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Beneficial Effect of Internal Hydrogen Bonding Interactions on the β-Fragmentation of Primary Alkoxyl Radicals. Two-Step Conversion of D-Xylo- and D-Ribofuranoses into L-Threose and D-Erythrose, Respectively

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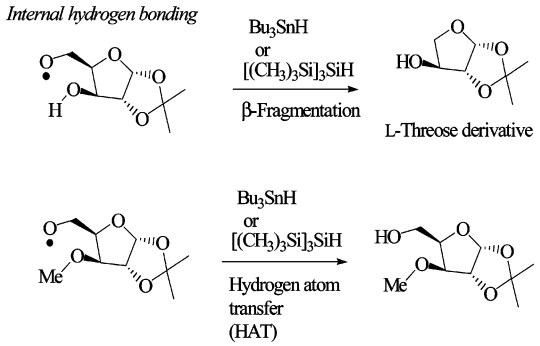
Received May 10, 2007



Primary alkoxyl free radicals were generated from their readily synthesized *N*-phthalimido derivatives under reductive conditions. Primary alkoxyl radicals derived from their corresponding xylo- and ribofuranose derivatives underwent, exclusively, an unusual β-fragmentation affording L-threose and D-erythrose derivatives, respectively. This occurs because the alkoxyl radical is capable of achieving an internal hydrogen-bonding interaction leading to a stable six-membered ring intramolecular hydrogen-bonded structure. When the hydroxyl group is protected, the β-fragmentation pathway is prevented and the hydrogen atom transfer (HAT) pathway occurs. Computational studies provided strong support for the experimental observations.

Introduction

Alkoxyl free radicals are very important and highly reactive intermediates that are present in atmospheric,[1] biological,[2] and synthetic processes.[3] In synthetic chemistry, alkoxyl radicals have been employed in many chemical transformations, including radical-mediated ring expansion (eq 1),[3f,g,i,k,n] radical-mediated fragmentation of carbohydrates (eq 2),[3h,4] internal (and external) hydrogen atom transfer (eq 3),[3a,b,h,i,l,m,5] and radical-mediated ring closing reactions (eq 4).[3j,l,66] Generally, the driving force for these reactions resides in the formation of the more

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(2) (a) Halliwell, B.; Gutteridge, J. M. C. *Free Radicals in Biology and Medicine*; Clarendon Press: Oxford, 1989. (b) Sies, H. *Oxidative Stress, Oxidants and Antioxidants*; Academic Press: New York, 1991. (c) Breen, A. P.; Murphy, J. A. *Free Radic. Biol. Med.* **1995**, *18*, 1033. (d) Finkel, T.; Holbrook, N. J. *Nature* **2000**, *408*, 239.

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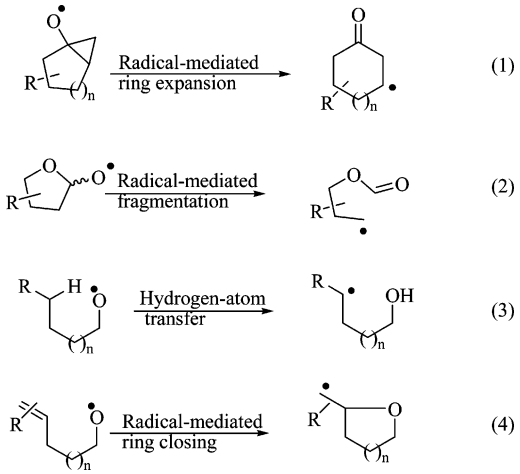
10.1021/jo0709551 CCC: $37.00
Published on Web 09/27/2007

