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Enantioselective Synthesis of *N*-Cbz-Protected 6-Amino-6-deoxymannose, -talose, and -gulose

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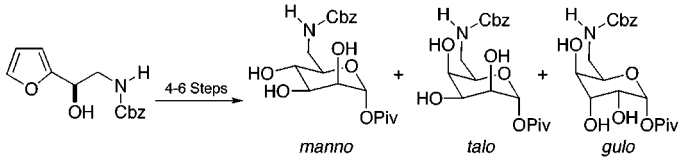
ABSTRACT

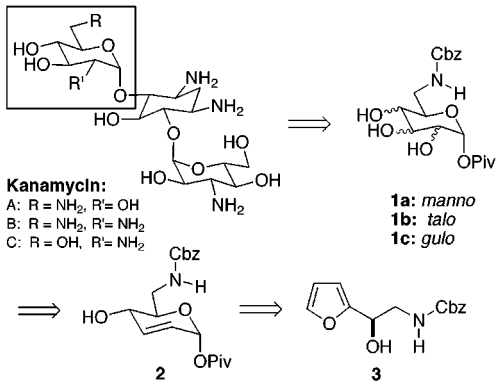


The enantioselective synthesis of three 6-amino-6-deoxy sugars has been achieved in six to eight steps from furfural. A sequence of diastereoselective oxidation and reduction reactions produced Cbz-protected 6-aminomannose from furfuryl alcohol 3. The incorporation of a Mitsunobu reaction into the reaction sequence allows for the selective synthesis of both *N*-Cbz-protected 6-aminotalose and 6-aminogulose. The overall procedure allows for the synthesis of either enantiomer of these three aminosugars.

Since their identification in the 1950s, the aminoglycosides have been an important class of antibiotics in the fight against infections.[1] The aminoglycosides consist of a large class of mono- and bis-glycosidated diaminocyclitols such as kanamycins A−C[2] (Scheme 1) and others.[3] These compounds belong to a class of broad spectrum antibacterial compounds that are currently used to treat various Gram-negative and Gram-positive infections, as well as tuberculosis.[3] Although these antibiotics have high toxicity (nephrotoxicity and ototoxicity)[4] associated with their use, they are still administered because there are no alternatives.[5] Along with their continued use as antibiotics, aminoglycosides are being screened as potential anti-HIV compounds.[6]

The increased incidence of bacterial resistance has created a great need for new antibacterial compounds.[5] The rapid escalation of the incidence of multiple-antibiotic-resistant pathogens is now raising very serious concerns worldwide.[7,8] The synthesis and evaluation of new aminoglycoside ana-

Scheme 1



(1) Goodman-Gilman, A.; Goodman, L. S.; Rall, T. W.; Murad, F. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*; MacMillan Publishing Co: New York, 1985.

(2) For the first synthesis of kanamycin A, see: Nakajima, M. Hasegawa, A. Kurihara, N.; Shibata, H.; Ueno, T.; Nishumura, D. *Tetrahedron Lett.* **1968**, *9*, 623−627.

(3) Hooper, I. R. The Naturally Occurring Aminoglycoside Antibiotics. In *Aminoglycoside Antibiotics*; Hooper, I. R., Umezawa, H., Eds.; Springer-Verlag: NewYork, 1982.

(4) Ruppersberg, J. P. *HNO* **1997**, *45*(3), 111−112.

(5) Brickner, S. J. *Chem. Ind.* **1997**, 131−135.

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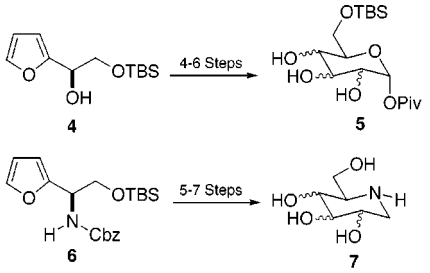
Scheme 2



logues will greatly increase our understanding of how to control bacterial infections and resistance.[9]

