Synthesis of α-Iodoalkyl Esters and α-Iodoalkyl Carbonates from Carbohydrates. Formation of Convenient Chiral Synthetic Intermediates

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In previous papers from this laboratory, we have described the formation of glycopyran-1-*O*-yl and glycofuran-1-*O*-yl radicals by reaction of carbohydrate anomeric alcohols with hypervalent iodine reagents in the presence of iodine.[1] Under very mild conditions, these intermediates undergo a C1−C2 *β*-fragmentation reaction to give a C2 radical. In the previously reported examples of this reaction, all the substrates possessed an ether group at C2. In these cases, the C2 radical was always oxidized by an excess of the reagent to give an oxonium ion (Scheme 1, eq 1), which may be trapped intermolecularly by an acetate anion from the medium to give an acetyl alkyl acetal.[1a] Intramolecular trapping by hydroxyl, carboxyl, or amide groups is also possible.[1b−e]

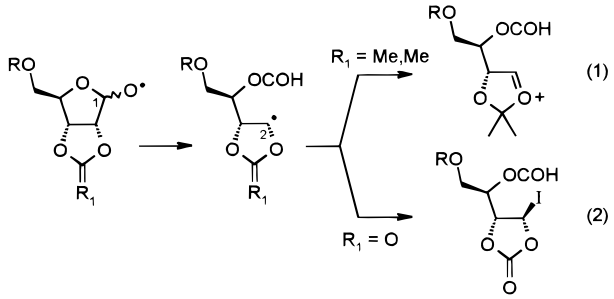
With these results in mind, we reasoned that the presence of a stronger electron-withdrawing group at C2 should decrease the electron-density at this position and the oxidation of the C2-radical should be more difficult. The competitive trapping of the intermediate radical by atoms of iodine from the reaction medium might then be possible. In this paper, we describe a study that shows how α-iodoalkyl esters and α-iodoalkyl carbonates can be obtained using, respectively, esters and carbonates as electron-withdrawing groups (eq 2). The exchange between iodide and other halogens (Finkelstein reaction) is the only method that has been employed for the synthesis of α-iodoalkyl esters.[2] α-Iodoalkyl carbonates have also been prepared from halide exchange and the 1-iodoethyl phenyl carbonate by reaction of acetaldehyde with phenyl carbonoiodidate.[3] All these substances have a limited stability, and to the best of our knowledge, they have not been previously used as synthetic intermediates. In Table 1 we compare the reaction of several carbohydrates of the threose and erythrose series, possessing either an ether or an ester group at C2, with the system (diacetoxyiodo)benzene/iodine. As shown in entry 1, the 2,3-*O*-isopropylidene-D-ribose derivative **1** is transformed under the conditions cited into the erythrose acetyl acetal derivative **2** in good yield and with excellent selectivity.[1a] On the other hand, under the same conditions the 2,3-carbonate **3** gave exclusively the α-iodoalkyl carbonate **4** as an inseparable 4:1 mixture of 1*R* and 1*S* isomers (entry 2). It is worth noting that, in this case, no products coming from addition of acetate to an oxonium ion (eq 1) were detected and that the product formed is better explained by a radical reaction (eq 2). Compound **4** is a stable crystalline solid that can be purified by chromatography and stored for months in the refrigerator.

Table 1. Reaction of Carbohydrates with DIB/I_2[a]

entry	substrate	product	yield (%)
1	**1** R = Me,Me	**2** R_1 = Me,Me; R_2 = OAc	84 (19:1)[b]
2	**3** R = O	**4** R_1 = O, R_2 = I	63 (4:1)
3	**5** R = Me	**6** R_1 = Me, R_2 = OAc	78 (3:1)
4	**7** R = Bz	**8** R_1 = Bz, R_2 = I	81 (1.5:1)
5	**9** R = Ac	**10** R_1 = Ac, R_2 = I	67 (7:1)
6	**11** R = Me	**12** R_1 = Me, R_2 = OAc	94 (2:1)
7	**13** R = Bz	**14** R_1 = Bz, R_2 = I	35 (4:1)[c]
8	**15** R = Me	**16** R_1 = Me, R_2 = OAc	85 (1:1)
9	**17** R = Bz	**18** R_1 = Bz, R_2 = I	63 (1:1)

[a] All reactions were performed in dry CH_2Cl_2 (35 mL) at room temperature under nitrogen containing (diacetoxyiodo)benzene (DIB) (2 mmol) and iodine (1.2 mmol) per mmol of substrate. Ratios were determined by ^{1}H NMR analysis, and where assigned the major isomer is illustrated. [b] See ref 1a. [c] Partially hydrolyzed during silica gel chromatography.

Scheme 1



To further extend the scope of the described method, we have investigated the feasibility of applying this methodology to hexoses of the glucose (entries 3−7) and galactose types (entries 8 and 9). In all cases when the substituent at C2 was an ether (entries 3, 6, and 8) α-acetoxy ethers were formed, and when it was an ester (entries 4, 5, 7, and 9) α-iodo esters were obtained, while mixtures of both products were not observed in any case. Two features of these reactions deserve a brief comment: first, the unexpected selectivity of the acetate **10** (7:1) compared with that

(1) (a) Armas, P.; Francisco, C. G.; Suárez, E. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 772−774. (b) Armas, P.; Francisco, C. G.; Suárez, E. *J. Am. Chem. Soc.* **1993**, *115*, 8865−8866. (c) Armas, P.; Francisco, C. G.; Suárez, E. *Tetrahedron Lett.* **1993**, *34*, 7331−7334. (d) Francisco, C. G.; González, C.; Suárez, E. *J. Org. Chem.* **1998**, *63*, 2099−2109. (e) Francisco, C. G.; Freire, R.; González, C.; Suárez, E. *Tetrahedron: Asymmetry* **1997**, *8*, 1971−1974.

