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ONE-CARBON EXTRUSION FROM CARBOHYDRATES VIA C1-ALKOXY RADICAL FRAGMENTATION. AN EASY ACCESS TO ERYTHROSE AND THREOSE

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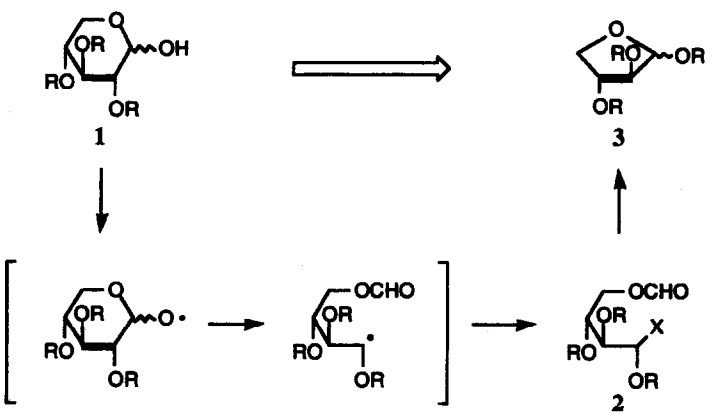
Abstract: *Generation and fragmentation of the C1-alkoxy radicals of pyranose derivatives are nicely promoted by (diacetoxyiodo)benzene or lead tetraacetate in the presence of iodine catalyst under mild conditions to give the corresponding mixed-acetal formates, which are further converted to the furanose derivatives by acid-catalyzed transacetalization.*

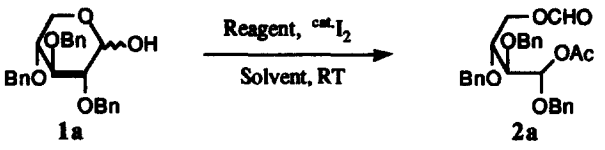
Recent renewed interest in carbohydrate chemistry has partly arisen from the synthetic challenge offered by complex organic molecules such as macrolides and polyether antibiotics, because carbohydrates, with their well-defined stereochemistry at numerous chiral centers, may be logical choices as chiral starting materials or building blocks for such complex natural products.[1] When carbohydrates which are expensive or rare in nature are required, C1 carbon extrusion from easily available substrates with desired stereochemistry at appropriate chiral centers may be adopted as a most straightforward way.[2] For this approach, we have developed a new reaction sequence: formation and fragmentation of anomeric alkoxy radicals (1→2) followed by acid-catalyzed trans-acetalization (2→3) (Scheme I), and applied it to the synthesis of erythrose and threose.[3-5]

Scheme I.



First, the reaction of 2,3,4-tri-*O*-benzyl-D-xylopyranose (1a)[6] with (diacetoxyiodo)benzene was carried out in the presence of a catalytic amount of iodine in dichloromethane. (Eq. 1) As shown in Table 1, the fragmentation proceeded smoothly at room temperature especially when two equivalents of the hypervalent iodine reagent and 0.2 equivalent of the catalyst were used (entry 4).[7] The products were obtained as a

diastereomeric mixture of the mixed-acetal formates (**2a**) in 1:1.2~1:2.4 ratio. As a solvent, toluene and THF can also be used without serious decrease of the yield. The use of one equivalent of lead tetraacetate in place of (diacetoxyiodo)benzene also gave **2a** in good yield under similar conditions. (Entry 10)



1a **2a** (1)

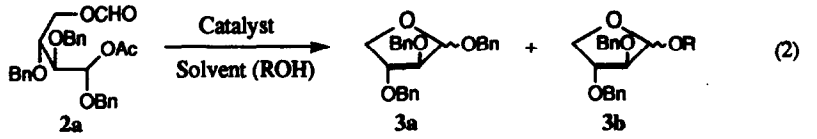
Table 1. Radical Fragmentation of 2,3,4-Tri-*O*-benzyl-D-xylopyranose (**1a**)

Entry	Reagent [a] (eq)	I_2 (eq)	Solvent	Time (h)	Yield [b] (%)
1	A (1.2)	0.2	CH_2Cl_2	4.5	65
2	A (1.6)	0.2	CH_2Cl_2	3.5	82
3	A (2.0)	0.1	CH_2Cl_2	16	83
4	A (2.0)	0.2	CH_2Cl_2	2	89
5	A (2.0)	0.2	Benzene	0.5	78
6	A (2.0)	0.2	Toluene	1.5	90
7	A (2.0)	0.2	THF	4	85
8	A (2.0)	0.2	Et_2O	14	62
9	B (0.5)	0.2	CH_2Cl_2	14	52
10	B (1.0)	0.2	CH_2Cl_2	0.4	82

a) A: $PhI(OAc)_2$; B: $Pb(OAc)_4$. b) Isolated yield of **2a**.

