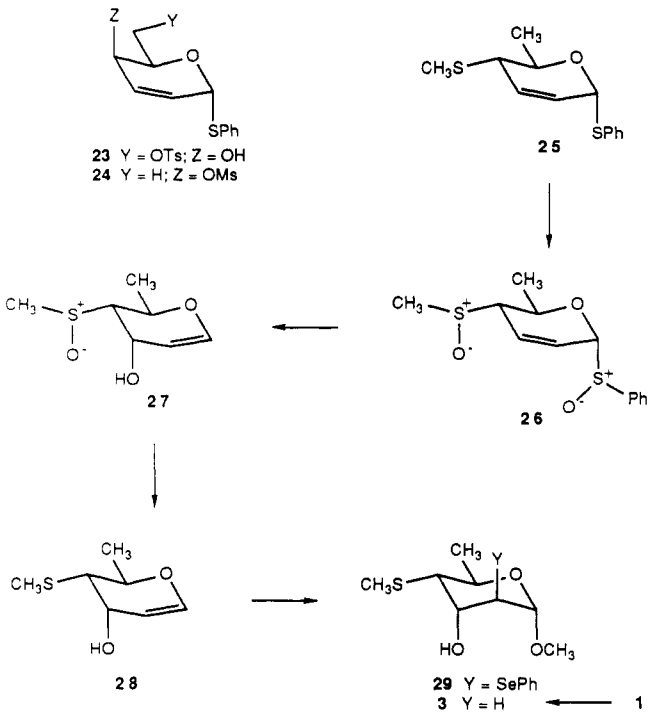
Scheme III



While additional investigations will be required to delineate the scope and mechanism of the new glycal synthesis, it has already been used to advantage in reaching the desired target system **3**. For this purpose, we returned to the galactal derived sulfide **19**. Twofold deacetylation (sodium methoxide–methanol, room temperature) was followed by treatment with dibutyltin oxide and tosyl chloride in chloroform. There was thus obtained in 60% yield the monotosylate **23**.[9] Reduction of the latter with lithium aluminum hydride followed by mesylation (mesyl chloride, triethylamine, CH_2Cl_2, 0 °C) afforded **24** (Scheme III). The bis thio compound **25**[9] was obtained (70% overall from **23**) upon reaction of **24** with sodium methanethiolate. Reaction of **25** with 2.1 equiv of mCPBA followed by exposure of the bis sulfoxide **26** to diethylamine afforded monosulfoxide **27**. It is interesting to note that the rate of [2,3]-rearrangement[11,12] of the anomeric phenylsulfinyl function of **26** is apparently much more rapid than is the hypothetical corresponding reaction of the methanesulfinyl group. The anomeric effect would favor rearrangement in the observed sense.[14] Moreover, the rate of the observed [2,3]-process may be further enhanced by virtue of the axial character of the phenylsulfinyl group as opposed to the equatorial nature of the methanesulfinyl unit.

Glycal **28**[9] (64% overall from **25**) was obtained by reduction of **27** with lithium aluminum hydride. Methoxyselenation[15] (PhSeCl, MeOH, toluene, 0 °C) of **28** afforded **29**, which upon reduction with Ph_3SnH–AIBN [2,2′-azobis(2-methylpropionitrile)], provided the methyl glycoside **3** (53% overall from **28**).[15] The same compound was obtained by treatment of esperamicin with methanolic HCl.[1] The NMR spectra (300 MHz) and optical rotations [synthetic sample $[\alpha]_D$ ($CHCl_3$, *c* 0.61) +270°, degradation product $[\alpha]_D$ ($CHCl_3$, *c* 0.275) +273°] are the same.

In summary, a new route to glycals of the type **4** or **5** has been developed. The method has been applied to the synthesis of glycal **28**, a possible intermediate for the total synthesis of the esperamicin trisaccharide **2**. Methoxyselenation–reduction was used to convert **28** to the α-methyl glycoside **3**, obtained by degradation of esperamicin.[1] *This synthesis rigorously establishes the absolute configuration of the thiosugar residue of esperamicin.*[16]

Acknowledgment. This research was supported by PHS Grant CA28824. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by NSF Chemistry Division Grant CHE7916210. An NIH Postdoctoral Fellowship to M.D.W. (Grant 1F32CA08641-01) is gratefully acknowledged.

