JOC Article

Intra- and Intermolecular 1,3-Dipolar Cycloaddition of Sugar Ketonitrones with Mono-, Di-, and Trisubstituted Dipolarophiles

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The 1,3-dipolar cycloaddition of sugar ketonitrones is a useful synthetic procedure to build up nitrogenated quaternary centers in terms of scope (substrate, dipolarophile, inter- and intramolecular versions), yield, and regio- and stereoselectivity. The hybrid ONIOM (B3LYP/6-31G(d):AM1) theoretical method followed by single-point energy calculations at the B3LYP/6-31G(d) level adequately perform to model this cycloaddition for the relatively large ketosugar precursors commonly used.

Introduction

Since their introduction by Huisgen in 1960,[1] the 1,3-dipolar cycloaddition remains the single most powerful method for the construction of five-membered heterocycles.[2,3] Despite its early discovery and considerable posterior development, some aspects of this transformation remain relatively unattended, even for nitrones, the most commonly applied 1,3-dipole. In particular, use of ketonitrones has been rare, despite their synthetic potential,[4] when compared with the extensive studies and broad synthetic applications described for nitrones derived from aldehydes. Such a trend is especially pronounced in the carbohydrate field where most efforts were dedicated to the study and exploitation of the reaction on sugar aldonitrones,[5] while for nitrones derived from ketosugars the process, schematically il-

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(1) For an account on Rolf Huisgen's contributions to organic chemistry emphasizing 1,3-dipolar cycloaddditions, see: Sustmann, R. *Heterocycles* **1995**, *40*, 1−18. The entire issue is specially devoted to R. Huisgen.

(2) For general treatises on 1,3-dipolar cycloadditions, see: (a) *Cycloaddition Reactions in Organic Synthesis*; Carruthers, W., Ed.; Tetrahedron Organic Chemistry Series; Pergamon Press: New York, 1990; Vol. 8, pp 269−314. (b) Padwa, A. Intermolecular 1,3-Dipolar Cycloaddition. In *Comprehensive Organic Synthesis*; Trost, B., Ed.; Pergamon Press: New York, 1992; Chapter 4.9, pp 1069−1109. Wade, P. A. *Intramolecular 1,3-Dipolar Cycloadditions.* In *Comprehensive Organic Synthesis*; Trost, B., Ed.; Pergamon Press: New York, 1992; Chapter 4.10, pp 1111−1168 .See also: (c) *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press, Inc.: London, 1988; Vol. 1; 1990; Vol. 2; 1993; Vol. 3. For metal-catalyzed 1,3-dipolar cycloadditions, see: (d) Gothelf, K. V. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jorgensen, K. A., Eds.; Wiley-VCH: Weinheim, 2002; Chapter 6, pp 211−247. Kanemasa, S. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jorgensen, K. A., Eds.; Wiley-VCH: Weinheim, 2002; Chapter 7, pp 249−300. For reviews on the 1,3-dipolar cycloaddition of nitrones, see: (e) Frederickson, M. *Tetrahedron* **1997**, *53*, 403−425. (f) Confalone, P. N.; Huie, E. M. *Org. React.* **1988**, *36*, 1−173. (g) Torseel, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; Feuer, H., Ed.; VCH: Weinheim, 1988. For a recent review on asymmetric 1,3-dipolar cycloadditions, see: (h) Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *863*, 3−909.

(3) The mechanism of the 1,3-dipolar cycloaddition is discussed from a historical perspective (1935−1995) in: (a) Houk, K. N.; González, J.; Li, Y. *Acc. Chem. Res.* **1995**, *28*, 81−90. See also: Valentin, C. D.; Freccero, M.; Gandolfi, R.; Rastelli, A. *J. Org. Chem.* **2000**, *65*, 6112−6120.

(4) (a) White, J. D.; Blakemore, P. R.; Korf, E. A.; Yokochi, A. F. T. *Org. Lett.* **2001**, *3*, 413−415, (b) Snider, B. B.; Lin, H. *Org. Lett.* **2000**, *2*, 643−646, (c) Williams, G. M.; Roughley, S. D.; Davies, J. E.; Holmes, A. B. *J. Am. Chem. Soc.* **1999**, *121*, 4900−4901. (d) Werner, K. M.; de los Santos, J. M.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1999**, *64*, 686−687; 4865−4873. (e) Snider, B. B.; Lin, H. *J. Am. Chem. Soc.* **1999**, *121*, 7778−7786. (f) Marotta, E.; Righi, P.; Rosini, G. *Tetrahedron Lett.* **1998**, *39*, 1041−1044.

(5) For the 1,3-dipolar cycloaddition of glycosyl aldonitrones, see: (a) Fisera, L.; Al-Timari, V. A. R.; Ertl, P. In *Cycloaddition Reactions in Carbohydrate Chemistry*; Giuliano, R. M., Ed.; ACS Symposium Series No. 494; American Chemical Society: Washington, DC, 1992; Chapter 11. For the intramolecular cycloaddition of sugar-derived aldonitrones, see: (b) Sharma, G. V. M.; Reddy, K. R.; Sankar, A. R.; Kunwar, A. C. *Tetrahedron Lett.* **2001**, *42*, 8893−8896. (c) Shing, T. K. M.; Zhong, Y.-L. *Tetrahedron* **2001**, *57*, 1573−1579. (d) Pal, A.; Bhattacharjya, A.; Mukhopadhyay, R. *Tetrahedron Lett.* **2000**, *41*, 10135−10139. (e) Collins, P. M.; Ashwood, M. S.; Eder, H.; Wright, S. H. B.; Kennedy, D. J. *Tetrahedron Lett.* **1990**, *31*, 2055−2058. (f) Ferrier, R. J.; Prasit, P. *J. Chem. Soc., Chem. Commun.* **1981**, 983−985. (g) Bernet, V. B.; Vasella, A. *Helv. Chim. Acta* **1979**, *62*, 1990−2016 and references therein. For intermolecular cycloadditions of sugar aldonitrones, see, for example: (h) Borrachero, P.; Cabrera-Escribano, F.; Diáñez, M. J.; Estrada, M. D.; Gómez-Guillén, M.; Castro, A. L.; Pérez-Garrido, S.; Torres, M. I. *Tetrahedron: Asymmetry* **2002**, *13*, 2025−2038. (i) Kuban, J.; Kolarovic, A.; Fisera, L.; Jager, V.; Humpa, O.; Prónayová, N.; Ertl, P. *Synlett* **2001**, 1862−1865. (j) Silva, A. M. G.; Tomé, A. C.; Neves, M. B. P. M. S.; Silva, A. M. S.; Cavaleiro, J. A. S.; Perrone, D.; Dondoni, A. *Tetrahedron Lett.* **2002**, *43*, 603−605. For a discussion of the applications of cycloaddition reactions in the transformation of carbohydrate derivatives into functionalized cyclohexanes and cyclopentanes, see: (k) Ferrier, R. J.; Middleton, S. *Chem. Rev.* **1993**, *93*, 2779−2831. For the application of the 1,3-dipolar cycloaddition of sugar aldonitrones to prepare cycloheptane derivatives, see: (l) Bar, N. C.; Roy, A.; Achari, B.; Mandal, S. B. *J. Org. Chem.* **1997**, *62*, 8948−8951. (m) Marco-Contelles, J.; De Opazo, E. *J. Carbohydr. Chem.* **2002**, *21*, 201−218. For reviews on asymmetric 1,3 dipolar cycloadditions, including sugar-derived aldonitrones, see ref 2e,h.

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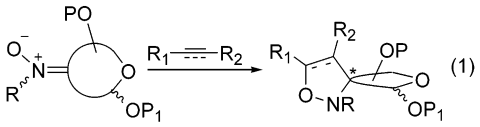
lustrated in eq 1 for the intermolecular case on a protected cyclic sugar, remained unexplored.[6,7]



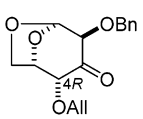
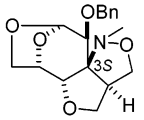
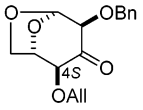
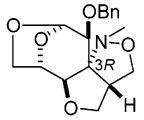
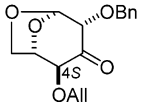
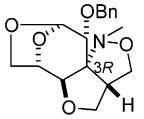
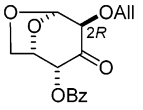
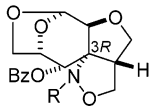
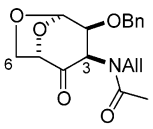
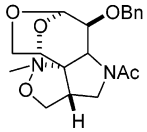
Noticing the potential of this transformation to build nitrogenated quaternary centers on synthetic precursors of biologically relevant targets having such structural motif, we carried out a preliminary study with several allyl-substituted ketohexoses. Our results clearly demonstrated that the intramolecular cycloaddition of sugar-derived ketonitrones was indeed a suitable process to prepare highly oxygenated heterocyclic systems (Table 1; Table 2, entry 1). We also reported one example on the a priori more difficult intermolecular version (Table 3, entry 1).[8] Notwithstanding the good results obtained in the preliminary study using plain allyl ethers, full application of the methodology would require in general the use of more substituted dipolarophiles. Moreover, while the intramolecular approach initially appears attractive in terms of yield and regio- and stereoselectivity, the intermolecular version could provide a potentially superior strategy. In this last case, tethering and untethering operations would not be required, thus allowing quick exploration of a nitrone cycloaddition as a key step in a synthetic pathway by confronting such nitrone to a battery of dipolarophiles.

We have consequently extended our initial work to evaluate the inter- and intramolecular cycloaddition of a selected group of ketofuranonitrones using differently substituted dipolarophiles. A theoretical study was also conducted to explain the observed regio- and stereochemistry when starting from 3-*O*-allyl-5-oxo-*β*-D-glucofuranoses.

Results and Discussion

Cycloaddition Precursors: Selection and Preparation. As can be seen in Scheme 1, preparation of (−)-tetrodotoxin (**1**),[9] (+)-lactacystin (**2**),[10] and (+)-myriocin (**3**)[11] from suitable protected sugar derivatives, e.g., **I**, **II**, and **III**, would require, as one of the key steps, the formation of a nitrogenated quaternary center, either at position C3 of **I** (later C8a in TTX) or at C5 in both **II** and **III** (meant to be C4 of lactacystin and C2 of myriocin, respectively). Accordingly, most of the ketosugar precursors we selected for this study (Chart 1) were C3- and C5-keto derivatives. A brief description of their preparation follows.

TABLE 1. Intramolecular Cycloaddition of Ketopyranonitrones

Entry	Ketone precursor	Cycloadduct Isolated yield
1	 **4a**	 **19a** 78%
2	 **4b**	 **19b** 77%
3	 **4c**	 **19c** 65%
4	 **4d**	 **19d** R = CH_3 79% **19d'** R = Bn 61%
5	 **4e**	 **19e** 52%

As for the ketopyranoses, ketone **4a** was prepared from 1,6-anhydro-2,3-*O*-isopropylidene-*β*-D-mannopyranose (**6**)[12] by efficient and uneventful two-step conversion to the known diol **8a**,[13] followed by selective benzylation at C2 and final oxidation (Scheme 2). Room-temperature epimerization of **4a** with DBU in toluene afforded ketones **4b**

(6) For a recent review on the 1,3-dipolar cycloaddition of carbohydrate derived aldo and ketonitrones covering the period 1990−June 2002, see: Osborn, H. M. I.; Gemmel, N.; Harwood, L. M. *J. Chem. Soc., Perkin Trans. 1* **2002**, *22*, 2419−2438.

(7) At the outset of our studies, we found only a single application of this transformation to sugar ketonitrones: Tronchet, J. M. J.; Mihaly, M. E. *Helv. Chim. Acta* **1972**, *55*, 1266−1271. Chattopadhyaya subsequently reported on the 1,3-dipolar cycloaddition of thymidine-derived ketonitrones: (a) Hossain, N.; Papchikhin, A.; Plavec, J.; Chattopadhyaya, J. *Tetrahedron* **1993**, *49*, 10133−10156. (b) Rong, J.; Roselt, P.; Plavec, J.; Chattopadhyaya, J. *Tetrahedron* **1994**, *50*, 4921−4936.

(8) Torrente, S.; Noya, B.; Paredes, M. D.; Alonso, R. *J. Org. Chem.* **1997**, *62*, 6710−6711.