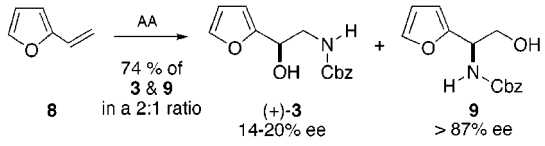
Analysis of the aminoglycosides reveals two common structural motifs, a 2-deoxystreptamine core and variously substituted aminosugars (Scheme 1). Wong and Mobashery have demonstrated the importance of the 6-amino-6-deoxysugar for both ribosomal RNA binding and antibiotic activity.[5,10] Previous structure−activity studies of the aminoglycoside antibiotics have used semisynthesis techniques to remove hydroxyl groups from the existing aminoglycosides and strategically added functional groups of interest.[11] We felt a complementary approach would be to start with a drastically simplified structure and to sequentially increase its stereochemical and functional complexity. To implement this strategy, we desired a flexible route to D- and L-6-amino-6-deoxysugars that allows for the synthesis of various stereoisomers and deoxy analogues.

Recently, our group has had success at using asymmetric catalysis for the synthesis of D- and L-sugars and iminosugars from the achiral vinylfuran via chiral furans **4** and **6** (Scheme 2).[12,13] Four hexoses of the type **5** were derived from monoprotected diol **4** in four−six steps. Similarly, two iminosugars of type **7** were prepared in five−seven steps from Cbz-protected furfurylamine **6**. Both furans **4** and **6** were easily prepared as either enantiomer by the Sharpless asymmetric dihydroxylation reaction (AD)[14] and aminohydroxylation reaction (AA),[15] respectively. Buoyed by this success, we decided to investigate a related strategy toward Cbz-protected 6-amino-6-deoxysugars **1** from pyran **2**. Thus we envisioned pyran **2** arising via an Achmatowicz strategy[16] from furfuryl alcohol **3** (Scheme 1). Ultimately we envision this route allowing access to unnatural *C*-2/*C*-3-dideoxy-6-aminosugars.

Traditionally, 6-amino-6-deoxysugars are obtained from an azide displacement of a protected *C*-6-halosugar followed by reduction to the free amine.[2,17,18] Because we desired access to both enantiomers of various 6-aminosugars, we were interested in testing the viability of an Achmatowicz approach (**2** from **3**) to these aminoglycoside intermediates[16] (Scheme 1), where the initial asymmetry will be derived from furan **3**. Herein we report our successful efforts at the conversion of furfural into either enantiomer of *N*-Cbz-protected *β*-pivaloyl-6-aminomannose **1a** and the corresponding talose and gulose isomers **1b** and **1c**.

Previously we found that *N*-Cbz-protected amino alcohol **3** was produced (42% yield) as the major regioisomer (2:1 ratio) from the asymmetric aminohydroxylation (AA) of vinylfuran, however in low enantioexcess.[19] Using the $(DHQ)_2PHAL$ ligand the minor isomer (+)-**9** was produced in greater than 87% enantiomeric excess,[20] while the major isomer (+)-**3** was formed with 14% enantiopurity (Scheme 3). Accordingly, the pseudoenantiomeric ligand

Scheme 3



AA: NaClNCbz, 4% OsO_4 / 5% $(DHQ)_2PHAL$, *t*-BuOH/H_2O

$(DHQD)_2PHAL$ provided the enantiomer (−)-**3** in a slightly higher enantiomeric excess (20%) and (−)-**9** in a similar enantiomeric excess (> 87%). Although the use of

(6) (a) Green, M. R. *AIDS Res. Rev.* **1993**, *3*, 41−55. (b) Alper, P. B.; Hendrix, M.; Sears, P.; Wong, C.-H. *J. Am. Chem. Soc.* **1998**, *120*, 1965−1978.

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(8) For instance, worldwide *Streptococcus pneumoniae* is responsible for 1.2 million deaths per year in children under the age of 5, see: (a) Bruyn G. A. W.; Zegers, B. J. M.; van Furth, R. *Clin. Infect. Dis.* **1992**, *14*, 251−262. (b) Janoff, E. N.; Rubins, J. B. *Microb. Drug Resist.* **1997**, *3*, 215−232. Even more alarming is that *Mycobacterium tuberculosis* is estimated to cause 3 million deaths per year, see: (c) Swartz, M. N. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 2420−2427.