Supplementary Material Available: ^1H NMR, IR, HRMS, optical rotation, and melting point data for compounds **11**, **13**, **17**, **19**, **23**, **25**, **28**, and **3** (2 pages). Ordering information is given on any current masthead page.

(14) Curran, D. P.; Suh, Y.-G. *J. Am. Chem. Soc.* **1984**, *106*, 5002.
(15) For examples of the synthesis of 2-deoxy glycosides from glycals, see: (a) Lemieux, R. U.; Fraser-Reid, B. *Can. J. Chem.* **1964**, *42*, 539. (b) Lemieux, R. U.; Fraser-Reid, B. *Can. J. Chem.* **1964**, *42*, 547. (c) Thiem, J. *Trends in Synthetic Carbohydrate Chemistry*; Horton, D., Hawkins, L. D., McGarvey, G. J., Eds.; ACS Symposium Series 386; American Chemical Society: Washington, DC, 1989; Chapter 8 and references therein. For leading references to alkoxyselenation reactions of glycals, see: (d) Jaurand, G.; Beau, J.-M.; Sinäy, P. *J. Chem. Soc., Chem. Commun.* **1981**, 572. (e) Jaurand, G.; Beau, J.-M.; Sinäy, P. *J. Chem. Soc., Chem. Commun.* **1982**, 701. (f) Beau, J.-M.; Jaurand, G.; Esnault, J.; Sinäy, P. *Tetrahedron Lett.* **1987**, 1105.
(16) The absolute configuration of **3** has also been determined by single-crystal X-ray analysis of its *p*-bromobenzoate: Golik, J.; Clardy, J. Unpublished results.

On the Conversion of Biologically Interesting Amines to Hydroxylamines

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Summary: Oxidation of amines to hydroxylamines with 2,2-dimethyldioxirane is described. This new method is utilized to prepare disaccharide hydroxylamine **13**.

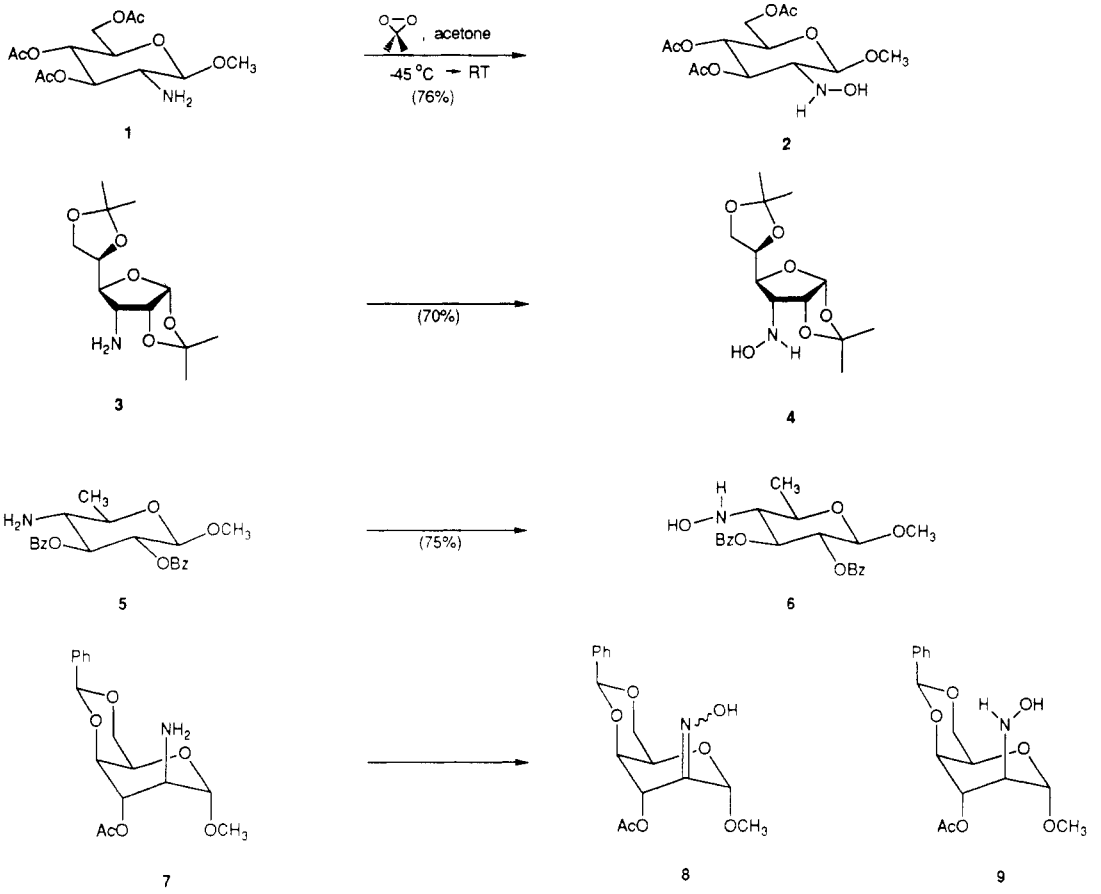
One of the many fascinating features of the trisaccharide of esperamicin[1] is the presence of a hydroxylamino sugar glycosidically linked to a sulfur-containing sugar. In the previous paper[2] we have described some new chemistry which produced a potential glycosyl donor variation of the thiosugar. Herein we concern ourselves with chemistry designed to produce equatorial hydroxylamino sugars. In particular, we wondered about the possibility that hydroxylamino sugars might be accessible by direct oxidation of the corresponding amines. In this way, the relatively