SCHEME 1. Common Alkoxyl Radical Reactions



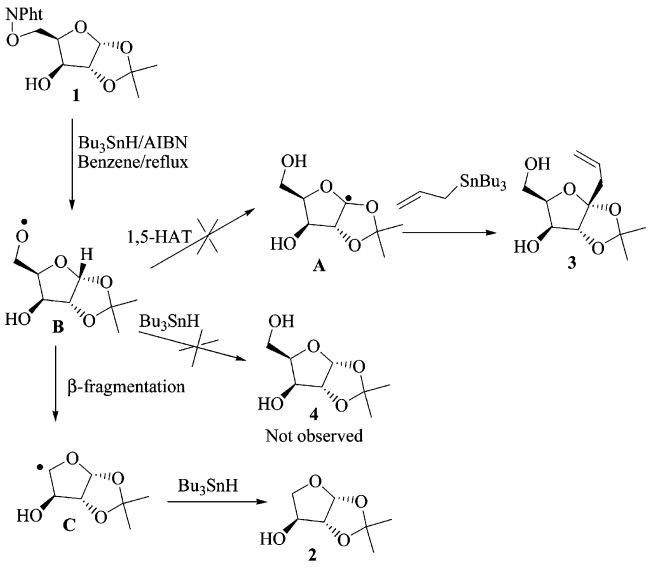
stable alkyl radical.[7] Therefore, these reactions are usually controlled by thermodynamic stability of the formed products, although solvent effects and intrinsic geometric properties are also important factors (Scheme 1).[8]

For example, Houk found by computational methods that *β*-fragmentations of some alkoxyl radicals do not always depend on the stability of the formed alkyl radical and that particular bond interactions can sometimes slow the rate of *β*-fragmentation.[9]

Results and Discussion

As part of an ongoing research project on the generation of primary alkoxyl radicals, we were trying to generate the 1,2-*O*-isopropylidenexylofuranose-1-yl radical **A** (Scheme 2) from its corresponding radical **B** in order to test its reactivity with allyltributyltin (**1**→**3**). However, we observed an unexpected result. Under classical tin conditions (Bu_3SnH/AIBN), when 5-*N*-phthalimido-1,2-*O*-isopropylidene-α-D-xylofuranose **1**[10] was

SCHEME 2. Proposed Reaction



NPht = Phthalimido
HAT = Hydrogen Atom Transfer

treated with allyltributyltin, it gave 1,2-*O*-isopropylidene-L-threose **2**[4g,11] as a single product in very good yield. Not even traces of the hydrogen atom transfer (HAT) product **4** were detected (Scheme 2).

This unexpected result aroused our attention, not only because of the apparent synthetic importance of the chiral building blocks, 1,2-*O*-isopropylidene-L-threose **2**,[11] but also because new findings on the *β*-fragmentation of alkoxyl radicals might be uncovered. In this regard, Suárez and Hernández[12] previously reported *β*-fragmentation of primary alkoxyl radicals under oxidative conditions (PhI or DIB in the presence of I_2); however, neither experimental nor theoretical efforts were carried out to clarify their unusual results.[13] Although the scope of this work did not specifically address their results, we believe that our results may offer interesting findings not previously considered in alkoxyl radical chemistry.

First, we needed to know if the presence of the allyltributyltin caused the unexpected *β*-fragmentation reaction. To address this question, the reaction was conducted with only Bu_3SnH and a catalytic amount of AIBN in refluxing benzene, and the result was identical. We considered that the presence of the internal free hydroxyl group might be responsible for *β*-fragmentation. To probe this, other alkoxyl radical precursors (**5**,[10] **8**, and **10**) were synthesized from their respective commercially available carbohydrate precursors applying Kim's methodology[6b] and subsequently treated under different reaction conditions (Table 1).

We reasoned that varying the polarity of the solvent (benzene, THF, and CH_3CN) and using a less efficient hydrogen atom

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(6) (a) Johns, A.; Murphy, J. A. *Tetrahedron Lett.* **1988**, *29*, 837. (b) Kim, S.; Lee, T. A.; Song, Y. *Synlett* **1998**, 471. (c) Hartung, J.; Hiller, M.; Schmidt, P. *Liebigs Ann.* **1996**, 1425. (d) Hartung, J.; Hiller, P.; Schmidt, P. *Chem. Eur. J.* **1996**, *2*, 1014. (e) Hartug, J.; Kneuer, R. *Eur. J. Org. Chem.* **2000**, 1677.

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(8) (a) Bacha, J. D.; Kochi, J. K. *J. Org. Chem.* **1965**, *30*, 3272. (b) Walling, C.; Wagner, P. J. *J. Am. Chem. Soc.* **1963**, *85*, 2333. (c) Walling, C.; Padwa, A. *J. Am. Chem. Soc.* **1963**, *85*, 1593. (d) Choo, K. Y.; Benson, S. W. *Int. J. Chem. Kinet.* **1981**, *13*, 833.

(9) Wilsey, S.; Dowd, P.; Houk, K. N. *J. Org. Chem.* **1999**, *64*, 8801.

