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Azetidine Iminosugars from the Cyclization of 3,5-Di-*O*-triflates of α-Furanosides and of 2,4-Di-*O*-triflates of β-Pyranosides Derived from Glucose

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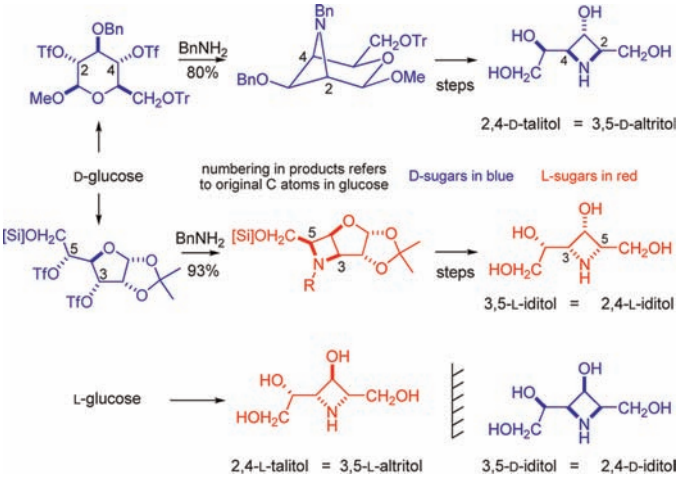
ABSTRACT



Primary amines with either 3,5-di-*O*-ditriflates of α-furanosides or 2,4-di-*O*-triflates of β-pyranosides form bicyclic azetidines in high yield.

Applications of azetidines[1] include use in polymeric materials[2] and in a wide range of bioactive compounds.[3] Natural and synthetic azetidine carboxylic acids[4] are common proline substitutes and components of nonproteinogenic amino acids and are being studied as a new class of foldamers.[5] Accordingly there is much current

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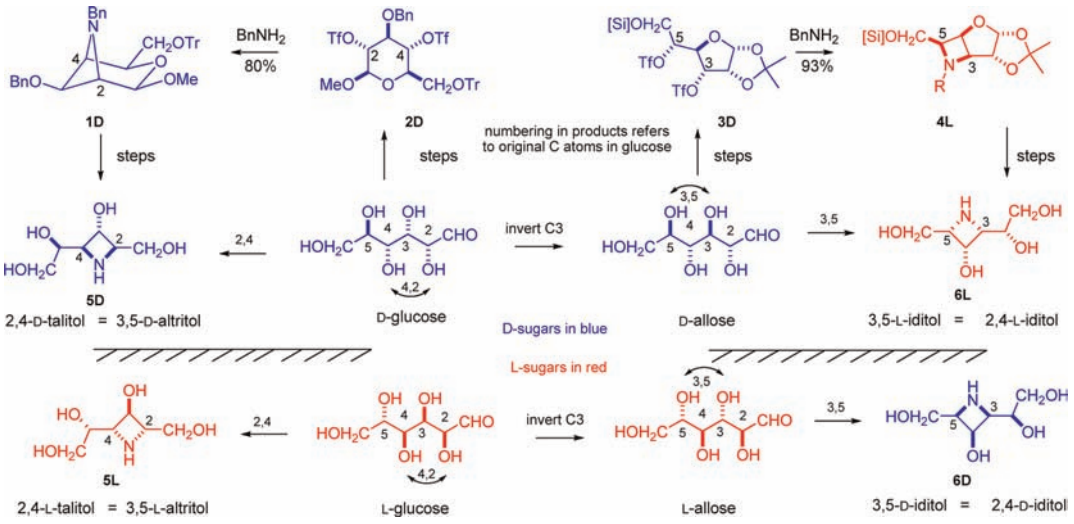
Scheme 1. Strategy for the Synthesis of Azetidine 2,4-Dideoxy-2,4-iminohexitols from Glucose



interest in the different strategies for the synthesis of azetidines.[6]