(2) (a) Geraghty, N. W. A. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Pergamon Press: New York, 1995; Vol. 4, pp 51−60. See also related glycosyl iodides: (b) Gervay, J.; Nguyen, T. N.; Hadd, M. J. *Carbohydr. Res.* **1997**, *300*, 119−125. (c) Schmid, U.; Waldmann, H. *Tetrahedron Lett.* **1996**, *37*, 3837−3840. (d) Gervay, J.; Hadd, M. J. *J. Org. Chem.* **1997**, *62*, 6961−6967.

(3) Senet, J.-P.; Sennyey, G.; Woodem, G. P. *Synthesis* **1988**, 407−410.

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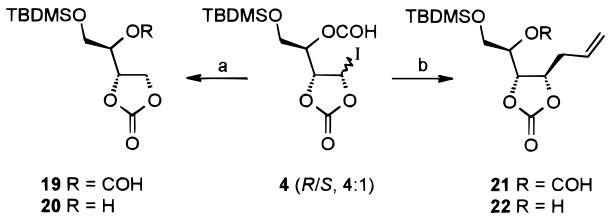
of the benzoate **8** (1.5:1) (entries 4 and 5); second, the remarkable stability of the products, especially of the iodine compounds. All are sufficiently stable to be purified by silica gel chromatography and stored under nitrogen at low temperature, with the exception of compound **14**, which could not be purified by this technique without substantial hydrolysis to the corresponding aldehyde.

Compound **4** belongs to a class of *meso*-erythritol derivatives that have become asymmetric by substitution. Since these compounds are important four-carbon chiral building blocks in natural products synthesis,[4] we have initiated the study of this α-iodo carbonate as a synthetic intermediate. We are particularly interested in the reactivity of the carbon-centered radical generated by rupture of the C−I bond. The reduction of compound **4** with tributyltin hydride led to carbonate **19** containing a small amount of the alcohol **20** in 89% overall yield (Scheme 2). This could be a good two-step method to transform a carbohydrate into the corresponding alditol with one less carbon. Radical intermolecular allylation is also possible following the Keck and Yates procedure;[5] reaction of the 4:1 mixture of compound **4** with allyltributylstannane in the presence of AIBN gave the allyl derivative **21** along with the alcohol **22**. Absolute selectivity was observed in the crude reaction mixture, with only the *anti*-stereoisomer being obtained.

Scheme 2[a]



[a] Key: (a) Bu_3SnH (2.5 equiv), AIBN (0.2 equiv), PhH, reflux, 1 h, 89% [**19** (71%), **20** (18%)]; (b) allyltributyltin (3 equiv), AIBN (0.2 equiv), PhH, reflux, 3 h, 74% [**21** (45%), **22** (29%)].

Moreover, α-acetoxy ethers react with a variety of carbon nucleophiles (e.g., allylsilanes) in the presence of a Lewis acid.[6] We therefore now have the opportunity to carry out either cationic or radical allylations from α-acetoxy ethers or α-iodo esters obtained from the same carbohydrate by simply changing the protective group at C2.

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Supporting Information Available: Supporting Information Available: Experimental procedures and characterization data for compounds **4**, **6**, **8**, **10**, **12**, **14**, **16**, and **18**−**22** (5 pages).

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(4) (a) Flasche, M.; Scharf, H.-D. *Tetrahedron: Asymmetry* **1995**, *6*, 1543−1546. (b) Pottie, M.; De Lathauwer, G.; Vandewalle, M. *Bull. Soc. Chim. Belg.* **1994**, *103*, 285−294. (c) Pottie, M.; Van der Eycken, J.; Röper, H.; Vandewalle, M. *Tetrahedron: Asymmetry* **1991**, *2*, 329−330. (d) Le Merre, Y.; Gravier-Pelletier, C.; Dumas, J.; Depezay, J. C. *Tetrahedron Lett.* **1990**, *31*, 1003−1006. (e) Abushanab, E.; Vemishetti, P.; Leiby, R. W.; Singh, H. K.; Mikkilineni, A. B.; Wu, D. C.-J.; Saibaba, R.; Panzica, R. P. *J. Org. Chem.* **1988**, *53*, 2598−2602.

(5) (a) Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829−5831. (b) Keck, G. E.; Enholm, E. J.; Yates, J. B.; Wiley: M. R. *Tetrahedron* **1985**, *41*, 4079−4094.

(6) (a) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Pergamon Press: Oxford, 1995; Chapter 2, pp 54−67. (b) Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545−8599. (c) Rychnovsky, S. D.; Powell, N. A. *J. Org. Chem.* **1997**, *62*, 6460−6461. (d) Dahanukar, V. H.; Rychnovsky, S. D. *J. Org. Chem.* **1996**, *61*, 8317−8320. (e) Rychnovsky, S. D.; Skalitzky, D. J. *Synlett* **1995**, 555−556. (f) Boons, G.-J.; Eveson, R.; Smith, S.; Stauch, T. *Synlett* **1996**, 536−538.