(9) (−)-Tetrodotoxin is a natural toxin that selectively blocks voltage-gated sodium channels with high affinity: Tetrodotoxin, Saxitoxin and the Molecular Biology of the Sodium Channel. In *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 acomplished: (a) Kishi, Y.; Fukuyama, T.; Aratani, M.; Nakatsubo, F.; Goto, T.; Inoue, S.; Tanino, H.; Sugiura, S.; Kakoi, H. *J. Am. Chem. Soc.* **1972**, *94*, 9219−9221. For other synthetic studies, see: (b) Nishikawa, T.; Urabe, D.; Yoshida, K.; Iwabuchi, T.; Asai, M.; Isobe, M. *Org. Lett.* **2002**, *4*, 2679−2682 and references therein. For our own synthetic efforts, see: (c) Noya, B.; Paredes, M. D.; Ozores, L.; Alonso, R. *J. Org. Chem.* **2000**, *65*, 5960−5968. (d) Noya, B.; Alonso, R. *Tetrahedron Lett.* **1997**, *38*, 2745−2748. See also ref 14.

(10) (+)-Lactacystin, initially reported as the first nonprotein neurotrophic factor due its biological relevance to its unique ability to specifically inhibit the 20S proteasome: (a) Omura, S.; Fujimoto, T.; Otoguro, K.; Matsuzaki, K.; Moriguchi, R.; Tanaka, H.; Sasaki, Y. *J. Antibiot.* **1991**, *44*, 113−116. (b) Fenteany, G.; Schreiber, S. L. *J. Biol. Chem.* **1998**, *273*, 8545−8548. (c) Fenteany, G.; Standaert, R. F.; Lane, W. S.; Choi, S.; Corey, E. J.; Schreiber, S. L. *Science* **1995**, *268*, 726−731. For recent reviews, mainly focused on synthetic aspects, see: (d) Masse, C. E.; Morgan, A. J.; Adams, J.; Panek, J. S. *Eur. J. Org. Chem.* **2000**, *14*, 2513−2528. (e) Corey, E. J.; Li, W.-D. *Chem. Pharm. Bull.* **1999**, *47*, 1−10.

TABLE 2. Intramolecular Cycloaddition of Ketofuranonitrones

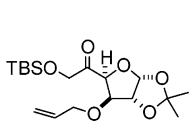
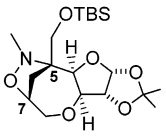
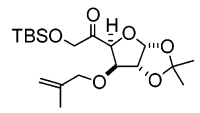
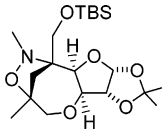
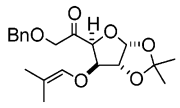
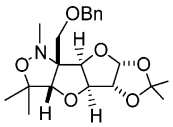
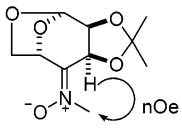
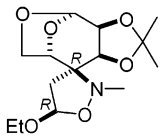
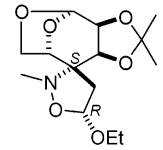
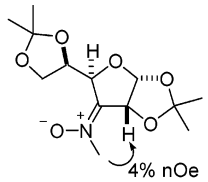
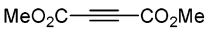
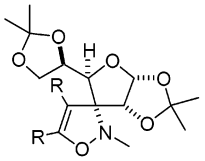
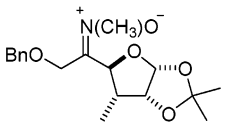
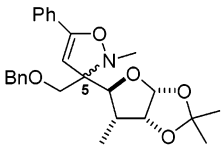
Entry	Ketone precursor	Cycloadduct Isolated yields
1	 **4i**	 **19i** 69%
2	 **4j**	 **19j** 37%
3	 **4k**	 **19k** 43%

TABLE 3. Intermolecular Cycloaddition of Ketonitrones 5f, 5g, and 5l

Entry	Ketonitrone Dipolarophile	Cycloadduct Isolated yield
1	 **5f** 	 **19f** 62%  **19f'** 11%
2	 **5g** 	 **19g** 68% R = CO_2Me
3	 **5l**	 **19l** 60%

and **4c** in 42% and 26% yields, respectively. Ketone **4d** was synthesized through a sequence similar to that employed for **4a** through intermediates **8b**[14] and **9b** (Scheme 2). Ketone **4e** was prepared from epoxide **10**,[15] through successive benzylation to **11**,[16] epoxide opening with *N*-allylamine, *N*-acylation, and C4-oxidation (Scheme 3). In our case, we first obtained **10** as a side product on preparing 1,6-anhydro-β-D-mannopyranose by selective C6 tosylation of β-D-mannose followed by base-induced internal S_N2 displacement by the anomeric hydroxyl group.[12,17] To get larger quantities of **10**, we found it convenient to use an excess of tosyl chloride.[18] Although we did not optimize this process for the preparation of **10** because we also required 1,6-anhydro-β-D-mannopyranose as the precursor of **6**, researchers using **10** with preparative purposes[19] could find it interesting to further study this one-pot, two-step procedure as an alternative to the standard five-step protocol developed by Cerny.[15] Ketopyranose **4f**[20] and ketofuranoses **4h**[21] and **4l**[22] are known compounds, while ketone **4g** is commercially available.

(11) For the biological significance of myriocin, see, for example: Chen, J. K.; Lane, W. S.; Schreiber, S. L. *Chem. Biol.* **1999**, *6*, 221−235 and references therein. For its total synthesis, see: (a) Banfi, L.; Beretta, M. G.; Colombo, L.; Gennari, C.; Scolastico, C. *J. Chem. Soc., Chem. Commun.* **1982**, 488−490. (b) Banfi, L.; Beretta, M. G.; Colombo, L.; Gennari, C.; Scolastico, C. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1613−1619. (c) Yosikawa, M.; Yokokawa, Y.; Okuno, Y.; Murakami, N. *Chem Pharm. Bull.* **1994**, *42*, 994−996; *Tetrahedron* **1995**, *51*, 6209−6228. (d) Sano, S.; Kobayashi, Y.; Kondo, T.; Takebayashi, M.; Maruyama, S.; Fujita, T.; Nagao, Y. *Tetrahedron Lett.* **1995**, *36*, 2097−2100. (e) Hatakeyama, S.; Yoshida, M.; Esumi, T.; Iwabuchi, Y.; Irie, H.; Kawamoto, T.; Yamada, H.; Nishizawa, M. *Tetrahedron Lett.* **1997**, *38*, 7887−7890. (f) Oishi, T.; Ando, K.; Inomiya, K.; Sato, H.; Iida, M.; Chida, N. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1927−1947. (g) Lee, K.-Y.; Oh, C.-Y.; Kin, Y.-H.; Joo, J.-E.; Ham, W.-H. *Tetrahedron Lett.* **2002**, *43*, 9361−9363. Formal synthesis: (h) Rao, A. V. R.; Gurjar, M. K.; Devi, T. R.; Kumar, K. R. *Tetrahedron Lett.* **1993**, *34*, 1653−1656. (i) Deloisy, S.; Thang, T. T.; Olesker, A.; Lukacs, G. *Tetrahedron Lett.* **1994**, *35*, 4783−4786. (j) Deloisy, S.; Thang, T. T.; Olesker, A.; Lukacs, G. *Bull. Chem. Soc.* **1996**, *133*, 581−585. (k) Torrente, S.; Alonso, R. *Org. Lett.* **2001**, *3*, 1985−1987.

(12) Zottola, M. A.; Alonso, R.; Vite, G. D.; Fraser-Reid, B. *J. Org. Chem.* **1989**, *54*, 6123−6125. Although expensive, 1,6-anhydro-2,3-*O*-isopropylidene-β-D-mannopyranose is now commercially available from various vendors.

(13) For the alternative removal of the isopropylidene group of **7a** with pyridinium *p*-toluenesulfonate to give **8a**, see: Van Rijsbergen, R.; Anteunis, M. J. O.; De Bruyn, A. *J. Carbohydr. Chem.* **1983**, *2*, 395−404.

(14) Alonso, R. A.; Burgey, C. S.; Rao, B. V.; Vite, G. D.; Vollerthun, R.; Zottola, M. A.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1993**, *115*, 6666−6672.

(15) Dolezalova, J.; Trnka, T.; Cerny, M. *Collect. Czech. Chem. Commun.* **1982**, *47*, 2415−2422. Cerny, M.; Stanek, J., Jr. *Adv. Carbohydr. Chem.* **1977**, *34*, 23−177.

(16) (a) Mikkelsen, L. M.; Krintel, S. L.; Jimenez-Barbero, J.; Skrydstrup, T. *J. Org. Chem.* **2002**, *67*, 6297−6308. (b) Kroutil, J.; Trnka, T.; Budesinsky, M.; Cerny, M. *Collect. Czech. Chem. Commun.* **1998**, *63*, 813−825.

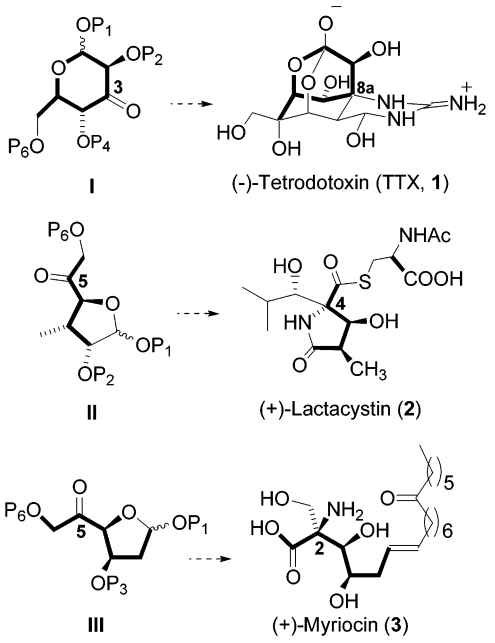
(17) Epoxide **10** would be the result of double tosylation of D-mannose at C6 and C3, followed by base-induced 1,6-anhydro bridge formation and (most likely, subsequent) 3,4-epoxide formation.

(18) Using 2.2 equiv of TsCl, we obtained yields of **10** up to 20% (Els de Hoog, E. Student from the University of Utrecht, unpublished results).

(19) 1,6:3,4-Dianhydro-β-D-altropyranose (**10**) is a useful building block for the preparation of a variety of mannose derivatives. See, for example: (a) Reference 16a. (b) Holla, E. W.; Sinnwell, V.; Klaffke, W. *Synlett* **1992**, *5*, 413−414.

(20) Horton, D.; Jewell, J. S. *Carbohydr. Res.* **1966**, *2*, 251−60. Horton, D.; Jewell, J. S.; Just, E. K.; Wander, J. D. *Carbohydr. Res.* **1971**, *18*, 49−56. Lindberg, B. *Methods Carbohydr. Chem.* **1972**, *6*, 323−325. Fischer, J. C.; Horton, D. *Carbohydr. Res.* **1977**, *59*, 477−503.

SCHEME 1[a]



[a] Boldfaced bonds identify corresponding fragments on targets **1**−**3** and their ketosugar precursors **I**−**III**.

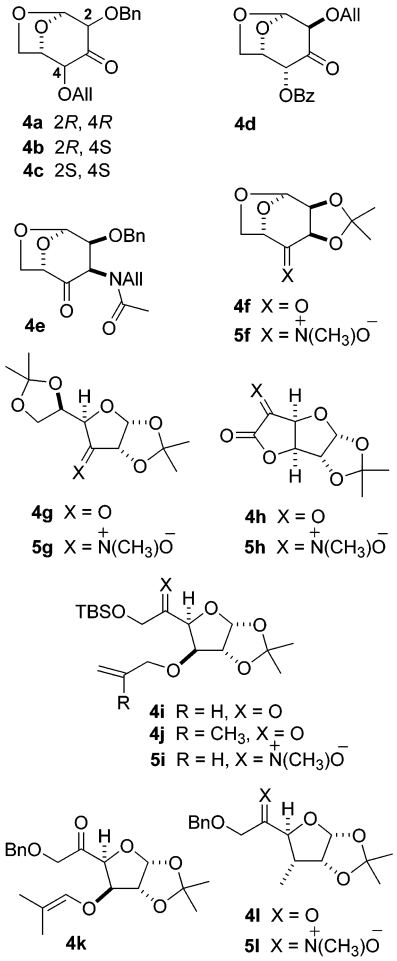
Ketofuranose derivatives **4i**−**k** with mono-, di-, and trisubstituted olefins tethered at O3 were prepared from commercial 1,3−5,6-diisopropylidene-β-D-glucofuranose (DAG, **15**) through known **16b**,[23] **16c**,[23] and **18a**[24] using standard transformations (Scheme 4).

Intramolecular Dipolar Cycloadditions. As previously described, treatment of ketopyranoses **4a**−**c** with *N*-methyl hydroxylamine hydrochloride and pyridine in ethanol in the presence of 4 Å molecular sieves, initially at room temperature and then at 45−55 °C, led to cycloadducts **19a**, **19b**, and **19c** in 78%, 77%, and 65% yields (Table 1). In particular, the efficient cycloadditions of **4b** and **4c**, in which the dipolarophile must approach the intermediate nitrone from its more hindered concave face, were especially noteworthy.

