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Novel Polyhydroxylated Cyclic Nitrones and *N*-Hydroxypyrrolidines through BCl_3-Mediated Deprotection

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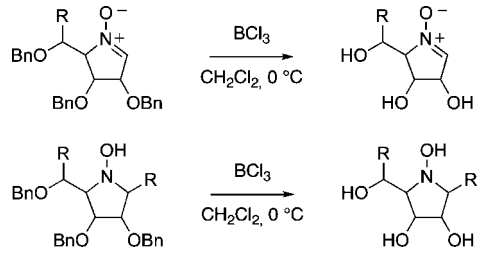
ABSTRACT



A general method to prepare a new class of carbohydrate-derived, enantiomerically pure polyhydroxypyrroline *N*-oxides from their alkoxy (protected) derivatives is presented. Boron trichloride is shown to cleave efficiently benzyl ethers and ketals without affecting the imine *N*-oxide functionality of nitrones. The same reagent (BCl_3) also allowed the efficient synthesis of a polyhydroxylated *N*-hydroxypyrrolidine, giving access to a novel class of *N*-hydroxyiminosugars.

Polyhydroxylated heterocycles containing an endocyclic nitrogen atom are coined by the general term of *iminosugars*.[1] Iminosugars have demonstrated outstanding biological activities as glycosidase inhibitors and, more generally, as glycoprocessing enzyme modulators.[2] Since the inhibition of glycoprocessing enzymes has potential applications in the development of antiviral,[3] anticancer,[4] and metabolic disorder[5] therapies, iminosugars have attracted much attention. In particular, polyhydroxylated pyrrolidines and pyrrolines (five-membered ring iminosugars) are among the most potent inhibitors of individual glycoprocessing enzymes (Figure 1).[6]

In contrast to the intense research devoted to iminosugars and to their structure−function relationship, little or no attention has been given to their *N*-oxygenated analogues. Very few polyhydroxylated pyrrolidine *N*-oxides[7] (**I**) and

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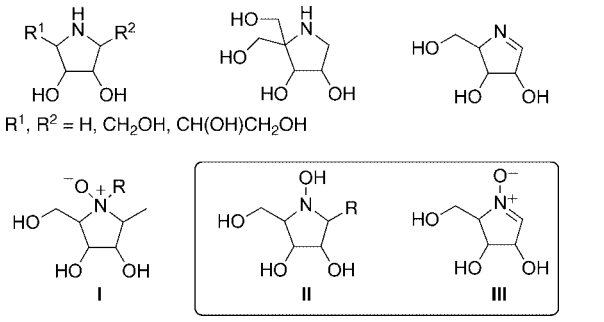

Figure 1. Pyrrolidine iminosugars and *N*-oxy analogues.

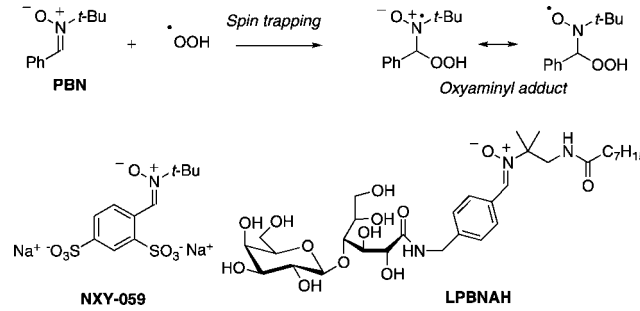

Figure 2. PBN: spin-trapping activity and hydrophilic derivatives.

N-hydroxy-pyrrolidines[6g,8] (**II**) have been reported. Remarkably, only a single letter describes the obtention of a polyhydroxylated endocyclic nitrone, in the course of structural studies on the enediyne antibiotic esperamycin A_1.[9]

Nitrones share with imines[10,11] the sp^2 character at the pseudoanomeric position (beneficial to mimic oxocarbenium-like transition states) and with tertiary amine *N*-oxides the zwitterionic character.[12] Notwithstanding these potentially advantageous properties, the biological activity of polyhydroxylated nitrones related to iminosugars has never been evaluated, although numerous polyalkoxylated nitrones have been used by chemists as synthetic intermediates.[13]

In addition, nitrones have been recognized as protective agents against oxidative stress in biological systems.[14] While α-phenyl-*N*-*tert*-butylnitrone (PBN) is the most studied nitrone with respect to spin-trapping properties,[15] several hydrophilic derivatives, such as NXY-059[16] and LPBNAH,[17] have been designed for better distribution (Figure 2). Interestingly, the activity of nitrones as antioxidants is dependent on their lipophilicity/hydrophilicity balance as recently demonstrated by the group of Pucci.[18] Highly water-soluble nitrones are still scarce in the literature, and their physicochemical properties have not been investigated in detail.

