5} = 6.5$ Hz, and NOE between H-2 and H-5). In addition to the azide-transfer product **12**, a 15% yield of the diazo-transfer product **13** was also obtained.[27] Although diazo compounds are useful synthetic intermediates,[28] only a few diazo sugars have so

(14) Bernasconi, C.; Cottier, L.; Descotes, G.; Rémy, G. *Bull. Soc. Chim. Fr.* **1979**, *5*−*6*. II-332-II-336.
(15) Bovin, N. V.; Zurabyan, S. É.; Khorlin, Y. *Carbohydr. Res.* **1981**, *98*, 25−35.
(16) Boullanger, P.; Martin, J.-C.; Descotes, G. *J. Heterocycl. Chem.* **1975**, *12*, 91−93.
(17) For example: (a) Bolitt, V.; Mioskowski, C.; Lee, S.-G.; Falck, J. R. *J. Org. Chem.* **1990**, *55*, 5812−5813. (b) Sabesan, S.; Neira, S. *J. Org. Chem.* **1991**, *56*, 5468−5472. (c) Wild, R.; Schmidt, R. R.; *Liebigs Ann. Chem.* **1995**, 755−763. (d) Barnes, N. J.; Probert, M. A.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **1996**, 431−438. (e) Bettelli, E.; Cherubini, P.; D'Andrea, P.; Passacantilli, P.; Piancatelli, G. *Tetrahedron* **1998**, *54*, 6011−6018.
(18) For example: (a) Hackert, M. L.; Jacobson, R. A. *Acta Crystallogr.* **1971**, *B27*, 203−109. (b) Nelson, C. R. *Carbohydr. Res.* **1982**, *106*, 155−159. (c) Walaszek, Z.; Horton, D.; Ekiel, I. *Carbohydr. Res.* **1982**, *106*, 193−201. (d) Hürzeler, M.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1993**, *76*, 995−1012.
(19) See the Experimental Section for ^{1}H NMR data of **2**, **6**, and tri-*O*-benzyl-2-deoxy-D-galactose.
(20) Conformations are symbolized by the first letter of the general ring shape, e.g., chair = *C*; boat = *B*. A reference plane is selected to have the maximum number of ring atoms. Superscript and subscript numbers describe the atoms above and below the reference plane, respectively (see Figure 1).
(21) Mlynarski, J.; Banaszek, A. *Tetrahedron* **1999**, *55*, 2785−2794.
(22) Harmon, R. E.; Wellman, G.; Gupta, S. K. *J. Org. Chem.* **1973**, *38*, 11−16.
(23) Dondoni, A.; Scherrmann, M.-C. *J. Org. Chem.* **1994**, *59*, 6404−6412.
(24) Grundler, G.; Schmidt, R. R. *Liebigs Ann. Chem.* **1984**, 1826−1847.
(25) The one-pot procedure was given in the Experimental Section.
(26) Kinzy, W.; Schmidt, R. R. *Carbohydr. Res.* **1987**, *166*, 265−276.
(27) The diazo transfer reaction using trisyl azide has been reported for hindered enolates under phase transfer conditions: Lombardo, L.; Mander, L. *Synthesis* **1980**, 368−369.

far been synthesized from the corresponding keto sugars[29] and aldoximes[30] in a stepwise fashion. According to Evans et al.,[10] the use of *p*-nitrobenzenesulfonyl azide may lead to diazo transfer with minimal competing azide transfer.

Conclusion

We have shown that electrophilic azidation of enolates derived from 2-deoxyaldono-1,5-lactones is a highly stereoselective route to 2-azido-2-deoxyaldono-1,5-lactones. This enol-azidation reaction, coupled with the subsequent in situ reduction of lactone to lactol, provides a highly stereoselective alternative to the existing methods for the synthesis of 2-azido-2-deoxyaldoses. Further extension of the azide transfer reaction to the synthesis of various aminosugars and their analogues is currently under way.

Experimental Section

General. All commercial materials were used without purification. THF and CH_2Cl_2 were distilled from sodium benzophenone ketyl and CaH_2, respectively, under positive pressure of dry argon. Trisyl azide was prepared as reported.[22] All the reactions were performed under an argon atmosphere. ^{1}H NMR spectra were recorded using either a Bruker AM360, Bruker ARX400, or Bruker Avance 500 spectrometer in $CDCl_3$ with TMS as internal reference. Gradient NOESY experiments were performed to determine the presence of interaction due to the NOE. Signal assignments were done by extensive decoupling experiments. HRMS (FAB) were recorded on a VG Analytical 70VSE spectrometer.

