

Enantioselective Synthesis of 2-Deoxy- and 2,3-Dideoxyhexoses

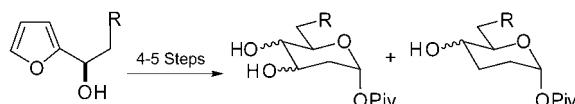
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ABSTRACT



The enantioselective syntheses of C-6 *O*-TBS- and *N*-Cbz-protected 2-deoxy- and 2,3-dideoxysugars have been achieved in 6–8 steps from furfural. A combination of chemo-, regio-, and diastereoselective oxidation and reduction reactions produced deoxysugars with various C-6 substitution. A key development of this route was the use of *o*-nitrobenzenesulfonylhydrazide (NBSH) as a diimide precursor. These overall procedures allow for the synthesis of eight deoxysugars in either enantiomeric form.

Since their identification in the 1950s the aminoglycosides have been an important class of antibiotics in the fight against infections.¹ Aminoglycosides consist of a large class of mono- and bisglycosidated diaminocyclitols such as kanamycins A–C² and others (Figure 1).³ The increased incidence

Arbekacin and dibekacin are deoxysugar analogues of kanamycin that were developed to overcome the problems of enzymatic resistance.³ Removing the hydroxyl groups at C-3 and C-4 of kanamycin produces an antibiotic that still binds to the ribosome but is no longer inactivated by the enzymes that resistant bacteria have evolved to counter them. Unfortunately, even these new antibiotics are succumbing to bacterial resistance.^{6b} Our approach to finding new

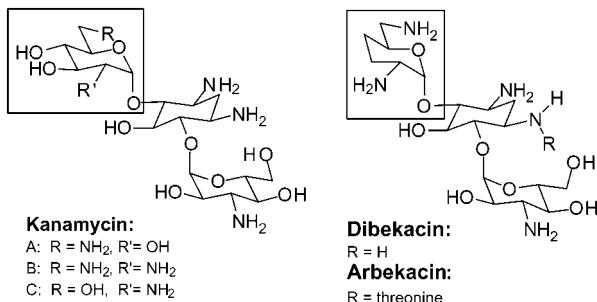


Figure 1.

of bacterial resistance has created a great worldwide need for new antibacterial compounds to fight multiple-antibiotic-resistant pathogens.^{4–6} The synthesis and evaluation of new aminoglycoside analogues will greatly increase our understanding of how to control bacterial infections and bacterial antibiotic resistance.⁷

(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.; Nishimura, D. *Tetrahedron Lett.* **1968**, 9, 623.

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

(4) Brickner, S. *J. Chem. Ind.* **1997**, 131.

(5) Miller, G. H.; Sabatelli, F. J.; Hare, R. S.; Glupczynski, Y.; Mackey, P.; Shlaes, D.; Shimizu, K.; Shaw, K. J.; Bauerfeind, A.; Schweighart, S.; Shannon, K.; Patzer, J.; Molinari, G.; Schito, G. C.; Gomezlus, R.; Gomezlus, S.; Ferreira, H.; Sousa, J. C.; Vaz, M. J. M.; Collatz, E.; Bismuth, R.; Lambert, T.; Courvalin, P.; Minozzi, C.; Klugman, K. *Clin. Infect. Dis.* **1997**, 24, S46.

(6) 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. (b) Janoff, E. N.; Rubins, J. B. *Microb. Drug Resist.* **1997**, 3, 215. 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.

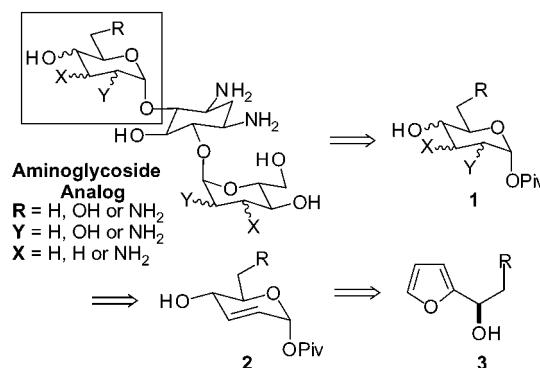
(7) Umezawa, H.; Kondo, S. *Mechanisms of Resistance to Aminoglycoside Antibiotics*. In *Aminoglycoside Antibiotics*; Hooper, I. R., Umezawa, H., Eds.; Springer-Verlag: New York, 1982.

antibiotics is to mimic nature by synthesizing novel deoxyaminosugars then to couple them to an aminocyclitol core. These new aminoglycoside analogues may be the next generation of nonresistant antibiotics.

