Oxa- and Azabicyclo[4.1.0]heptenes as New Synthons for C-Disaccharide and Alkaloid Synthesis. Reactivity Trends with Carbon Nucleophiles

Tomas Hudlicky,* Xinrong Tian, Kurt Königsberger, and Jacques Rouden

Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061

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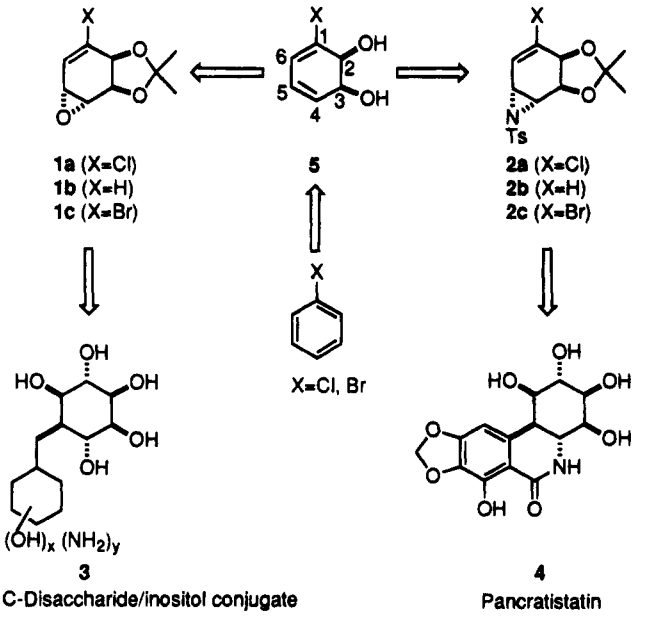
Summary: Homochiral vinyloxiranes and vinylaziridines were reacted with a series of organometallic reagents in order to determine the regio- and stereoselectivity of the ring opening with carbon nucleophiles.

The behavior of both acyclic and cyclic vinyloxiranes toward carbon nucleophiles has been well studied, and ample parameters are now available for the control of regioselectivity.[1,2] Although the opening of N-activated aziridines with various kinds of nucleophiles such as organocopper reagents[3] or Grignard reagents[4] has been reported and recently summarized,[3g] the reactions of vinylaziridines with nucleophiles have been limited to ring opening with iodide and subsequent rearrangements to pyrrolines,[1a] save for one example.[1b] In connection with a program that utilizes synthons **1** and **2** in rational approaches to C-disaccharides such as **3** and their amino derivatives, as well as to *Amaryllidaceae* alkaloids such as pancratistatin (**4**), Scheme 1, it became crucial to understand the modes of reactivity of the two title compounds toward carbon nucleophiles.

Synthons **1** and **2** are readily available by means of our published biocatalytic protocol—oxidation of haloarenes with microbial dioxygenase—followed by functionalization of the C4—C5 olefin in cyclohexadiene diols such as **5** to either **1**[5] or **2**.[6] In this paper we report the initial findings relevant to the pursuits of the goals delineated in Scheme 1. Despite the volume of literature on the synthetic utility of cyclohexadiene-*cis*-diols of type **5**[7] and their facile functionalization, reports of successful attachment of carbon residues to the inositol framework

Scheme 1



are rare, confined thus far to only one report on the opening of a conduritol epoxide with acetylide.[8]

Two series of compounds were examined for their reactive tendencies: the epoxides and aziridines containing either the vinyl chloride unit (**1a**, **2a**) or their dehalogenated forms (**1b**, **2b**). The two series were scrutinized in parallel in order to assess the influence of the electron-withdrawing properties of the halogen atom on the regioisomeric outcome of the reaction. Treatment of **1a** with phenyllithium resulted in the formation of an elimination product **6**,[9] whereas aziridine **2a** did not show any elimination under these conditions as it requires Lewis acid activation. Reactions of **1a** with Grignard reagents and cuprates furnished products of both S_N2 and S_N2' opening, Table 1. The expected S_N2' mode was predominant with epoxide **1b**, which lacks the bulky, electron-withdrawing halogen atom. Only in one instance (entry 5) was the normal opening mode observed in low yield with a small nucleophile. The *syn*-stereochemistry of the S_N2' additions to **1** and **2** exhibited by the Gilman reagents and the cuprates derived from

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(1) (a) For a recent review see: Hudlicky, T.; Reed, J. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, GB, 1991; Vol. 5, p 899. (b) During revision of the manuscript a communication on ring opening of vinyl aziridines appeared: Ibuka, T.; Nakai, K.; Habashita, H.; Hotta, Y.; Fujii, N.; Mimura, N.; Miwa, Y.; Taga, T.; Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 652.

(2) For recent literature see: (a) Chini, M.; Crotti, P.; Flippin, L. A.; Macchia, F.; Pineschi, M. *J. Org. Chem.* **1992**, *57*, 1405. (b) Chini, M.; Crotti, P.; Flippin, L. A.; Gardelli, C.; Macchia, F. *J. Org. Chem.* **1992**, *57*, 1713.