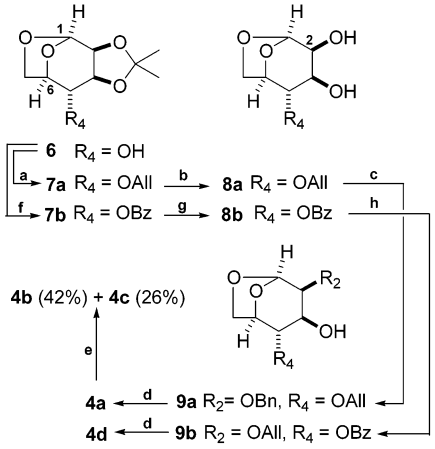
Of outmost importance for synthetic purposes, no α-epimerization occurred under the reaction conditions. As a consequence, a single stereoisomer resulted from each of the ketosugar precursors **4a**, **4b**, and **4c**; i.e., the configuration at the newly created quaternary center at C3, *S* in **19a**, and *R* in **19b** and **19c** was completely determined by that of the tethering center, C4, at the cycloaddition precursor: *R* in **4a** and *S* in **4b** and **4c**.

Similarly, the configuration at C2 of the 2-*O*-allyl mannopyranose derivative **4d** fully dictated the resulting configuration at C3 on its cycloadduct **19d**. Use of *N*-benzylhydroxylamine hydrochloride to generate the ketonitrone from **4d** led to a similar result, and cycloadduct **19d′** was obtained instead. At this point, we decided to address the N−O bond cleavage, a synthetic

CHART 1. Cycloaddition Precursors



SCHEME 2[a]



[a] Reagents: (a) (i) NaH, THF, (ii) CH_2=$CHCH_2Br$, *n*-Bu_4NI, 98%; (b) $AcOH_{aq}$ (30%), quant; (c) (i) *n*-Bu_2SnO, PhH, Δ, (ii) BnBr, *n*-Bu_4NI, Δ, 53%; (d) Dess−Martin periodinane, *t*-BuOH, CH_3CN, 92% for **4a**, 96% for **4d**; (e) DBU, $PhCH_3$, rt; (f) Py, BzCl, 0 °C → rt, 99%, ref 14; (g) $AcOH_{aq}$, quant., ref 14; (h) (i) *n*-Bu_2SnO, PhH, Δ, (ii) CH_2=$CHCH_2Br$, *n*-Bu_4NI, Δ, 85%.

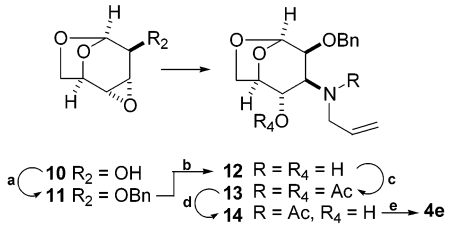
(21) Yoshikawa, M.; Murakami, N.; Yokokawa, Y.; Inoue, Y.; Kuroda, Y.; Kitagawa, I. *Tetrahedron* **1994**, *50*, 9619−9628. Csuk, R.; Schaade, M. *Tetrahedron* **1994**, *50*, 3333−48. Anzeveno, P. B.; Creemer, L. J. *Tetrahedron Lett.* **1990**, *31*, 2085−2088.

(22) (a) Chida, N.; Takeoka, J.; Ando, K.; Tsutsumi, N.; Ogawa, S. *Tetrahedron* **1997**, *53*, 16287−16298. (b) Oikawa, Y.; Tanaka, T.; Horita, K.; Noda, I.; Nakajima, N.; Kakusawa, N.; Hamada, T.; Yonemitsu, O. *Chem. Pharm. Bull.* **1987**, *35*, 2184−2195.

(23) Arnold, T.; Orschel, B.; Reissig, H. U. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1033−1035.

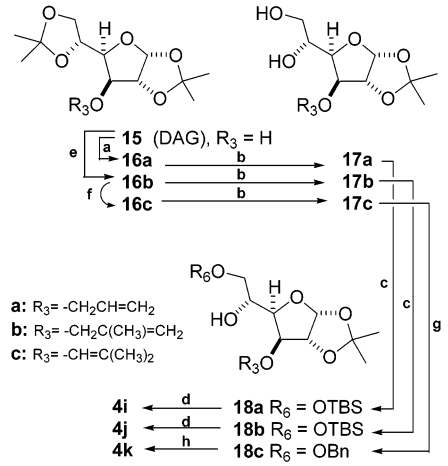
(24) Das, S. K.; Mallet, J.-M.; Esnault, J.; Driguez, P.-A.; Duchaussoy, P.; Sizun, P.; Herault, J.-P.; Herbert, J.-M.; Petitou, M.; Sinay, P. *Chem. Eur. J.* **2001**, *7*, 4821−4834.

SCHEME 3[a]



[a] Reagents: (a) (i) NaH, THF, (ii) BnBr;[16a] (b) CH_2=$CHCH_2NH_2$, DMF, 120 °C, 65%; (c) Ac_2O, Et_3N, DMAP, AcOEt, 91%; (d) K_2CO_3, CH_3OH, 98%; (e) PCC, CH_2Cl_2, 55%.

SCHEME 4[a]



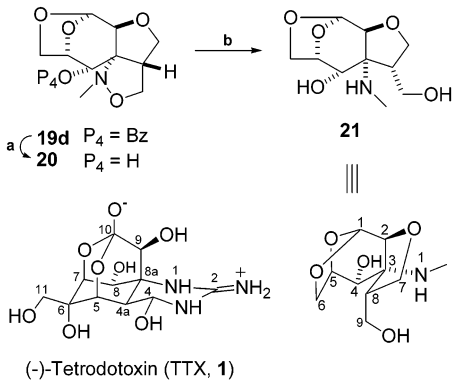
[a] Reagents: (a) (i) NaH, THF, (ii) CH_2=$CHCH_2Br$, *n*-Bu_4NI, 98%;[36] (b) $AcOH_{aq}$ (30%), quant for **17a**,[25] 98% for **17b**, quant for **17c**; (c) imidazole, TBSCl, DMF, 70% for **18a**,[24] 90% for **18b**; (d) PCC, CH_2Cl_2, 80% for **4i**, 58% for **4j**; (e) (i) NaH, THF, (ii) CH_2=$C(CH_3)CH_2Br$, *n*-Bu_4NI, 99%; (f) DMSO, K-*t*-BuO, 100 °C, 78%; (g) (i) *n*-Bu_2SnO, PhH, Δ, (ii) BnBr, *n*-Bu_4NI, Δ, 55%; (h) Dess−Martin periodinane, *t*-BuOH, CH_3CN, 70%.

operation needed at some time along the synthetic scheme, should this transformation be used as a key step to prepare (−)-tetrodotoxin. While all our attempts to reduce the N−O bond in **19d** and in its silylated analogue at C4 (Scheme 5, P_4 = *t*-$BuPh_2Si$) gave either unreacted starting material or mixtures of products,[25] the isoxazolidine ring could be successfully opened in alcohol **20** on treatment with Zn dust in 60% aqueous acetic acid. Noteworthy, intermediate **21** has every carbon atom required for the natural product except C2 and C11. Besides, its centers at positions 2, 3, 4, and 5 all have the required configuration for C9, C8a, C8, and C7 in the toxin, and positions 7 and 9 are adequately differentiated to make position 8 adequate precursor for C4a (Scheme 5).

As the last ketopyranose for this study, we selected the derivative **4e** as a particularly difficult test for the transformation because of the extreme steric hindrance associated with the pseudoaxial disposition of the nitrogen substituent at C3 in close proximity to the C6 ether-bridge. Although the yield was sensibly lower than for the previous cases, the tetracyclic pyrrolidine **19e** was indeed isolated in 52%.

Next, we investigated the utility of the 1,3-dipolar cycloaddition for the construction of a nitrogen-bearing quaternary center at position C5 with ketofuranose **4i**.

SCHEME 5[a]



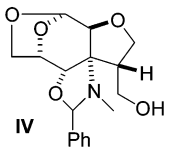
[a] Reagents: (a) $NaOH_{aq}$ 1%−CH_3OH (1:9), 98%; (b) Zn, $AcOH_{aq}$ 60%, Δ, 81%.

While formation of up to six cycloadducts is possible, we only observed the formation of the tetracyclic bridged oxepane **19i** (Table 2, entry 1, 69%), and none of its stereoisomer with inverted configuration at C5 and C7, or any of the four alternative fused tetrahydropyrane isomers of type **T** (Scheme 6). Cycloaddition of **4j**, where the dipolarophile is now disubstituted, also took place, although in a comparatively diminished yield (37%). The result was, however, analogous to that of **4i** in terms of regio- and stereoselectivity: we could only isolate the bridged-oxepane cycloadduct **19j** (Table 2, entry 2). Trisubstitution was also allowed, and the intramolecular cycloaddition of **4k** proceeded exclusively to the fused isoxazolidine−tetrahydrofuran system **19k** (Table 2, entry 3).

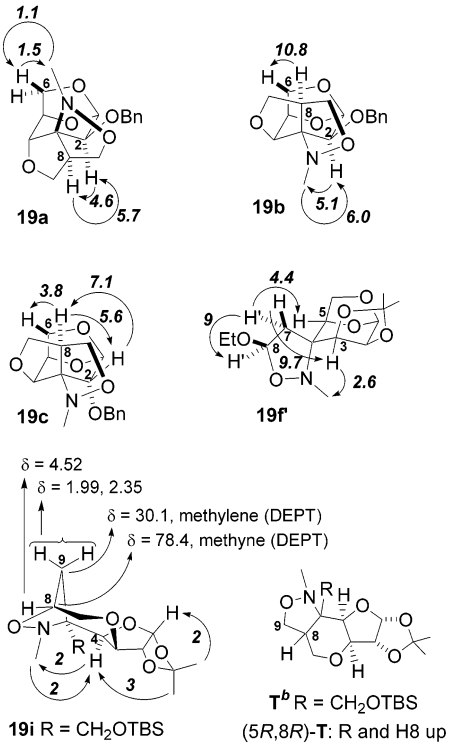
Through this work, structural determination of the cycloadducts was based on extensive NMR spectroscopy, particularly 1D NOE and 2D NOESY experiments (e.g., Scheme **6**), which also allowed for unequivocal nuclear resonance assignments. Identification of cycloadducts **19i** and **19j** as bridged-oxepanes instead of fused tetrahydropyranes **T**, directly derives from analysis of their NMR signals corresponding to positions 8 and 9 (Scheme **6** for **19i**, Experimental Section for **19j**).

Intermolecular Cycloadditions. Our first experiments for the intermolecular version of the cycloaddition

(25) Conditions tried for **19d** include: catalytic hydrogenation with either Pd/C or $Pd(OH)_2$/C, Zn/AcOH, Al/Hg, Na/Hg, and Sm_2I. Besides unreacted **19d** (30−90%), we could only isolate and identify oxazolidine **IV**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.41 (m, 5H), 5.51 (d, J = 2.8 Hz, 1H), 4.80 (s, 1H), 4.70 (m, 1H), 4.50 (s, 1H), 4.27 (dd, $J \approx J'$ = 8.4 Hz, 1H), 4.15 (d, J = 2.8 Hz, 1H), 4.03−3.96 (m, 2H), 3.86 (dd, J = 11.7 Hz, J' = 6.2 Hz, 1H), 3.80−3.73 (m, 2H), 3.77 (m, 2H), 3.34 (s ancho, 1H), 2.77 (m, 1H), 2.18 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 137.6, 129.7, 128.7, 127.8, 100.1, 97.5, 80.8, 75.6, 75.5, 71.4, 70.9, 65.4, 61.4, 46.6, 32.2. The silylated analogue at C4 of **19d** (Scheme 5, P_4 = *t*-$BuPh_2Si$) was inert to catalytic hydrogenation −Pd/C and $Pd(OH)_2$−, and on treatment with either Zn in refluxing TFA−EtOH (1:1), or Na/naphthalene in THF. Complex mixtures were obtained with $NiCl_2$ and $LiAlH_4$ at low temperature. Reduction with Zn (400 mol %) in refluxing 60% aqueous acetic acid was not reproducible and rendered variable mixtures of silylated and desilylated, reduced and nonreduced products of difficult separation.



