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Intramolecular 1,5- versus 1,6-Hydrogen Abstraction Reaction Promoted by Alkoxy Radicals in Carbohydrate Models

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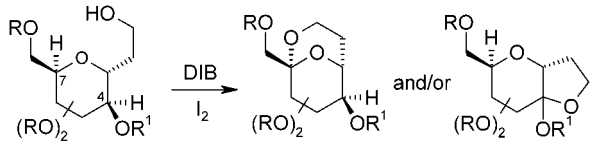
ABSTRACT



R¹ = alkyl, acyl

The alkoxy radical generated by reaction of 3,7-anhydro-2-deoxyoctitols with (diacetoxyiodo)benzene (DIB) and iodine abstracts regioselectively either the proton at C7 or that at C4 depending on the electronegativity of the substituent at C4. The correct election of this substituent can switch the reaction to give 2,9-dioxabicyclo[3.3.1]nonane or hexahydro-2*H*-furo[3,2-*b*]pyran ring systems.

The intramolecular hydrogen abstraction (IHA) reaction promoted by alkoxy radicals has attracted considerable interest among synthetic organic chemists since it offers the remarkable possibility of carrying out remote free radical functionalizations of unactivated carbons.[1] The 1,5-hydrogen atom transfer (HAT) is by far the most common reaction and is particularly useful for the synthesis of tetrahydrofuran derivatives.[2] 1,6-HAT has also been frequently observed, but high yields are only obtained when the hydrogen to be removed is bonded to an oxygen-substituted carbon.[3,4]

Earlier reports from this laboratory have described the synthesis of 1,6-dioxaspiro[4.5]decane and 1,7-dioxaspiro-[5.5]undecane ring systems, starting from carbohydrates with a primary alkoxy radical attached respectively to a trimethylene or tetramethylene tether extended from the C1 of the sugar, through an IHA reaction.[5] We have also found that electron-withdrawing group (EWG) substituents inhibit oxidation of the radical in the alkoxy radical β-fragmentation reaction, allowing faster reaction with radical species present in the medium.[6,7]

(1) Recent reviews: (a) Majetich, G. *Tetrahedron* **1995**, *51*, 7095−7129. (b) Feray, L.; Kuznetsov, N.; Renaud P. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, pp 246−278. (c) Robertson, J.; Pillai, J.; Lush, R. K. *Chem. Soc. Rev.* **2001**, *30*, 94−103.

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(3) (a) Danishefsky, S. J.; Armistead, D. A.; Wincott, F. E.; Selnick, H. G.; Hungate, R. *J. Am. Chem. Soc.* **1989**, *111*, 2967−2980. (b) Brimble, M. A.; Farès, F. A. *Tetrahedron* **1999**, *55*, 7661−7706. (c) Concepción, J. I.; Francisco, C. G.; Hernández, R.; Salazar, J. A.; Suárez, E. *Tetrahedron Lett.* **1984**, *25*, 1953−1984.

(4) HAT reaction through eight-membered transition states or higher promoted by alkoxy radicals which suffer a severe entropic penalty are practically unknown. Recently an IHA through a nine-membered transition state between glucopyranose units in a disaccharide model has been observed in this laboratory: Francisco, C. G.; Herrera, A. J.; Kennedy, A. R.; Melián, D.; Suárez, E. *Angew. Chem., Int. Ed.* . **2002**, *41*, 860−862.

(5) (a) Martín, A.; Salazar, J. A.; Suárez, E. *J. Org. Chem.* **1996**, *61*, 3999−4006. (b) Dorta, R. L.; Martín, A.; Salazar, J. A.; Suárez, E.; Prangé, T. *J. Org. Chem.* **1998**, *63*, 2251−2261. For other IHA reactions in carbohydrate chemistry, see: (c) Descotes, G. *J. Carbohydr. Chem.* **1988**, *7*, 1−20. (d) Chatgilialoglu, C.; Gimisis, T.; Spada, G. P. *Chem. Eur. J.* **1999**, *5*, 2866−2876. (e) Robins, M. J.; Guo, Z.; Samano, M. C.; Wnuk, S. F. *J. Am. Chem. Soc.* **1999**, *121*, 1425−1433. (f) Francisco, C. G.; Herrera, A. J.; Suárez, E. *Tetrahedron: Asymmetry* **2000**, *11*, 3879−3882. (g) Francisco, C. G.; Herrera, A. J.; Suárez, E. *Tetrahedron Lett.* **2000**, *41*, 7869−7873.

