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syn Additions to 4α-Epoxypyranosides: Synthesis of L-Idopyranosides

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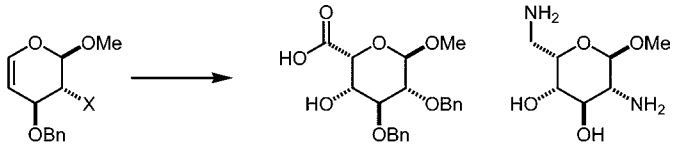
ABSTRACT



The *syn*-selective addition of organozinc compounds to 4α-epoxypyranosides (4α-EPs), generated from methyl β-D-glucoside or aminoglucoside, provides an efficient route to pyranosides with α-L-*ido* configurations, including L-iduronic acid, neosamine B, and higher monosaccharide derivatives.

Unsaturated pyranosides such as glycals are used extensively in carbohydrate and natural products synthesis.[1] One widespread application involves the formation of epoxyglycals by stereoselective addition of dimethyldioxirane (DMDO), which can be employed as glycosyl donor in the synthesis of *O*- and *C*-glycosides.[2] 4-Deoxypentenosides (4-DPs) bear a strong structural homology to glycals but retain a stereogenic anomeric center. The reactivity profile of 4-DPs is similar to that of glycals but is somewhat more selective with respect to stereocontrol. 4-DPs can be epoxidized by DMDO in a highly facioselective manner,[3,4] and 4β-epoxypyranosides (4β-EPs) can undergo *anti*-selective (S_N2) ring opening to generate novel pyranosides with an L-*altro* configuration.[3] 4α-Epoxypyranosides (4α-EPs), which can also be obtained with high stereoselectivity,[4] should be equally valuable as precursors to L-pyranosides. Here we demonstrate the utility of organozinc reagents for *syn*-selective ring opening of 4α-EPs into pyranosides with an L-*ido* configuration.

The efficient formation of α-*C*-glycosides via *syn*-selective ring openings of α-epoxyglycals has been achieved with mild organometallic reagents having a significant Lewis acid character, namely, those derived from aluminum,[5,6] boron,[5] titanium,[7] zirconium,[8] or zinc.[9] *Syn* delivery of the nucleophile is assumed to proceed by coordination and simultaneous activation of the epoxide by the metal center. Although many of these reagents are likely to be useful for *syn*-selective addition to 4-EPs,[10] organozinc halides (RZnX) are most appealing with respect to atom efficiency and functional group compatibility and can be generated by several different methods.[9,11]

4α-EPs **6** and **7** were derived in good yields from β-methyl-D-glucoside **1** and β-methyl-D-glucosaminoside **2**,

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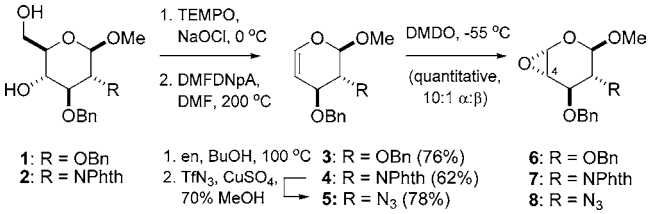
respectively, using an oxidation−decarboxylative elimination sequence.[3,10] Phthalimide **4** was transformed into azido derivative **5** by diazo transfer onto the intermediate free amine.[12] DMDO oxidations of 4-DPs **3**−**5** were carried out at −55 °C to produce 4α-EPs **6**−**8** with 10:1 α:*β* stereoselectivity and in quantitative yield (Scheme 1).[4] The 4α-EPs could be stored at −20 °C for several months without concern for decomposition.

Scheme 1. Synthesis of 4α-Epoxypyranosides[a]



[a] Selected abbreviations: DMDO = dimethyldioxirane; DMFDNpA = dimethylformamide dineopentyl acetal; en = ethylenediamine; Phth = phthalimide; TEMPO = tetramethylpiperidine oxide; TfN_3 = triflyl azide.

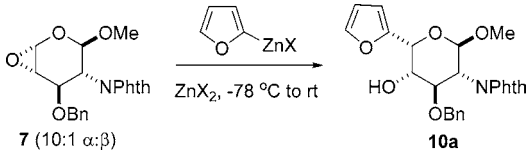
The most reliable *syn* additions were produced by generating RZnX species via the transmetallation of organolithium or Grignard reagents (see Supporting Information). Systematic examination of reaction conditions revealed that the presence of excess $ZnBr_2$ significantly improved the efficiency of addition (Table 1); adducts were produced in high yields using 2 equiv of RZnBr, whereas stronger Lewis acids such as $Zn(OTf)_2$ or BF_3−Et_2O were often incompatible with the epoxide. Furthermore, allyltrimethylsilane and other electron-rich olefins tended to react poorly with 4α-EPs in the presence of Lewis acids, in contrast to their efficacy as nucleophiles in *C*-glycoside synthesis. These studies suggest that $ZnBr_2$ promotes *syn* addition by forming an active complex with RZnBr (see below), rather than by direct activation of the epoxide. The activation of organometallic reagents by Lewis acids has been well documented over the years.[13]