Tri-*O*-benzyl-2-deoxy-D-galactopyranose[17e] (α/β = 3.5/1). ^{1}H NMR (500 MHz) δ 2.01 (ddd, 1, J = 12.0, 4.5, ∼0 Hz, H-2eqα), 2.15 (br d, 1, J = 12 Hz, H-2eqβ), 2.21 (ddd, 1, J = 12.0, 11.0, 4.0 Hz, H-2axα), 3.50 (dd, 1, J = 9.5, 5.5 Hz) and 3.58 (dd, 1, J = 9.5, 5.5 Hz) (2 × H-6α), 3.63 (dd, 1, J = 9.5, 6.0 Hz, H-6β), 3.81 (br s, 1, H-4β), 3.87 (br s, 1, H-4α), 3.98 (ddd, 1, J = 11.0, 4.5, 3.0 Hz, H-3α), 4.13 (ddd, 1, J = 5.5, 5.5, ∼0 Hz, H-5α), 5.45 (br d, 1, J = 4.0 Hz, H-1α).

Tri-*O*-benzyl-2-deoxy-D-galactono-1,5-lactone[13] (2). ^{1}H NMR (360 MHz) δ 2.88 (dd, 1, J = 17.5, 6.5 Hz, H-2eq), 2.97 (dd, 1, J = 17.5, 11.0 Hz, H-2ax), 3.66 (dd, 1, J = 9.0 5.5 Hz) and 3.75 (br t, 1, J = 9 Hz) (2 × H-6), 3.86 (ddd, 1, J = 11.0, 6.5, 1.5 Hz, H-3), 4.17 (br s, 1, H-4), 4.32 (br td, J = 5, 1 Hz, H-5).

Tri-*O*-benzyl-2-deoxy-D-glucono-1,5-lactone[14] (6). ^{1}H NMR (500 MHz) δ 2.74 (dd, 1, J = 15.0, 4.5 Hz, H-2eq), 2.84 (dd, 1, J = 15.0, 4.5 Hz, H-2ax), 3.70 (dd, 1, J = 10.5, 4.0 Hz) and 3.73 (dd, 1, J = 10.5, 4.0 Hz) (2 × H-6), 3.89 (dd, 1, J = 7.5, 4.5 Hz, H-4), 3.94 (dd, 1, J = 4.5, 4.5 Hz, H-3), 4.30 (ddd, 1, J = 7.5, 4.0, 4.0 Hz, H-5).

Tri-*O*-benzyl-2-azido-2-deoxy-*D*-galactono-1,5-lactone[23] (3). A solution of **2** (100 mg, 0.23 mmol) in THF (3 mL) was cooled to −90 °C and a 0.5 M solution of KHMDS in toluene (0.51 mL, 0.26 mmol) was added dropwise with vigorous stirring. After 15 min, a precooled 0.2 M solution of trisyl azide[21] in THF (1.5 mL, 0.3 mmol, −90 °C) was added dropwise. After another 2 min, AcOH (16 μL, 0.28 mmol) was added. The cooling bath was then removed and the mixture was stirred at room temperature overnight. After addition of H_2O (30 mL), the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined CH_2Cl_2 layers were dried and concentrated to dryness. Flash column chromatography on silica gel with hexanes−EtOAc (6:1) yielded known **3** (77 mg, 70%) as a colorless oil: $[\alpha]_D$ +63 (*c* 0.6, $CHCl_3$) [lit.[23] $[\alpha]_D$ +63.4 (*c* 1, $CHCl_3$)]; ^{1}H NMR (500 MHz) δ 3.67 (dd, 1, J = 10.5, 2.0 Hz, H-3), 3.65 (dd, 1, J = 10.0, 6.0 Hz) and 3.70 (dd, 1, J = 10.0, 9.0 Hz) (2 × H-6), 4.15 (br s, 1, H-4), 4.31 (ddd, 1, J = 9.0, 6.0, ∼0.5 Hz, H-5), 4.59 (d, 1, J = 10.5 Hz, H-2). HRMS: cacld for $C_{27}H_{27}N_3O_5$ + Na 496.1848, found 496.1839.

Tri-*O*-benzyl-2-azido-2-deoxy-D-mannono-1,5-lactone (7). Electrophilic azidation of **6** was carried out as described above to yield **7** (50%) as a colorless oil: $[\alpha]_D$ +6 (*c* 0.06, $CHCl_3$); ^{1}H NMR (500 MHz) δ 3.66 (d, 2, J = 4.5 Hz, 2 × H-6), 3.90 (dd, 1, J = 6.0, 1.5 Hz, H-4), 4.05 (dd, 1, J = 3.5, 1.5 Hz, H-3), 4.14 (d, 1, J = 3.5 Hz, H-2), 4.33 (m, 1, H-5). HRMS: cacld for $C_{27}H_{27}N_3O_5$ + Na 496.1848, found 496.1848.