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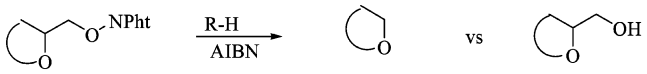
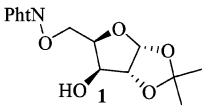
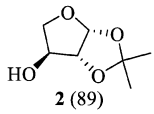
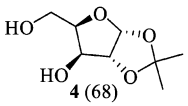
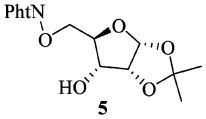
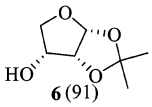
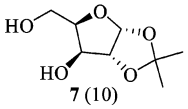
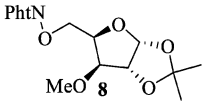
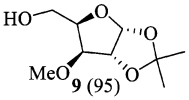
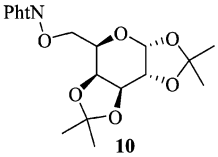
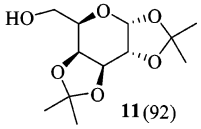
(13) They reasoned that *β*-fragmentation of primary alkoxyl radicals in carbohydrate chains occurs because the resulting radical is stabilized by the adjacent oxygen, which under oxidative conditions produces an oxycarbenium ion.

TABLE 1. *β*-Fragmentation versus HAT[a]



Entry	Substrate	Solvent	R-H	β-fragmentation product yield (%)[b]	HAT product yield (%)[b]
1	 **1**	Benzene	Bu_3Sn	 **2** (89)	NOT OBSERVED
2	**1**	Benzene	$[(Me_3)_3Si]_3Si$	**2** (78)	NOT OBSERVED
3	**1**	THF	Bu_3Sn	**2** (12)	 **4** (68)
4	**1**	CH_3CN	Bu_3Sn	**2** (18)	**4** (58)
5	 **5**	Benzene	Bu_3Sn	 **6** (91)	NOT OBSERVED
6	**5**	Benzene	$[(Me_3)_3Si]_3Si$	**6**(87)	NOT OBSERVED
7	**5**	THF	Bu_3Sn	**6**(74)	 **7** (10)
8	 **8**	Benzene	Bu_3Sn	------	 **9** (95)
9	**8**	Benzene	$[(Me_3)_3Si]_3Si$	------	**9** (89)
10	**8**	THF	Bu_3Sn	------	**9** (85)
11	 **10**	Benzene	Bu_3Sn	------	 **11** (92)
12	**10**	Benzene	$[(Me_3)_3Si]_3Si$	------	**11** (90)

[a] The reactions were performed in dry and degassed solvent at reflux temperature with 3.0×10^{-3} M of Bu_3SnH. Addition time 1h. [b] Yields determined after column chromatography.

donor ($[(Me_3)_3Si]_3SiH$) could provide evidence for the hypothesis of hydroxyl group participation in the *β*-fragmentation pathway. As anticipated, 5-*N*-phthalimido-1,2-*O*-isopropylidene-D-ribofuranose **5** afforded 1,2-*O*-isopropylidene-D-erythrose **6**[14] as a single product when either Bu_3SnH or $[(Me_3)_3Si]_3SiH$ was used (entries 5 and 6, Table 1), very similar as for **1 (**entries 1 and 2, Table 1). A dramatic decrease in the yield of the *β*-fragmentation products **2** and **6**, and subsequent increase in the yields of hydrogen atom transfer products **4** and **7** was observed when good hydrogen bond accepting solvents such as THF and CH_3CN were used (entries 3, 4 and 7). Interestingly, the 5-*N*-phthalimido-3-*O*-methyl-1,2-*O*-isopropylidene-D-xylofuranose **8**, and the 6-*N*-phthalimido-1,2:3,4-di-*O*-isopropylidene-D-galactopyranose **10** yielded only the hydrogen atom transfer products **9** and **11**, respectively, under different reaction conditions (entries 8−12, Table 1).

In the case of **8**, the exclusive formation of the hydrogen atom transfer product **9** may be due to both (1) a 1,6-internal hydrogen atom transfer (IHAT) from the methyl group to the alkoxyl radical followed by hydrogen atom transfer from Bu_3SnH to the respective alkyl radical **E** and (2) a 1,5-IHAT from the anomeric hydrogen atom to the alkoxyl radical followed by HAT from Bu_3SnH to the respective alkyl radical **F** (Scheme 3).