$$^{(\delta-)}R-{}^{(\delta+)}Zn-Br\cdots ZnBr_2$$

The addition of RZnX species to 4α-EPs **6**, **7**, and **8** proceeded with high selectivity (*syn*:*anti* > 20:1) for a variety of sp^2- and sp-carbon nucleophiles, producing the corresponding L-idopyranoside derivatives in good to high yields (Table 2). For example, 4α-EP **6** was converted into L-idopyranoside **9a** in 84% isolated yield, accompanied by a small amount of *anti* adduct and a product derived from the minor 4*β*-EP isomer (<5% combined yield).[14] 4α-EP **6** also reacted efficiently with activated sp^3-carbon nucleophiles such as allylzinc bromide (entry 7) but was less receptive to additions with (*Z*)-alkenylzinc agents (entries 10 and 13). These derivatives could be obtained with higher overall yields by partial hydrogenation of the corresponding alkynyl derivatives.

Several of the *syn* adducts in Table 2 were examined as intermediates for preparing L-idopyranosides with natural or unnatural configurations. In particular, we were interested to develop novel routes to L-iduronic acid, a vital component of heparin and heparan sulfate;[15] neosamine B, a 2,6-diaminopyranoside with L-*ido* configuration found in several aminoglycoside antibiotics;[16] and higher monosaccharides with structural analogy to sialic acid and other biologically active congeners.[17,18] Syntheses of these sugars typically involve manipulation of acyclic intermediates, either for epimerization of the C5 stereocenter in the cases of L-iduronic acid and neosamine B[19,20] or for chain extension at the reducing end in the case of higher monosaccharides.[17,21] In

Table 1. Selected Conditions for *syn* Addition of 2-Furylzinc Halides to 4α-Epoxypyranoside **7** in the Presence of ZnX_2[a]



entry	furylZnX (equiv)	ZnX_2 (equiv)	yield (%)[b]
1	2	$ZnCl_2$ (2)	41
2	2	$ZnCl_2$ (5)	60
3	4	$ZnCl_2$ (2)	64
4	10	$ZnCl_2$ (2)	76
5	2	$ZnBr_2$ (0)	56
6	2	$ZnBr_2$ (2)	67
7	**2**	**$ZnBr_2$ (5)**	**83**

[a] Preparation of 2-furylzinc halide in THF: (i) furan, *n*-BuLi, THF, −78 °C, 30 min; (ii) ZnX_2, THF, 0 °C, 30 min. Epoxide **7** was added as a CH_2Cl_2 solution at −78 °C, warmed to 0 °C, and then stirred for 2 h while warming to rt. [b] Isolated yields.

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(14) Addition to the 4*β*-EP isomer is presumed also to proceed with high *syn* selectivity.

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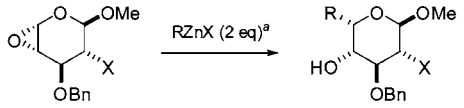
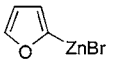
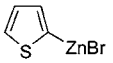
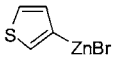
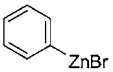
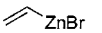
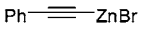
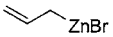
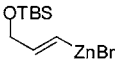
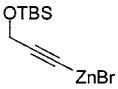
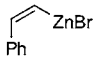
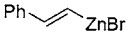
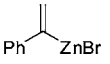
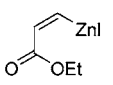
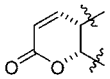
Table 2. *syn* Additions to 4α-Epoxypyranosides **6**−**8**[a]



6: X = OBn
7: X = NPhth
8: X = N_3

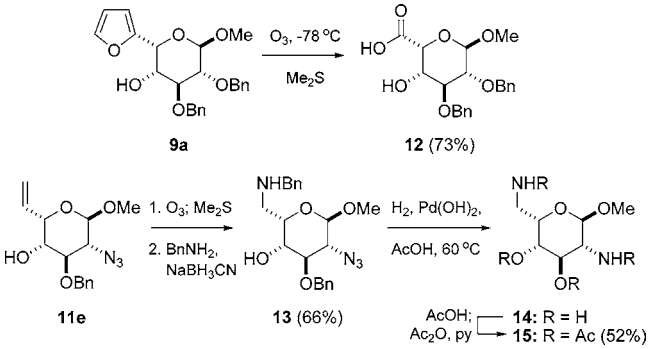
9: X = OBn
10: X = NPhth
11: X = N_3

entry	RZnX	prep method[b]	product	yield[c]
1		A	**9a** **10a**	84% 83%
2		A	**9b** **10b**	74% 83%
3		C	**9c** **10c**	69% 82%
4		B	**9d** **10d**	80% 83%
5		B	**9e** **10e** **11e**	69% 74% 58%
6		A	**9f** **10f**	77% 74%
7		B	**9g**	73%
8		C	**9h**	60%
9		A	**9i**	79%
10		C	**9j**	37%[d] (77%)[e]
11		C	**9k**	66%
12		C	**9l**	77%
13		D	 **9m**	23% (73%)[f]