SCHEME 6[a]

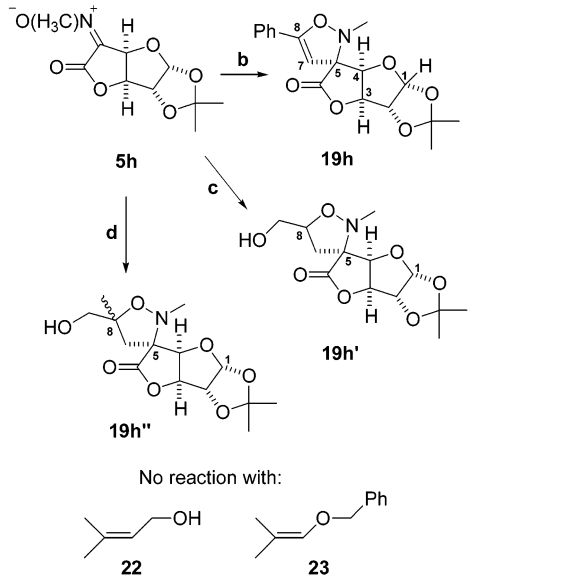


[a] Selected NOE enhancements (%) for representative cycloadducts (*italic*). [b]Non-observed fused-tetrahydropyran-type compounds potentially obtainable from 3-*O*-allyl-5-ketonitrones (only oxepanes **19i**,**j** were isolated).

were carried out with ketonitrone **5f** (Chart 1), obtained as a single stereoisomer (*E*) in the form of a white solid by treatment of known **4f** with MeNHOH·HCl in pyridine at 5 °C (97%). Gratifyingly, reaction of **5f** with ethyl vinyl ether in refluxing benzene for 8 h took place with complete regioselectivity, a result expected both from electronic and steric effects, to give cycloadducts **19f** and **19f′** in an acceptable 73% combined yield (Table 3, entry 1). Formation of the nitrogenated quaternary center proceeded, however, with modest stereoselectivity (**19f**/**19f′** = 6:1). To gain further insight into the reaction course, we independently subjected each of these products to the cycloaddition conditions; however, they were recuperated unaltered. It thus appears that the reaction is under kinetic control, and that the major cycloadduct **19f** is predominantly formed by the quicker reaction of the dipolarophile with the less hindered face of **5f**. Although irrelevant for most synthetic applications, it was curious to observe that the acetalic center was exclusively generated with the *R* configuration for both cycloadducts.

Intermolecular cycloaddition was also feasible with both electron-deficient and conjugated dipolarophiles as demonstrated with cyclic and acyclic ketonitrones **5g** and **5l** (Table 3, entries 2 and 3). Reaction of cyclic C3-ketonitrone **5g** with dimethyl acetylenedicarboxylate was completely stereoselective and yielded a single stereoisomer of the 4,5-isoxazoline **19g** in 68% yield. The configuration of the quaternary center was assigned based on ample precedent for the observed face-selectivity in reactions of structurally related systems.[26] On the other hand, treatment of the acyclic C5-ketonitrone **5l** with phenylacetylene gave **19l** in 60% yield. As it could be expected from the acyclic nature of the nitrone, the reaction was now only moderately stereoselective: **19l** was obtained as a 5.6:1 C5-epimeric mixture. We also isolated 26% of ketone **4l** (Chart 1) because of nitrone hydrolysis.

SCHEME 7. Intermolecular Cycloaddition of Ketonitrone 5h[a]



[a] Configuration at C5 on the cycloadducts was secured on the basis of NOE enhancements between H1 and the *N*-methyl group. [b]PhC≡CH, 82%. [c]CH_2=$CHCH_2OH$, 81%. [d]CH_2=$C(CH_3)CH_2OH$, 81%.

To further study the intermolecular reaction, in particular the degree of substitution allowed for the dipolarophile, we next selected the C5 ketonitrone **5h** (Scheme 7), both because of its easy availability (it was prepared as a single stereoisomer in just three steps from cheap commercial D-glucurono-6,3-lactone) and because high face-selectivity was expected for such a rigid tricyclic system. This would in turn facilitate the study while ideally producing attractive synthetic intermediates as single stereoisomers. These expectations were totally satisfied: complete regio- and stereocontrol was indeed observed on treatment of **5h** with phenylacetylene, which reacted only from the exo face of the nitrone. As an additional bonus, the reaction yield was comparatively better than for the previous studied cases; a single cycloadduct **19h** was isolated in 82% yield (Scheme 7). It is worth noting that C7−C8 oxidative cleavage of **19h** would render intermediates with the same pattern of substitution and stereochemistry at C5, C4, and C3 as (+)-myriocin has at C2, C3, and C4.

A similar trend was observed with another monosubstituted dipolarophile, allyl alcohol, and a disubstituted one, 2-methyl-2-propen-1-ol. Yields were high again, and isoxazolidines **19h′** and **19h″** were both obtained in 81% yield. The reaction proceeded with complete regioselectivity: the more substituted end of the dipolarophile ended up joined to the oxygen atom of the intermediate

(26) See, for example: (a) Rosenthal, A.; Sprinzl, M. *Can. J. Chem.* **1969**, *47*, 3941−3946; (b) *Tetrahedron Lett.* **2001**, *42*, 1499−1502.

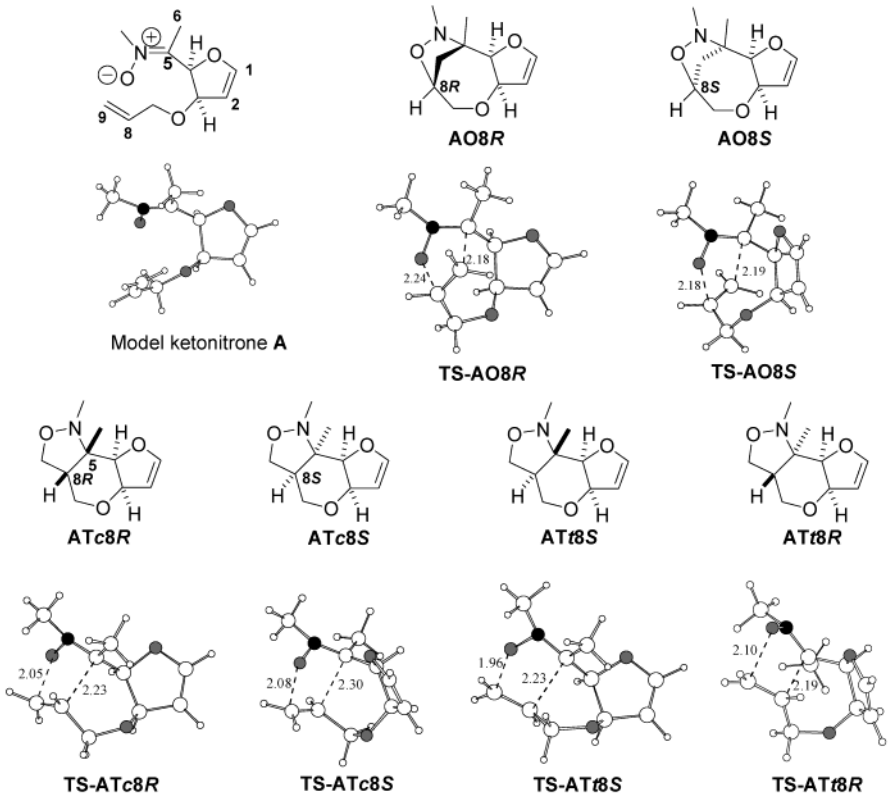


FIGURE 1. Nitrone A (simplified model for ketonitrone **5i**), its lower energy conformer, and its corresponding cycloadducts and transition states (B3LYP/6-31G(d)). Selected interatomic distances in Å.

ketonitrone. The process was also completely stereoselective at C5 in both cases. Regarding the additional stereocenter created at C8 during these two cycloadditions, it is noteworthy that only one configuration (undetermined) was obtained when using allyl alcohol as the dipolarophile; i.e., the sugar backbone is able to efficiently differentiate between the hydroxymethyl group and the hydrogen atom during the formation of the tertiary carbon center at C8, and **19h′** is consequently obtained as a single diastereoisomer. No substantial discrimination is made however, between the hydroxymethyl and the methyl groups of 2-methyl-2-propen-1-ol, and the quaternary center C8 in **19h″** is created with low diastereoselectivity (1.3:1).

We next studied the reaction with trisubstituted dipolarophiles. In particular, we selected 3-methyl-but-2-en-1-ol (**22**). We also chose trisubstituted enol ether (2-methyl-propenyloxymethyl)benzene (**23**),[27] first because on reaction with a C5-sugarketonitrone it would render a quaternary center with the substitution (+)-lactacystin requires at that center and also because its electron-rich character would probably favor its reaction with the electron-poor ketonitrone **5h**. However, either no reaction was observed, e.g., refluxing in toluene, or a complex mixture was obtained when the conditions were forced (heating at 160 °C in a sealed tube). Disubstitution on the dipolarophile looks in fact to be an upper limit because treatment of trisubstituted **23** and ketonitrone **5g** under high pressures[28] (40000 psi) also gave no cycloadducts.

Theoretical Study. In an attempt to evaluate the predictive power of common theoretical methods for the cycloaddition of ketonitrones, we decided to model the reaction of ketonitrone **5i** (Chart 1). This is a case of particular interest because of the rich array of cycloaddition pathways theoretically available to **5i**, which contrast the experimentally high regio- and stereoselectivity observed in the reaction, which only gave oxepane **19i** (Table 2, entry 1). For these studies, we initially selected nitrone **A** (Figure 1) as a simplified model for **5i**, where the OTBS and the $-OC(CH_3)_2O-$ groups of **5i** were replaced by a hydrogen atom at C6 and a double bond between positions C1 and C2, respectively. On cyclization, nitrone **A** could in principle give a total of six cycloadducts: (i) two **o**xepanes with either 8*R* or 8*S* configurations, **AO8*R*** and **AO8*S***; (ii) two **t**etrahydropyran-containing derivatives presenting cis fusion with the simultaneously formed isoxazolidine ring, **AT*c*8*R*** and **AT*c*8*S***; and (iii) their two trans-fused analogues, **AT*t*8*S*** and **AT*t*8*R*** (Figure 1).

In practice, every nitrone−olefin face relative-orientation is possible when the terminal end of the double bond (C9) overlaps the nitrone-oxygen, and transition states **TS-AT*c*8*R***, **TS-AT*c*8*S***, **TS-AT*t*8*S***, and **TS-AT*t*8*R***, leading to the four possible tetrahydropyrans, were found

(27) Trisubstituted enol ether **23** was prepared from commercial 2-methyl-2-propenol by protection of the hydroxyl group as the benzyl ether (NaH, THF, 0 °C → rt, 71%, 4 g scale), followed by double-bond isomerization (K^tBuO, DMSO, Δ, 47%, 1 g scale). For previously reported procedures, see: (a) Tietze, L. F.; Bachmann, J.; Wichmann, J.; Burkhardt, O. *Synthesis* **1994**, 1185−1194. (b) Earnshaw, C.; Wallis, C. J.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1979**, 3099−3106. (c) Adam, W.; Arias, L. A *Synthesis* **1979**, 388−390.

(28) Dicken, C. M.; DeShong, P. *J. Org. Chem.* **1982**, *47*, 2047−2051.

TABLE 4. Energies[a] at 1 atm and 298.15 K Computed for the Cycloaddition of Nitrone A[b] at the B3LYP/6-31G(d) Level

	$\Delta E^{\ddagger}$	$\Delta G^{\ddagger}$	ΔE	ΔG
TS-AO8*R*	21.6	25.2	−19.9	−12.6
TS-AO8*S*	30.0	33.2	−15.1	−8.4
TS-AT*c*8*R*	18.9	22.5	−16.1	−9.4
TS-AT*c*8*S*	29.5	32.7	−12.8	−6.2
TS-AT*t*8*S*	38.2	41.9	−13.0	−6.4
TS-AT*t*8*R*	45.8	49.9	−9.9	−3.6

[a] All values in kcal mol^{-1}. [b] See Figure 1.

with the B3LYP[29,30] density functional method using the 6-31G(d) basis set.[31] Alternatively, when C9 overlaps C5, *like* topicity (*Re-Re*, *Si-Si*) is structurally forbidden and transition states **TS-AO8*R*** and **TS-AO8*S***, corresponding to *Si-Re* and *Re-Si* nitrone−olefin approaches were found at the same level of theory. The calculated potential energy barriers (Table 4) identify as clearly disfavored, by as much as ∼8−27 kcal mol^{-1}, those pathways leading to oxepane **AO8*S*** and to tetrahydropyranes **AT*c*8*S***, **AT*t*8*S***, and **AT*t*8*R***, whose corresponding analogues were not isolated in the cyclization of nitrone **5i**. The calculation predicted, however, that model nitrone **A** would behave differently from **5i**, preferentially affording cis-fused tetrahydropyran **AT*c*8*R*** over the alternative oxepane **AO8*R*** (the analogue of isolated **19i**) because of a difference of 2.7 kcal mol^{-1}.