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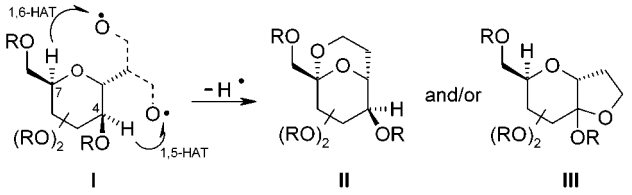
The purpose of the present work was to investigate whether substituents could be used to control the reaction course in an IHA reaction. With this aim, we have synthesized a number of carbohydrate models also possessing a primary alkoxy radical but attached at C1 of a pyranose *C*-glycoside by a shorter two-carbon tether (3,7-anhydro-2-deoxyoctitols). In these models the alkoxy radical may abstract hydrogens from two carbon atoms located in the pyranose ring:[8] from C7 through a seven-membered transition state (TS) and from C4 through in principle, a more favorable six-membered TS **I** (Scheme 1). It therefore offers an opportunity to study the

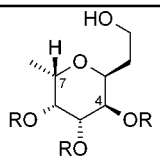
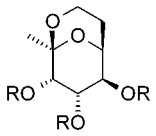
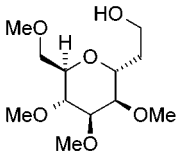
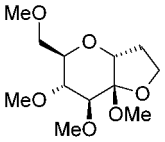
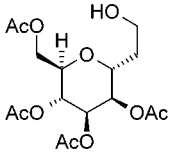
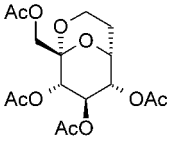
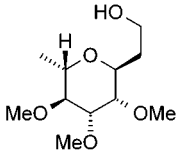
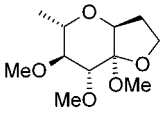
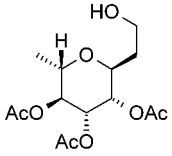
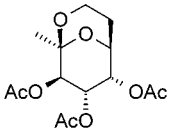
Scheme 1. Regioselectivity of the IHA Reaction



regioselectivity of the process (1,5- vs 1,6-HAT) and at the same time to develop new methodology for the synthesis of two especially interesting dioxabicyclic systems: 2,9-dioxabicyclo[3.3.1]nonane **II** and hexahydro-2*H*-furo[3,2-*b*]pyran **III**. These bicycles are substructural units of many natural products: an example is azaspiracid, a marine toxin which has both units in its molecule.[9]

Preparation of the required octitols was accomplished in two steps starting from suitably protected carbohydrates. A Lewis acid-mediated *C*-glycosidation with allyltrimethylsilane afforded the non-8-enitols, in general with high stereoselectivity,[10] which upon subsequent ozonolysis followed by reductive workup with $NaBH_4$ provided the alcohols **1**, **2**, **5**, **7**, **9**, and **11** in good yield. The IHA reactions were performed under the oxidative conditions stated in Table 1, with (diacetoxyiodo)benzene and iodine in CH_2Cl_2 at room temperature and irradiation with two 80-W tungsten filament lamps.

Table 1. IHA of 3,7-Anhydrooctitols[a]

entry	substrate	DIB mmol	time h	products	yield %
1	 **1** R = Ac	1.5	1	 **3** R = Ac	47
2	**2** R = Me	1.5	1.5	**4** R = Me	57
3	 **5**	1.3	1.25	 **6**	70
4	 **7**	1.6	2.75	 **8**	48
5	 **9**	1.5	4.5	 **10**	45[b]
6	 **11**	1.3	9	 **12**	53

[a] Octitol derivative (1 mmol) in CH_2Cl_2 (25 mL) containing (diacetoxyiodo)benzene (DIB) and iodine (1 mmol) was irradiated with two 80-W tungsten filament lamps at room temperature. [b] 2,8-Anhydro-1,7-dideoxy-3,4,5-tri-*O*-methyl-*β*-L-*altro*-oct-2-ulopyranose (11%) is also obtained.

