

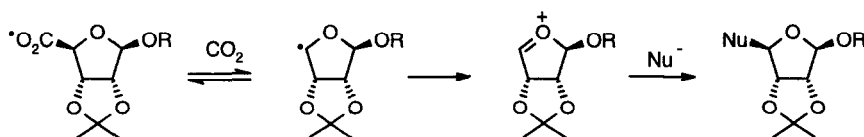
A Mild Oxidative Decarboxylation of Carbohydrate Acids

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Abstract: The oxidative decarboxylation of carbohydrate uronic or ulosonic acids with simultaneous replacement by an acetoxy group has been accomplished using the (diacetoxyiodo)benzene and iodine system under mild conditions. A general synthesis of derivatives of tetrodialdoses, and pentodialdoses in furanose or pyranose form is described. © 1997 Elsevier Science Ltd.

The oxidative decarboxylation of carbohydrate uronic or ulosonic acids may be of interest not only for descending the aldose series but also to provide chiral building blocks suitable for the synthesis of non-carbohydrate compounds.¹ The reagent and the reaction conditions should be mild enough to be compatible with most common carbohydrate protecting groups. We have used hypervalent iodine reagent in the presence of iodine to promote the oxidative decarboxylation of steroidal carboxylic acids² accompanied by a simultaneous replacement by iodine in a modified Hunsdiecker reaction.³ This reagent has also been used for the β -fragmentation of carbohydrate anomeric alkoxy radicals and proven to be compatible with most of the protective groups currently used in this type of compounds.⁴ The decarboxylation reaction would be favoured in carbohydrate systems since the initially formed C-radical (Scheme 1) could be oxidised with an excess of reagent to give an oxonium ion, that could be trapped by a nucleophile present in the medium shifting the equilibrium towards the decarboxylation.



Scheme 1

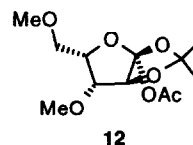
From hexuronic and penturonic acids, pentodialdoses and tetrodialdoses of the type shown in the Table could be obtained. These 1,5- and 1,4-dialdehydes have important applications as chiral building blocks in synthetic organic chemistry.⁵

The uronic and ulosonic acids were treated with the system (diacetoxyiodo)benzene (DIB) and iodine in the conditions shown in the Table 1 in order to generate the acyloxy radicals. An excess of DIB was required to oxidize the C-radical intermediate to the oxonium ion. The reaction conditions were determined with the readily available benzyl 2,3-*O*-isopropylidene- β -D-riburonic acid⁶ (**1**) which gave a mixture (89%) of two decarboxylated products, the β -D-*erythro*-tetrodialdo-1,4-furanose derivative **2**⁷ and the amide **3**⁷ (Table 1, entry 1). The proposed stereochemistry at C-4 is based on the observation that the *trans* coupling constant between H-3 and H-4 has a null value. The presence of iodine was necessary for the reaction to take place (entry 2), as expected for a radical decarboxylation.

The formation of the amide **3**, that is reminiscent of the Ritter-type reactions⁸ and seems to proceed by attack of the nitrogen atom of acetonitrile on the oxonium ion, is a good support for the proposed mechanism. A somewhat higher yield of amide is obtained using idosylbenzene instead of DIB in order to avoid the competition of other nucleophiles in the medium (entry 3). The decarboxylation occurs even at -15 °C under exposure to ambient light (entry 4).

To further investigate the scope of this methodology we have examined oxidative decarboxylation of various carboxylic acids (Table 1). It is interesting to point out the behaviour of the mannuronic acid derivatives **4** and **5**. While the methyl ether **4** gave the dialdose **6** in good yield (entry 5), the benzyl ether **5** gave the decarboxylated product **7** in lower yield (entry 6). We think that during the reaction of the latter a favoured side β -fragmentation of the C₅-radical intermediate, to give a benzyl radical, took place and the yield dropped to 58%. The oxonium ion can also be formed over a six-membered ring and the glucuronic acid derivative **8** decarboxylates smoothly to give the D-*xyl*o-pentodialdose **9** (entry 7).

Reaction of the 2,3-*O*-isopropylidene-4,6-di-*O*-methyl- β -L-*xyl*o-2-hexulosonic acid (**10**) gave the expected orthoester **12** which can be observed by ¹H NMR spectroscopy of the crude reaction mixture but is transformed into the lactone **11**⁷ by hydrolysis during the purification step (entry 8).



As can be observed (entries 1-7) in the dialdoses obtained by decarboxylation of uronic acids both masked aldehydes are differently protected. This may be of interest when the carbohydrates are to be employed as chiral building blocks and selective deprotection for further chemical transformations is required.