To demonstrate that 1,5- and 1,6-HAT processes do not accelerate the formation of the reduction product **9** and

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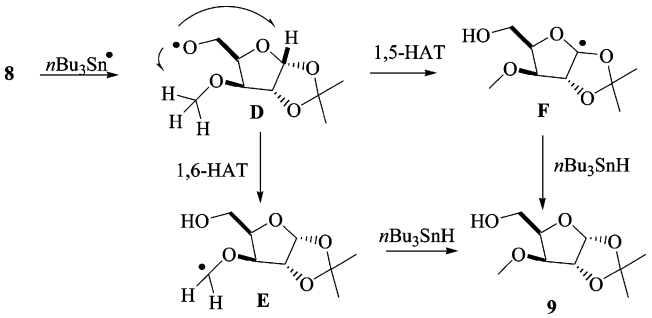
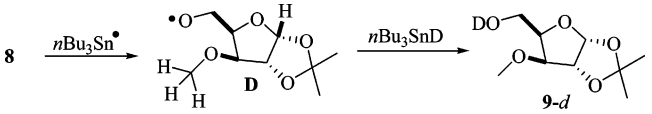
SCHEME 3. Plausible 1,5- and 1,6-HAT Reactions of Alkoxyl Radical D



SCHEME 4. Labeling Experiment



no deuterium incorporation at methyl group and anomeric position

consequently the inhibition of the respective *β*-fragmentation product (not shown), we conducted deuterium-labeling experiments. Treatment of the *N*-phathalimido **8** with *n*-Bu_3SnD under the same condition reactions as used with *n*-Bu_3SnH or $[(Me_3)_3Si]_3SiH$, it provided reduction product **9**, without deuterium incorporation at methyl group or anomeric position (Scheme 4).[15] This result is consistent with the suggestion that internal hydrogen bonding favors the *β*-fragmentation of a primary alkoxyl radical.

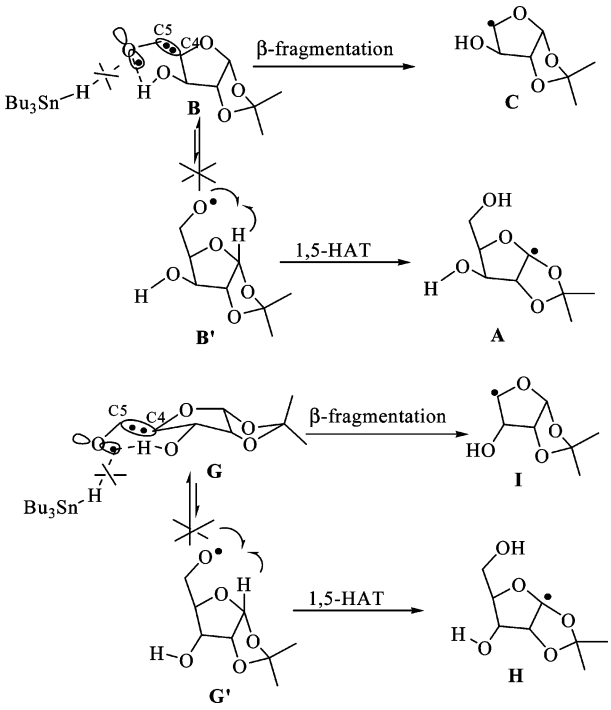
Therefore, in the light of above results, the hypothesis of internal hydroxyl group participation in the *β*-fragmentation process seems to be occurring. Accordingly, we propose that the semi-filled p-orbital (SOMO) of the alkoxyl radicals **B** and **G** (which are generated from *N*-phathalimide derivatives **1** and **5**, respectively) is interacting with the hydrogen atom of the hydroxyl group, forming, in the case of **B**, a six-membered boat conformation, and in the case of **G**, a six-membered chair conformation (Scheme 5). Thus, a parallel or pseudoparallel orientation between the semifilled p-orbitals of **B** and **G** and their respective C4−C5 bonding orbital is achieved, leading to hyperconjugative stabilization (Scheme 5).

