Fragmentation of Carbohydrate Anomeric Alkoxy Radicals. Tandem β-Fragmentation-Cyclization of Alcohols

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In recent years there has been a growing interest in carbohydrates as synthetic precursors to enantiomerically pure bioactive molecules because of their well-defined stereochemistry, highly functionalized nature, and distinct reactivities of the hydroxyl groups.[1] We consider worthwhile a general procedure to obtain cyclic carbohydrates, even those not easily accessible by other routes, with a masked hydroxy aldehyde, the elaboration of which may be conveniently timed and whose functionalities would each be eligible for further elaboration.

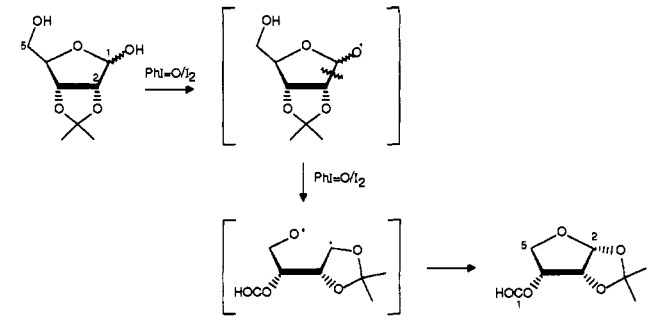
With these considerations in mind, we envisioned a novel, tandem strategy, illustrated in Scheme I, on a ribofuranose derivative, which involves the sequencing of two different reactions: (i) initial β-fragmentation reaction of the hemiacetal alcohol promoted by the formation of an anomeric alkoxy radical generated with the hypervalent iodine reagent/I_2 system under mild conditions[2] and (ii) intramolecular trapping of the C2 radical originated in the fragmentation step with a suitably positioned alcohol group. Cyclic aldotetroses or aldopentoses would be accessible using this methodology.

With this aim, the system iodosylbenzene/I_2 was used, and since carbon-centered radicals are inert toward hydroxyl groups,[3] an additional 1 mol/equiv of the hypervalent iodine reagent was used to promote the alkoxy radical that could eventually cyclize with the C2 radical in an intramolecular 1,5-diradical coupling reaction. In this way, varying ring sizes may be obtained by changing the location of the alcohol group.

The carbohydrate derivatives were treated with iodosylbenzene and iodine in cyclohexane or dichloromethane under the conditions specified in Table I.[4] The readily available 2,3-*O*-isopropylidene-D-ribofuranose (**1**)[5] gave 3-*O*-formyl-1,2-*O*-isopropylidene-α-D-erythrofuranose (**2**) (entry 1). Only one isomer at C1 was obtained, and the coupling constant of 3.9 Hz between H1 and H2 confirms a *cis* stereochemistry for these protons. When the reaction mixture was treated with potassium carbonate in methanol, the crystalline alcohol **3**[6] was isolated instead (entry 2). The interest in 1,2-*O*-isopropylidenetetrofuranoses as chiral templates has been established.[7]

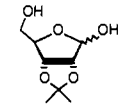
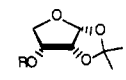
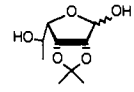
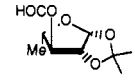
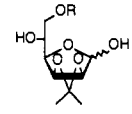
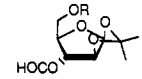
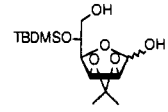
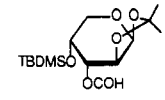
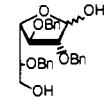
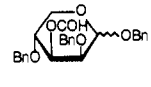
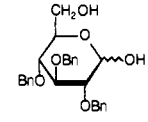
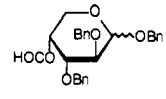
The reaction also occurs using a secondary alcohol group to trap the C radical; hence 2,3-*O*-isopropylidene-L-rhamnofuranose

Scheme I.[a] β-Fragmentation–Cyclization Reaction



[a] For sake of comparison, the pentose numbering is retained in the product.