Five, six, and seven ring iminosugars[7] as mimics of monosaccharides are the most general class of inhibitors of glycosidases and interact with many other enzymes and receptors concerned with carbohydrate processing. In contrast there are very few examples of azetidine imino sugars;[8] *N*-alkyl hydroxyazetidines have been designed as potent transition state analogue inhibitors of purine nucleoside phosphorylase with subnanomolar K_i.[9] Azetidine iminosugar analogues of pentoses have been found to be specific inhibitors of nonmammalian glycosidases.[10,11] DMDP, the most common natural iminosugar, is a 2,5-dideoxy-2,5-iminohexitol and is a bioactive mimic of fructose and glucose.[12] Reported examples of corresponding azetidine analogues, 2,4-dideoxy-2,4-iminohexitols, are rare.[13]

This paper reports the syntheses of analogues in which the azetidine ring was formed in excellent yield by amine double displacements of ditriflates at C2 and C4, or at C3 and C5, of protected hexoses [Scheme 1]. The *cis*-2,4-di-*O*-triflate pyranoside **2D** derived from D-glucose with benzylamine gave the bicyclic azetidine **1D** in 80% yield as a key intermediate in the synthesis of 3,5-dideoxy-3,5-imino-D-altritol **5D**.[14] Inversion of configuration at C3 of D-glucose to D-allose allowed the formation of a ditriflate **3D** in which the C3 OH group is *trans* to the carbon side chain; reaction of **3D** with benzylamine afforded the *cis*-fused azetidine **4L** in 93% yield, as a precursor to 2,4-dideoxy-2,4-imino-L-iditol **6L**. The L-enantiomers of many iminosugars have significant bioactivities compared to the corresponding D-natural products.[15] Accordingly, the enantiomers **5L** and **6D** were prepared by identical sequences from L-glucose, readily available from D-glucoheptonolactone.[16] The amine cyclization of such sugar-derived ditriflates is likely to provide an efficient general access to highly functionalized homochiral azetidines. Preliminary studies on the inhibition of glycosidases by **5** and **6** are described.

The β-pyranoside **12L**, with only the C2 and C4 hydroxyl groups unprotected, was the key intermediate in the synthesis of 2,4-dideoxy-2,4-imino-L-talitol **5L** from diacetone-L-glucose **7L** [Scheme 2]. Reaction of **7L** with benzyl bromide and sodium hydride in DMF gave the benzyl ether **8L** (88%). Hydrolysis with aqueous trifluoroacetic acid afforded the pyranose **9L** (81%). Acetylation with acetic anhydride in pyridine formed the tetraacetate **10Lβ** (75%) with a small amount of the α-anomer **10L**α. **10L** with hydrogen bromide in acetic acid, followed by treatment of the resulting crude bromide with methanol in the presence of silver carbonate, afforded the fully

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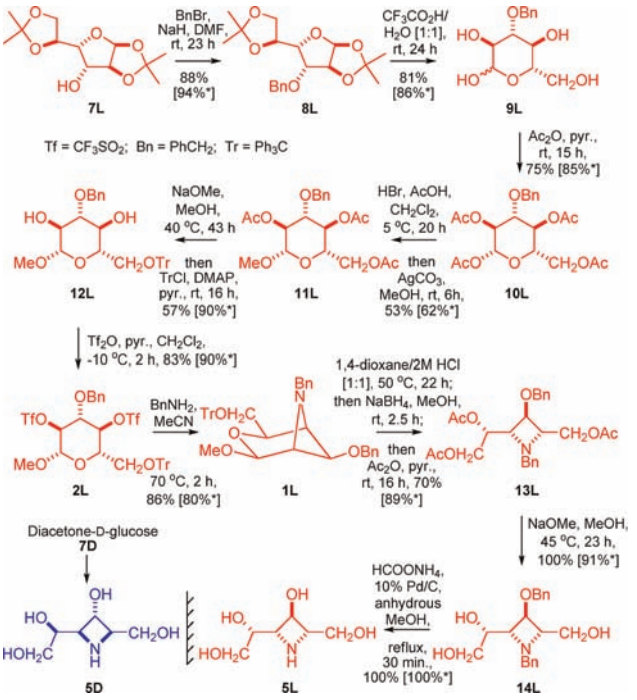
(14) The equivalence of 2,4-dideoxy-2,4-imino- and of 3,5-dideoxy-3,5-imino-hexitols is shown in Scheme 1. IUPAC carbohydrate nomenclature names **5** as 3,5-dideoxy-3,5-imino-altritol and **6** as 2,4-dideoxy-2,4-imino-iditol.