As is shown in Scheme 5, suitable conformations for 1,5-HAT (**B′** and **G′**) can be prevented by internal hydrogen bonding interactions. The apparent conformational equilibria for **B** ↔ **B′** and **G** ↔ **G′** is strongly directed toward **B** and **G** structures. Accordingly, if the overall chair and boat geometries are retained, these arrangements should lead, as postulated above, to hyperconjugative stabilization, and consequently, *β*-fragmentation. Besides considering the participation of hydrogen bond donation to the alkoxyl radical center, the HAT from Bu_3SnH or $[(Me_3)_3Si]_3SiH$ can also be prevented (Scheme 5).

It is important to mention that in atmospheric studies the participation of internal hydrogen bond donation to alkoxyl or peroxyl radical centers as a common motif in *β*-hydroxyperoxyl and *β*-hydroxyalkoxyl radicals have been postulated.[16] Furthermore, to the best of our knowledge, there have been no reports where internal hydrogen bonding interaction of an alkoxyl free

(15) It is important to mention that 35% of deuterium incorporation at anomeric position occurs when more diluted conditions (1.4×10^{-3} M) are used and addition of Bu_3SnD is very slow (3 h).

SCHEME 5. Hydrogen-Bonding Interactions Favoring the *β*-Fragmentation



radical is invoked as the driving force for a *β*-fragmentation process of an alkoxyl free radical. However, it has been reported that a large acceleration of *β*-fragmentation of alkoxyl radicals can be favored by intermolecular hydrogen bonding.[17] Therefore, we were obliged to use quantum chemical methods to provide evidence in support of the hypothesis above.

Computational Methods

The geometry of each stationary point was fully optimized using the Gaussian 03 software package[18] with the UHF/B3LYP/6-31+G-(d) method.[19] All stationary points were characterized as minima by calculating the harmonic vibrational frequencies using analytical second derivatives. All of structures were visualized using the Chemcraft 1.5 program. To save computational time, the two methyl

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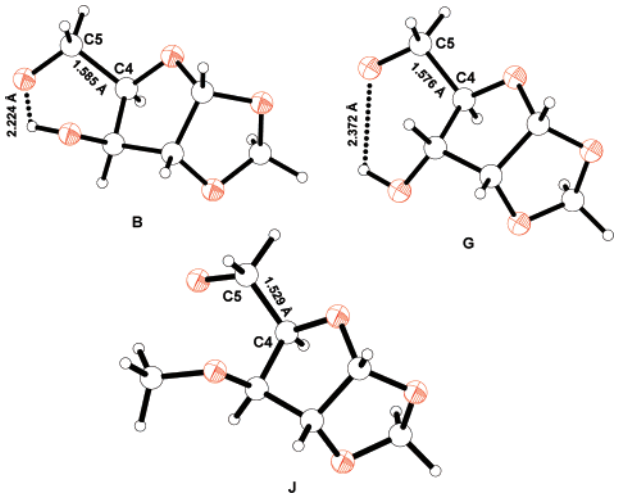

FIGURE 1. Optimized structures for **B**, **G**, and **J**.

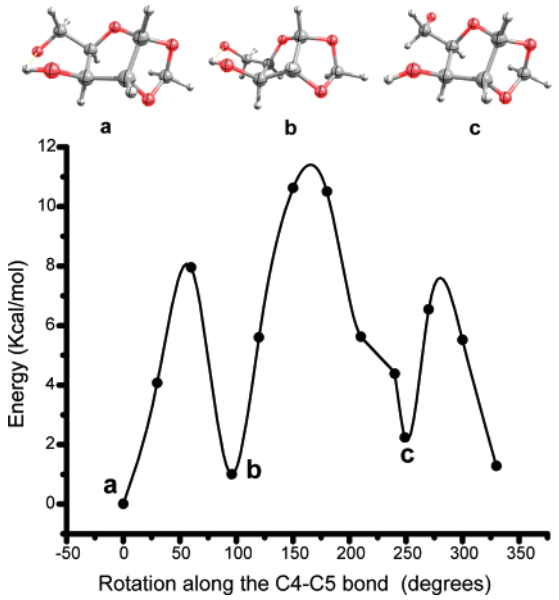

FIGURE 2. Potential energy surface for radical **B**.

groups of the 1,2-*O*-isopropylidene moiety of radicals **B**, **G**, and **J** were replaced by two hydrogen atoms. Free radical **J** which contains the C-3 hydroxyl group protected represents a good model for comparative investigation.

