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A GENERAL SYNTHESIS OF METHYL ALDULOSONATES USING TRIS (METHYLTHIO) METHYL LITHIUM AS THE ESTER ANION EQUIVALENT

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Abstract: A general procedure is described for the conversion of aldonolactones to their corresponding methyl 2-aldulosonates.

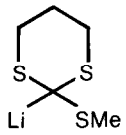
Certain aldulosonic acids play important roles in bacterial metabolism and virulence. For example, 3-deoxy-D-arabino-2-heptulosonic acid-7-phosphate is a precursor in aromatic amino acid biosynthesis, N-acetylneuraminic acid is a component of the capsular polysaccharides of certain uropathogenic bacteria, and 3-deoxy-D-manno-2-octulosonic acid is an ubiquitous and vital component of gram-negative outer membrane.

Our studies on such metabolites led to an interest in the synthesis of 2-ulosonic acids. Our strategy involved starting with suitably modified hexoses and elaborating them, via one carbon homologation, to 2-heptulosonic acids. We elected to study the addition of acylanion equivalents to aldonolactones as a means of achieving such transformations. Previous work[1] has shown that 1,3-dithiane reacts with 2,3,4,6-tetra-O-(trimethylsilyl)-D-glucono-1,5-lactone to afford 1-C-(1,3-dithian-2-yl)-α-D-glucopyranose, upon removal of the silyl protecting groups. We, however, desired intermediates with higher oxidation states, methanolysis of which would yield the methyl esters[2] of the desired ulosonates.

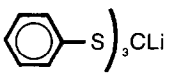
To this end, we studied the addition of lithio-2-methylthio-1,3-dithiane (**1**), tris(phenylthio)methyl lithium (**2**), tris(ethylthio)methyl lithium (**3**), and tris(methylthio) methyl lithium (**4**), to δ-valerolactone (**5**), as a model and to 3,4,6-tri-O-benzyl-2-deoxy-D-lyxono-1,5-lactone (**6**). Compounds **1** to **4** have previously been used as ester anion equivalents[3-6] and have been shown to add to ketones.

Compound **1** reacted with **5** to afford 2-C-(2-methylthio-1,3-dithian-2-yl)-tetrahydropyran-2-ol, but formed mainly the dithiane adduct, upon reaction with **6**. Compound **2** formed a stable anion, as previously reported,[2] reacted with **5** to form an adduct, which upon methanolysis, afforded the ester **7** but did not react with **6** or other aldonolactones, presumably due to unfavorable steric interactions. Addition of **3** to **6** was accompanied by significant formation of 3,4,6-tri-O-benzyl-2-deoxy-D-lyxo-hexopyranose, presumably resulting from reduction of the starting lactone by the reagent. The mechanism of the reduction may be analogous to that described for reaction of certain Grignard reagents with ketones.[8] This analogy suggested the use of **4**, which cannot undergo reductive side reactions.[9] We wish to report that **4** is an efficient acylanion equivalent, which allows for easy conversion of aldonolactones to methyl 2-aldulosonates.

Scheme 1



1



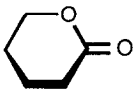
2

$(CH_3CH_2S)_3CLi$

3

$(CH_3S)_3CLi$

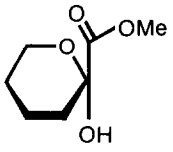
4



5

1 $(RS)_3CLi$

2 $HgO/HgCl_2/MeOH$

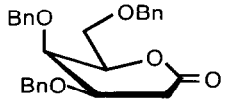
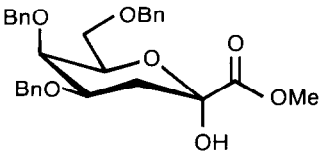
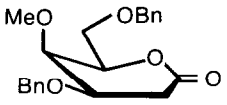
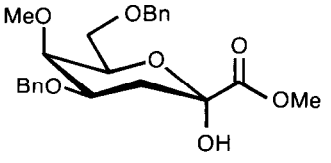
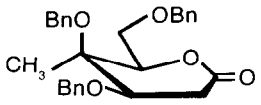
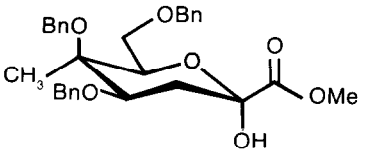
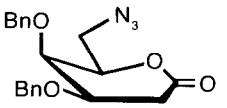
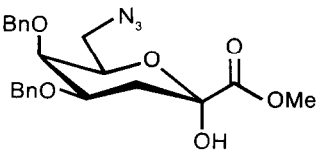
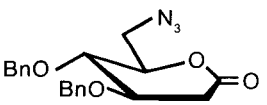
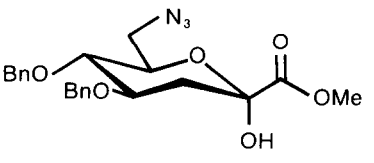
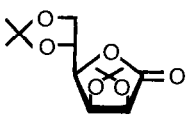
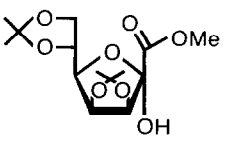


7

The synthesis of methyl 3,4,6-tri-O-benzyl-2-deoxy-D-lyxo-2-heptulosonate, **8** is a typical example; Tris (methylthio)methane (713.0 mg, 627.1 µl, 4.6 mmoles) was dissolved in dry THF (19.4 ml) and cooled to -78°C. One equivalent of n-butyllithium in hexane was added and the resulting mixture stirred under N_2 for 15 min. 3,4,6-tri-O-benzyl-D-lyxono-1,5-lactone **6** (665.4 mg; 1.5 mmoles), dissolves in dry THF (6.75 ml), was added to the reaction mixture via a syringe. The mixture was stirred at -78° for 4 hrs, allowed to warm gradually to -20° and quenched with saturated NH_4Cl solution. Chloroform was added to the mixture, the organic layer was separated, washed with water, dried over $MgSO_4$, filtered, and evaporated in vacuo. The crude product was dissolved in 95% aqueous methanol (7.3 ml). Yellow HgO (1.67 g, 7.7 mmoles) and $HgCl_2$ (5.39 g, 19.9 mmoles) were added and the mixture stirred at room temperature for 2.5 hrs. The reaction was monitored by TLC on silica gel, using hexane/EtOAc (7:3) as the solvent system. The crude reaction mixture was filtered through celite, evaporated in vacuo, and triturated with $CHCl_3$. The chloroform mixture was filtered to remove insoluble mercury salts and evaporated in vacuo to afford the crude ester, which was purified by flash chromatography, using Baker 40 µm silica gel and hexane/EtOAc (7:3) as the solvent. The colorless oil, (911.0 mg) was isolated in 40% yield. Some applications of this procedure are shown in Table 1.

Table 1

Conversion of Aldonolactones to Methyl 2-ulosonates

Lactone	Methyl 2-ulosonate	Yield, %
 **6**	 **8**	40
 **9**	 **10**	33
 **11**	 **12**	42
 **13**	 **14**	40
 **15**	 **16**	42
 **17**	 **18**	49

Reported yields in Table 1 are after purification by silica gel column chromatography. Structure proof was by mass spectrometry, ^{13}Cnmr and 360 mHZ pmr. The commonly used OH protecting groups, benzyl and isopropylidene groups, are compatible with this transformation, thereby demonstrating the potential utility of this procedure in multi-step syntheses.

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Acknowledgements

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