(3) (a) Eis, M. J; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 1153. (b) Duréault, A.; Tranchepain, I.; Greck, C.; Depezay, J. C. *Tetrahedron Lett.* **1987**, *28*, 3341. (c) Baldwin, J. E.; Adlington, R. M.; O'Neil, I. A.; Schofield, C.; Spivey, A. C.; Sweeney, J. B. *J. Chem. Soc., Chem. Commun*, **1989**, 1852. (d) Tanner, D.; Birgersson, C.; Dhaliwal, H. K. *Tetrahedron Lett.* **1990**, *31*, 1903. (e) Tanner, D.; He, H. M.; Somfai, P. *Tetrahedron* **1992**, *48*, 6069. (f) Ibuka, T.; Nakai, K.; Habashita, H.; Fujii, N.; Garrido, F.; Mann, A.; Chounan, Y.; Yamamoto, Y. *Tetrahedron Lett.* **1993**, *34*, 7421. (g) For a review see: Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599.

(4) (a) Kozikowski, A. P.; Ishida, H.; Isobe, K. *J. Org. Chem.* **1979**, *44*, 2788. (b) Onistschenko, A.; Buchholz, B.; Stamm, H. *Tetrahedron* **1987**, *43*, 565.

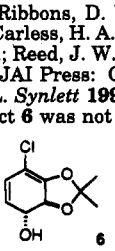
(5) (a) Hudlicky, T.; Fan, R.; Tsunoda, T.; Luna H.; Andersen, C.; Price, J. D. *Isr. J. Chem.* **1991**, *31*, 229. (b) Carless, H. A. *Tetrahedron Lett.* **1992**, *33*, 6379.

(6) (a) Yamada, Y.; Yamamoto, T.; Okawara, M. *Chem. Lett.* **1975**, 361. (b) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Org. Chem.* **1991**, *56*, 6744. (c) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328. (d) Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326.

(7) (a) Brown, S. M.; Hudlicky, T. In *Organic Synthesis: Theory and Practice*; Hudlicky, T., Ed.; JAI Press: Greenwich, CT, 1993; Vol. 2, p 113. (b) Widdowson, D. A.; Ribbons, D. W.; Thomas, S. D. *Janssen Chim. Acta* **1990**, *8*(3), 3. (c) Carless, H. A. J. *Tetrahedron: Asymmetry* **1992**, *3*, 795. (d) Hudlicky, T.; Reed, J. W. In *Advances in Asymmetric Synthesis*; Hassner, A., Ed.; JAI Press: Greenwich, CT, 1994.

(8) Ley, S. V.; Yeung, L. L. *Synlett* **1992**, 291.

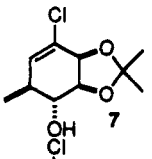
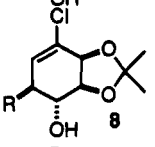
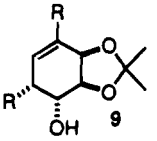
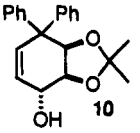
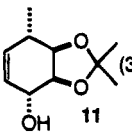
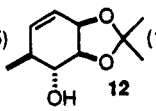
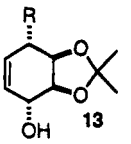
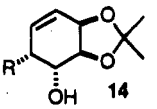
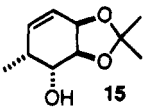
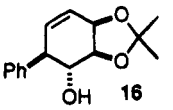
(9) The elimination product **6** was not stable at rt.



(10) Marshall, J. A. *Chem. Rev.* **1989**, *89*, 1503.

0022-3263/94/1959-4037$04.50/0

Table 1. Reactions of Vinyloxiranes

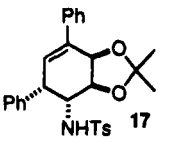
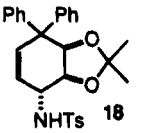
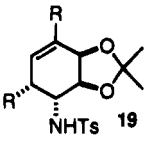
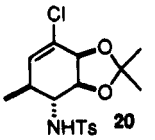
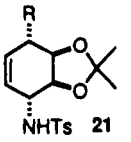
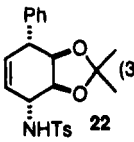
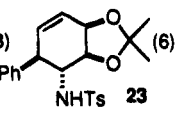
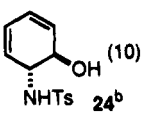
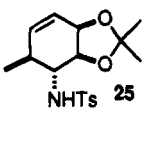
Entry / Electrophile	Nucleophile [a] / conditions	Product(s),[a] (%)
1 / **1a**	MeMgBr/ 10%CuI THF/-78°C to -40°C	 **7** (58)
2	RMgBr/10% CuI THF/-78°C to 0°C	 **8** (39)
3	R_2CuLi Et_2O/THF/-78°C to -40°C	 **9** (14) + **8** (4)
4	Ph_2CuLi/Et_2O/0°C	 **10** (8) + aromatic products
5 / **1b**	MeMgBr /10% CuI Et_2O/THF/-40°C	 **11** (35)  **12** (11)
6	RMgBr / 10% CuI THF/-78°C to -10°C	 **13** (83)
7	R_2CuLi Et_2O/THF/ -78°C to -40°C	 **14** (37) + **13** (5)
8	Me_2CuLi Et_2O/THF/-78°C	 **15** (30)
9	$PhSnMe_3/Pd(0)$ DMF/H_2O/rt	 **16** (10)

[a] R = cyclohexylmethyl.