A calculation with the real system was consequently in place to evaluate if the structural differences between **5i** and its model nitrone **A** could in fact account for the unexpectedly lower energy barrier calculated for transition state **TS-ATc8*R*** as compared to that of **TS-AO8*R***. To this end, the ONIOM[32] hybrid method was chosen. Nitrone **5i** was divided in two layers as shown in Figure 2. The first layer, which mainly included the atoms of the chain joining dipole and dipolarophile, was treated at B3LYP/6-31G(d); the second one was described with the semiempirical AM1 method.[33]

The energies of the stationary points obtained using the ONIOM method were recalculated through single-point calculations at the B3LYP/-6-31(d) level. As it can be inferred from the relative energies of transition states **TS-19i** and **TS-(5*R*,8*R*)-T**, and reaction products **19i** and (5*R*,8*R*)-**T** shown in Table 5, the formation of oxepane **19i** is more favorable both kinetically and thermodynamically than the formation of (5*R*,8*R*)-**T**. Comparison between the ONIOM and the single-point B3LYP

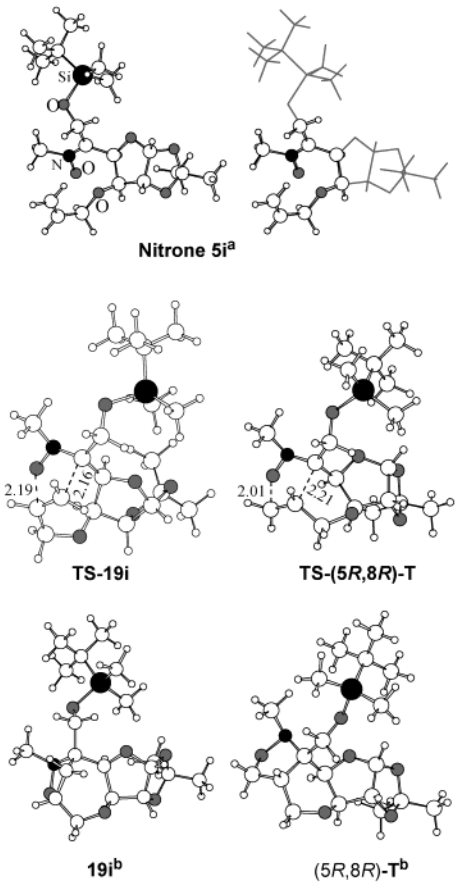


FIGURE 2. Nitrone **5i**: lower energy conformer (upper left), atoms included in the first layer of the ONIOM calculation (upper right), and transition states and corresponding reaction products. Selected interatomic distances in Å. (a) Chart 1. (b) Scheme 6.

TABLE 5. Energies[a] Relative to Reactant for the Stationary Points[b] Corresponding to the Cycloadditions of Ketonitrone 5i Obtained at the ONIOM(B3LYP/6-31G(d):AM1) Level

	ONIOM	B3LYP[c]
TS-19i	22.7	19.1
19i	−16.2	−21.5
TS-(5*R*,8*R*)-T	24.2	21.5
(5*R*,8*R*)-**T**	−8.9	−10.7

[a] In kcal mol^{-1}. [b] See Figure 2. [c] Computed at the ONIOM geometries.

energy values indicates that the former method seems to overestimate the potential energy barriers and to underestimate the reaction energies. Moreover, the difference of energy barriers computed at the B3LYP method, 2.4 kcal mol^{-1}, seems more reasonable than the 1.5 kcal mol^{-1} obtained at the ONIOM level of calculation, since only **19i** has been experimentally observed. Further analysis of the transition states **TS-19i** and **TS-(5*R*,8*R*)-T** shows that **TS-19i** can be directly related to the most stable conformation of nitrone **5i**. Both processes are exothermic and concerted, but relative bond lengths for the two forming bonds differ from one transition state to another: the C−C distance is slightly shorter than the C−O distance for **TS-19i**, whereas for **TS-(5*R*,8*R*)-T** the C−O distance is 0.20 Å shorter. The examination of the

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(30) For the use of the B3LYP method to model nitrone cycloadditions, see, for example: (a) Silva, M. A.; Goodman, J. M. *Tetrahedron* **2002**, *58*, 3667−3671. (b) Carda, M.; Portolés, R.; Murga, J.; Uriel, S.; Marco, J. A.; Domingo, L. R.; Zaragozá, R. J.; Röper, H. *J. Org. Chem.* **2000**, *65*, 7000−7009. (c) Cossío, F. P.; Morao, I.; Jiao, H.; Schleyer, P. *J. Am. Chem. Soc.* **1999**, *121*, 6737−6746. (d) Magnuson, E. C.; Pranata, J. *J. Comput. Chem.* **1998**, *19*, 1795. See also: (e) Jorgensen, K. A. Theoretical Calculations of Metal-Catalyzed Cycloaddition Reactions. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jorgensen, K. A., Eds.; Wiley-VCH: Weinheim, 2002 and references therein.
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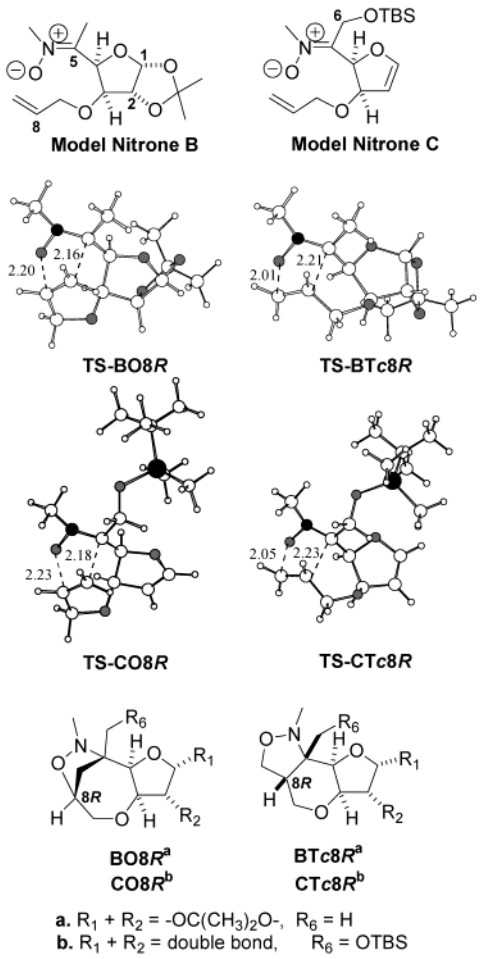

FIGURE 3. Model ketonitrones B and C, their transition states, and corresponding cycloadducts at ONIOM(B3LYP/6-31G(d):AM1).

corresponding transition vectors show that the bond involving the vinyl terminal carbon atom is formed in the first place in both cases.

Finally, it was of interest to compute model nitrones **B** and **C** (Figure 3) to separately consider the effects of the isopropylidene group at C1−C2 and of the OTBS group at C6 on the energy barriers leading, either to the corresponding oxepanes **BO8*R*** and **CO8*R*** or to the tetrahydropyrans **BT*c*8*R*** and **CT*c*8*R***. Analysis of the potential energy barriers appears to indicate that each group individually contribute in the same sense to diminish the difference between both competing pathways (**TS-O8*R*** and **TS-T*c*8*R***), when compared with model nitrone **A** ($\Delta\Delta E^{\ddagger} = 2.7$ kcal mol^{-1} for model **A**, 1.9 for model **B**, and 0.9 for model **C**, at the ONIOM level, Table 6). While a bigger effect looks to be associated with the presence of the OTBS group at C6 (model **C**) at the ONIOM(B3LYP/6-31(d):AM1) level, single-point recalculations at the B3LYP/-6-31(d) level afforded essentially the same energy barriers for the oxepane and the tetrahydropyran pathways in both models **B** and **C**. At this last level, it thus appears that the individual presence of either the OTBS group at C6 or the isopropylidene at C1−C2 equally contributes to the relative energy barriers completely leveling both pathways, while their combined effect (nitrone **5i**) definitively makes the oxepane pathway (**TS-19i**) the preferred one.

TABLE 6. Potential Energy Barriers[a] Computed for the Reactions of Model Nitrones B and C at the ONIOM(B3LYP/6-31G(d):AM1) Level

model	TS[b]	ONIOM	B3LYP[c]
B	**TS-BO8*R***	21.2	18.5
	TS-BT*c*8*R*	19.3	18.9
C	**TS-CO8*R***	23.6	21.8
	TS-CT*c*8*R*	22.7	21.6
A[d]	**TS-AO8*R***		21.6
	TS-AT*c*8*R*		18.9
5i[e]	**TS-19i**	22.7	19.1
	TS-(5*R*,8*R*)-T	24.2	21.5

[a] In kcal mol^{-1}. [b] See Figure 3. [c] Computed at the ONIOM geometries for **5i** and models B and C. [d] Data from Table 4 (showed for comparison). [e] Data from Table 5 (showed for comparison).

Conclusions

In summary, 1,3-dipolar cycloaddition of sugar-derived ketonitrones efficiently perform to create nitrogenated quaternary centers with yields ranging from moderate to good ones. Intra- and intermolecular variants are possible. Mono- and disubstituted dipolarophiles can be used when the reaction is run intermolecularly; trisubstitution is also allowed in the intramolecular case.

Intramolecularly, complete regio- and stereochemical control on the cycloaddition outcome can be performed by adequately choosing the position and relative configuration of the dipolarophile-attachment point, as well as the length of the tether chain connecting dipole and dipolarophile in the sugar substrate. For the particular case of the two 3-*O*-allyl 5-ketoglucofuranonitrones studied, only bridged oxepane systems were formed and none of the alternative fused tetrahydropyrans. As for the intermolecular cases considered, the regioselectivity was complete using nonsymmetrically substituted dipolarophiles. Stereoselectivity was better for rigid keto derivatives. The case of ketonitrone **5h** is highly illustrative: it is quickly available from cheap commercial sources and it undergoes cycloaddition with a variety of dipolarophiles in high yields and with complete stereocontrol in the formation of the quaternary center. A theoretical study performed to model the intramolecular cycloaddition of 3-*O*-allyl C5- ketofuranonitrones unveiled the need to consider every substituent, even those located relatively far away from the reacting center, when discriminating between energetically close reacting pathways. Extreme care should be consequently exercised in simplifying the real systems when performing such calculations. Use of hybrid methods appears as an attractive alternative. In particular, the ONIOM(B3LYP/6-31(d):AM1) method followed by single-point calculations at the B3LYP/6-31(d) level appears to adequately treat the cycloaddition of these relative-large systems, while keeping the calculation cost to reasonable limits. Its application to similar cycloadditions is expected to further validate its predictive power for synthetic endeavors.[34] It is also expected that this cycloaddition type, because of its wide scope, smooth reaction conditions and efficient regio and stereocontrol, besides the existence of well-developed synthetic routines to prepare differentially protected ketosugars, will be advantageously used, both inter and

intramolecularly, as a reliable key step for the preparation of targets endowed with nitrogen-bearing quaternary centers. In this respect, it should also be indicated that, although this study was mostly conducted with C3 and C5 ketosugars because of our particular synthetic interests, the nitrogenated quaternary center could in principle be formed at any other positions of a sugar backbone, provided a keto group can be previously installed on it (e.g., at C4 as in Table 1, entry 5).

Experimental Section

Computational Study. All calculations have been done performed the Gaussian-98 program.[35] Molecular geometries have been fully optimized. Harmonic vibrational frequencies were calculated for all stationary points to characterize them as energy minima (all frequencies are real) or transition states (one and only one imaginary frequency).

Cycloadduct 19a. MeNHOH·HCl (250 mg, 2.9 mmol), pyridine (161 μL, 1.9 mmol), and molecular sieves (4 Å, 100 mg) were added to a solution of **4a** (145 mg, 0.5 mmol) in ethanol (1 mL). After 36 h at rt and 6 h at 45 °C, the reaction mixture was filtered, diluted with water, and extracted with CH_2Cl_2. The organic extracts were combined, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Column chromatography (15% and 40% AcOEt−hexane) of the crude residue gave **19a** as an oil (124 mg, 78%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.36−7.29 (m, 5H, ArH), 5.46 (d, J = 2.2 Hz, 1H, H1), 4.72 (AB_q, Ar-CH_2), 4.63 (d, J_{5-6exo} = 5.5 Hz, 1H, H5), 4.24 (dd, J_{gem} = 9.2 Hz, J = 7.1 Hz, 1H, H7′), 4.19 (d, J_{gem} = 7.3 Hz, 1H, H6endo), 4.08 (dd, J_{gem} = 8.7 Hz, J = 7.0 Hz, 1H, H9′), 3.86 (d, $J_{1,2}$ = 2.2 Hz, 1H, H2), 3.69 (dd, J_{gem} = 9.2 Hz, J = 4.4 Hz, 1H, H7), 3.57 (dd, J_{gem} = 8.7 Hz, J = 2.1 Hz, 1H, H9), 2.88 (s, 3H, CH_3), 2.83 (m, 1H, H8). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 137.7 (Ar_{ipso}), 128.5 (C_{meta}), 128.0 (C_{para}), 127.8 (C_{orto}), 99.1 (C1), 79.9 (C4), 78.4 (C2), 75.6 (C5), 73.7 (C7), 73.4 (C10), 70.1 (C9), 66.0 (C6), 56.1 (C8), 40.6 (NCH_3). MS *m*/*z*: 319 (25, M^+), 228, 213, 183, 91 (100, C_7H_7), 68. Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.386. Found: C, 63.71; H, 6.75; N, 4.32. $[\alpha]_D$ = −58.2 (0.82, CH_2Cl_2).