protected β-glucoside **11L** (53%). Sodium methoxide in methanol removed the acetate protecting groups in **11L** to allow subsequent protection of the primary alcohol by treatment with trityl chloride in pyridine in the presence of DMAP to afford the diol **12L** (57%). Esterification of the free hydroxyl groups in **12L** with triflic anhydride in dichloromethane in the presence of pyridine afforded the ditriflate **2L** (83%) which with benzylamine in acetonitrile underwent a highly efficient cyclization to produce the bicyclic azetidine **1L** in 86% yield. All attempts to get the α-anomer of **2L** to undergo a similar cyclization in a significant yield were unsuccessful; further studies are in progress to determine the propensity of similar anomeric pyranose ditriflates to form azetidines. Hydrolysis of **1L** with aqueous hydrochloric acid in dioxane removed both the trityl and anomeric protecting groups; reduction of the crude lactol with sodium borohydride in methanol and subsequent acetylation of the resulting triol with acetic anhydride in pyridine afforded the triacetate **13L** (70%), allowing easy purification. Removal of the acetates from **13L** by sodium methoxide in methanol gave **14L** (100%); subsequent transfer hydrogenation with ammonium formate in anhydrous methanol in the presence of 10% palladium on charcoal removed both benzyl groups from **14L** to form the target azetidine **5L**[17] {100%, $[\alpha]_D^{25}$ +15.5 (*c* 0.49, H_2O) for the hydrochloride salt} in an overall yield of 8% from **7L**. The enantiomer **5D** {$[\alpha]_D^{25}$ −13.9 (*c* 0.44, H_2O) for the hydrochloride salt} was prepared by a similar procedure in 22% overall yield from diacetone-D-glucose **7D**.

The synthesis of 2,4-dideoxy-2,4-imino-L-iditol **6L**, an epimer of **5L**, *via* azetidine ring formation between C3 and C5 [Scheme 3], required initial epimerization of C3 in diacetone glucose **7D** to the allose **15D**.[18] Selective removal of the exocyclic acetonide in **15D** by hydrolysis with aqueous acetic acid afforded the triol **16D** (81%). Reaction

Scheme 2. Synthesis of Azetidines **5L** and **5D**[a]



[a] * = yield for enantiomers prepared from **7D**.

of **16D** with *tert*-butyldimethylsilyl chloride in DMF gave the silyl ether **17D** (94%), which on esterification of the free hydroxyl groups at C3 and C5 formed the ditriflate **3D** (98%). Reaction of the ditriflate **3D** with benzylamine in the presence of diisopropylethylamine (DIPEA) gave the fused azetidine **4L** (93%). Treatment of **4L** with aqueous trifluoroacetic acid removed both the silyl and isopropylidene protecting groups; reduction of the resulting lactol with sodium borohydride in water afforded a triol **19L**, which was isolated as the nonpolar triacetate **18L** [68% overall yield from **4L**]. Removal of the esters from **18L** with sodium methoxide in methanol gave **19L** (98%), which on hydrogenolysis of the *N*-benzyl group by transfer hydrogenation formed the iminoiditol **6L**[19] {$[\alpha]_D^{25}$ −6.2 (*c* 0.5, MeOH) for the hydrochloride salt} (100%). The overall yield of **6L** from **15D** was 46%. The enantiomer **6D** {$[\alpha]_D^{25}$