(1) (a) Golik, J.; Clardy, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3461. (b) Golik, J.; Dubay, G.; Groenewald, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3462.

(2) Wittman, M. D.; Halcomb, R. L.; Danishefsky, S.; Golik, J.; Vyas, D. *J. Org. Chem.*, preceding paper in this issue.

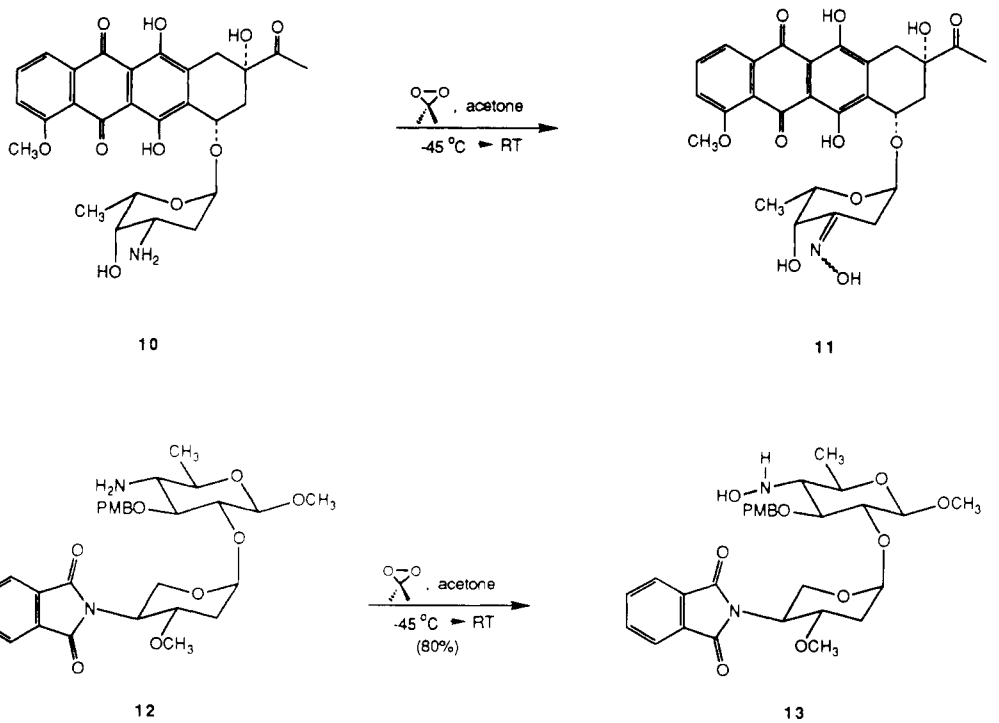
0022-3263/90/1955-1981$02.50/0

Scheme I



1 2 3 4 5 6 7 8 9

Scheme II



10 11 12 13

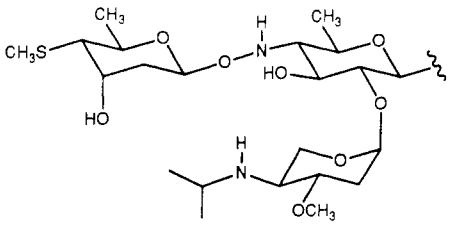
well developed capacity for preparing stereochemically homogeneous amino sugars could be used, obviating the necessity for a stereoselective oxime reduction.[3] Alternatively, hydroxylamines have been obtained from the corresponding amines by a sequence involving imine formation, oxidation, and oxaziridine hydrolysis.[4] A direct oxidation would not only simplify the synthetic procedure but also enable synthesis of hydroxylamino sugars with

(3) For reduction of oximes to hydroxylamino sugars, see: (a) Tronchet, J. M. J.; Habashi, F.; Fasel, J.-P.; Zosimo-Landolfo, G.; Barbalat-Rey, F.; Moret, G. *Helv. Chim. Acta* **1986**, *69*, 1132. (b) Tronchet, J. M. J.; Bizzozero, N.; Geoffroy, M. *Carbohydr. Res.* **1989**, *191*, 138.

(4) Polonski, T.; Chimiak, A. *Tetrahedron Lett.* **1974**, *28*, 2453.

functionality not compatible with oxaziridine hydrolysis.

A particularly attractive possibility as a potential oxidizing agent would be 2,2-dimethyldioxirane—a reagent of increasing importance in synthesis.[5] We have found that the use of stoichiometric amounts of 2,2-dimethyldioxirane will oxidize most amines to the hydroxylamines without further oxidation to the nitro compounds as reported by Murray[6] (the hydroxylamines of amines **7** and **10** were not observed).