Representative Experimental Procedure. A solution of *p*-methoxybenzyl 2,3-*O*-isopropylidene-5-*O*-methyl- α -D-mannofuranosiduronic acid (**4**) (75 mg, 0.204 mmol) in dry acetonitrile (8 ml) containing (diacetoxyiodo)benzene (164 mg, 0.51 mmol) and iodine (62 mg, 0.245 mmol) was stirred at room temperature (20 °C) for 30 min. The reaction mixture was then poured into aqueous solution of sodium thiosulphate, extracted with EtOAc, dried over Na₂SO₄ and concentrated. The residue was purified by chromatotron chromatography over neutral alumina (*n*-hexane-EtOAc, 90:10) to give *p*-methoxybenzyl 2,3-*O*-isopropylidene-5-*O*-methyl-5-*O*-acetyl- α -D-*lyx*o-pentodialdo-1,4-furanoside (**6**) (69 mg, 0.18 mmol, 88 %).

Table 1. Decarboxylation of uronic and usulonic acids

Entry	Substrate	Conditions ^a			Products	Yield (%)
		DIB (mmol)	I ₂ (mmol)	time (h)		
1	1	3	1.2	0.5	2 R = AcO 3 R = AcNH	53 36
2		3	0	24		no reaction
3		3^b	1.2	8	3 R = AcNH	48
4		3^{c,d}	1.2	5	2 R = AcO 3 R = AcNH	9 57
5	4 R = Me	2.5^c	1.2	0.5	6 R = Me	88
6	5 R = Bn	2.5	1.2	1	7 R = Bn	58
7	8	3	1.2	2	9	63
8	10	2.2^c	1.2	1	11	86

a) All reactions were performed in dry acetonitrile at rt under irradiation with two 100 W tungsten-filament lamps; mmol of DIB and I₂ per mmol of substrate. b) Iodosylbenzene was used. c) Irradiation was omitted. d) Reaction at -15 °C. DIB = (diacetoxyiodo)benzene.

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- Schmidt, R. R.; Karl-Heinz, J.; Hermentin, P. *Chem. Ber.* **1978**, *111*, 3311-3324.
- Compound (2): m.p. 93-94.5 °C (*n*-hexane-EtOAc); $[\alpha]_D -34.4^\circ$ (CHCl₃); IR (CCl₄) 1761, 1749 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) 1.34 (3H, s), 1.48 (3H, s), 2.03 (3H, s), 4.49 (1H, d, *J* 11.7 Hz), 4.71 (1H, d, *J* 11.7 Hz), 4.76 (1H, d, *J* 4.7 Hz), 4.80 (1H, d, *J* 4.7 Hz), 5.30 (1H, s), 6.27 (1H, s), 7.32-7.35 (5H, m); ¹³C NMR (CDCl₃, 50.3 MHz) 21.01 (q), 24.93 (q), 26.26 (q), 69.25 (t), 84.07 (d), 84.16 (d), 102.85 (d), 108.62 (d), 113.01 (s), 127.94 (d), 128.01 (2 x d), 128.47 (2 x d), 136.83 (s), 169.51 (s); MS *m/z* 293 (M⁺-CH₃, 20%). Anal. Calcd. for C₁₆H₂₀O₆: C, 62.31; H, 6.54. Found: C, 62.17; H, 6.75. Compound (3): m.p. 83-84.5 °C (*n*-hexane-EtOAc); $[\alpha]_D -18.2^\circ$; IR 1702 cm⁻¹; ¹H NMR 1.30 (3H, s), 1.47 (3H, s), 1.82 (3H, s), 4.60 (1H, d, *J* 11.4 Hz), 4.62 (1H, d, *J* 5.4 Hz), 4.72 (1H, d, *J* 5.4 Hz), 4.73 (1H, d, *J* 11.4 Hz), 5.22 (1H, s), 5.97 (1H, m, NH), 7.33-7.38 (5H, m); ¹³C NMR 23.22 (q), 24.90 (q), 26.21 (q), 69.54 (t), 84.27 (d), 84.71 (d), 87.32 (d), 107.86 (d), 112.88 (s), 128.11 (2 x d), 128.28 (d), 128.73 (2 x d), 136.67 (s), 169.04 (s); MS *m/z* 292 (M⁺-Me, 7%). Anal. Calcd for C₁₆H₂₁O₅N: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.32; H, 6.93; N, 4.42. Compound (11): $[\alpha]_D -54.4^\circ$; IR 3575, 3461, 1796 cm⁻¹; ¹H NMR 3.37 (3H, s), 3.54 (3H, s), 3.61 (1H, dd, *J* 2.8, 11.2 Hz), 3.69 (1H, dd, *J* 2.7, 11.2 Hz), 4.16 (1H, dd, *J* 7.9, 7.9 Hz), 4.63 (1H, ddd, *J* 7.9, 2.8, 2.7 Hz), 4.67 (1H, d, *J* 7.9 Hz); ¹³C NMR 58.74 (q), 59.50 (q), 69.26 (t), 72.05 (d), 77.08 (d), 82.40 (d), 175.51 (s); MS *m/z* 176 (M⁺, 3%). Anal. Calcd for C₇H₁₂O₅: C, 47.71; H, 6.87. Found: C, 47.46, H, 7.06.
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