[a] See Supporting Information for reaction conditions. [b] A: (i) RH (4 equiv), *n*-BuLi (2 equiv), THF, −78 °C; (ii) $ZnBr_2$ (7 equiv), THF, 0 °C. B: RMgBr (2 eq), $ZnBr_2$ (7 equiv), 0 °C. C: (i) RBr or RI (2 equiv), *t*-BuLi (4 equiv), Et_2O, −78 °C; (ii) $ZnBr_2$ (7 equiv). D: RI (2 equiv), Zn (activated powder), THF, 45 °C. [c] Isolated yields. [d] **9f** formed as a byproduct (40% yield). [e] Yield in 2 steps via **9f**. [f] Yield in 4 steps via **9i**.

comparison, 4-EPs enable the stereoselective installation of carbon fragments at C5 with retention of the pyranose ring and anomeric configuration.

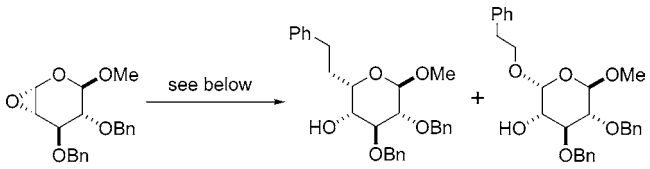
Scheme 2. Synthesis of L-Iduronic Acid and Neosamine B Methyl Glycosides



9a **12** (73%) **11e** **13** (66%) **14:** R = H **15:** R = Ac (52%)

L-Iduronic acid methyl glycoside **12** was prepared in 73% yield from 2-furyl adduct **9a** by ozonolysis with Me_2S workup (Scheme 2). Neosamine B methyl glycoside **14** was derived in 3 steps from **11e** (the C5 vinyl adduct of 4α-EP derivative **8**) by ozonolysis, reductive amination, and hydrogenation, and fully characterized as peracetate **15**.

Scheme 3. Addition of Mono- and Dialkylzinc Species to 4α-Epoxypyranoside **6**



6 **16** **17**

$PhCH_2CH_2ZnBr$, $ZnBr_2$ [a]	<10%	52%
$Ph(CH_2CH_2)_2Zn$ [b]	43%	24%

[a] Epoxide **6** added as a CH_2Cl_2 solution at −78 °C to $PhCH_2CH_2ZnBr$ (4 equiv) and $ZnBr_2$ (3 equiv) in THF, slowly warmed to −30 °C, and then stirred for 12 h at −30 °C. [b] Epoxide **6** added at −78 °C to $(PhCH_2CH_2)_2Zn$ (4 equiv) in THF, slowly warmed to −30 °C, and then stirred for 4 h at 0 °C.

Reactions involving unactivated alkylzinc halides and dialkylzincs did not proceed as smoothly under comparable reaction conditions. For example, phenethylzinc bromide and diphenethylzinc gave low to fair yields of expected L-idopyranoside **16** accompanied by significant amounts of C5 phenethoxy adducts **17** (Scheme 3), an indication of the oxidative sensitivity of alkylzinc species.[22] Rigorous removal of oxygen from the reaction mixture did not improve the ratio of C- to O-addition products, implying that alkylzincs