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(17) Selected data for a HCl salt of 3,5-dideoxy-3,5-imino-D-altritol **5D**: δ_H (D_2O, 500 MHz): 3.62−3.65 (1H, dd, H6, $J_{6,5}$ 5.1 Hz, J_{gem} 12.1 Hz), 3.68−3.71 (1H, dd, H6′, $J_{6',5}$ 4.1 Hz, J_{gem} 12.1 Hz), 3.88−3.92 (1H, dd, H1, $J_{1,2}$ 4.1 Hz, J_{gem} 13.3 Hz), 3.91−3.95 (1H, dd, H1′, $J_{1',2}$ 4.8 Hz, J_{gem} 13.3 Hz), 4.06−4.09 (1H, a-dt, H5, $J_{5,6'}$ 4.1 Hz, $J_{5,6}/J_{5,4}$ 5.3 Hz), 4.30−4.32 (1H, dd, H4, $J_{4,5}$ 5.5 Hz, $J_{4,3}$ 7.2 Hz), 4.33−4.36 (1H, a-dt, H2, $J_{2,1}/J_{2,1'}$ 4.4 Hz, $J_{2,3}$ 7.2 Hz), 4.57−4.60 (1H, t, H3, $J_{3,4}/J_{3,2}$ 7.2 Hz); δ_C (D_2O, 125 MHz): 58.4 (C1), 62.6 (C6), 64.9 (C3), 67.4, 67.6 (C2 and C4), 68.8 (C5).

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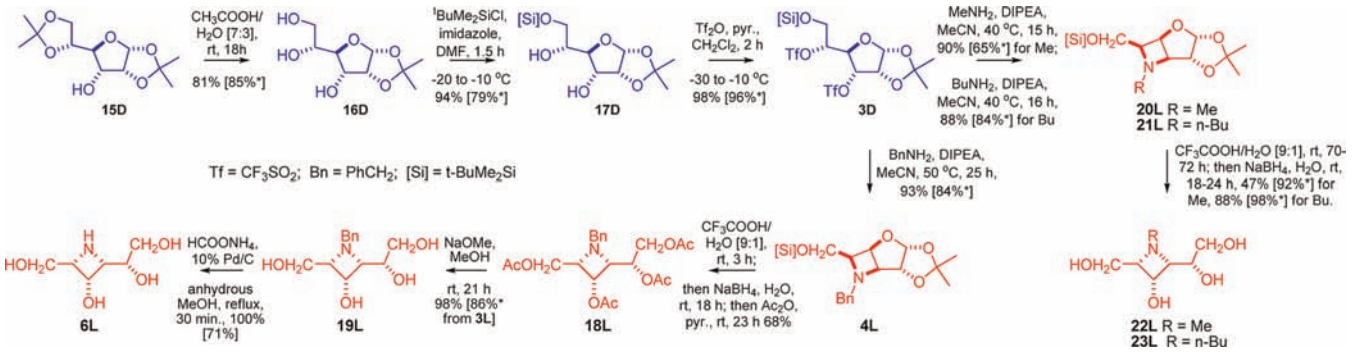
(19) Selected data for 3,5-dideoxy-3,5-imino-D-altritol **6L**: mp 101−102 °C; δ_H (D_2O, 400 MHz): 3.45−3.50 (1H, dd, H6, $J_{6,5}$ 6.3 Hz, J_{gem} 11.9 Hz), 3.62−3.66 (1H, dd, H6′, $J_{6',5}$ 3.5 Hz, J_{gem} 11.9 Hz), 3.63−3.67 (1H, dd, H1, $J_{1,2}$ 6.3 Hz, J_{gem} 11.3 Hz), 3.82−3.87 (1H, dd, H1′, $J_{1',2}$ 7.0 Hz, J_{gem} 11.3 Hz), 3.84−3.88 (1H, dd, H4, $J_{4,3}$ 6.3 Hz, $J_{4,5}$ 8.6 Hz), 3.94−3.99 (1H, ddd, H5, $J_{5,6'}$ 3.5 Hz, $J_{5,6}$ 6.3 Hz, $J_{5,4}$ 8.7 Hz), 3.99−4.04 (1H, a-dt, H2, $J_{2,3}/J_{2,1}$ 6.4 Hz, $J_{2,1'}$ 7.0 Hz), 4.62−4.65 (1H, a-t, H3, $J_{3,2}/J_{3,4}$ 6.4 Hz); δ_C (D_2O, 100 MHz): 60.3 (C4), 60.5 (C2), 61.0 (C1), 63.4 (C6), 68.0 (C3), 71.8 (C5). Selected data for HCl salt of 3,5-dideoxy-3,5-imino-D-altritol **6 L**: δ_H (D_2O, 400 MHz): 3.56−3.60 (1H, dd, H6, $J_{6,5}$ 5.2 Hz, J_{gem} 12.2 Hz), 3.68−3.72 (1H, dd, H6′, $J_{6',5}$ 3.5 Hz, J_{gem} 12.2 Hz), 3.95−4.00 (1H, dd, H1, $J_{1,2}$ 5.3 Hz, J_{gem} 12.7 Hz), 4.05−4.10 (1H, dd, H1′, $J_{1',2}$ 7.2 Hz, J_{gem} 12.7 Hz), 4.28−4.32 (1H, ddd, H5, $J_{5,6'}$ 3.5 Hz, $J_{5,6}$ 5.2 Hz, $J_{5,4}$ 8.1 Hz), 4.56−4.59 (1H, dd, H4, $J_{4,3}$ 6.7 Hz, $J_{4,5}$ 8.1 Hz), 4.63−4.67 (1H, m, H2), 4.79−4.82 (1H, a-t, H3, $J_{3,2}/J_{3,4}$ 6.5 Hz); δ_C (D_2O, 100 MHz): 57.2 (C1), 63.0 (C6), 64.0, 64.0 (C2 and C4), 66.3 (C3), 67.4 (C5).