In this paper, we disclose a method to prepare polyhydroxylated cyclic nitrones from polyalkoxy precursors that are themselves readily prepared from commercially available carbohydrates.[13] Such cyclic nitrones are generally prepared by (i) introduction of ethers or isopropylidene ketals to protect hydroxyl groups in carbohydrates and (ii) cyclization by intramolecular *N*-alkylation of an oxime function placed at the anomeric center. Benzyl ethers have proved particularly convenient in such sequences, as benzyl groups are stable to a large variety of chemical treatments but can be removed by hydrogenolysis.[19] Consequently, benzyl protection of hydroxyl groups has been commonly used for the synthesis of carbohydrate-derived nitrones.[13,20]

The deprotection of benzyloxy-substituted nitrones could not be effected by hydrogenolysis as the nitrone functionality does not resist such conditions.[21] We thus considered another method for benzyl ether cleavage, previously used in carbohydrate chemistry, that involves treatment of benzyl ethers with boron trichloride.[22] It should be noted that substrates containing nitrone or hydroxylamine functions have never been subjected to such treatment. At first, this

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(11) Nectrisine (FR-900484) is an example of potent α-mannosidase and glucosidase inhibitor, exhibiting immunomodulator activity: (a) Hibata, T.; Nakayama, O.; Tsurumi, Y.; Okuhara, M.; Terano; H.; Ohsaka, M. *J. Antibiot.* **1988**, *41*, 296. (b) Kim, Y. J.; Takatsuki, A.; Kogoshi, N.; Kitahara, T. *Tetrahedron* **1999**, *55*, 8353.

(12) Such zwitterionic character was proposed to allow better interaction with the putative carboxylate and carboxylic acid residues in active sites of glycosidases due to stronger electrostatic interactions. However, this hypothesis has yet to be validated as the previously prepared polyhydroxylated piperidine and pyrrolidine *N*-oxides exhibited weak or unsignificant activity against glycosidases: (a) Dong, W.; Jespersen, T.; Bols, M.; Skrydstrup, T.; Sierk, M. R. *Biochemistry* **1996**, *35*, 2788. See also ref 8a, c.

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(14) For a review, see: (a) Floyd, R. A. *Adv. Pharm.* **1997**, *38*, 361.

(15) Janzen, E. G.; Kotake, Y.; Hinton, R. D. *Free Radical Biol. Med.* **1992**, *12*, 169, and references therein.

(16) Nitrone NXY-059 (Astra Zeneca) has been in phase III clinical trials as a neuroprotective agents for the treatment of cerebral ischemias: (a) Lapchak, P. A.; Song, D.; Wei, J.; Zivin, J. A. *Exp. Neurol.* **2004**, *188*, 279.

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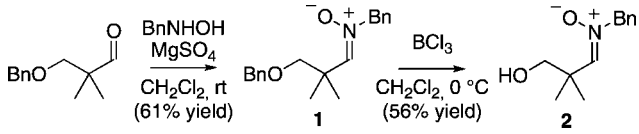
method was tested on nitrone **1**, prepared from 3-(benzyloxy)-2,2-dimethylpropanal[23] (Scheme 1). When **1** was

Scheme 1. Nitrone Debenzylation in the Presence of BCl_3



treated with 1 equiv of BCl_3, incomplete reaction was observed, but when the reagent was used in excess (3 equiv) the *O*-benzyl-deprotected nitrone **2** was isolated as the sole product; both the nitrone functionality and the *N*-benzyl substituent remained unaffected under these conditions.