Tri-*O*-benzyl-2-azido-2-deoxy-D-galactopyranose[24] (4). A solution of **3** (100 mg, 0.21 mmol) in THF (5 mL) was cooled to −78 °C and a pre-cooled 1 M solution of DIBALH in toluene (0.23 mL, 0.23 mmol) was added dropwise. After 30 min, H_2O (30 mL) was added and the mixture was warmed to room temperature. The mixture was acidified by a few drops of 6 M HCl and stirred for 15 min. The product was extracted with CH_2Cl_2 (3 × 30 mL), dried, and concentrated to dryness. Flash column chromatography on silica gel with toluene−acetone (20:1) yielded known **4** (95 mg, 95%) as a colorless oil: α/β = ∼2/1; ^{1}H NMR (500 MHz) δ 2.86 (br s, 1, OHα), 3.23 (br s, 1, OHβ), 3.35 (dd, 1, J = 10.5, 3.0 Hz, H-3β), 3.47−3.60 (m, 5H, H-5β, 2 × H-6α, 2 × H-6β), 3.76 (dd, 1, J = 10.5, 8.0, H-2β), 3.87 (br d, 1, J = 3 Hz, H-4β), 3.92−3.98 (m, 3, H-2α, H-3α, H-4α), 4.16 (br t, 1, J = 6 Hz, H-5α), 5.32 (br d, 1, J = 1 Hz, H-1α).

Tri-*O*-benzyl-2-azido-2-deoxy-D-mannopyranose (8). DIBALH reduction of **7** under the same condition as above yielded **8** (87%) as a colorless oil; α/β = 3.5/1; ^{1}H NMR (500 MHz) δ 3.65 (m, 2, 2 × H-6α), 3.69 (m, 2, 2 × H-6β), 3.71 (dd, 1, J = 9.0, 3.5 Hz, H-3β), 3.78 (dd, 1, J = 9.0, 9.0 Hz, H-4α), 3.82 (dd, 1, J = 9.5, 9.5 Hz, H-4β), 3.92 (dd, 1, J = 4.0, 2.5 Hz, H-2α), 3.93 (m, 1, H-2β), 3.99 (ddd, 1, J = 9.5, 5.0, 2.5 Hz, H-5α), 4.10 (dd, 1, J = 9.0, 4.0 Hz, H-3α), 4.69 (br s, 1, H-1β), 5.19 (br s, 1, H-1α). HRMS: cacld for $C_{27}H_{29}N_3O_5$ + Na 498.2005, found 498.2010.

One-Pot Procedure (2→3→4 and 6→7→8). A solution of **3**/**6** in THF was cooled to −90 °C and a 0.5 M solution of KHMDS (1.1 equiv) was added dropwise with vigorous stirring. After 15 min, a pre-cooled 0.2 M solution of trisyl azide in THF (1.2 equiv, −90 °C) was added dropwise. After another 2 min, AcOH (1.2 equiv) was added and the mixture was warmed gradually to room temperature (overnight). The mixture was again cooled to −70 °C and precooled DIBALH (2 equiv) was added. After 30 min, H_2O was added and the mixture was warmed to room temperature. The mixture was then acidified by a few drops of 6 M HCl and stirred for 15 min. The product was extracted with CH_2Cl_2 and purified by flash column chromatography on silica gel with toluene−acetone (20:1).

Di-*O*-benzyl-2-deoxy-4-*O*-(tetra-*O*-benzyl-β-D-galactopyranosyl)-D-glucono-1,5-lactone (11). A mixture of **10** (1.06 g, 1.18 mmol), PCC (0.8 g, 3.63 mmol), and molecular sieves (4 Å) in CH_2Cl_2 (20 mL) was stirred at room temperature for 1 h. After addition of ether (500 mL) and subsequent filtration, the mixture was concentrated to dryness. Flash column chromatography on silica gel with hexanes−EtOAc (4:1) yielded **11** (0.82 g, 80%) as a colorless syrup together with the lactal **9**[17e] (0.13 g, 15%). **11**: $[\alpha]_D$ +12.7 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz) δ 2.81 (dd, 1, J = 16, 3.0 Hz, H-2eq), 2.86 (dd, 1, J = 16, 3.0 Hz, H-2ax), 3.55 (dd, 1, J = 9.5, 2.5 Hz, H-3′), 3.50−3.60 (m, 3, H-5′, 2 × H-6′), 3.70 (dd, 1, J = 12.0, 5.0 Hz,) and 3.78 (dd, 1, J = 12.0, 4.5 Hz,) (2 × H-6), 3.84 (dd, 1, J = 9.5, 8.0 Hz, H-2′), 3.96 (br d, 1, J = 3 Hz, H-4′), 4.15 (dd, 1, J = 6.0, 2.5 Hz, H-4), 4.27 (br q, 1, J = 3 Hz, H-3), 4.42 (br q, J = 5 Hz, H-5), 4.46 (d, 1, J = 8.0 Hz, H-1′). HRMS: cacld for $C_{54}H_{56}O_{10}$ + Na 887.3756, found 887.3748.