Structure activity relationship analysis of the carbohydrate portions of the aminoglycosides in terms of antibiotic resistance reveals two common structural motifs that impart prolonged bioactivity: the presence of both deoxyaminosugars and deoxysugars (Figure 1). The replacement of a hydroxyl group with an amino group installs an improved hydrogen-bond acceptor. In contrast, the removal of a hydroxyl group imparts in vitro stability by lessening the abilities of naturally occurring glycosidase enzymes to degrade the structure.³ This approach can be used by synthetic chemists to improve binding and to overcome the accompanying resistance that all antibiotics eventually incur.

For the past 5 years our group has been developing methods for the enantioselective synthesis of carbohydrates with the goal of accessing uniquely functionalized aminoglycoside antibiotics (Scheme 1). Previous structure activity

Scheme 1



studies of the aminoglycoside antibiotics have used semi-synthesis techniques to strategically remove hydroxyl groups from the existing aminoglycosides, followed by the addition of functional groups of interest.⁸ A complementary approach is to start with a drastically simplified structure and to sequentially increase its stereochemical and functional complexity (e.g., **2** to **1**). To implement this strategy, a flexible route to D- and L-sugars that allows for the synthesis of various stereoisomers and deoxyanalogs was developed. Having successfully addressed the synthesis of sugars,⁹ iminosugars,¹⁰ and aminosugars (Scheme 2),¹¹ our next goal was to apply this methodology to the catalytic asymmetric synthesis of deoxysugars.

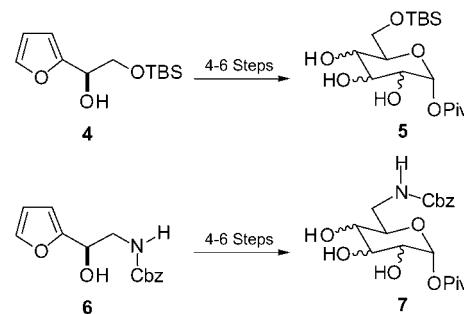
(8) (a) Umezawa, S.; Tsuchiya, T. Total Synthesis and Chemical Modification of the Aminoglycoside Antibiotics. In *Aminoglycoside Antibiotics*; Hooper, I. R., Umezawa, H., Eds.; Springer-Verlag: New York, 1982. (b) Okuda, T.; Ito, Y. Biosynthesis and Mutasynthesis of Aminoglycoside Antibiotics. In *Aminoglycoside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

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

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

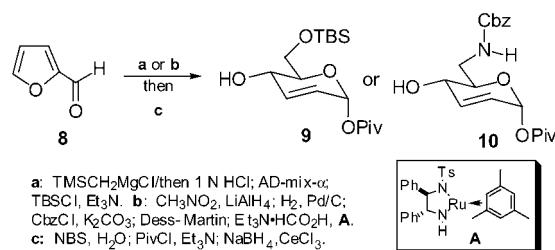
(11) Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 3899.

Scheme 2



Recently, our group has successfully employed asymmetric catalysis for the synthesis of D- and L-sugars and iminosugars from the achiral vinylfuran via chiral furans **4** and **6** (Scheme 2).⁹⁻¹¹ Four hexoses of the type **5** were prepared from monoprotected diol **4** in 4–6 steps, as well as the analogous C-6 aminosugars **7** from furan **6**. Similarly this route should allow for access to unnatural C-2/C-3 dideoxysugars. We envisioned that C-2 and C-2/C-3 deoxysugars could be derived from the same intermediates **9** and **10** (Scheme 3)

Scheme 3



that were used for the syntheses of **5** and **7**. Reported herein are our successful efforts at the conversion of intermediates **9** and **10** into both C-2 deoxysugars and C-2/C-3 dideoxysugars. This approach allows for access to either enantiomer of *N*-Cbz-protected and *O*-TBS-protected C-2 deoxy-*allo*- and deoxy-*galactosugars* and C-2/C-3 dideoxy-*gluco*- and *galacto*-sugars.