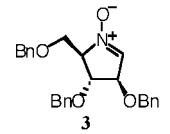
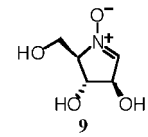
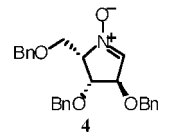
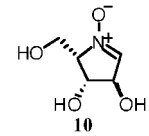
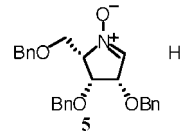
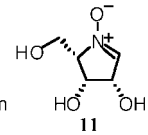
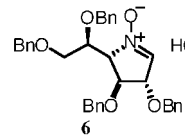
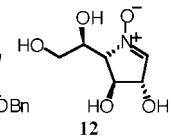
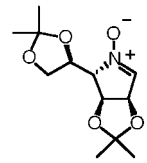
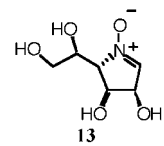
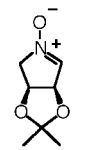
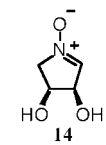
The method was then applied to polyalkoxy-substituted nitrones **3**,[20a,24] **4**,[25] **5**,[20c] and **6**[26] readily obtained from l-xylose, d-arabinose, d-ribose, and d-glucose, respectively (Table 1). Using excess BCl_3, *O*-debenzylation of nitrones **3**−**5** was performed to yield the corresponding polyhydroxyl nitrones **9**–**11** in good yields (entries 1−3). The branched nitrone exhibiting the galacto configuration (**6**) was also deprotected in good yield (entry 4).

In a similar fashion, isopropylidene protected nitrones **7**[27] and **8**,[28] prepared respectively from d-mannose and l-erythrose, were smoothly transformed to nitrones **13** and **14**, respectively (entries 5 and 6).

Encouraged by the success of this method for preparing polyhydroxylated nitrones, we next examined the possibility of deprotecting *N*-hydroxypyrrolidines. Such compounds can be obtained from nitrones by nucleophilic additions[29] or reductive coupling with electrophiles.[30]

Secondary hydroxylamines are sensitive compounds, prone to dehydration in acidic conditions. However, when the cyclic *N*-hydroxypyrrolidine **15**[20b] was treated in the above-

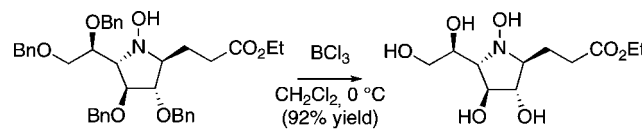
Table 1. BCl_3-Mediated *O*-Dealkylation of Polyalkoxy Carbohydrate-Derived Endocyclic Nitrones[a]

entry	starting nitrones	products	equivalents BCl_3	yield[b] (%)
1	 **3**	 **9**	9	97
2	 **4**	 **10**	9	85
3	 **5**	 **11**	9	74
4	 **6**	 **12**	12	91
5	 **7**	 **13**	12	88
6	 **8**	 **14**	6	57

[a] Conditions: BCl_3 (1 M in hexanes), CH_2Cl_2, 0 °C, 17 h. See the Supporting Information. [b] Isolated yields.

described conditions to deprotect benzyl ethers, the corresponding polyhydroxylated *N*-hydroxypyrrolidine **16** was isolated in 92% yield (Scheme 2).

Scheme 2. *N*-Hydroxypyrrolidine Debenzylation using BCl_3



15 (ref. 20b) **16**

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In conclusion, the use of BCl_3 as a Lewis acid promotes efficient cleavage of benzyl ethers and isopropylidene ketals in nitrones and in a *N*-hydroxypyrrolidine.[31] The described method thus opens a route to two new classes of enantiopure polyhydroxylated cyclic nitrones and polyhydroxylated *N*-hydroxypyrrolidines. Such products could find useful applications as novel glycomimetics and/or as water-soluble radical-trapping agents (in the case of nitrones). Biological evaluations in both these directions are now possible as a consequence of the easy access to these compounds.

(31) Some of the work described herein has been patented: Py, S.; Desvergnes, S.; Vallée, Y. (Université Joseph Fourier−CNRS), FR2902097, 2007; *Chem. Abstr.* 2007, *148*, 54460.

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Supporting Information Available: Experimental procedures, compounds characterization data, and copies of ^1H NMR and ^{13}C NMR for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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