As the synthesis of the 2,9-dioxabicyclo[3.3.1]nonane system has never been reported from an IHA reaction, we decided to perform preliminary experiments to verify the feasibility of this methodology. Alcohols **1** and **2** derived from L-fucose were selected since C4 abstraction is stereochemically blocked and the reaction, in a conformationally restricted $^1C_4$ pyranose ring, should proceed exclusively by abstraction of the hydrogen at C7 (entries 1 and 2). In both cases the reaction proceeded smoothly to give the expected dioxabicyclic products **3** and **4**, respectively, in moderate yield.

In entry 3 we describe an IHA reaction over a *C*-glycoside derived from D-mannose **5**. In this case a restricted $^4C_1$ conformation of the pyranose ring allows the hydroxy radical at C1 to abstract the axial hydrogens located at either the C4 or C7 positions. The hexahydro-2*H*-furo[3,2-*b*]pyran

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(7) An example of the influence of the substituents in the 1,5-HAT reaction compared with competing *β*-fragmentation of alkoxy radicals has been published: Allen, P. R.; Brimble, M. A.; Farès, F. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2403−2411.

(8) No products arising from the geometrically possible abstraction of the hydrogen at C5 have been detected in the examples described in this Letter. Probably the abstraction at C7 is favored by steric and stereoelectronic factors. For studies on stereoelectronic effects in intermolecular hydrogen abstraction reactions, see: (a) Malatesta, V.; Ingold, K. U. *J. Am. Chem. Soc.* **1981**, *103*, 609−614. (b) Beckwith, A. L. J.; Easton, C. J. *J. Am. Chem. Soc.* **1981**, *103*, 615−619.

(9) (a) Satake, M.; Ofuji, K.; Naoki, H.; James, K. J.; Furey, A.; McMahon, T.; Silke, J.; Yasumoto, T. *J. Am. Chem. Soc.* **1998**, *120*, 9967−9968. (b) Aiguade, J.; Hao, J.; Forsyth, C. J. *Org. Lett.* **2001**, *3*, 979−982. (c) Nicolaou, K. C.; Pihko, P. N.; Diedrichs, N.; Zou, N.; Bernal, F. *Angew. Chem., Int. Ed.* **2001**, *40*, 1262−1265.

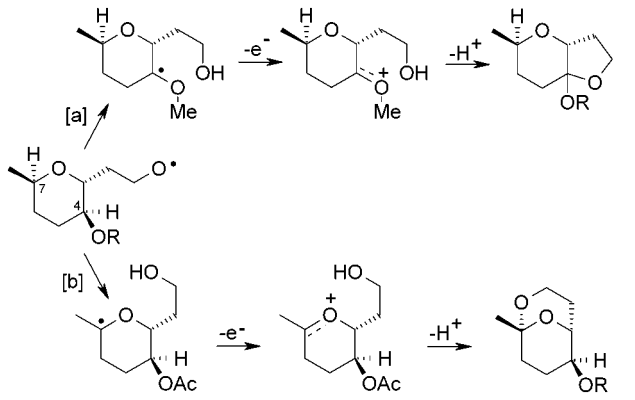
(10) (a) Luengo, J. I.; Gleason, J. G. *Tetrahedron Lett.* **1992**, *33*, 6911−6914. (b) Giannis, A.; Sandhoff, K. *Tetrahedron Lett.* **1985**, *26*, 1479−1482. (c) Richter, P. K.; Tomaszewski, M. J.; Miller, R. A.; Patron, A. P.; Nicolaou, K. C. *J. Chem. Soc., Chem. Commun.* **1994**, 1151−1152.

derivative **6**, coming from transfer of the hydrogen at C4, was formed exclusively. The *cis* stereochemistry of the ring junction was determined by ^{1}H NMR studies including coupling constant analysis and NOESY experiments. The influence of the protective group at C4 was subsequently studied in entry 4 of Table 1. The substitution of the methyl ether by an acetyl group (such as compound **7**) affected the regiochemical course of the reaction; the H-C7 was now transferred and the 2,9-dioxabicyclo[3.3.1]nonane derivative **8** was obtained instead. Although the yield was moderate, no other compounds could be detected in the reaction mixture.