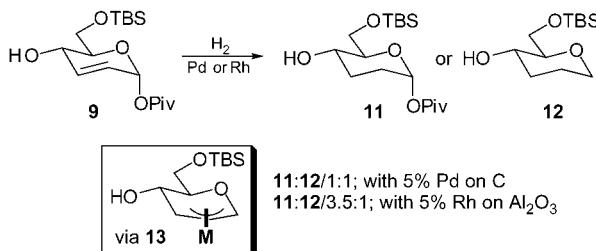
Our earlier work has shown that the C-6 *O*-TBS-protected and C-6 *N*-Cbz-protected pyran allylic alcohols **9** and **10** were diastereoselectively produced from furfural in 47% and 14% yields, respectively (Scheme 3).¹¹ The asymmetry of **9** was effectively introduced by a Sharpless dihydroxylation of vinylfuran (>90% ee).¹² In contrast, the asymmetry of **10** was ineffectively introduced in terms of enantio- and regioselectivity by the Sharpless aminohydroxylation; however, very high enantioexcess (>98% ee) was achieved with the Noyori hydrogenation of a furyl ketone.^{13,14}

(12) The enantioselectivity was increased to >98% after recrystallization of the furan diol bisbenzoate.

(13) For specific conditions, see ref 11 and (a) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521. For catalyst preparation, see: (b) Haack, K.-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 285.

With the establishment of enantioselective routes to both allyl alcohols **9** and **10**, the use of transition-metal-catalyzed hydrogenation reactions was investigated for the conversion of **9** into the dideoxysugar **11** (Scheme 4). Our preference

Scheme 4



for the direct hydrogenation reaction of **9** and **10** was ameliorated by concerns with competing hydrogenolysis (via **13**) of the allylic ester or ether bonds.¹⁵ In fact, when pyran **9** was subjected to typical palladium on carbon hydrogenation conditions (1 atm of H₂, 10% Pd/C in MeOH) a significant amount of the hydrogenolysis product **12** was found (87% of a 1:1 ratio of **11** and **12**).¹⁶ Switching the catalyst from Pd/C to Rh/alumina resulted in less but still a significant proportion of hydrogenolysis. Thus when exposing **9** to 1 atm of H₂ in the presence of 10% Rh on Al₂O₃ in EtOAc, a 90% yield of a 3.5:1 ratio of **11** and **12** was isolated. Although pure fractions of **11** could be isolated by silica gel column chromatography, a more pragmatic route to **11** was desired. In addition, the C-6 *N*-Cbz group of **10** would likely not survive the hydrogenation conditions.

A practical solution was realized by the use of a diimide to reduce the dihydropyan ring. Hence, exposing **9** to an excess of potassium azodicarboxylate (10–15 equiv) and acetic acid (20–30 equiv) in MeOH gave a good yield (93%) of pivolate **11**.^{17,18} Because of our concerns with the potential acid sensitivity of **11** in the presence of acetic acid, we searched for an alternative procedure for the generation of diimide. Initially, benzenesulfonylhydrazide was examined as a diimide source, but the high temperature required for the reaction was undesirable.¹⁹

With the hope that a better leaving group would allow for a more facile generation of diimide, we turned to the

(14) The absolute stereochemistries and enantioexcesses of **4** and **6** were determined by Mosher's method; see: (a) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143. (b) Yamaguchi, S.; Yasuhara, F.; Kabuto, K. T. *Tetrahedron* **1976**, *32*, 1363.

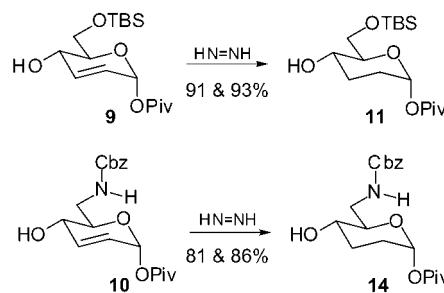
(15) These model studies were carried out on the anomeric pivolate because of the propensity of allylic esters to undergo hydrogenolysis reactions. Thus a procedure established on this substrate should have the greatest substrate generality.