Cycloadduct 19b. MeNHOH·HCl (604 mg, 7.23 mmol), pyridine (390 μL, 4.82 mmol), and molecular sieves (4 Å, 40 mg) were added to a solution of **4b** (70 mg, 0.24 mmol) in EtOH (4 mL). After 36 h at rt and 16 h at 65 °C, the reaction was worked up as described for **19a**. Chromatography (1% CH_3OH−CH_2Cl_2) gave **19b** (oil, 60 mg, 77%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.41−7.26 (m, 5H, ArH), 5.28 (d, J = 2.5 Hz, 1H, H1), 4.79 (d, J = 11.7 Hz, 1H, Ar-CH_2), 4.69 (d, J = 11.7 Hz, 1H, Ar-CH_2), 4.47 (m, 1H, H5), 4.32 (m, 2H, H7, H4), 4.04 (d, J_{gem} = 8.3 Hz, 1H, H6endo), 3.98 (dd, J = 7.7 Hz, J = 5.4 Hz, 1H, H9), 3.81 (m, 1H, H7), 3.72 (m, 2H, H6exo, H9), 3.64 (m, 1H, H8), 3.55 (d, J = 1.9 Hz, 1H, H2), 2.72 (s, 3H, NCH_3). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 138.0 (Ar_{ipso}), 128.4 (C_{meta}), 127.9 (C_{para}), 127.8 (C_{orto}), 99.3 (C1), 78.4 (C3), 76.6, 76.0 (C2, C4, C5), 74.8, 71.9 (C9, C7), 73.2 (OCH_2Bn), 65.5 (C6), 50.5 (C8), 37.7 (NCH_3). MS (EI): 321 (0.05, M^+ + 2), 320 (1.5, M^+ + 1), 319 (7.84, M^+), 91 (100, C_7H_7). HRMS (EI): 319.1416, calcd for $C_{17}H_{21}NO_5$ 319.1419. Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.386. Found: C, 63.89; H, 6.68; N, 4.32. $[\alpha]_D$ = −50.4 (1.01, CH_2Cl_2).

Cycloadduct 19c. Compound **19c** was obtained (chromatography: 1% MeOH/CH_2Cl_2, oil, 48 mg, 65%) from ketone **4c** (67 mg, 0.23 mmol), MeNHOH·HCl (582 mg, 6.97 mmol), pyridine (375 μL, 4.64 mmol), and molecular sieves (40 mg) in EtOH (4 mL, 24 h at rt, 6 h at 55 °C), as reported for **19b**. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.41−7.26 (m, 5H, ArH), 5.27 (d, J = 1.5 Hz, 1H, H1, 4.94 (d, J = 11.8 Hz, 1H, Ar-CH_2), 4.68 (d, J = 11.8 Hz, 1H, Ar-CH_2), 4.61 (d, J = 6.1 Hz, 1H, H4), 4.50 (m, 1H, H5), 4.32 (dd, J_{gem} = J_{7-8} = 9.0 Hz, 1H, H7), 3.93 (d, J_{gem} = 8.5 Hz, 1H, H6endo), 3.86 (dd, J_{gem} = 8.9 Hz, J = 3.5, 1H, H9′), 3.74 (d, J_{gem} = 8.9 Hz, 1H, H9), 3.64 (m, 2H, H6exo, H7), 3.49 (d, $J_{1,2}$ = 1.5 Hz, 1H, H2), 3.17 (m, 1H, H8), 2.83 (s, 3H, NCH_3). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 138.1 (Ar_{ipso}), 128.4 (C_{meta}), 128.2 (C_{para}), 127.8 (C_{orto}), 101.0 (C1), 79.5, 73.9 (C2, C4), 75.0 (C5), 74.9, 74.8 (C9, C7), 69.3 (C10), 64.7 (C6), 53.3 (C8), 40.1 (NCH_3). MS (EI): 320 (0.5, M^+ + 1), 319 (2.52, M^+), 91 (100, C_7H_7). HRMS (EI): 319.1429, calcd for $C_{17}H_{21}NO_5$ 319.1419. Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.386. Found: C, 63.92; H, 6.74; N, 4.37.

Cycloadduct 19d. A solution of ketone **4d** (564 mg, 1.85 mmol), MeNHOH·HCl (474 mg, 5.56 mmol, 300 mol %), and dry Py (0.52 mL, 6.48 mmol, 350 mol %) in dry CH_2Cl_2 (16 mL) was heated to reflux in a 25 mL one-necked round-bottomed flask fitted with a reflux condenser and a $CaCl_2$ tube. After consumption of the starting material (28 h) as monitored by TLC (AcOEt−hexane, 25:75), the reaction mixture was poured into water (10 mL), and the aqueous layer was decanted and further extracted with CH_2Cl_2. The combined organic extracts were concentrated, and the resulting solid residue was dissolved in AcOEt. Washing with brine, drying over Na_2SO_4, filtration, elimination of the solvents, and chromatographic purification afforded the isoxazolidine **19d** (oil, 485 mg, 79%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.07 (m, 2H; ArH_{orto}), 7.58 (m, 1H; ArH_{para}), 7.46 (m, 2H; ArH_{meta}), 5.55 (d, $J_{1,2}$ = 2.3 Hz, 1H; H1), 5.47 (s, 1H; H4), 4.65 (m, 1H; H5), 4.52 (dd, $J_{7,7'}$ = 8.3 Hz, 1H; H7endo#), 4.36 (br s, 1H; H2), 4.11 (d, $J_{6,6'}$ = 8.3 Hz, 1H; H6endo), 3.91 (dd, $J_{9,9'}$ = 8.9 Hz, $J_{9,8}$ = 3.5 Hz, 1H; H9exo∧), 3.84−3.80 (m, 2H; H9′∧, H6exo), 3.65 (dd, $J_{7,7'}$ = 7.6 Hz, $J_{7,8}$ = 4.5 Hz, 1H; H7exo#), 3.05 (m, 1H; H8), 2.73 (s, 3H; NCH_3). (#,∧: these assignments could be interchanged). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 165.6 (Ph*C*OO-), 132.7 (Ar, C_{orto}), 129.8 (Ar, C_{para}), 129.6 (Ar, C_{ipso}), 128.4 (Ar, C_{meta}), 101.9 (C1), 76.6 (C2), 75.8 (C5), 74.8 (C7), 73.9 (C4), 72.9 (C3), 70.5 (C9), 66.0 (C6), 54.7 (C8), 40.3 (N*C*H_3). IR (film, NaCl): 1720 cm^{-1} (m, PhCO). MS *m*/*z*: 334 [6, $(M + 1)^+$], 333 (31, M^+), 228 [7, $(M - PhCO)^+$], 207, 149, 140, 105 [100, $(PhCO)^+$], 77 (31, Ph^+). Anal. Calcd for ($C_{17}H_{19}NO_6$): C, 61.26; H, 5.76; N, 4.20. Found: C, 61.36; H, 6.00; N, 4.31.

Cycloadduct 19d′. Compound **19d′** was obtained (oil, 372 mg, 61%) from ketone **4d** (456 mg, 1.5 mmol), BnNHOH·HCl (370 mg, 2.25 mmol, 150 mol %), and dry Py (0.24 mL, 3.0 mmol, 200 mol %) in dry CH_2Cl_2 (13 mL) as described for **19d**. ^{1}H NMR (CDCl3, 500 MHz) δ: 8.03 (m, 2H; ArHorto-PhCO), 7.50 (m, 1H; ArHpara-PhCO), 7.36 (m, 2H; ArH_{meta}-PhCO), 7.04 (m, 5H; H10), 5.60 (d, $J_{1,2}$ = 2.7 Hz, 1H; H1), 5.59 (d, $J_{4,5}$ = 1.2 Hz, 1H; H4), 4.69 (m, 1H; H5), 5.57 (dd, $J_{7,7'}$ = $J_{7,8}$= 8.3 Hz, 1H; H7), 4.50 (d, $J_{2,1}$ = 2.7 Hz, 1H; H2), 4.15 (2 d, 2H; H6endo, H10), 3.95 (d, $J_{10,10'}$ = 13.7 Hz, 1H; H10′), 3.92 (dd, $J_{9,9'}$ = 8.9 Hz, $J_{9,8}$ = 3.8 Hz, 1H; H9), 3.83 (m, 2H; H6exo, H9′), 3.72 (dd, $J_{7,7'}$ = 7.8 Hz, $J_{7,8}$ = 4.5 Hz, 1H; H7′), 3.14 (m, 1H; H8).^{13}C NMR ($CDCl_3$, 125 MHz) δ: 165.7 (Ph*C*OO−), 137.7 (Ar, C_{ipso}-NCH_2Ph), 133.2 (Ar, C_{para}-PhCOO−), 129.7 (Ar, C_{orto}-

(34) Ideally, theoretical calculations would be used to decide among different synthetic pathways when pursuing a given target. The synthetic work reported by Shing's group on zoapatanol: Shing, T. K. M.; Wong, C.-H.; Yip, T. *Tetrahedron*: *Asymmetry* **1996**, *7*, 1323−1340, where two approaches, both involving a 1,3-dipolar cycloaddition as the key step, needed to be consecutively tested to reach the required molecular-skeleton, adequately illustrates this issue.

(35) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, Revision A.9; Gaussian, Inc.: Pittsburgh, PA, 1998. http://www.Gaussian.com.

(36) For an alternative procedure, see: Smith, A. B., III; Rivero, R. A.; Hale, K. J.; Vaccaro, H. A. *J. Am. Chem. Soc.* **1991**, *113*, 2092−2112.

PhCOO−), 129.5 (Ar, C_{ipso}-PhCOO−), 128.4 (Ar, C_{meta}-PhCOO−), 127.9, 127.8, 126.7 (Ar-CH_2Ph), 101.9 (C1), 77.4 (C2#), 76.0 (C5#), 74.9 (C7), 73.9 (C4), 73.4 (C3), 70.8 (C9), 66.0 (C6), 57.2 (C10), 54.6 (C8). (#: these assignments could be interchanged). MS *m/z*: 410 [8, $(M + 1)^+$], 409 (30, M^+), 333 [0.1, $(M + 1 - Ph)^+$], 304 [0.5, $(M - PhCO)^+$], 105 (100, $PhCO^+$), 91 [95, $(PhCH_2)^+$], 77 (77, Ph^+). Anal. Calcd for ($C_{23}H_{23}NO_6$): C, 67.47; H, 5.67; N, 3.42. Found: C, 67.20; H, 5.80; N, 3.50.

Isoxazolidine 20. Benzoate **19d** (2.7 g, 8.04 mmol) was hydrolyzed with 1% aqueous NaOH−CH_3OH (1:9, 45 mL). The reaction mixture was filtered through Celite, the solids carefully reextracted with hot methanol, the organic extracts concentrated, and the residue redissolved in CH_2Cl_2. Drying over anhydrous Na_2SO_4 and concentration gave an oily residue. Chromatography gave **20** (1.8 g, 98%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.41 (d, $J_{1,2}$= 2.7, 1H; H1), 4.69 (m, 1H; H5), 4.54 (br, 1H; OH), 4.43 (dd, $J_{7,7'} = J_{7endo,8} = 8.5$, 1H; H7endo), 4.17 (dd, $J_{9,9'} \approx J_{9endo,8} \approx 8.3$, 1H; H9endo), 3.93 (m, 3H; H2, H6endo, H9exo), 3.75 (m, 2H; H4, H6exo), 3.64 (dd, $J_{7,7'} = 8.3$, $J_{7exo,8} =$ 4.4, 1H; H7exo), 3.11 (m, 1H; H8), 2.73 (s, 3H; NCH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 101.0 (C1), 79.5 (C3), 76.3, 76.1, 73.9, 72.9 (C7, C9), 70.1, 65.8 (C6), 54.2 (C8), 39.2 (N*C*H_3). LRMS *m/z*: 321 $[(M + 2)^+$; 0.1], 230 $[(M + 1)^+$; 13], 229 (M^+; 100), 186, 140, 127, 98, 82, 68.