(9) Umezawa, H.; Kondo, S. Mechanisms of Resistance to Aminoglycoside Antibiotics. In *Aminoglycoside Antibiotics*; Hooper, I. R., Umezawa, H., Eds.; Springer-Verlag: New York, 1982.

(10) Roestamadji, J.; Grapsas, I.; Mobashery, S. *J. Am. Chem. Soc.* **1995**, *117*, 11060−11074.

(11) (a) Umezawaa, S.; Tsuchiya, T. Total Synthesis and Chemical Modification of the Aminoglycoside Antibiotics. In *Aminoglycoside Antibiotics*; Hooper, I. R., Umezawa, H., Eds.; Springer-Verlag: NewYork, 1982. (b) Okuda, T. Ito, Y. Biosynthesis and Mutasynthesis of Aminoglycoside Antibiotics. In *Aminoglycoside Antibiotics*; Hooper, I. R., Umezawa, H., Eds.; Springer-Verlag: NewYork, 1982.

(12) (a) Harris, J. M.; Keranen, M. D.; O'Doherty, G. A. *J. Org. Chem.* **1999**, *64*, 2982−2983. (b) Harris, J. M.; Keranen, M. D.; Nguyen, H.; Young, V. G.; O'Doherty, G. A. *Carbohydr. Res.* **2000**, *328*, 17−36.

(13) Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 401−404.

(14) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547.

(15) (a) Sharpless, K. B.; Patrick, D. W.; Truesdale, L. K.; Biller, S. A. *J. Am. Chem. Soc.* **1975**, *97*, 2305−2306. (b) Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 451−454.

(16) An Achmatowicz reaction is the oxidative rearrangement of furfuryl alcohols to 2-substituted 6-hydroxy-2*H*-pyran-3(6*H*)-ones. (a) Achmatowicz, O.; Bielski, R. *Carbohydr. Res.* **1977**, *55*, 165−176. (b) Grapsas, I., K.; Couladouros, E. A.; Georgiadis, M. P. *Pol. J. Chem.* **1990**, *64*, 823−826. For its use in carbohydrate synthesis, see: ref 12 and the following. (c) Balachari, D.; O'Doherty, G. A. *Org. Lett.* **2000**, *2*, 863−866. (d) Balachari, D.; O'Doherty, G. A. *Org. Lett.* **2000**, *2*, 4033−4036.

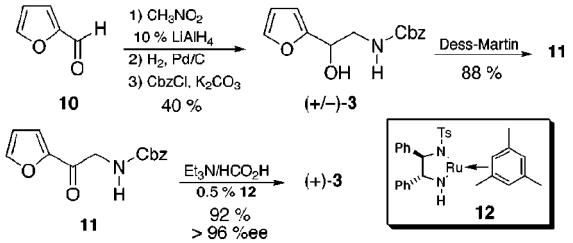
(17) (a) Ponpipom, M. M.; Hanessian, S. *Can. J. Chem.* **1972**, *50*, 246−252. (b) Ponpipom, M. M.; Hanessian, S. *Can. J. Chem.* **1972**, *50*, 253−258.

(18) Recently, Herscovici reported the use of this approach to structures related to **2** by a six-step route from triacetyl-D-glucal, see: Herscovici, J.; Egron, M. J.; Quenot, A.; Leclercq, F.; Leforestier, N.; Mignet, N.; Wetzer, B.; Scherman, D. *Org. Lett.* **2001**, *3*, 1893−1896.

$(DHQ)_2AQN$ as a ligand in the AA has been reported to achieve a reversal of regioselectivety,[21] its use in the AA of vinylfuran produced results similar to those of $(DHQ)_2PHAL$ (1:2 ratio of regioisomers favoring the furfuryl alcohol; furfurylamine, 74% ee; furfuryl alcohol, 14% ee).[22,23]

While the aminohydroxylation provided enough material to investigate the Achmatowicz reaction sequence, we still desired a more practical and enantioselective approach to **3**. Racemic aminoalcohol **3** was readily prepared from furfural via a Henry reaction[24]/hydrogenation/Cbz-protection sequence (**10** to (±)-**3**, Scheme 4). This procedure routinely