(16) Product **12** could be derived from an *in situ* acid-catalyzed elimination reaction of the anomeric pivolate of **11** followed by hydrogenation of the resulting enolether. This possibility was discounted for the Rh/Al₂O₃ reaction, when it was shown that **11** was untouched when re-exposed to the hydrogenolysis conditions.

(17) Prepared by the method of Heck: Dieck, H. A.; Heck, R. F. *J. Org. Chem.* **1975**, *40*, 1083. Also see: Pasto, D. J. *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: 1991; Vol. 40, p 91.

(18) If any starting material was detected by ¹H NMR, it was easily converted to product by re-subjecting the crude product to the reaction conditions.

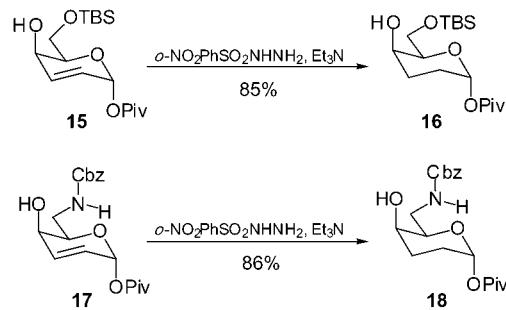
Scheme 5



Diimide: KO₂CN₂CO₂K, AcOH or *o*-NO₂PhSO₂NHNH₂, Et₃N

decomposition of *o*-nitrobenzenesulfonylhydrazide (NBSH) in the presence of triethylamine.²⁰ Our choice of the *o*-nitrobenzenesulfinate anion as a leaving group was made easy by the fact that Myers and Zheng had reported a simple preparation of the labile NBSH.²¹ In fact, exposing **9** to an excess (2–5 equiv) of a 1–2 molar ratio of NBSH and triethylamine in CH₂Cl₂ gave a good yield (91%) of pivolate **11**.²⁰ Not surprisingly, the C-6 *N*-Cbz-protected pyran **10** reacted under both diimide conditions to give very good yields (86% from potassium azodicarboxylate/AcOH and 81% from NBSH/Et₃N) of **14**. Both sets of reaction conditions gave clean products without the use of silica gel chromatography.

Scheme 6



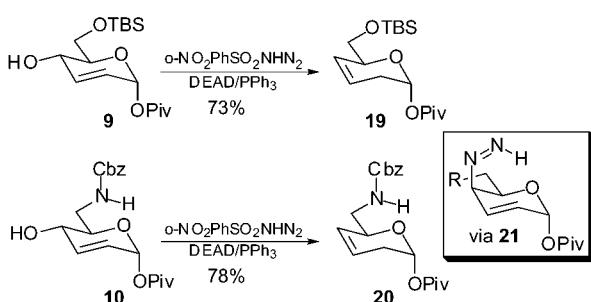
The C-4 epimeric allylic alcohols **15** and **17** were easily prepared from the corresponding isomers (**9** and **10**) via a Mitsunobu/hydrolysis sequence (*p*-nitrobenzoic acid/DEAD/PPh₃, then Et₃N/MeOH). Utilizing the same diimide reduction conditions on allylic alcohols **15** and **17** provided excellent yields of the tetrahydropyrans **16** and **18**. The axial alcohols **16** and **18** were routinely isolated in high yields from **15** (85% from NBSH/Et₃N) and **17** (86% from NBSH/Et₃N).

(19) For a report on the high-temperature use of other benzenesulfonylhydrazides as diimide precursors see: Cusack, N. J.; Reese, C. B.; Risi, A. C.; Rozpeikar, B. *Tetrahedron* **1976**, *32*, 2157.

(20) To the best of our knowledge this is the first use of NBSH as a diimide precursor for an alkene reduction, although Hunig had previously shown that NBSH decomposes to diimide; see: Hunig, S.; Muller, H. R.; Their, W. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 271.

(21) For the preparation of NBSH: Myers, A. G.; Zheng, B.; Movassaghi, M. *J. Org. Chem.* **1997**, *62*, 7507.