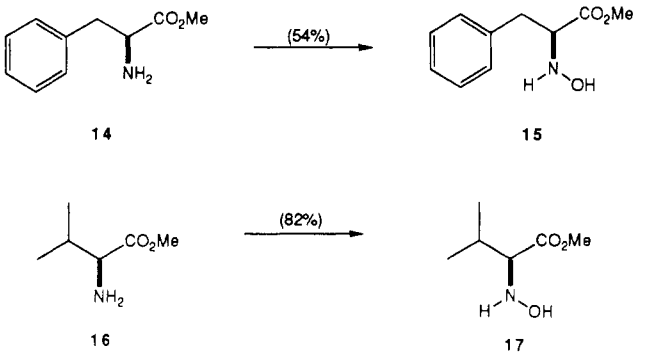


Esperamicin trisaccharide

Reaction of the β-methyl glycoside of 3,4,6-triacetylglucosamine (**1**)[7a] with 2,2-dimethyldioxirane as prepared by Murray[5b] was carried out in acetone from −45 °C to room temperature. There was isolated a 61% yield of the hydroxylamine **2**.[7b,8] The structure of **2** follows from its NMR spectrum, which indicates no change from **1** in the number or multiplicity of carbon-bound protons, and its mass spectrum (*m/e* 335) which indicates a net gain of 16 mass units.[9]

Similarly the 3-aminoallofuranose **3**[10] afforded the corresponding hydroxylamine **4**[3a] (70% yield) while the 4-amino derivative **5**[11] gave **6**[8] in 75% yield (Scheme I).

Scheme III



In contrast to the straightforward oxidation of amines with 2,2-dimethyldioxirane, we were unable to oxidize amine **5** to hydroxylamine **6** using *m*-chloroperoxybenzoic acid, nor were we able to reduce the corresponding nitro compound to the hydroxylamine with Zn/NH_4Cl.

Some potential complications may be foreshadowed by the failure of the benzylidene 2-aminoidose derivative **7**[12] to react in the usual way. Instead of the expected **9**, there was obtained a mixture of starting material and oxime **8**.[13] Likewise, oxidation of daunomycin **10**[14] provided the oxime **11** (Scheme II). While the reasons for the over oxidation of amines **7** and **10** are unknown, the method appears to be well suited for the oxidation of complex amines such as **12**. Thus disaccharide amine **12**[15] is oxidized to the corresponding hydroxylamine **13**.

