Intramolecular 1,3-Dipolar Cycloadditions of Sugar Ketonitrones: A Convenient Method for Stereoselective Formation of Nitrogenated Quaternary Centers

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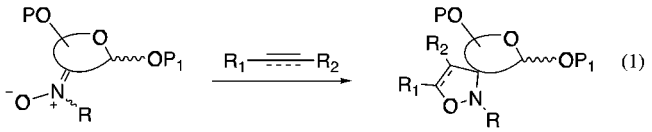
Cycloaddition reactions are among the most important transformations in organic chemistry.[1] Currently, they are the focus of much interest in the carbohydrate field,[2] where the use of some of them has hitherto been rare or, at most, limited. A case in point is the 1,3-dipolar cycloaddition of ketonitrones, which is schematically illustrated for a protected cyclic sugar in eq 1.



Our interest in this reaction stems from our studies toward the synthesis of (−)-tetrodotoxin (TTX, **1**)[3,4] and (+)-lactacystin (**2**).[5] Specifically, we envisaged that it might be of utility in the formation of the nitrogenated quaternary centers at positions C8a and C5 of **1** and **2**, respectively (Figure 1).

Although use of the 1,3-dipolar cycloaddition of aldonitrones has been widespread,[2,6] at the outset of this study

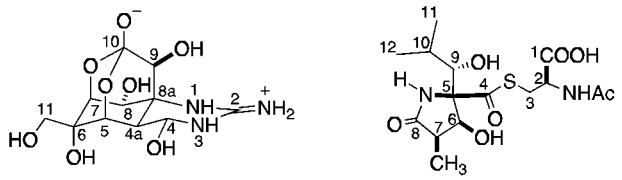
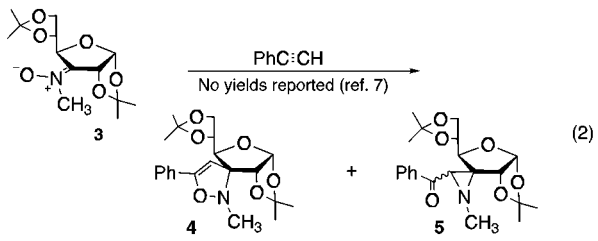


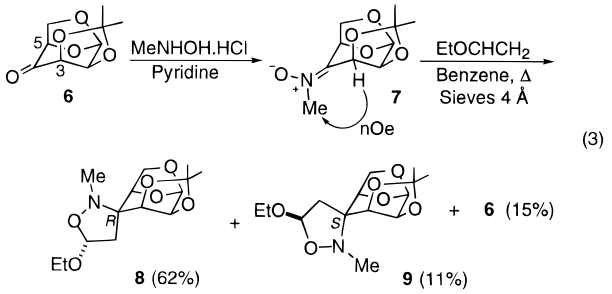
Figure 1.

we found only a single application of this transformation of the more hindered sugar-ketonitrones: the cycloaddition of *N*-methylketonitrone **3** to phenylacetylene, which gives the isoxazolidine **4** and the aziridine **5** (eq 2).[7]



Herein we report the first results of our investigation of the 1,3-dipolar cycloaddition of ketonitrones, which show that this reaction is a synthetically useful procedure for the stereocontrolled generation of nitrogenated quaternary centers in sugar substrates.

Initial experiments were carried out with ketonitrone **7**, which was prepared from the known 4-oxo-mannopyranose derivative **6**[8] (eq 3). Gratifyingly, reaction of **7**



with ethyl vinyl ether took place regioselectively to give cycloadducts **8** and **9** in an acceptable 73% combined yield. Formation of the nitrogenated quaternary center proceeded, however, with modest stereoselectivity (**8**:**9** = 6:1).

Next, we explored an intramolecular version of this reaction. Cycloaddition of compound **10**, which has a 4-*O*-allyl group as the internal dipolarophile (entry 1, Table 1), proceeded with yield similar to that of the intermolecular reaction, but in this case a single stereoisomer was isolated. Spectroscopic analysis of this product strongly suggested it to be the adduct **11**. Nonetheless, to rule out isomeric products such as **13** and **15**, which could have been formed by α-epimerization of ketone **10** prior to the intramolecular cycloaddition, the corresponding epimeric ketones **12** and **14** were subjected

(1) (a) For a general treatise see *Cycloaddition Reactions in Organic Synthesis*; Carruthers, W., Ed.; Tetrahedron Organic Chemistry Series, Vol. 8, Pergamon Press: New York, 1990. (b) See also *Advances in Cycloaddition*; Vol. 1 (1988), Vol. 2 (1990), and Vol. 3 (1993); Curran, D. P., Ed.; Jai Press Inc.: London. (c) An extensive review of the synthetic utility of cycloaddition reactions can be found in *Comprehensive Organic Synthesis*; Trost, B., Ed.; Pergamon Press: New York, 1992; Vol. 5. In Vol. 4 of the same collection, A. Padwa reviews intermolecular 1,3-dipolar cycloadditions (Chapter 4.9, pp 1069−1109), and P. A. Wade reviews intramolecular 1,3-dipolar cycloadditions (Chapter 4.10, pp 1111−1168). See also Confalone, P. N.; Huie, E. M. *Org. React.* **1988**, *36*, 1−173. (d) The mechanisms of two of the most important cycloaddition reactions (the Diels−Alder reaction and the 1,3-dipolar cycloaddition) are discussed from a historical perspective (1935−1995) in Houk, K. N.; González, J.; Li, Y. *Acc. Chem. Res.* **1995**, *28*, 81−90.