Thus, electronic structures **B** and **G** have shown the intramolecular hydrogen bonding with a distance of 2.22 Å and 2.37 Å for **B** and **G**, respectively (Figure 1). Additional important information extracted from this theoretical calculation is the C4−C5 bond distance for the radicals **B**, **G**, and **J**. As in case of **B** and **G** where the internal hydrogen bonding is present, so does hyperconjugative interactions, bond distances are considerably longer (1.585 Å for **B** and 1.576 Å for **G**) than radical **J** (1.529 Å). This means that C4−C5 bond distances for radical **B** and radical **G** are 0.056 Å and 0.047 Å, respectively, longer than radical **J**; therefore, this provides additional proof for the favorable β-fragmentations in **B** and **G**.

Additionally, we computed structures and energies of other conformers for radical **B** in order to demonstrate that the hydrogen-bonded structure possesses a local minimum and thereby the driving force for β-fragmentation. Therefore, by computing the potential energy surface for radical **B** (at the same level of theory) along the C4−C5 bond, we found two other minima (**b** and **c**, Figure 2). Interestingly, rotamer **b** showed another internal hydrogen-bonding

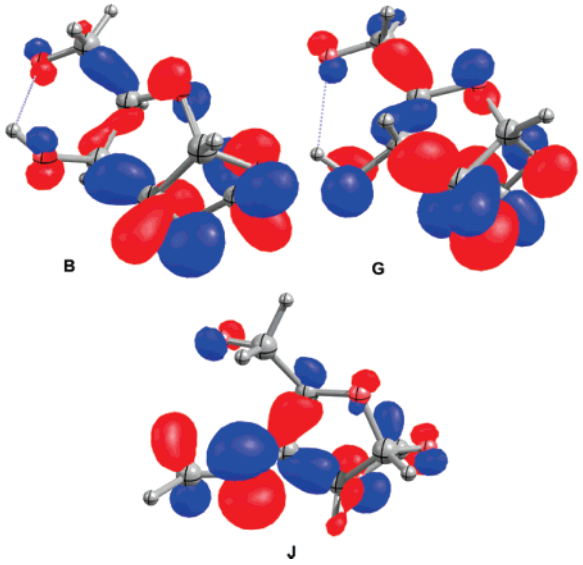

FIGURE 3. Electron-wave distribution SOMO for **B**, **G**, and **J**.

TABLE 2. NBO Analysis (Second-Order Perturbation Theory) of Hyperconjugative Interactions, $n\pi O \rightarrow \sigma^*_{C4-C5}$ and $n\pi O \rightarrow \sigma^*_{H-O}$, in Free Radical Structures B, G, and J

donor orbital	acceptor orbital	$E(2)$ (kcal/mol)	$\epsilon_i - \epsilon_j$ (au)	F_{ij} (au)
structure **B**				
$n_\pi O$	σ^*_{C4-C5}	5.10	0.68	0.074
$n_\pi O$	σ^*_{C5-H}	4.93	0.72	0.076
$n_\pi O$	σ^*_{H-O}	1.49	0.77	0.043
structure **G**				
$n_\pi O$	σ^*_{C4-C5}	4.73	0.69	0.072
$n_\pi O$	σ^*_{C5-H}	4.67	0.71	0.073
$n_\pi O$	σ^*_{H-O}	0.62	0.82	0.029
structure **J**				
$n_\pi O$	σ^*_{C5-H}	4.91	0.73	0.076
$n_\pi O$	σ^*_{C4-C5}	4.64	0.75	0.074

interaction leading now to a different conformation (chair). In addition, it is important to notice that the C4−C5 bond length in the structures that lack the H-bond have an average value of 1.527 Å, whereas where the structures with a H-bond is present, the C4−C5 bond has an average value of 1.577 Å. This reveals that the C4−C5 bond is debilitated by the hydrogen-bonding interactions.

The natural bond orbital (NBO) analysis[20] clearly shows the difference of the electronic distribution for the SOMO for radicals **B**, **G**, and **J**. Note that radicals **B** and **G** have very similar electronic distribution onto oxygen radical, thus permitting free movement toward the C4−C5 antibonding orbital and thereby providing further support of the hyperconjugative interactions that favor the β-fragmentation process (see Figure 3 and Table 2).