It was of interest to explore the oxidation of other biologically interesting amines to hydroxylamines by the aforedescribed method. Oxidation of amino acid derivatives **14** and **16** to **15** and **17**,[4] respectively (Scheme III), without racemization is suggestive of an excellent future for this reaction. While the full scope and quality of the process remain to be explored, it seems likely to have significant impact in the oxidation of amines and usefulness particularly in the esperamicin–calicheamicin area.

Acknowledgment. This research was supported by PHS Grant CA28824. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by NSF Chemistry Division Grant CHE9716210. An NIH Postdoctoral Fellowship to M.D.W. (Grant 1F32CA08641-01) is gratefully acknowledged.

Supplementary Material Available: ^1H NMR, IR, HRMS, optical rotation, and melting point data for compounds **2**, **4**, **6**, **8**, **11**, **13**, **15**, and **17** (3 pages). Ordering information is given on any current masthead page.

(5) (a) Curci, R.; Fiorentino, M.; Troisi, L.; Edwards, J. O.; Pater, R. H. *J. Org. Chem.* **1980**, *45*, 4758. (b) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847. (c) Adam, W.; Chan, Y.-Y.; Cremer, D.; Gauss, J.; Scheutzow, D.; Schindler, M. *J. Org. Chem.* **1987**, *52*, 2800. (d) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187. (e) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205. (f) We have prepared and stored up to 100 mL of 0.1 M solutions of 2,2-dimethyldioxirane without incident.

(6) For the oxidation of amines to nitro compounds using 2,2-dimethyldioxirane, see: (a) Murray, R. W.; Jeyaraman, R.; Mohan, L. *Tetrahedron Lett.* **1986**, *27*, 2335. (b) Murray, R. W.; Singh, M. *Tetrahedron Lett.* **1988**, *29*, 4677. (c) Zabrowski, D. L.; Moormann, A. E.; Beck, K. R. *Tetrahedron Lett.* **1988**, *29*, 4501. (d) Murray, R. W.; Rajadhyaksha, S. N.; Mohan, L. *J. Org. Chem.* **1989**, *54*, 5783. Reference 4d cites such an oxidation of a pyrolidine. To our knowledge there are no previous reports of an oxidation of a primary amine to a hydroxylamine with 2,2-dimethyldioxirane. During publication, Murry reported the oxidation of secondary amines to hydroxylamine could be accomplished with 2,2-dimethyldioxirane see: Murry, R. W.; Singh, M. *Synth. Commun.* **1989**, *19*, 3509.

(7) (a) Yamasaki, T.; Kubota, Y.; Tsuchiya, T.; Umezawa, S. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3190. (b) The following procedure is representative: The amine **1** (0.129 mol) in acetone (2 mL) at −45 °C was treated with the dioxirane (1.2 mL, 0.9 M in acetone) and slowly warmed to ambient temperature over 2 h to provide hydroxylamine **2** (24 mg) and recovered amine (76% based on recovered amine).

(8) Each hydroxylamine reported has been characterized by ^1H NMR, IR, and high-resolution mass spectrometry.

(9) In addition, there is observed a characteristic upfield shift (Δ 0.2 ppm) of the resonance of the proton on the carbon bearing the hydroxylamine relative to the corresponding amine.

(10) Malik, A.; Nighat, A.; Roosz, M.; Voelter, W. *J. Chem. Soc., Chem. Commun.* **1984**, *22*, 1530.

(11) Stevens, C. L.; Ransford, G. H.; Nemec, J.; Cahoon, J. M.; Pillai, P. M. *J. Org. Chem.* **1974**, *39*, 298.

(12) Guthrie, R. D.; Liebmann, J. A. *J. Chem. Soc., Perkin Trans 1* **1974**, 650.

(13) The structure of oxime **8** was supported by the absence of one of the carbon bound protons and by high-resolution mass spectroscopy.

(14) We gratefully acknowledge the National Cancer Institute for a generous gift of daunomycin.

(15) The preparation of the amino disaccharide **10** of relevance to esperamicin, will be disclosed shortly.