Scheme 4

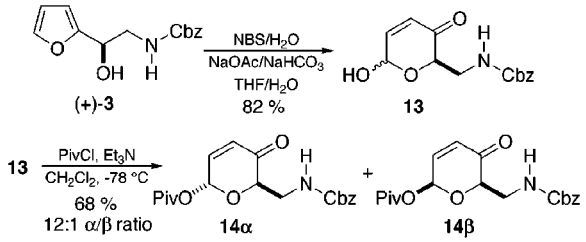


provided multigram quantities of racemic **3** in a 40% overall yield and with the use of only one chromatographic purification. While we initially investigated the use of an asymmetric Henry reaction[25] to provide **3**, the reduction of the nitro group gave significant amounts of partially reduced byproducts. Thus, we desired a more reliable method to induce the asymmetry.

A highly practical procedure was finally found when we decided to induce the asymmetry in **3** via an asymmetric reduction of ketone **11**. Exposing racemic **3** to Dess−Martin reagent (1.1 equiv in CH_2Cl_2) gave an 88% yield of ketone **11**. While we had only modest success with the oxazaborolidine-catalyzed asymmetric borane reduction[26] of ketone **11** (68% yield and 78% ee with 1 equiv of catalyst at room temperature),[27] we found that a Noyori reduction of **11** furnished excellent results.[28] In practice, treating a neat admixture of Et_3N/HCO_2H (5:2) and ketone **11** to the Noyori reagent system (0.5 mol % of **12** in a neat 5:2 ratio of Et_3N/HCO_2H)[29] gave (+)-**3** in excellent yield and enantioexcess (92% yield, >96% ee).

Employing the Achmatowicz reaction on furan **3**[30] produced dihydropyranone **13** in an excellent yield (82%, 1.05 equiv of NBS, 1 equiv of NaOAc and 2 equiv of $NaHCO_3$, Scheme 5).[12] Our preference is for the NBS procedure, but

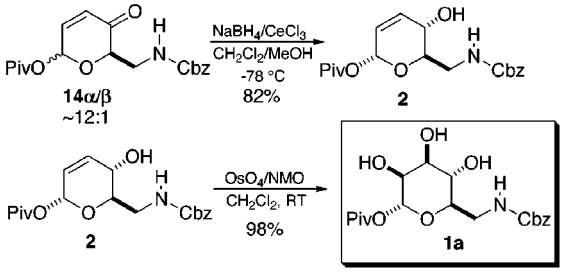
Scheme 5



alternative oxidants such as mCPBA also convert **3** to **13**. The anomeric hydroxyl of pyranone **13** was then protected as the pivaloate (PivCl, Et_3N, −78 °C), providing a 68% yield of a 12:1 mixture of anomers **14**α and **14**β.[31]

With the stereochemistry set at *C*-1 and *C*-5, the other three stereocenters were diastereoselectively added in two remaining steps (Scheme 6). The pivaloate **14**α was subjected

Scheme 6



to Luche reduction conditions ($NaBH_4$, $CeCl_3$, −78 °C) to give the allylic alcohol **2** (82% yield) with complete stereocontrol.[12,32] Diastereoselective osmium-catalyzed dihydroxylation of olefin **2** (5% OsO_4, $NMO_{(aq)}$, in CH_2Cl_2) occurred from the less hindered face to afford the *manno*-triol **1a** in a 98% yield. The relative stereochemistry of **1a**

(19) This is an improved procedure and yield from our previously published results, see: Bushey, M. L.; Haukaas, M. H.; O'Doherty, G. A *J. Org. Chem.* **1999**, *64*, 2984−2985.

(20) At a smaller scale, the level of enantio-induction has been as high as 94%, as determined by Mosher ester analysis. (a) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143−2147. (b) Yamaguchi, S.; Yasuhara, F.; Kabuto, K. T. *Tetrahedron* **1976**, *32*, 1363−1367.

(21) Tao, B.; Schlingloff, G.; Sharpless, K. B. *Tetrahedron Lett.* **1998**, *39*, 2507−2510.