Acid-catalyzed successive transesterification-transacetalization of the primary product (**2a**) leading to the corresponding furanosides (**3a** and **3b**) was examined with various catalysts and solvents. (Eq. 2) As shown in entry 4 of Table 2, when an ethanol solution of a diastereomeric mixture of **2a** (1:1.2) was treated with 15% aqueous perchloric acid and one equivalent of methanol at room temperature, the corresponding benzyl 2,3-di-*O*-benzyl-D-threofuranosides (**3a**) were obtained predominantly in 90% yield as a mixture of C1 isomers (1:1.2) accompanied by a small amount of the ethyl furanosides (**3b**, R=Et).[8] On the other hand, the methyl furanosides (**3b**, R=Me) were selectively produced by refluxing **2a** with a drop of concentrated sulfuric acid in methanol for 1.5 h. (Entry 7) No isomerization occurred on the C2 asymmetric carbon under these conditions.[9]

Similarly, 2,3,4-tri-*O*-benzyl-D-arabinopyranose and 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose were selectively converted into the corresponding erythrofuranosides, **4a** or **4b**,[9,10] and arabinofuranosides, **5a** or **5b**, respectively, in high yields. (Scheme II) The latter example clearly shows that the method is particularly useful for obtaining furanoside derivatives of pentoses or higher carbohydrates in pure form because the corresponding pyranoside isomers are not produced at all under the reaction conditions.



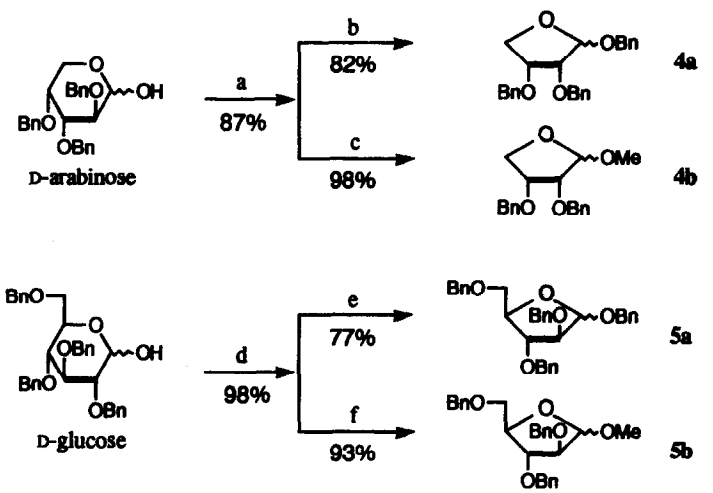
(2)

Table 2. Acid-Catalyzed Transacetalization of **2a**

Entry	Catalyst	Solvent	Temp	Time	Yield[a] (%)/ 3a	3b
1	PPTS[b]	MeOH	RT	6 days	81	7
2	p-TsOH	MeOH	RT	1.5 h	77	7
3	6% $HClO_4$	EtOH	RT	5 days	87	3
4	15% $HClO_4$[c]	EtOH	RT	5.5 h	90	5
5	CSA[d]	MeOH	50°C	3 days	7	85
6	conc. H_2SO_4	MeOH	RT	5.5 days	—	94[e]
7	conc. H_2SO_4	MeOH	Refl	1.5 h	—	95[e]

a) Determined by ^1H NMR analysis of the mixture of **3a**+**3b**. b) Pyridinium *p*-toluenesulfonate.
c) MeOH (1eq) was added. d) Camphorsulfonic acid. e) Isolated yield.