Scheme 3. Synthesis of Azetidines **6L** and **6D**[a]



[a] * = yield for enantiomers prepared from **15L**.

+12.1 (*c* 0.5, MeOH) for the hydrochloride salt} was also prepared from diacetone-L-allose **15L** by a similar route in an overall yield of 33%.

N-Alkylation of imino sugar mimics can affect their biological properties significantly;[20] the ring closure of the ditriflate **3D** proceeded in good yield with a number of amines, allowing access to *N*-alkyl azetidines. Reaction of the ditriflate **3D** with methylamine in acetonitrile in the presence of DIPEA formed the protected azetidine **20L** (90%); with butylamine under the same conditions **21L** was obtained (88%), illustrating the general efficiency of the ring closure. Hydrolysis of **20L** with aqueous trifluoroacetic acid followed by reduction with sodium borohydride gave the *N*-methyl azetidine **22L** (47%); similar treatment of **20L** afforded the *N*-butyl analogue **23L** (88%).

Inhibition by the azetidine iminosugars of the activity of the following glycosidases was studied:[21] α-glucosidases (rice, yeast, rat intestinal maltase, *A. niger*), β-glucosidases (almond, bovine liver), α-galactosidase (coffee beans), β-galactosidase (bovine liver), α-mannosidase (Jack bean), β-mannosidase (snail), α-L-rhamnosidase (*P. decumbens*), α-L-fucosidase (bovine kidney), trehalase (porcine kidney), and amyloglucosidases (*A. niger*, *Rhizopus sp*). The *N*-benzyl-D-iditol **19D** showed potent and specific inhibition of rice and rat intestinal maltase [IC_{50} 27 and 71 μM, respectively] whereas the parent D-iditol **6D** showed no inhibition. The imino-L-talitol **5L** was a moderate inhibitor of rice and rat intestinal maltase [IC_{50} 481 and 176 μM, respectively]. The imino-L-iditol **6L** showed weak but selective α-galactosidase inhibition [IC_{50} 416 μM].

In summary, bicyclic azetidines may be formed by high yielding cyclizations of ditriflates of both pyranosides and furanosides. While this paper has illustrated the value of this strategy in the synthesis of iminosugar azetidines, this strategy may provide a general approach to the synthesis of enantiomerically pure highly functionalized azetidines and, in particular, allow easy access to a new range of azetidine carboxylic acids.

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Supporting Information Available. Experimental procedures and full spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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