Scheme 7



To gain access to the C-2 deoxysugars we hoped to diastereoselectively oxidize alkenes **19** and **20** (Scheme 7). Thus we investigated the use of Myers' reductive 1,3-transposition reaction²² to reduce the allylic alcohol **9** and **10** to alkenes **19** and **20**. This rearrangement reaction seemed ideal for an equatorial allylic alcohol because the reductive rearrangement requires an axial allylic diazene as depicted in **21**.²³ Thus exposing **9** to 2 equiv of a 1:1:1 ratio of NBSH, PPh₃, and DEAD at -30 °C in *N*-methylmorpholine gave a 73% yield of alkene **19**. The allylic alcohol **10** reacted under similar conditions (2.5 equiv) to give a 78% yield of alkene **20**.

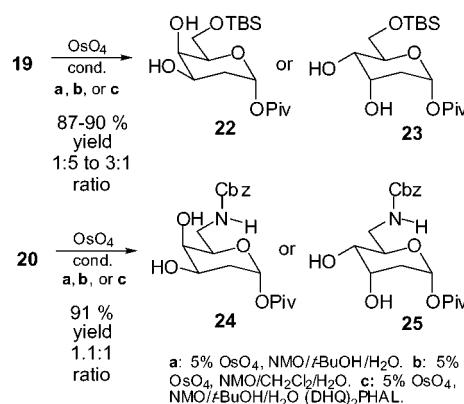
With access to the two desired alkenes **19** and **20**, we next explored their reactivity under typical dihydroxylation conditions (Scheme 8). From our previous studies, the steric effects of the axial anomeric pivaloate was expected to control the facial selectivity, resulting in the C-2 deoxy galactosugars **22** and **24**. Surprisingly, treatment of pyran **19** to modified "Upjohn Conditions" (5 mol % OsO₄, 50% NMO_(aq)/CH₂Cl₂; Scheme 8 condition a), afforded a 1.5:1 ratio of C-2-deoxysugars **22/23**. The *galacto*-diol **22** was the predominant isomer, isolated in a 52% yield along with 35% of the diastereomeric *allo*-diol **23**. Nearly identical stereoselectivities were observed for the C-6 *N*-Cbz series **20** in CH₂Cl₂. Thus exposing **20** to the same conditions provided a 1:1:1 ratio of C-2-deoxysugars **24/25** with the *galacto*-diol **24** as the isomer (47% yield) and the diastereomeric *allo*-diol **25** (44%) as the minor.

We have previously found a significant solvent dependence of the facial selectivity of the dihydroxylation for substrates with C-6 *N*-Cbz substitution.¹¹ However, only small variations in the selectivity were observed for the dihydroxylations

(22) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492. Myers, A. G.; Zheng, B. *Tetrahedron Lett.* **1996**, *37*, 4841.

(23) We have already shown that the allylic alcohol **9** and **10** are ideal substrates for the Mitsunobu reaction; see refs 9 and 11.

Scheme 8



of **19** and **20**. For instance, the use of *t*-BuOH as solvent increased the facial selectivity for **24** over **25** from a 1.5:1 ratio to 2:1 with a slightly higher combined yield (83%). While changing solvents was found to have very little effect on the stereoselectivities, adding a more hindered ligand had a significant affect. Thus, treating pyran **19** to OsO₄/NMO_(aq) in the presence of (DHQ)₂PHAL gave an improved ratio (3:1) with the *galacto*-diol **22** being the major isomer at >90% conversion. The relative configurations of **22–25** were determined by examining relevant coupling constants from the ¹H NMR. Particularly diagnostic for the 2-deoxygalactose stereochemistry in **22** and **24** were the large *J* values (~12.5 Hz) for the diaxial protons at C-2 and C-3. Conversely, both **23** and **25** displayed large *J* values (>8 Hz) for the diaxial protons at C-4 and C-5, which is indicative of the 2-deoxyallose stereochemistry.

In summary, we have developed two practical reaction sequences for the preparation of four C-2 deoxysugars and four C-2/C-3 dideoxysugars from pyrans **9** and **10**. These routes are amenable to multigram scale preparation. We hope these new routes to D- and L-sugars will be beneficial for the synthesis of unnatural aminoglycosides.

Acknowledgment. We thank the Arnold and Mabel Beckman Foundation and the National Institute of General Medical Sciences (1R01 GM63150-01A1) for their generous support of our program.

Supporting Information Available: Complete experimental procedures and spectral data (MP, IR, ¹H NMR, ¹³C 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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