Diol 21. Isoxazolidine **20** (645 mg, 2.81 mmol) and Zn dust (775 mg, 1.26 mmol, 400 mol %) were refluxed in 60% aqueous AcOH (18 mL). Once consumed (TLC, MeOH/CH_2Cl_2, 10:90, R_{f22}= 0.14), the solvents were evaporated, the residue dissolved in CH_3OH and treated with 3 N aqueous ammonia. The salts were filtrated, and the filtrate was concentrated. Last traces of water were eliminated by azeotropic distillation with toluene. Chromatography gave **21** as a white solid (521 mg, 81%). ^{1}H NMR ($CDCl_3$−CD_3OD, 3:1, 300 MHz) δ: 5.27 (d, $J_{1,2}$ = 2.5, 1H; H1), 4.47 (m, 1H; H5), 4.14 (dd, $J_{7,7'} \approx J_{7,8} \approx 9.2$, 1H; H7), 4.04 (s, 1H; H4), 3.98 (d, $J_{2,1} = 2.5$, 1H; H2), 3.88 (d, $J_{6,6'} = 8.5$, 1H; H6endo), 3.7−3.5 (m, 4H; H6exo, H7′, H9), 2.55 (s, 3H; NCH_3), 2.54 (m, 1H; H8). ^{13}C NMR ($CDCl_3$−CD_3OD, 3:1, 75 MHz) δ: 99.9 (C1), 78.8, 77.8, 70.2 (C7), 68.9, 67.2 (C3), 65.8 (C6), 57.8 (C9), 47.9 (N*C*H_3), 30.1 (C8). LRMS *m/z*: 232 $[(M + 1)^+$; 6], 231 (M^+; 46), 200 $[(M - CH_2OH)^+$; 6], 188, 164, 149, 129 (100), 98, 85, 70, 57.

Cycloadduct 19e. It was obtained (oil, 43 mg, 52%) from ketone **4e** (77 mg, 0.23 mmol), MeNHOH·HCl (388 mg, 4.63 mmol), pyridine (241 μL, 2.99 mmol), and molecular sieves (50 mg) in EtOH (0.7 mL), following the procedure reported for **19a**. Total reaction time 15 h at room temperature and 15 h at 60 °C. Mixtures of AcOEt−hexane of increasing polarity (25%, 50%, 70%), were used for chromatography. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.36−7.27 (m, 5H, ArH), 5.39 (d, J_{1-2} = 1.6 Hz, 1H, H1), 4.65 (d, J = 11.5 Hz, 1H, H10), 4.53 (d, J = 11.5 Hz, 1H, H10′), 4.25 (d, $J_{5-6exo} = 4.7$ Hz, 1H, H5), 4.17 (dd, $J_{gem} = 8.9$ Hz, $J_{9-8} = 7.5$ Hz, 1H, H9), 4.08 (d, $J_{gem} = 8.1$ Hz, 1H, H6endo), 4.02 (d, $J_{3-2} = 7.1$ Hz, 1H, H3), 3.89 (dd, $J_{gem} = 8.9$ Hz, $J_{9'-8} = 4.6$ Hz, 1H, H9′), 3.80 (dd, $J_{gem} = 8.1$ Hz, $J_{6exo-5} = 4.7$ Hz, 1H, H6exo), 3.75 (dd, $J_{gem} = 13.0$ Hz, J_{7-8} = 4.3 Hz, 1H, H7), 3.46 (dd, $J_{gem} = 13.0$ Hz, $J_{7'-8} = 9.5$, 1H, H7′), 3.34 (dd, $J_{2-3} = 7.1$ Hz, $J_{2-1} = 1.6$ Hz, 1H, H2), 3.25 (m, 1H, H8), 2.59 (s, 3H, −N*CH*$_3$), 2.14 (s, 3H, −CO*CH*$_3$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 168.7 (CO), 136.6 (C_{ipso}), 128.6 (C_{meta}), 128.3 (C_{para}), 128.2 (C_{ortho}), 98.1 (C1), 80.8 (C2), 78.1 (C4), 75.8 (C5), 72.9 (C9#), 72.7 (C10#), 68.1 (C6), 60.2 (C8), 49.1 (C7), 47.9 (C3), 38.6 (−N*C*H_3), 22.2 (−CO*C*H_3). MS (EI): 361 (0.07, $M^+ + 1$), 360 (0.89, M^+), 168 (29), 91 (100, C_7H_7). HRMS (EI): 360.1685, calcd for $C_{19}H_{24}N_2O_5$ 360.1673.

Cycloadducts 19f and 19f′. A solution of the nitrone **5f** (120 mg, 0.53 mmol) in benzene (5 mL) was added to a suspension of molecular sieves (80 mg) in ethyl vinyl ether (1 mL, 5.26 mmol). After 38 h at rt and refluxing for 8 h, the reaction mixture was filtered. Column chromatography (AcOEt/hexane 20%, 30%, 50%) gave **19f** (oil, 99 mg, 62%), **19f′** (oil, 17 mg, 11%), and some starting ketone **4f** (18 mg, 15%). **19f.** ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.43 (m, 1H, H8), 5.30 (d, J_{1-2} = 2.7 Hz, 1H, H1), 4.57 (m, 1H, H5), 4.41 (d, $J_{6endo-6exo} = 7.2$ Hz 1H, H6endo), 4.08 (d, $J_{3-2} = 5.4$ Hz, 1H, H3), 4.00 (dd, $J_{2-1} = 2.7$ Hz, $J_{2-3} = 5.4$ Hz, 1H, H2), 3.80 (dq, 1H, H9′), 3.74 (dd, $J_{6exo-6endo} \approx J_{6exo-5} = 7$ Hz, 1H, H6exo), 3.50 (dq, 1H, H9), 2.86 (s, 3H, NCH_3), 2.60 (dd, $J_{gem} = 13.9$ Hz, $J = 2.8$ Hz, 1H, H7′), 2.42 (dd, $J_{gem} = 13.9$ Hz, $J = 6.6$ Hz, 1H, H7), 1.59 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.21 (t, $J = 7.1$ Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 111.2 (*C*$(CH_3)_2$), 105.2 (C8), 99.5 (C1), 75.9 (C3), 74.4 (C2, C5), 69.2 (C4), 64.9 (C6), 64.3 (C9), 44.4 (C7), 41.8 (*C*H_3−N), 25.9, 25.8 (CH_3, CH_3), 15.1 (C10). MS (EI): 301 (68, M^+), 256 (53, $M^+ - (^-ON^+$-Me)), 214 (62), 200 (42), 159 (100), 142 (82). Anal. Calcd for $C_{14}H_{23}NO_6$: C, 55.81; H, 7.69; N, 4.65. Found: C, 55.48; H, 7.65; N, 4.53. $[\alpha]_D$= −128.2 (1.07, CH_2Cl_2). **19f′.** ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.33 (dd, $J = 6.6$ Hz, $J = 3.7$ Hz, 1H, H8), 5.26 (m, 1H, H1), 4.42 (dd, $J_{6endo-6exo} = 7.2$ Hz, $J_{6endo-5} = 0.9$ Hz, 1H, H6endo), 4.31 (m, 1H, H3), 4.09 (d, 1H, H5), 3.96 (dd, $J_{2-1} = 2.7$ Hz, J_{2-3} = 5.3 Hz, 1H, H2), 3.82 (dq, $J = 7.1$, 9.5 Hz, 1H, H9), 3.66 (dd, $J_{6exo-6endo} = 7.2$ Hz, $J_{6exo-5} = 5.9$ Hz, 1H, H6exo), 3.50 (dq, J = 7.1, 9.5 Hz, 1H, H9′), 3.06 (s, 3H, CH_3N), 3.00 (dd, $J_{gem} = 13.8$ Hz, $J = 6.6$ Hz, 1H, H7′), 2.20 (dd, $J = 13.8$, 3.7 Hz, 1H, H7), 1.57 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.21 (t, $J = 7.1$ Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 111.3 (*C*$(CH_3)_2$), 106.1 (C8), 99.6 (C1), 75.7, 75.2, 74.7 (C2, C3, C5), 69.5 (C4), 64.8 (C6), 64.1 (C9), 44.7 (C7), 41.7 (N-*C*H_3), 25.9, 25.8 (CH_3, CH_3), 15.1 (C10). MS (EI): 301 (16.6, M^+), 256 (14, $M^+ - (ON^+$-Me)), 214 (17), 200 (11.6), 159 (40), 142 (28), 58 (100). MS (CI): 304 (2, $M^+ + 3$), 303 (15.6, $M^+ + 2$), 302 (100, $M^+ + 1$). HRMS (CI): 302.1603, calcd for $C_{14}H_{24}NO_6$ 302.1611. $[\alpha]_D = +8.14$ (1.18, CH_2Cl_2).

Cycloadduct 19g. A solution of the nitrone **5g** (150 mg, 0.52 mmol) and dimethyl acetylenedicarboxylate (1 mL, 8.25 mmol) in dry benzene (1 mL) was stirred at rt for 8 h. The solvent was removed; column chromatography (AcOEt−hexane 25:75, 40:60) gave **19g** (oil, 153 mg, 68%). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 5.94 (d, $J = 3.6$ Hz, 1H, H_1), 4.87 (d, $J = 3.6$ Hz, 1H, H_2), 4.31 (d, $J = 7.6$ Hz, 1H, H_4), 4.08 (dd, 1H, H_6*), 3.95−3.72 (m, 2H, H_6*, H_5*), 3.85 (s, 3H, $-OCH_3$), 3.71 (s, 3H, $-OCH_3$), 3.14 (s, 3H, CH_3), 1.54, 1.40, 1.32, 1.31 (s, s, s, s, 4 CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 162.5, 159.0 (C=O, C=O), 154.4 (C=), 112.3, 109.3, 105.4 (C=), 104.3 (C_1), 83.7, 80.4, 79.8 (C_4*, C_3, C_2), 73.4 (C_5*), 67.6 (C_6), 53.0 (CH_3O), 52.9 (CH_3O), 42.1 (CH_3), 26.4, 26.1, 25.9, 24.9 (CH_3, CH_3, CH_3, CH_3). *: these assignments could be interchanged. MS (EI): 429 (5.3, M^+), 414 (68, $M^+ - CH_3$), 85 (100). MS (FAB$^+$): 430 ($M^+ + 1$). HMRS (FAB$^+$): calcd for $C_{19}H_{28}NO_{10}$ 430.1713, found 430.1704.

Cycloadduct 19h. A solution of nitrone **5h** (100 mg, 0.41 mmol) and phenylacetylene (135 μL, 1.23 mmol) in dry benzene (3 mL) was refluxed for 5 h. Additional phenylacetylene (3 equiv) was added and the reaction mixture refluxed for 6 h. The solvent was removed. Crystallization (AcOEt) afforded **19h** (116 mg, 82%, mp = 175 °C dec). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.52 (m, 2H, ArH), 7.37 (m, 3H, ArH), 5.98 (d, J = 3.6 Hz, 1H, H_1), 5.07 (s, 1H, H_7), 4.85 (m, 3H, H2, H3, H4), 3.22 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 1.35 (s, 3H, CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 171.7 (C_6), 157.6 (C_8), 130.2, 128.5, 126.0 (Ar), 127.1 (C_{ipso}), 113.4 (C), 106.8 (C_1), 89.2 (C_7), 82.3, 82.1, 82.0 (C_2, C_3, C_4), 79.1 (C_5), 42.3 (NCH_3), 26.9, 26.5 (CH_3, CH_3). MS (EI): 347 (11.5, $M^+ + 2$), 346 (3.5, $M^+ + 1$), 345 (14, M^+), 204 (100), 77 (55, C_6H_6). HRMS (EI) 345.1197, calcd for $C_{18}H_{19}NO_6$ 345.1212. Anal. Calcd for $C_{18}H_{19}NO_6$: C, 61.01; H, 5.57; N, 3.99. Found: C, 61.25; H, 5.74; N, 4.20. $[\alpha]_D = +218.6$ (0.7, CH_2Cl_2).

Cycloadduct 19h′. A solution of the nitrone **5h** (20 mg, 0.082 mmol) and allyl alcohol (1 mL) was refluxed for 2 h. The solvent was removed. Flash chromatography (AcOEt/hexane 40%, 50%, 85%) gave **19h′** (oil, 20 mg, 81%). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 5.98 (d, $J = 3.7$ Hz, 1H, H_1), 4.85 (d, $J = 2.7$ Hz, 1H, H_4), 4.80 (d, $J = 3.7$ Hz, 1H, H_2), 4.77 (d, $J = 2.7$ Hz, 1H, H_3), 4.42 (m, 1H, CHO), 3.87 (m, 1H, CH_2OH), 3.64 (m, 1H, CH_2OH), 2.99 (s, 3H, CH_3N), 2.70 (m, 1 H, OH), 2.51 (m,

2H, CH_2), 1.51 (s, 3H, CH_3), 1.35 (s, 3H, CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 171.9 (C=O), 113.3 ($C(CH_3)_2$), 106.7 (C_1), 83.4, 82.0, 81.9 (C_2, C_3, C_4), 76.2 (*C*HO), 71.6 (C_5), 64.4 (CH_2OH), 39.4 (CH_2), 26.8, 26.4 (CH_3, CH_3). MS (FAB$^+$): 302 ($M^+ + 1$). HRMS (FAB$^+$): 302.1249, calcd for $C_{13}H_{20}NO_7$ 302.1239. $[\alpha]_D$ = +9.16 (0.24, CH_2Cl_2).