(22) The absolute stereochemistry and the level of enantioexcesses of **3** and **6** were determined by the method of Mosher, see ref 20a.

(23) Our optimized variation from the typical Sharpless procedure was to the use the sodium salt of *N*-chlorobenzylcarbamate as the limiting reagent, providing a good yield of a mixture of regioisomers (74%). Thus, the volatile and inexpensively produced vinylfuran in 30% excess allowed for more efficient use of the more costly catalyst and chiral ligand. This procedure routinely provided a ~40% yield of the furfuryl alcohol **3** and a 21% yield of the TBS-protected regioisomer, see ref 19.

(24) Youn, S. W.; Kim, Y. H. *Synlett* **2000**, 880−882.

(25) (a) Iseki, K.; Oishi, S.; Sasai, H.; Shibasaki, M. *Tetrahedron Lett.* **1996**, *37*, 9081−9084. (b) Sasai, H.; Tokunaga, T.; Watanabe, S.; Suzuki, T.; Itoh, N.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 7388−7389.

(26) (a) Yadav, J. S.; Reddy, P. T.; Hashim, S. R. *Synlett* **2000**, 1049−1051. (b) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986−2012.

(27) In our hands, the TON (turn over numbers) for the catalytic (10%) use of the oxazaborolidine was too low for practical use.

(28) (a) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521−2522. For catalyst preparation, see: (b) Haack, K.-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 285−288.

(29) For good conversions on large scale, a 0.5 M CH_2Cl_2 solution of ketone **11** was reduced with **12** and 2 equiv of Et_3N and 5 equiv of HCO_2H at elevated temperatures (50 °C) with no reduction in enantiopurity and yield, see: Cossy, J.; Eustache, F.; Dalko, P. I. *Tetrahedron Lett.* **2001**, *42*, 5005−5007.

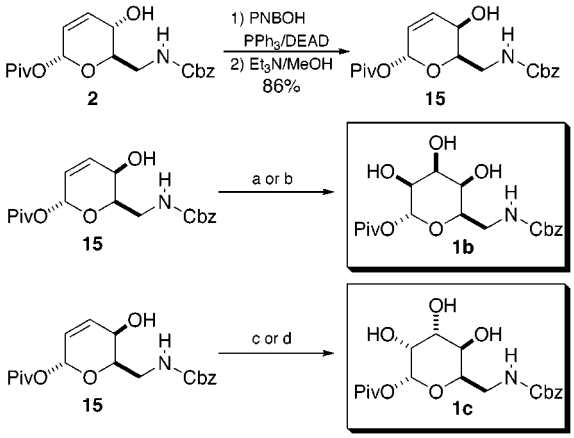
was confirmed by examination of the appropriate coupling constants and comparison to a similarly protected mannose sugar.[12] Data that were particularly indicative of the *manno*-stereochemistry were the *trans*-diequatorial coupling constant between H1−H2 (J = 1.5 Hz), the *cis*-equatorial/axial coupling constant between H2−H3 (J = 3.0 Hz), and the two *trans*-diaxial coupling constant between H3−H4 and H4−H5 (J = 9.5 and 9.5 Hz) (see Supporting Information).

With the successful synthesis of the mannose sugar **1a**, we next explored the viability of this approach to the talose and gulose sugars **1b** and **1c**, respectively. As with our conversion of furan diol **4** to gulose/talose sugars **5** (Scheme 2), we envisioned that access to pyran **15** would be required. From these previous studies, we expected the gulose sugar **1c** to result from a facial selective dihydroxylation reaction of pyran **15**. Similarly, the talose sugar **1b** should be produced from a hydroxy-directed dihydroxylation of pyran **15**.