Grignard reagent reflects the effect of the acetonide group, which directs the nucleophilic attack to the less hindered α-face. This observation contrasts with the expected *anti* - opening of vinyloxirane reported in the literature.[10] Detailed investigations will be required to distinguish between the mechanistic possibilities. Opening of **1b** with phenyltrimethyltin under Pd(0) catalysis[11] afforded the product of a formal S_N2 reaction, **16**, in low yield. The stereochemistry of the products was determined by NOE difference spectroscopy as well as by analysis of coupling constants and comparison with similar systems. The preparations of **7**–**9** as well as **13** bode well for applications in the synthesis of C-disaccharides and cyclitol conjugates once the conditions are optimized for these reactions.

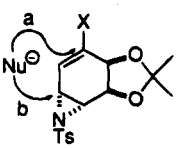
The behavior of aziridines **2a** and **2b** was similar, Table 2. No normal opening was observed for lithium

Table 2. Reactions of Vinylaziridines

Entry / Electrophile	Nucleophile [a] / conditions	Product(s),[a] (%)
1 / **2a**	Ph_2CuLi THF/-78°C to RT	 **17** (52)
2	Ph_2Cd/THF/50°C	 **18** (50)
3	Ph_2Zn/THF/ Et_2O/RT	**17** + **18** 3 : 1 (36)
4	R_2CuLi/Et_2O/THF -78°C to -40°C	 **19** (89)
5	MeMgBr/CuI THF/Et_2O/ -45°C	 **20** (53)
6 / **2b**	R_2CuLi/Et_2O/THF -78°C to -40°C	 **21** (76)
7	Ph_2CuLi/THF -78°C to RT	 **22** (38)  **23** (6)
8	$Ph_2CuCNLi_2$/ THF/-78°C	**23** (23)
9	$PhMe_3Sn/Pd(0)$ DMF/H_2O/RT	**23** (19)  **24**[b] (10)
10	MeMgBr/CuI THF/Et_2O/ -45°C	 **25** (29)

[a] R = cyclohexylmethyl. [b] See ref 12.

cuprates, except for a low amount of **23** identified as a byproduct. As with epoxide **1a**, Grignard reagents preferentially yielded products of normal S_N2 opening (path b). The use of cyanocuprates with **2b** allowed for a reasonable initial yield of **23**, whose synthesis serves as a model for an approach to pancratistatin. An interesting byproduct isolated from the Pd(0) catalyzed opening of **2b** with trimethylphenyltin was the *trans*-amino alcohol **24**, which may find use as an amino sugar synthon.[12]



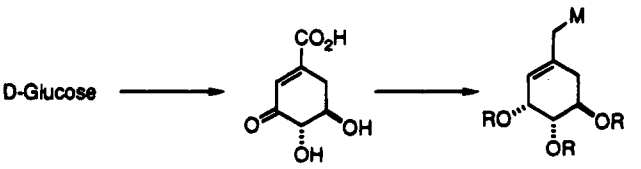
2a, X=Cl
2b, X=H

The exploratory results reported in this paper are exciting and will be carefully optimized and incorporated

(11) For details on the mechanism of this reaction see: Tueting, G. R.; Echavarren, A. M.; Stille, J. K. *Tetrahedron* **1989**, *45*, 979.

(12) Compound **24** was also obtained in 50–60% yield when **2c** was reduced with sodium naphthalide in dimethoxyethane.

into the compendium of synthetic methods.[13] For an approach to *Amaryllidaceae* alkaloids the cuprate derived from the aryl residue reported by Heathcock[14] will be used.[15] For an approach to C-disaccharides containing aminocyclitol units, products **19**, **21**, and **22** of this model study are ideally suited. The cyclohexylmethyl moiety will be replaced with **29** derived from dehydroshikimate **28**, which is now available biocatalytically via the shikimic acid pathway.[16] We will report on the optimization and further applications in due course.



28 **29**

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Supplementary Material Available: Experimental procedures and copies of ^1H and ^{13}C NMR spectra of **2a–c** and **7–25** (58 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(13) A full discussion of the mechanistic aspects of this work will be included in a full paper.

(14) Lopes, R. S. C.; Lopes, C. C.; Heathcock, C. H. *Tetrahedron Lett.* **1992**, *33*, 6775.

(15) The aryl unit reported by Heathcock[14] and required for pancratistatin (**4**) has been successfully added to **2b** in 49% yield: Hudlicky, T.; Tian, X.; Königsberger, K.; Rouden, J. Unpublished results.

(16) (a) Draths, K. M.; Pompliano, D. L.; Conley, D. L.; Frost, J. W.; Berry, A.; Disbrow, G. L.; Staversky, R. J.; Lievense, J. C. *J. Am. Chem. Soc.* **1992**, *114*, 3956. (b) Draths, K. M.; Ward, T. L.; Frost, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 9725.