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Synthesis of L-Sugars from 4-Deoxypentenosides

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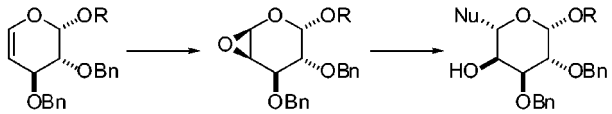
ABSTRACT



4-Deoxypentenosides, which are readily derived from D-sugars, resemble glycals in structure and reactivity and can undergo stereoselective epoxidation and S_N2 nucleophilic addition to produce L-sugars in pyranosidic form.

L-Sugars, designated as such by the configuration of the stereogenic carbon most remote from the aldehydo/keto functionality,[1] have been a subject of enduring scientific interest. L-Sugars in their pyranosidic forms are important constituents of antibiotics[2] and clinically useful agents such as heparin;[3] they have also demonstrated potential as noncaloric sweeteners[4] and selectively toxic insecticides.[5] Numerous synthetic approaches toward L-pyranosides have been reported, including de novo syntheses,[6] homologation of shorter-chain sugars,[7] and epimerization of readily available D-sugars.[8] Most strategies involving the latter employ an acyclic intermediate to establish the C5 stereocenter, which often leads to a mixture of products upon cyclization. Several groups have reported epimerization of the critical stereocenter without opening the pyranose ring,[9] but overall, an efficient synthetic route to L-pyranosides has been lacking.

Here we introduce a direct and potentially general approach to L-pyranosides via 4-deoxypentenosides (4,5-unsaturated pentopyranosides). These unsaturated sugars bear a strong resemblance to glycals, a widely used intermediate in the synthesis of oligosaccharides[10] and a variety of natural products.[11] Indeed, the methodology reported herein suggests that 4-deoxypentenosides and glycals have similar reactivity profiles: both can be stereoselectively epoxidized by dimethyldioxirane (DMDO) and can react with carbon nucleophiles with inversion of configuration. We demonstrate this with a stereoselective, two-step synthesis of L-altropyranoside derivatives bearing a diverse range of functional groups at C5.

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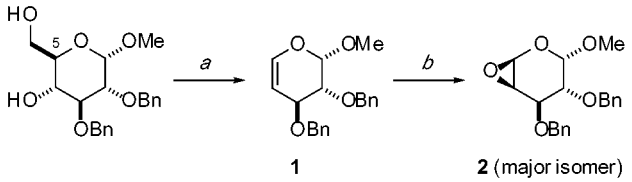
Scheme 1[a]



1 2 (major isomer)

[a] Reaction conditions: (a) (i) TEMPO (5 mol %), KBr (10 mol %), *n*-Bu_4NBr (5 mol %), NaOCl, $NaHCO_3$, CH_2Cl_2/H_2O, 0 °C; (ii) *N*,*N*-dimethylformamide dineopentyl acetal (5 equiv), toluene, 120 °C (70% overall yield). (b) 0.1 M DMDO in acetone, CH_2Cl_2, −55 °C (quantitative yield).

4-Deoxypentenoside **1** was prepared from the corresponding methyl α-D-glucoside in 70% yield by a two-step oxidation−decarboxylative elimination, modified from a procedure reported by Zemlicka and co-workers (see Scheme 1).[12] Several methods for epoxidation were investigated; however, the sensitivity of the resulting 4,5-epoxypyranosides to acidic hydrolysis precluded purification by silica chromatography, placing considerable limitations on the choice of reagents and reaction media (see Table 1 for selected conditions). Nevertheless, we observed that epoxidation of **1** with DMDO at −55 °C proceeded quantitatively with β:α selectivities of approximately 10:1, as determined by ^1H NMR spectroscopy (300 MHz, C_6D_6) and the ensuing product ratios (see below). Epoxidation stereoselectivity was strongly affected by the transannular substituents, which can influence both the pentenoside ring conformation and the local steric environment; for example, epimerization at C1 or C2 resulted in high selectivity for the α face (see Table 2).[13]

Table 1. Selected Epoxidation Conditions for 4-Deoxypentenoside **1**

condition[a]	β:α selectivity
MMPP, $NaHCO_3$, CH_2Cl_2, rt	NR
m-CPBA, $NaHCO_3$, CH_2Cl_2/H_2O, 0 °C	2:1
$CF_3C(OO)Me$/trifluoroacetone, CH_2Cl_2, −78 °C	5:1
DMDO/acetone, CH_2Cl_2, −20 °C (4 h)	5:1
DMDO/acetone, CH_2Cl_2, −55 °C (48 h)	10:1

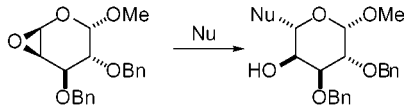
[a] MMPP = magnesium monoperoxyphthalate; *m*-CPBA = *m*-chloroperoxybenzoic acid; DMDO = 2,2-dimethyldioxirane.