Di-*O*-benzyl-2-azido-2-deoxy-4-*O*-(tetra-*O*-benzyl-β-D-galactopyranosyl)-D-mannono-1,5-lactone (12) and Di-O-benzyl-2-deoxy-2-diazo-4-O−(tetra-*O*-benzyl-β-D-galactopyranosyl)-D-glucono-1,5-lactone (13). Electrophilic azidation of **11** was carried out as described above except that the reaction was done at −78 °C. After workup, flash column chromatography on silica gel with hexanes−EtOAc (4:1) yielded **12** (60%) as a colorless oil together with **13** (15%) as a colorless oil. **12**: $[\alpha]_D$ −4.3 (*c* 1.5, $CHCl_3$); ^{1}H NMR (400 MHz) δ 3.44 (dd, 1, J = 8.0, 2.5 Hz, H-3′), 3.45−3.50 (m, 3, H-5′, 2 × H-6′), 3.61 (br d, 2, J = 5 Hz, 2 × H-6), 3.74 (dd, 1, J = 9.5, 8.0 Hz, H-2′), 3.86 (br d, 1, J = 2.5 Hz, H-4′), 3.98 (d, 1, J = 3.0 Hz, H-2), 4.06 (dd, 1, J = 6.5, 1.5 Hz, H-4), 4.24 (d, 1, J = 8.0 Hz, H-1′), 4.21−4.27 (m, 1,

(28) Some reviews on diazo chemistry: (a) Regitz, M. *Synthesis* **1972**, 351−373. (b) Doyle, M. P.; McKervey, M. A. *Chem. Commun.* **1997**, 983−989.

(29) For example: (a) Horton, D.; Just E. K. *Chem. Commun.* **1969**, 1116−1117. (b) Horton, D.; Philips, K. D. *Carbohydr. Res.* **1972**, *22*, 151−162. (c) Kurz, G.: Lehmann, J.; Thieme, R. *Carbohydr. Res.* **1985**, *136*, 125−133.

(30) Briner, K.; Vasella, A. *Helv. Chim. Acta* **1989**, *72*, 1371−1382.

H-5), 4.39−4.41 (m, 1, H-3). HRMS: cacld for $C_{54}H_{55}N_3O_{10}$ + Na 928.3785, found 928.3799. **13**: $[\alpha]_D$ +6.5 (*c* 0.87, $CHCl_3$); ^{1}H NMR (400 MHz) δ 3.42−3.54 (m, 4, H-3′, H-5′, 2 × H-6′), 3.76 (br d, 2, J = 6 Hz, 2 × H-6), 3.79 (dd, 1, J = 9.5, 8.0 Hz, H-2′), 3.86 (br d, 1, J = 2.5 Hz, H-4′), 4.23 (br t, 1, J = 3.5 Hz, H-4), 4.48 (d, 1, J = 8.0 Hz, H-1′), 4.83 (d, 1, J = 2.5 Hz, H-3). HRMS: cacld for $C_{54}H_{54}N_2O_{10}$ + Na 913.3676, found 913.3652.

Acknowledgment. We thank Dr. Joseph C. Walsh for his contribution to ^{1}H NMR investigations. We also thank Jennifer Leung and Philippa Reichert for technical assistance. This work was supported by the Crump Institute for Molecular Imaging and the Department of Molecular and Medical Pharmacology, UCLA School of Medicine. The Norton Simon Fund at UCLA and partial support from NSF (CHE 9974928) are also acknowledged.

Supporting Information Available: ^{1}H NMR spectra of compounds **2**−**4**, **6**−**8**, and **11**−**13** as well as NOE data of **6**, **7**, **11**, and **12**. This material is available free of charge via the Internet at http://pubs.asc.org.

JO005728C