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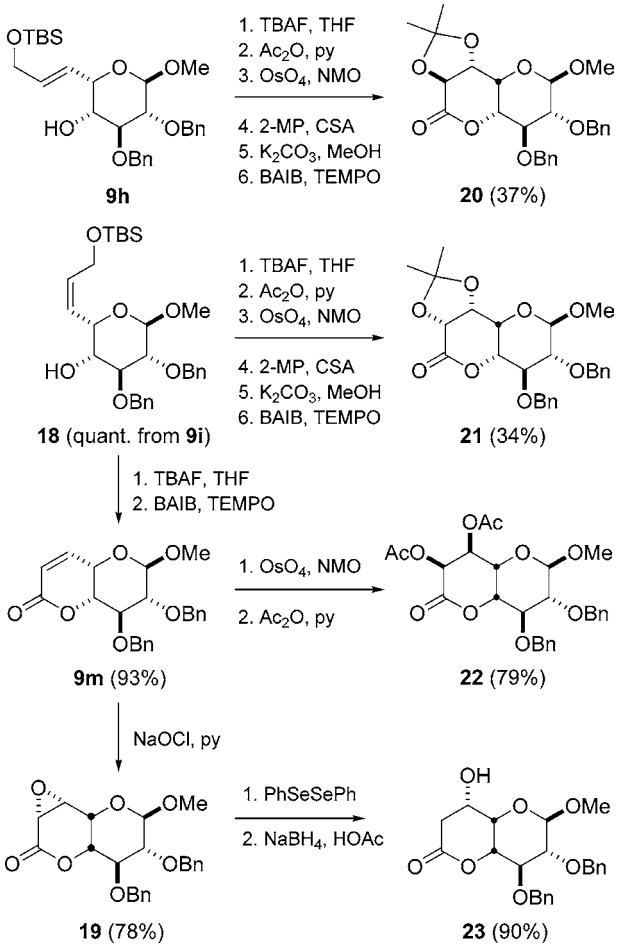
could be oxidized by the 4-EPs or an unidentified byproduct of the DMDO reaction (Scheme 1).[23]

L-Idopyranosides with C5 alkyl substituents can be prepared with considerable structural diversity and in synthetically useful yields via the *syn* addition of alkenyl groups. We illustrate this with the stereoselective syntheses of several octopyranoside derivatives, all with L-*ido* configuration but stereochemically divergent at C6 and C7. Compounds **20** and **21** were prepared respectively from *trans*-allylic ether **9h** and *cis*-allylic ether **18** (via reduction of propargylic ether **9i**) by catalytic osmylation, with diastereomeric ratios of 5:1 and 6:1 favoring the desired product (Scheme 4). The configurations of octopyranosides **20** and **21** were tentatively assigned as D-*threo*-L-*ido* and L-*erythro*-L-*ido* with the stereochemical relationship of C5 and C6 being *erythro* in each case, according to the empirical rule developed by Kishi and co-workers.[24] The stereochemical assignments were

Scheme 4. Stereoselective Synthesis of Octopyranosides with L-*ido* Configuration[a]



[a] Selected abbreviations: BAIB = bisacetoxyiodobenzene; CSA = camphorsulfonic acid; MP = methoxypropene; NMO = morpholine *N*-oxide; TBS = *tert*-butyldimethylsilyl; TEMPO = tetramethylpiperidinoxy radical.

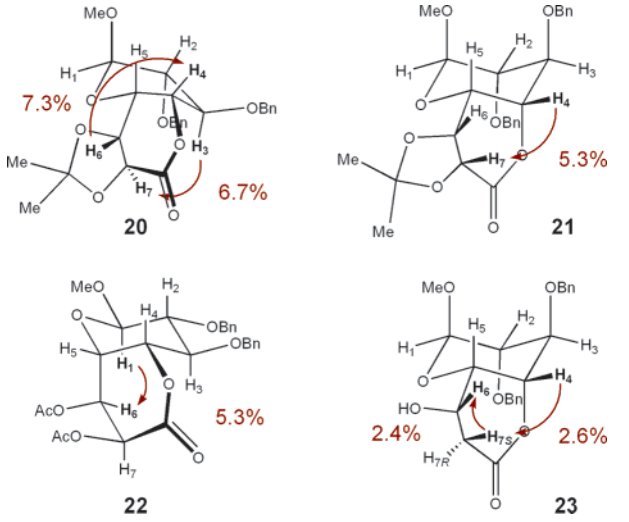


Figure 1. Stereochemical assignments of bicyclic lactones **20**−**23**. Conformations are drawn to emphasize NOE interactions.

confirmed by nuclear Overhauser enhancement (NOE) measurements (Figure 1). The osmylation of α,β-unsaturated lactone **9m**, which was expected to proceed with selectivity opposite to that of **18**, yielded a single diastereomer that was assigned as D-*erythro*-L-*ido* by NOE analysis of diacetate **22**. Compound **9m** could also be oxidized stereoselectively into epoxide **19** by hypochlorite oxidation[25] and converted cleanly by phenylselenol reduction[26] into 7-deoxyoctopyranoside **23**, whose C6 configuration was assigned to be L-*glycero* by NOE measurements.

In conclusion, $ZnBr_2$-mediated *syn* additions to 4α-epoxypyranosides provide a general and efficient route to natural and unnatural L-idopyranosides.

Acknowledgment. This work was supported by the National Institutes of Health (GM-06982). The authors also gratefully acknowledge support from the Purdue Cancer Center and the Purdue interdepartmental NMR facility, and Mr. Zhihong Huang (Purdue Univ.) for helpful discussions on organozinc chemistry.

Supporting Information Available: Experimental procedures and spectroscopic characterization of compounds **9a**−**23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) In some instances the deoxygenated reactant (4-DP **3**) could be recovered in low yield.

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