Essentially, Table 2 shows selected interactions between filled (donor) Lewis-type NBOs and empty (acceptor) non-Lewis NBOs and estimating their energetic importance by second-order perturbation theory. In this case, Table 2 summarizes $E(2)$ energies between the oxygen lone pair $n_\pi O$, from the alkoxyl radical with C4−C5, C5−H, or H−O antibonds. It is noteworthy that higher values for structures **B** and **G**, are for $n_\pi O \rightarrow \sigma^*_{C4-C5}$ interactions, while the higher value of $E(2)$, in structure **J** is for the $n_\pi O \rightarrow \sigma^*_{C5-H}$ interaction. This explains the elongation of C4−C5 bonds in structures **B** and **G** discussed above.

(20) (a) Foster, P.; Weinhold, F. *J. Am. Chem. Soc*. **1980**, *102*, 7211. (b) Reed, A. E.; Weinhold, F. *J. Chem. Phys*. **1983**, *78*, 4066. (c) Reed, A. E.; Weihstock, R. B.; Weinhold, F. *J. Chem. Phys*. **1985**, *83*, 735. (d) Reed, A. E.; Weinhold, F. *J. Chem. Phys*. **1985**, *83*, 1736. (e) Reed, A. E.; Curtis, L. A.; Weinhold, F. *Chem. Rev*. **1988**, *88*, 899.

Although in this work it has been demonstrated that *β*-fragmentation of a primary alkoxyl radical is favored by an internal hydrogen-bonding interaction between the semifilled p-orbital (rather than the lone pair of the alkoxyl radical) and a hydroxyl group, the previous *β*-fragmentation of a primary alkoxyl radical observed by Suarez and Hernández cannot be explained on the basis of the present study. Evidently, the driving force that governs the *β*-fragmentation in our reductive conditions is completely different to that of their oxidative conditions. However, from a mechanistic point of view, this *β*-fragmentation of primary alkoxyl radicals under reductive conditions contradicts the previous assumption which postulated that the driving force for *β*-fragmentation of a primary alkoxyl radical in carbohydrate chains resides in the formation of a stable alkyl radical with an adjacent oxygen which eventually form an oxycarbenium ion.[12]

In summary, a novel and highly efficient two step conversion of D-xylo and D-ribofuranose derivatives into L-threose and D-erythreose derivatives, respectively, is reported. The key step for these syntheses is a very unusual *β*-fragmentation of primary alkoxyl radicals derived from their corresponding *N*-phthalimido derivatives. Interestingly, internal hydrogen bonding has shown to be the driving force for such reactions.

Experimental Section

General Procedure for the Synthesis of L-Threose and D-Erythrose Derivatives 2 and 6, Respectively. The *β*-Fragmentation Protocol. 5-*N*-Phthalimido-1,2-*O*-isopropylidene-α-D-xylofuranose **1** (100 mg, 0.29 mmol) was dissolved in dry and degassed benzene (50 mL), and the resulting solution was heated at 80 °C before addition of a solution of Bu_3SnH (112 mg, 0.39 mmol) and AIBN (20 mg) in dry and degassed benzene (50 mL) dropwise (1 h approximately). After the addition was complete, the reaction mixture was stirred for 4 h and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (230−400 mesh) with ether−EtOAc (v/v = 3/1) to afford 1,2-*O*-isopropylidene-D-threose **2**[4g,11] in 89% yield as white solid: mp = 84−85 °C; $[\alpha]_D$ = +16.6 (*c* 1.0, $CHCl_3$) [lit.[4g] $[\alpha]_D$ = +13.4 (*c* 0.8)]; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 1.34 (s, 3H), 1.47 (s, 3H), 3.87 (dd, 1H, *J* = 9.6, 0.8 Hz), 4.08 (dd, 1H, *J* = 10.4, 3.2 Hz), 4.26 (d, 1H, *J* = 2.8 Hz), 4.50 (d, 1H, *J* = 3.6 Hz), 5.95 (d, 1H, *J* = 3.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 26.1, 26.6, 72.8, 77.3, 84.9, 105.1, 111.9.

Acknowledgment. We thank Dr. Rodney A Fernandez of the Indian Institute of Technology, Bombay, for helpful discussions. This work was supported by PROMEP-BUAP and I.Q.-UNAM.

Supporting Information Available: Experimental procedures, analytical data, copies of ^{1}H NMR and ^{13}NMR spectra for unknown compounds, and Cartesian coordinates for **B**, **G**, and **J**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0709551