Cycloadduct 19h″. A solution of the nitrone **5h** (20 mg, 0.082 mmol) and 2-methyl-2-propen-1-ol (2 mL) was refluxed for 8 h. Removal of the solvent and flash chromatography (AcOEt/hexane 40%, 50%) gave **19h$_a$″** (12 mg, 46%) and **19h$_b$″** (9 mg, 35%) as oils. **19h$_a$″.** ^{1}H NMR (250 MHz, $CDCl_3$) δ: 5.96 (d, J = 3.1 Hz, 1H, H_1), 4.77−4.72 (m, 3H, H_2, H_3, H_4), 3.63 (d, J = 12.0 Hz, 1H, CH_2OH), 3.35 (m, 1H, CH_2OH), 2.96 (s, 3H, NCH_3), 2.80 (d, J = 12.6 Hz, 1H, CH_2), 2.53 (d, J = 10.6 Hz, 1H, OH), 2.16 (d, J = 12.6 Hz, 1H, CH_2), 1.51 (s, 3H, CH_3), 1.34 (s, 3H, CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 172.1 (C=O), 113.3 ($C(CH_3)_2$), 106.8 (C_1), 84.0, 82.1, 81.6 (C_2, C_3, C_4), 81.5 (C), 72.2 (C_5), 66.0 (CH_2), 45.6 (CH_2), 40.2 (N−CH_3), 26.8, 26.4, 23.5 (CH_3, CH_3, CH_3). MS (FAB$^+$): 316 ($M^+ + 1$). HRMS (FAB$^+$): 316.1396, calcd for $C_{14}H_{22}NO_7$ 316.1396. $[\alpha]_D$ = −60.8 (0.44, CH_2Cl_2). **19h$_b$″.** ^{1}H NMR (mixture with **19h$_a$″**, 250 MHz, $CDCl_3$) δ: 5.95 (s, 1H, H_1), 4.86−4.72 (m, 3 H, H_2, H_3, H_4), 3.76 (d, J = 10.9 Hz, 1H, CH_2OH), 3.54 (m, 1 H, CH_2OH), 3.42 (m, 1H, OH), 2.98 (s, 3H, NCH_3), 2.70 (d, J = 12.5 Hz, 1H, CH_2), 2.29 (d, J = 12.5 Hz, 1H, CH_2), 1.52 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.25 (s, 3H, CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 171.9 (C=O), 113.5 ($C(CH_3)_2$), 106.8 (C_1), 83.7, 81.9, 81.9 (C_2, C_3, C_4), 81.0 (C), 71.9 (C_5), 70.9 (CH_2), 46.5 (CH_2), 40.5 (NCH_3), 26.8, 26.4, 21.4 (CH_3, CH_3, CH_3). MS (FAB$^+$): 316 ($M^+ + 1$).

Cycloadduct 19i. Compound **19i** was obtained (oil, 126 mg, 69%) from ketone **4i** (169 mg, 0.45 mmol), MeNHOH·HCl (227 mg, 2.72 mmol), pyridine (146 μL, 1.81 mmol), and molecular sieves (100 mg) in EtOH (5 mL), as reported for **19a**. Total reaction time 48 h at rt. Mixtures of AcOEt−hexane of increasing polarity (15%, 20%, 50%, 70%) were used for chromatography. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.82 (d, J_{1-2} = 3.7 Hz, 1H, H1), 4.52 (m, 1H, H8), 4.37 (d, J_{1-2} = 3.7 Hz, 1H, H2), 4.25 (br, s, 1H, H4), 4.13 (s, 1H, H3), 4.03 (d, $J_{6-6'}$ = 10.9 Hz, 1H, H6), 3.64 (d, $J_{6'-6}$ = 10.9 Hz, 1H, H6′), 3.57 (d, $J_{7-7'}$ = 12.6 Hz, 1H, H7), 3.52 (dd, $J_{7'-7}$ = 12.6 Hz, $J_{7'-8}$ = 2.5 Hz, 1H, H7′), 2.71 (s, 3H, NCH_3), 2.35 (d, 1H, H9), 1.99 (m, 1H, H9′), 1.44 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 0.87 (s, 9H, $C(CH_3)_3$), 0.06 (s, 3H, CH_3), 0.06 (s, 3H, CH_3). ^{13}C NMR (C_6D_6, 125 MHz) δ: 111.5 ($C(CH_3)_2$), 104.5 (C1), 85.3 (C2), 82.9 (C4), 78.4 (C8), 77.7 (C3), 71.7 (C7), 71.0 (C5), 63.5 (C6), 40.2 (N-Me), 30.1 (C9), 27.0, 26.2 (CH_3, CH_3), 26.1 (C(CH_3)), 18.5 ($C(CH_3)$), −5.7, −5.2 ($SiCH_3$, $SiCH_3$). IR: 3416 (tertiary amine), 2930 (COC), 2358, 1465 (CH_3−), 784 (Ph−). MS (EI): 401 (17.8, M^+), 386 (10, M − H_2O), 344 (18.8, M−C_3H_5O), 213 (100), 131 (19, −OTBDMS). HRMS (EI): 401.2233, calcd for $C_{19}H_{35}NO_6Si$ 401.2238. $[\alpha]_D$ = −30.4 (0.80, CH_2Cl_2).

Cycloadduct 19j. Compound **19j** was obtained (oil, 8 mg, 37%) from ketone **4j** (20 mg, 0.05 mmol), MeNHOH·HCl (26 mg, 0.31 mmol), pyridine (16 μL, 0.2 mmol), and molecular sieves (20 mg) in EtOH (1 mL), as reported for **19a**. Total reaction time 2 h at reflux. Flash chromatography (AcOEt−hexane 10:90). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 5.84 (d, J = 3.7 Hz, 1H, H_1), 4.40 (d, 1H, H_2), 4.28 (s, 1H, H_4), 4.23 (s, 1H, H_3), 3.96 (d, J = 10.8 Hz, 1H, H_6), 3.68 (d, J = 10.8 Hz, 1H, $H_{6'}$), 3.46 (d, J = 12.3 Hz, 1H, H_7), 3.39 (d, J = 12.3 Hz, 1H, $H_{7'}$), 2.82 (s, 3H, NCH_3), 2.50 (d, J = 12.1 Hz, 1H, H_9), 1.78 (d, J = 12.1 Hz, 1H, $H_{9'}$), 1.46 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.29 (s, 3H, CH_3[1]), 0.88 (s, 9H, $C(CH_3)_3$), 0.08 (s, 6H, −$Si(CH_3)_2$). ^{13}C NMR (125 MHz, C_6D_6, 327 K) δ: 110.5 (($CH_3)_2C$-), 103.0 (C_1), 83.8, 81.0 (C_2, C_3, C_4), 74.7 (CH_2), 62.2 (CH_2), 39.8 (NCH_3), 28.7 (CH_2), 25.7 (($CH_3)_2$C−), 25.2 (($CH_3)_2$C−), 25.0 (C($CH_3)_3$), 24.0 (CH_3), 17.3 ($C(CH_3)_3$), −6.4, −5.0 (CH_3Si−). MS (FAB$^+$): 416 ($M^+ + 1$). HRMS: 415.2489, calcd for $C_{20}H_{38}NO_6Si$ 415.2471. $[\alpha]_D$ = −6.0 (0.82, CH_2Cl_2).

Cycloadduct 19k. Compound **19k** was obtained (oil, 30 mg, 43%) from ketone **4k** (65 mg, 0.18 mmol), MeNHOH·HCl (90 mg, 1.07 mmol), pyridine (60 μL, 0.72 mmol), and molecular sieves (50 mg) in EtOH (8 mL), as reported for **19a**. Total reaction time 8 h at reflux. Flash chromatography (AcOEt−hexane 10:90, 50:50). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37−7.26 (m, 5H, ArH), 5.91 (d, J = 3.7 Hz, 1H, H_1), 4.78 (d, J = 2.7 Hz, 1H, H_4*), 4.66 (d, J = 2.7 Hz, 1H, H_3*), 4.58 (m, 3H, H_2, CH_2), 4.10 (s, 1H, CH), 3.81 (ABq, J = 9.8 Hz, 2H, CH_2), 2.80 (s, 3H, NCH_3), 1.50 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.21 (s, 3H, CH_3). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 138.7 (C_{ipso}), 128.7, 127.8 (ArH), 112.3 (($CH_3)_2C$−), 106.7 (C_1), 97.1 (CH), 88.6, 83.7, 83.5 (C_2, C_3, C_4), 81.8 (C), 80.2 (C), 74.0 (CH_2), 68.5 (CH_2), 39.3 (N−CH_3), 27.5 (CH_3), 26.9 (CH_3), 25.3 (CH_3), 21.4(CH_3). MS (FAB$^+$): 392 ($M^+ + 1$). HRMS (FAB$^+$) 391.1999, calcd for $C_{21}H_{29}NO_6$ 391.1994. $[\alpha]_D$ = +24.8 (0.91, CH_2Cl_2).

Cycloadduct 19l. A solution of nitrone **5l** (134 mg, 0.40 mmol) and phenylacetylene (260 μL, 2.39 mmol) in toluene (2 mL) was heated at 50 °C. After 5 h, more phenylacetylene was added (4 equiv) and the reaction mixture stirred at 80 °C for 3 h. Removal of the solvent and flash chromatography (AcOEt/hexane 20%) gave cycloadducts **19la** (oil, 90 mg, 51%) and **19lb** (oil, 16 mg, 9%) in addition to ketone **4l** (36 mg, 26%). **19la.** ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.44 (m, 2H, ArH), 7.26 (m, 8H, ArH), 5.56 (d, J = 3.5 Hz, 1H, H_1), 5.17 (s, 1H, H_9), 4.56 (m, 3H, H_7, H_7, H_2), 4.14 (d, J = 9.5 Hz, 1H, H_4), 3.89 (d, J = 9.1 Hz, 1H, H_6), 3.78 (d, J = 9.1 Hz, 1H, H_6), 2.98 (s, 3H, NCH_3), 2.64 (m, 1H, H_3), 1.51 (s, 3H, $C(CH_3)_2$), 1.35 (s, 3H, $C(CH_3)_2$), 1.11 (d, J = 6.8 Hz, 3H, CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 152.9 (C_8), 138.3, 128.7 (C_{ipso}, C_{ipso}), 128.9, 128.3, 128.3, 127.5, 127.4, 125.5 (ArH), 111.4 ($C(CH_3)_2$), 104.5 (C_9), 95.5 (C_1), 85.0, 84.3 (C_2, C_4), 75.0 (C_5), 73.4, 70.7 (C_7, C_6), 38.1 (NCH_3), 27.1, 26.6 (C($CH_3)_2$), 11.4 (CH_3). MS (EI): 438 (0.5, $M^+ + 1$), 362 (47), 326 (100), 105 (70), 91 (86, C_7H_7). Anal. Calcd for $C_{26}H_{31}NO_5$: C, 71.37; H, 7.14; N, 3.19. Found: C, 71.16; H, 7.22; N, 2.81. **19lb.** ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.50 (m, 2H, ArH), 7.31 (m, 8H, ArH), 5.67 (d, J = 3.4, 1H, H_1), 4.97 (s, 1H, H_9), 4.55 (s, 1H, H_7), 4.53 (s, 1H, H_7), 4.46 (m, 1H, H_2), 4.22 (d, J = 9.8, 1H, H_4), 3.82 (d, J = 10.4, 1H, H_6), 3.70 (d, J = 10.4, 1H, H_6), 2.89 (s, 3H, N−CH_3), 2.05 (m, 1H, H_3), 1.51 (s, 3H, $C(CH_3)_2$), 1.31 (s, 3H, $C(CH_3)_2$), 1.26 (d, J = 6.8, 3H, CH_3). MS (EI): 362 (6), 316 (37), 105 (66), 91 (100, C_7H_7).

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Supporting Information Available: General experimental methods, detailed preparation procedures for all cycloaddition precursors, and ^{1}H, ^{13}C, DEPT, NOE, and 2-D NMR spectra of selected compounds. Cartesian coordinates and total energies of all stationary points obtained in the computational study. This material is available free of charge via the Internet at http://pubs.acs.org.

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