Table 2. Substituent Effects on 4-Deoxypentenoside Epoxidation

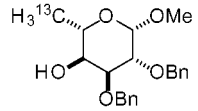
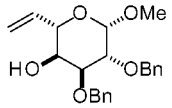
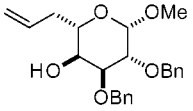
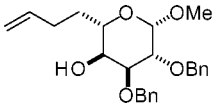
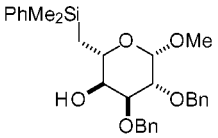
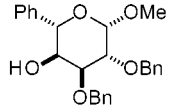
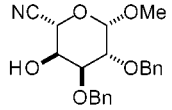
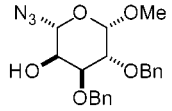
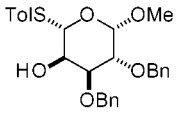
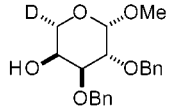
configuration	β:α selectivity
α-methyl gluco (**1**)	10:1[a]
α-isopropyl gluco	8:1[a]
β-isopropyl gluco	1:5[b]
α-methyl manno	>1:20[b]

[a] DMDO (0.1 M) in acetone/CH_2Cl_2, −55 °C. [b] DMDO (0.1 M) in acetone/CH_2Cl_2, 0 °C.

Table 3. Nucleophilic Ring-Opening of β-Epoxide **2**



2 (10:1 β:α) **3a-j** (major product)

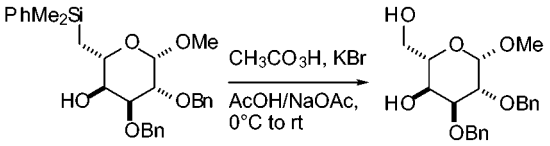
entry	nucleophile	react cond	product	yield
a	$^{13}CH_3MgI$	A		57%[b]
b	MgBr	B		78%[c]
c	MgCl	B		70%[b]
d	MgBr	B		52%[b]
e	$PhMe_2Si$ MgCl	B		86%[b]
f	MgBr	A		69%[c]
g	KCN	C		68%[b]
h	NaN_3	C		77%[b]
i	4-MePhSLi	D		72%[c]
j	$LiAlD_4$	E		69%[c]

[a] Reaction conditions: (A) 3.5 equiv of Nu, 1.5 equiv of CuI, THF, −10 °C. (B) 3.5 equiv of Nu, 0.1 equiv of CuI, THF, −10 °C. (C) 10−20 equiv of Nu in aq DMF, rt. (D) 9.0 equiv of Nu in THF, 0°C. (E) 5.0 equiv of Nu in Et_2O, rt. [b] Mixture of diastereomers = 10:1 L-altro/D-gluco. [c] Isolated yield.

Epoxypyranoside **2** was evaluated for its reactivity under S_N2 conditions with a broad set of nucleophiles. β-Epoxide ring-opening was observed to proceed in many cases with complete regioselectivity and inversion of stereochemistry at C5, producing the corresponding L-altro derivatives as the major products (see Table 3).[14,15] In particular, Cu(I)-assisted Grignard additions proceeded with both high yields and stereocontrol.[16] Similar nucleophiles have been reported to react with α-epoxyglycals and related intermediates with inversion of configuration at C1.[11b−d,17] Heteroatomic nucleophiles were also observed to add in an S_N2 fashion, yielding novel 1,5-bisacetals. It should be noted that several of the products in Table 3 can be readily converted to genuine L-hexopyranosides; for example, a Tamao−Fleming oxidation[18] on dimethylphenylsilane **3e** yields L-altropyranoside **4** in 75% yield (see Scheme 2).

The 4-deoxypentenoside route toward L-sugars offers some distinct advantages over other synthetic methods: (i) it can be used to install both natural and unnatural substituents at C5; (ii) it is an efficient method for introducing isotopic labels and can be used to prepare 6-[^{13}C]-hexopyranosides;[19] and (iii) it provides direct access to protected L-pyranosides with fixed anomeric configurations and may be adapted directly toward the construction of 1,4-linked saccharides such as the glycosaminoglycans. We anticipate that 4-deoxypentenosides will also be useful as synthetic intermediates toward higher-order or exotic sugars and other complex tetrahydropyrans.[11]

Scheme 2



3e **4**

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Supporting Information Available: Experimental procedures for the synthesis of compounds **1**−**4**, plus selected ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) The product of entry **i** is formally a 5*S*-[^{2}*H*]-L-arabinoside. It should be mentioned that additions to the minor α-epoxide isomer also proceeded with inversion at C5 to yield the corresponding D-gluco derivatives.

(15) Stereochemistry was assigned on the basis of ^{1}H NMR coupling constants of both the major and minor stereoisomers, supplemented by nuclear Overhauser effect experiments (see Supporting Information).

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