Scheme II.



a) $PhI(OAc)_2$, I_2, CH_2Cl_2, RT, 2 h. b) 15% $HClO_4$, MeOH (1eq), EtOH, RT, 8 h.
c) conc. H_2SO_4, MeOH, reflux, 1 h. d) $Pb(OAc)_4$, I_2, CH_2Cl_2, RT, 20 min.
e) 14% NH_4OH, MeOH, RT, 2 h; 15% $HClO_4$, RT, 2 h. f) conc. H_2SO_4, MeOH, reflux, 12 h.

We believe that the present one-carbon extrusion method would be generally applicable to a wide range of carbohydrates and related compounds.

References and Notes

1. Hanessian, S. *"Total Synthesis of Natural Products: The Chiron Approach"*, in Organic Chemistry Series, Vol. 3, ed by Baldwin, Pergamon Press, Oxford, **1983**.
2. For the previous works, see Hough, L.; Richardson, A. C. *"The Carbohydrates"* Vol. 1A eds by Pigman, W.; Horton, D. 2nd ed. Academic Press, San Diego, **1972**, 127-138.
3. Presented at the 63rd Semiannual Meeting of the Chemical Society of Japan, Osaka, March 31, **1992**.
4. In the course of the preparation of our manuscript, Suárez and his co-workers have reported that such radical fragmentation takes place on both pyranose and furanose derivatives with the aid of equimolar amount of (diacetoxyiodo)benzene and iodine. Armas, P.; Francisco, C. G.; Suárez, E. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 772.
5. For other alkoxy radical fragmentations, see for example, a) Schreiber, S. L. *J. Am. Chem. Soc.* **1980**, *102*, 6163. b) Ochiai, M.; Iwaki, S.; Ukita, T.; Nagao, Y. *Chem. Lett.* **1987**, 133. c) Nishida, A.; Takahashi, H.; Takeda, N.; Yonemitsu, O. *J. Am. Chem. Soc.* **1990**, *112*, 902. d) Ellwood, C. W.; Pattenden, G. *Tetrahedron Lett.* **1991**, *32*, 1591. e) Arencibia, M. T.; Freire, R.; Perales, A.; Rodriguez, M. S.; Suárez, E. *J. Chem. Soc., Perkin Trans. 1*, **1991**, 3349 and references cited therein.
6. Prepared from methyl β-D-xylopyranoside (purchased from Aldrich Co. Ltd.) according to the conventional methods.
7. A mixture of **1a** (42.2 mg, 0.1 mmol), (diacetoxyiodo)benzene (64.3 mg, 0.2 mmol), and iodine (5.4 mg, 0.02 mmol) in dichloromethane (2 mL) was stirred for 2 h at room temperature. To the resulting light reddish purple suspension was added an aqueous $Na_2S_2O_3$ solution and the crude product was extracted with dichloromethane, washed with water, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was purified by preparative TLC on silica gel to give 42.8 mg (89%) of **2a** as a colorless oil. Selected ^{1}H-NMR spectral data are as follows: δ=7.92 and 7.90 (1:2.4, s, 1H, formyl), 4.18-4.33 (m, 4H, methylene-C4), 2.01 and 1.96 (1:2.4, s, 3H, acetyl) ppm.
8. To a solution of **2a** (45.9 mg, 0.096 mmol) in ethanol (1 mL) was added methanol (4 μL, 0.096 mmol) and a drop of 15% aqueous $HClO_4$ solution and the mixture was stirred for 5.5 h at room temperature. The reaction mixture was neutralized by the addition of a saturated $NaHCO_3$ solution, extracted with ether, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the crude products were purified by preparative TLC on silica gel to give 35.0 mg of a mixture of **3a** and **3b**.
9. It was confirmed by comparing the ^{1}H- and ^{13}C-NMR spectral data of **3a** with those of **4a** and also with the reported ^{13}C-NMR spectral data of other methy glycofuranoside derivatives [Ritchie, R. G. S.; Cyr, N.; Korsch, B.; Koch, H. J.; Perlin, A. S. *Can. J. Chem.* **1975**, *53*, 1424]. The observed chemical shifts of C1 carbons: δ=105.39 (α-isomer of **3a**), 99.39 (β-isomer of **3a**), 98.47 (α-isomer of **4a**), and 105.21 (β-isomer of **4a**) ppm.
10. Another method for the conversion of an arabinose derivative to the corresponding erythrose derivative, see Ballou, C. E. *J. Am. Chem. Soc.* **1957**, *79*, 165.

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