Table I. Tandem β-Fragmentation–Cyclization Reaction[a]

entry	substrate[b]	solvent[c]	conditions: Ph—I=O (mmol)	conditions: I_2 (mmol)	conditions: time (h)	products	yield (%)
1	 1	CH_2Cl_2	3	1	5.5	 2 R = COH	36
2		CH_2Cl_2	3	1	5.5[d]	3 R = H	40
3	 4	Cy	2	1	20	 5	40
4	 6 R = TBDMS	Cy	2	1	2.5	 8 R = TBDMS	60
5	7 R = TBDPS	Cy	2	1	2.5	9 R = TBDPS	89
6	 10	Cy	2	1	16[e]	 11	65
7	 12	Cy	2	1	20[f]	 13	70
8		CH_2Cl_2	2.5	1	40		94
9	 14	Cy	2	1	20	 15	86

[a] 0.2–0.3 mmol scale at 20 °C. [b] TBDMS = *tert*-butyldimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl. Bn = benzyl. [c] Cy = cyclohexane.[d] A saturated solution of K_2CO_3/MeOH was added to the reaction mixture. [e] 60 °C. [f] 40 °C.

(1) (a) Hanessian, S. *Total Synthesis of Natural Products. The Chiron Approach*; Pergamon Press: Oxford, 1983. (b) Hanessian, S.; Rauncourt, G. *Pure Appl. Chem.* **1977**, *49*, 1201. (c) Inch, T. D. *Tetrahedron* **1984**, *40*, 3161–3213. (d) Bhat, K. L.; Chen, S.-Y.; Joullié, M. M. *Heterocycles* **1985**, *23*, 691–729. (e) *Trends in Synthetic Carbohydrate Chemistry*; Horton, D., Hawkins, L. D., Eds.; American Chemical Society: Washington, DC, 1989.

(2) (a) Freire, R.; Marrero, J. J.; Rodríguez, M. S.; Suárez, E. *Tetrahedron Lett.* **1986**, *27*, 383–386. (b) Freire, R.; Hernández, R.; Rodríguez, M. S.; Suárez, E.; Perales, A. *Ibid.* **1987**, *28*, 981–984. (c) Francisco, C. G.; Freire, R.; Rodríguez, M. S.; Suárez, E. *Ibid.* **1987**, *28*, 3397–3400. (d) Arencibia, M. T.; Freire, R.; Perales, A.; Rodríguez, M. S.; Suárez, E. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3349–3360. (e) de Armas, P.; Francisco, C. G.; Suárez, E. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 772–774.

(3) (a) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237–1286. (b) Brun, P.; Waegell, B. In *Reactive Intermediates, Vol. 3*; Abramovitch, R. A., Ed.; Plenum Press: New York, 1983; p 367.

(4) The following procedure is typical for the synthesis of **9**: a solution of 6-*O*-(*tert*-butyldiphenylsilyl)-2,3-*O*-isopropylidene-D-mannofuranose (**7**) (100 mg, 0.218 mmol) in dry cyclohexane (24 mL) containing iodosylbenzene (96 mg, 0.43 mmol) and iodine (55 mg, 0.218 mmol) was stirred at room temperature (20 °C) for 2.5 h. The reaction mixture was then poured into water and extracted with ether. The organic layer was washed with aqueous sodium thiosulfate and water. Chromatography of the residue (Chromatotron, Merck silica gel 60 PF 254, *n*-hexane/ethyl acetate 65:35 v/v) gave **9** (88 mg, 89%).

(5) Kaskar, B.; Heise, G. L.; Michalak, R. S.; Vishnuvajjala, B. R. *Synthesis* **1990**, 1031–1032.

(6) *Carbohydrates*; Collins, P. M., Ed.; Chapman and Hall: London, 1987; p 210.

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(4)[8] was transformed into 5-deoxy-1,2-*O*-isopropylidene-β-L-arabinofuranose (**5**) (entry 3), and 6-*O*-(*tert*-butyldimethylsilyl)-(**6**)[9] and 6-*O*-(*tert*-butyldiphenylsilyl)-3-*O*-isopropylidene-D-mannose (**7**)[9] were transformed into the corresponding arabinofuranose derivatives **8** and **9** (entries 4 and 5). In those cases where low yields were observed (entries 1–3), no side products or possible intermediates containing iodine could be characterized from the crude reaction.