Exposure of **2** to the Mitsunobu reaction conditions (PPh_3, DEAD, *p*-nitrobenzoic acid (PNBOH))[33] yielded a *p*-nitrobenzoate ester[34] (91%), which was selectively hydrolyzed with Et_3N in MeOH to yield the axial alcohol **15** (95%, Scheme 7). Surprisingly, treatment of pyran **15** to conditions identical to those for the conversion of pyran **2** to the *manno*-triol **1a** (5 mol % of OsO_4, 50% NMO_{aq}/CH_2Cl_2; Scheme 7, condition a) afforded a 6:1 ratio of sugars **1b**/**1c** with the all-syn *talo*-triol **1b** being the predominant isomer isolated in a 60% yield along with the recovery of 22% starting material **15**. These stereochemical assignments were confirmed by comparison with the results of the hydroxy-directed dihydroxylation. Exposure of allylic alcohol **15** to Donohoe's conditions[35] ($TMEDA{\cdot}OsO_4$, CH_2Cl_2; Scheme 7, condition b) exclusively afforded the expected all-syn triol **1b** (47% yield).

The facial selectivity for dihydroxylation in CH_2Cl_2 probably can be attributed to solvent effects on conformation. This was evident from the dihydroxylation of **15** in more polar solvents (acetone and *t*-BuOH). Substituting the more polar solvent acetone for CH_2Cl_2 gave of a 3:2 mixtures of

Scheme 7



a: 5 mol% OsO_4, 50% NMO/CH_2Cl_2; **b:** 1 equiv $TMEDA{\cdot}OsO_4$, CH_2Cl_2; **c:** 5 mol% OsO_4, 50% NMO/*t*-BuOH; **d:** 5 mol% OsO_4, 50% NMO/acetone

triols **1c**/**1b** in a low isolated yield (33%; Scheme 7, condition d), with the *gulo*-triol being the major isomer. This switch in selectivity was further increased upon the use of the polar/hydrogen donating solvent *t*-BuOH (Scheme 7, condition c). Treatment of **15** with 5% OsO_4/NMO_{aq} in *t*-BuOH afforded a 58% yield of a 6:1 mixture of the *gulo*- (50%) and *talo*-triols (8%), respectively. The relative configurations of **1b** and **1c** were determined by examining relevant coupling constants and NOE's from a series of ^1H NMR, ^1H,^1H-COSY, and HMQC experiments. Particularly diagnostic of the stereochemistry was the larger coupling constants between H1−H2 (J = 4.0 Hz) for the *gulo*-sugar **1c** than that for the *talo*-sugar **1b** (J = 1.5 Hz) and the W-coupling between H2 and H4 (J = 1.5 Hz) of talose triol **1b**.

In summary, we have developed a practical five-step synthesis of both D- and L-6-amino-6-deoxymannose from furfural (14% overall yield, 45% from **3**). This route is amenable to multigram scale preparation. Similarly we have also extended this methodology to D- and L-talose and gulose in comparable yields (23% and 19% from **3**). We feel this new route to L-sugars will be very beneficial for the synthesis of unnatural aminoglycosides.

Acknowledgment. We thank the Arnold and Mabel Beckman Foundation for their generous support of our program. We would also like to thank William W. Brennessel (University of Minnesota X-ray Crystallographic Laboratory) for help with X-ray structural determination.

Supporting Information Available: Complete experimental procedures and spectral data (MP, IR, ^1H NMR, ^{13}C NMR, HRMS, and/or EA) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(30) The preceding reaction sequences have been preformed on both (+)-**3** and (−)-**3**; for simplicity reasons we are only drawing the results for (+)-**3**.

(31) By performing the reaction at higher temperatures (0 °C), the minor isomer pivaloate **14**β could also be obtained in higher yields as part of a 3:2 ratio, still favoring of the α-anomer **14**α. At this point the anomers were separated by medium-pressure liquid chromatography (MPLC, 20% EtOAc/hexanes, UV detection) which produced baseline separation.

(32) A simpler purification procedure resulted by carrying the ∼8% impurity of the minor diastereoisomer through to the reduction step. The β-anomer **14**β presumably hydrolyzed when subjected to the Luche conditions; thus when samples of **14**α were reduced with small amounts of the β-anomer present, only diastereomerically pure samples of **2** were detected after silica gel chromatography.

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(34) The relative stereochemistry of the *p*-nitrobenzoate ester was confirmed by single-crystal X-ray analysis, see Supporting Information.

(35) Donohoe, T. J.; Moore, P. R.; Waring, M. J.; Newcombe, N. J. *Tetrahedron Lett*. **1997**, *38*, 5027−5030.