(2) (a) For a monograph, see *Cycloaddition Reactions in Carbohydrate Chemistry*; Giuliano, R. M., Ed.; ACS Symposium Series No. 494, 1992. (b) For a discussion of the applications of cycloaddition reactions in the transformation of carbohydrate derivatives into functionalized cyclohexanes and cyclopentanes, see Ferrier, R. J.; Middleton, S. *Chem. Rev.* **1993**, *93*, 2779−2831.

(3) *Tetrodotoxin, Saxitoxin and the Molecular Biology of the Sodium Channel; Annals of The New York Academy of Sciences*; Kao, C. Y., Levinson, S. R., Eds.; New York Academy of Sciences: New York, 1986; Vol. 479. To date only one total synthesis of tetrodotoxin in racemic form has been accomplished: Kishi, Y.; Aratani, M.; Fukuyama, T.; Nakatsubo, F.; Goto, T.; Inoue, S.; Tanino, H.; Sugiure, S.; Kakoi, H. *J. Am. Chem. Soc.* **1972**, *94*, 9217. *Ibid.* **1972**, *94*, 9219.

(4) We recently reported a free radical approach to the formation of the quaternary C8a center of this molecule: Noya, B.; Alonso, R. *Tetrahedron Lett.* **1997**, *38*, 2745. This paper lists references relating to the main attempts at development of a total synthesis of the enantiomerically pure toxin and to the recent isolation of new congeners.

(5) (+)-Lactacystin was recently reported as the first non-protein neurotrophic factor: Omura, S.; Fujimoto, T.; Otoguro, K.; Matsuzaki, K.; Moriguchi, R.; Tanaka, H.; Sasaki, Y. *J. Antibiot.* **1991**, *44*, 113. For a discussion of the main attempts at total synthesis of (+)-lactacystin, see Casiraghi, G.; Rassu, G.; Zanardi, F. *Chemtracts-Org. Chem.* **1994**, 266−272. See also: Fenteany, G.; Standaert, R. F.; Lane, W. S.; Choi, S.; Corey, E. J.; Schreiber, S. L. *Science* **1995**, *268*, 726 and references cited therein.

(6) For the 1,3-dipolar cycloaddition of glycosyl aldonitrones, see Fisera, L.; Al-Timari, V. A. R.; Ertl, P. in ref 2a, Chapter 11. For a recent review of asymmetric cycloadditions of nitrones, including sugar-derived aldonitrones, see Frederickson, M. *Tetrahedron* **1997**, *53*, 403.

(7) Tronchet, J. M. J.; Mihaly, M. E. *Helv. Chim. Acta* **1972**, *55*, 1266. See also ref 11.

(8) Cerny, M.; Stanek, J., Jr. *Adv. Carbohydr. Chem.* **1977**, *34*, 23−177.

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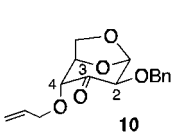
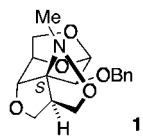
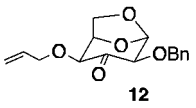
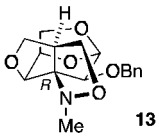
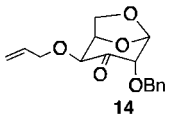
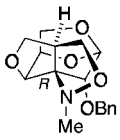
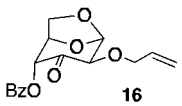
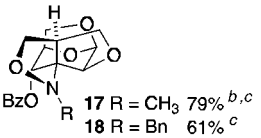
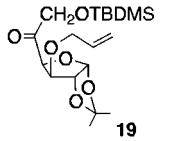
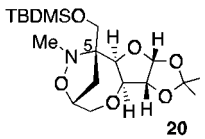
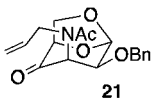
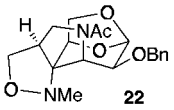
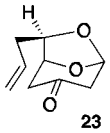
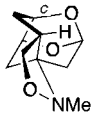
Table 1. Intramolecular Cycloaddition of Ketosugar Nitrones[a]

Entry	Ketone precursor	Cycloadducts	Isolated yield
1	 **10**	 **11**	78%
2	 **12**	 **13**	77%
3	 **14**	 **15**	65%
4	 **16**	 **17** R = CH_3 79%[b,c] **18** R = Bn 61%[c]	
5	 **19**	 **20**	69%
6	 **21**	 **22**	52%
7	 **23**	 **24**	49%[c]

[a] Cycloadditions were carried out by treatment of the ketone precursor with excess MeNHOH·HCl or BnNHOH·HCl and pyridine in ethanol in the presence of 4 Å molecular sieves, initially at rt and then at 45−65 °C. [b] See ref 9. [c] CH_2Cl_2 was used as solvent; no molecular sieves were employed.

to independent cycloaddition reactions (entries 2 and 3, Table 1). In each case, a single adduct different from **11** was isolated; identification of these adducts as **13** and **15** confirmed that no epimerization had taken place under the reaction conditions. Regarding yields, the efficient cycloadditions of **12** (77%) and **14** (65%), in which the dipolarophile must approach the nitrone molecule from its more hindered concave face, are especially noteworthy.