This reaction can also be extended to the synthesis of carbohydrates in the pyranose form via a 1,6-diradical coupling as shown in Table I (entries 6–9). For instance, 5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-D-mannofuranose (**10**)[10] was transformed into the arabinopyranose derivative **11** (entry 6). A coupling constant of 3.4 Hz between the H1 and H2 established the expected *cis* stereochemistry for the isopropylidene group at this position.

In this reaction, the formation of a carbohydrate in furanose or pyranose form is dependent on the situation of the hydroxyl group but not on any tautomeric equilibrium, e.g., both arabinose forms are easily obtained by this method (compare entries 4 and 5 with 6).

A similar situation is found in the reaction of 2,3,5-tri-*O*-benzyl-D-galactofuranose (**12**),[11] which is transformed into the D-lyxopyranose derivative **13** (entries 7 and 8). In this case, better yields were obtained when dichloromethane was used as solvent, probably due to greater solubility of the substrate. Compound **13** was found as an α,β mixture (ca. 1:1) of glycosides, as expected.

Another differently protected arabinopyranose derivative **15** can be obtained in good yield from 2,3,4-tri-*O*-benzyl-D-glucopyranose (**14**)[12] as an α,β mixture of glycosides (ca. 1:1).

As may be inferred from Table I, the reaction proceeds under mild conditions, which are compatible with the protective groups most widely used in carbohydrate chemistry. Furthermore, the regioselectivity observed in the fragmentation step should be pointed out as well as the fact that the reaction behavior does not depend on the C2 configuration, the protective group at this position, or the ring size.

This reaction may be a very valuable general procedure for descending the aldose series step by step and for preparing specific furanose or pyranose forms of aldotetroses and aldopentoses which are sometimes difficult to achieve by other methods. The obtained products with a protected anomeric hydroxyl group and an easily hydrolyzable formate group may be of interest when carbohydrates are to be employed as chiral templates or chiral auxiliaries and further chemical transformations are required.

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Supplementary Material Available: Analysis data for compounds **3**, **5**, **8**, **9**, **11**, **13**, and **15**, including mp, $[\alpha]_D$ values, IR, ^1H NMR, ^{13}C NMR, and mass spectra (5 pages). Ordering information is given on any current masthead page.

(7) (a) Sulikowski, M. M.; Ellis Davies, G. E. R.; Smith, III, A. B. *J. Chem. Soc., Perkin Trans. 1* **1992**, 979–989. (b) Smith, A. B., III; Sulikowski, G. A.; Fujimoto, K. *J. Am. Chem. Soc.* **1989**, *111*, 8039–8041. (c) Smith, A. B., III; Sulikowski, G. A.; Sulikowski, M. M.; Fujimoto, K. *J. Am. Chem. Soc.* **1992**, *114*, 2567–2576.

(8) Gelas, J.; Horton, D. *Heterocycles* **1981**, *16*, 1587–1601.

(9) Prepared from 2,3-*O*-isopropylidene-D-mannofuranose (see *Carbohydrates*; Collins, P. M., Ed.; Chapman and Hall: London, 1987; p 299) and the corresponding silyl chloride/imidazole/DMF.

(10) Prepared from 1-*O*-benzoyl-2,3-*O*-isopropylidene-α-D-mannofuranose (see *Carbohydrates*; Collins, P. M., Ed.; Chapman and Hall: London, 1987; p 300), selective benzoylation at C6, protection of C5 alcohol with *tert*-butyldimethylsilyl triflate/2,6-di-*tert*-butylpyridine, and deprotection of the benzoyl groups with diisobutylaluminum hydride.

(11) Prepared from 1,6-anhydro-α-D-galactofuranose (see Angyal, S. J.; Beveridge, R. J. *Aust. J. Chem.* **1978**, *31*, 1151–1155), tribenzylation, and treatment with acetic anhydride/zinc iodide followed by hydrolysis.

(12) Zemplén, G.; Csürös, Z.; Angyal, S. *Berichte* **1937**, *70*, 1848–1856. Prepared from 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose (see *Carbohydrates*; Collins, P. M., Ed.; Chapman and Hall: London, 1987; p 52), tribenzylation, and treatment with acetic anhydride/zinc iodide followed by hydrolysis.