The results obtained with two differentially protected 3,7-anhydro-2,8-dideoxyoctitols **9** and **11** derived from L-rhamnose are shown in entries 5 and 6. The IHA reaction proceeded analogously; the ester group at C4 inhibited the reactions originated by hydrogen transfer from this position and functionalization occurred at C7 through a seven-membered TS. The results obtained in the cyclization of compound **9** deserve a brief comment. Although the reaction gave mainly the expected product **10** corresponding to a H-C4 hydrogen transfer, a minor product, 2,8-anhydro-1,7-dideoxy-3,4,5-tri-*O*-methyl-β-L-*altro*-oct-2-ulopyranose, coming from a H-C7 hydrogen abstraction was also obtained.

A mechanism to explain the observed regioselectivity of these IHA reactions is depicted in Scheme 2. When the

Scheme 2. Mechanism of IHA of 3,7-Anhydro-2-deoxyoctitols



substituent at C4 was an electron-releasing group (R = alkyl), the alkoxy radical abstracted preferentially the hydrogen at this carbon atom through a six-membered TS. The [4.3.0]bicycle was subsequently formed, after oxidation of the C4 radical and intramolecular attack of the nucleophilic alcohol (path [a], entries 3 and 5). Nevertheless, the situation changed dramatically when R was an EWG (R = acyl). The electrophilic alkoxy radical abstracted exclusively the hydrogen on the electron-richer C7 despite the less favorable seven-membered TS, and the reaction went exclusively through path [b] to give the [3.3.1]bicycle (entries 4 and 6).[11] No compounds derived from abstraction of the hydrogen at C4 were detected in this case.

Interestingly, compound **5** reacts more selectively than its pseudo-enantiomer **9** with which the only difference is the 8-methoxy group. Probably the presence of a supplementary β-oxygen retards further the rate of hydrogen abstraction at C7, favoring the exclusive abstraction at C4.[12]

With these examples we have now demonstrated the possibility of using an EWG substituent to avoid the intramolecular functionalization on a favored position and trigger the reaction in a less favored carbon atom. Indeed, the correct choice of the C4 substituent has been the switch to either 1,5-HAT or 1,6-HAT control in the reaction and hence to the specific synthesis of 2,9-dioxabicyclo[3.3.1]-nonane or hexahydro-2*H*-furo[3,2-*b*]pyran ring systems.[13] As observed, the reaction which may be conceptually considered to be an intramolecular glycosidation is, in reality, a selective oxidation of specific carbons of the carbohydrate skeleton and constitutes a mild procedure for the synthesis of protected uloses, which are not readily accessible by other methods.

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Supporting Information Available: A complete description of experimental details and products characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) For studies of the influence of polar factors on the intermolecular hydrogen abstraction reactions, see: (a) Beckwith, A. L. J.; Zavitsas, A. A. *J. Am. Chem. Soc.* **1995**, *117*, 607−614. (b) Zavitsas, A. A.; Chatgilialoglu, C. *J. Am. Chem. Soc.* **1995**, *117*, 10645−10654. (c) Kaushal, P.; Mok, P. L. H.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1663−1670. For an example of correlation between proximity in the ground state and regioselectivity in an IHA reaction, see ref 2c.

(12) Evidence for a deactivating influence of a β-oxygen in the intermolecular hydrogen abstraction reaction has been described: (a) Busfield, W. K.; Grice, I. D.; Jenkins, I. D.; Monteiro, M. J. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1071−1077. (b) Busfield, W. K.; Grice, I. D.; Jenkins, I. D. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1079−1086.

(13) Bicyclic ketals can be easily converted into the corresponding bicyclic ethers by stereoselective reduction: (a) Takemoto, Y.; Furuse, S.-i.; Hayase, H.; Echigo, T.; Iwata, C.; Tanaka, T.; Ibuka, T. *Chem. Commun.* **1999**, 2515−2516. (b) Nicolaou, K. C.; Hwang, C.-K.; Nugiel, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 4136−4137.