These results also clearly show that the stereochemistry of the reaction can be controlled by tethering the dipolarophile to one of the sugar hydroxyl groups. Use of the α C4-hydroxyl for this purpose, as in **10**, allowed the exclusive formation of the C3*S* adduct **11**, while tethering the allyl group to the *β* C4-hydroxyl, as in **12** and **14**, gave the C3*R* isomers **13** and **15**, respectively.

Having established the feasibility of the cycloaddition procedure, we next evaluated its suitability for the formation of the N−C8a bond in (−)-tetrodotoxin. Treatment of **16** with MeNHOH·HCl and pyridine in CH_2Cl_2 gave the desired cycloadduct **17** in good yield (79%, entry 4, Table 1).[9] The more versatile *N*-benzyl derivative **18** could be prepared similarly. Except for the C11-hydroxymethyl group, all the carbon atoms in TTX are present in intermediates **17** and **18**, and those destined to form the C4a, C7, C8, C8a and C9 centers already possess the required configuration (Figure 2).

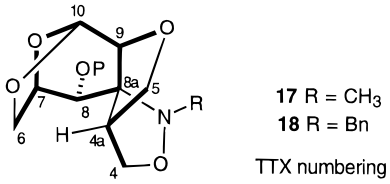


Figure 2. Alternative view of **17** and **18** to facilitate comparison with (−)-tetrodotoxin.

Next, we investigated the utility of the 1,3-dipolar cycloaddition for the construction of a nitrogen-bearing quaternary center at position C5 of the α-D-glucofuranose derivative **19**.[10,11] The tetracyclic adduct **20** was obtained as the main product in 69% yield, the formation of the bridged isoxazolidine being in keeping with the results obtained for cycloaddition of structurally related aldonitrones.[12,13]

Finally, two additional cycloaddition experiments were performed (entries 6 and 7, Table 1). Although the yields for these reactions are moderate, they serve to illustrate the potential of this methodology for the preparation of a variety of heterocyclic and carbocyclic systems.

In summary, we have shown that nitrones derived from ketosugars can undergo both inter- and intramolecular 1,3-dipolar cycloadditions to afford carbohydrate derivatives containing nitrogenated quaternary centers at various positions (e.g. C4 in **8**, C3 in **11**, and C5 in **20**). It was also shown that the stereochemistry of the reaction could be efficiently controlled by tethering the dipolarophile to a sugar hydroxyl group. Thus this methodology was successfully used to prepare synthetic precursors of (−)-tetrodotoxin, and to form a quaternary center at C5 of a glucofuranose derivative, which may have implications for the synthesis of (+)-lactacystin. Additional cycloaddition reactions examined (entries 6 and 7, Table 1) extend the utility of this method for the preparation of other heterocyclic and carbocyclic systems from carbohydrates.[2b]

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Supporting Information Available: Experimental procedures and characterization data are provided for new compounds (34 pages).

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(9) A solution of ketone **16** (564 mg), MeNHOH·HCl (474 mg, 300 mol %), and dry pyridine (0.52 mL, 350 mol %) in dry CH_2Cl_2 (16 mL) was refluxed for 28 h. The organic phase was washed with water, dried, and concentrated. Flash chromatography of the residue afforded isoxazolidine **17** (485 mg, 79%).

(10) Formation of a nitrogenated quaternary center at position C5 of a glucofuranose derivative analogous to **19** (by trichloroacetimidate rearrangement), and final conversion to (+)-lactacystin, has recently been reported: Chida, N.; Takeoka, J.; Tsutsumi, N.; Ogawa, S. *J. Chem. Soc., Chem. Commun.* **1995**, 793.

(11) In the course of this work, a related 1,3-dipolar cycloaddition was reported for the furanose of nucleoside derivatives: Rong, J.; Roselt, P.; Plavec, J.; Chaltopadhyaya, J. *Tetrahedron* **1994**, *50*, 4921.

(12) (a) Datta, S.; Chattopadyay, P.; Mukhopadhyay, T.; Bhattacharjya, A. *Tetrahedron Lett.* **1993**, *34*, 3585. (b) Shing, T. K. M.; Wong, C.; Yip, T. *Tetrahedron: Asymmetry* **1996**, *7*, 1323.

(13) The high yield obtained in the cycloaddition of **19** strongly suggests that a synthetic approach to (+)-lactacystin and/or lactacystin analogues based on this methodology would be viable (see also note 10).