useful alternative to the classical Horner–Wadsworth–Emmons reaction.

Acknowledgment. We would like to thank Walter Johnson, Priscilla Offen, and Scott Dixon at SK&F for exact mass determination, NOE studies, and MO calculations, respectively, and both Paul Gassman and Larry Overman for stimulating discussions.

Supplementary Material Available: IR and NMR data given for *E*-**3a**, *E*-**5a**, *E*-**6**, *E*-**7**, *E*-**8** (R″ = Me), *E*-**9**, *E*-**10**, *Z*-**10**, *E*-**11**, *E*-**12**, *E*-**13**, *Z*-**13**, *Z*-**14** (R = H), *E*-**14** (R = H), *E*/*Z*-**14** (R = Me), with high-resolution mass spectral data for new compounds (2 pages). Ordering information is given on any current masthead page.

A Route to Glycals in the Allal and Gulal Series: Synthesis of the Thiosugar of Esperamicin A_1

Mark D. Wittman, Randall L. Halcomb, and Samuel J. Danishefsky*
Department of Chemistry, Yale University, New Haven, Connecticut 06511
Jerzy Golik and Dolatrai Vyas
Bristol-Myers Squibb Company, Wallingford, Connecticut 06492
Received December 7, 1989

Summary: Axial anomeric sulfoxides generated via thiophenol Ferrier rearrangement of glucal and galactal derivatives are used to synthesize glycals of the gulal and allal series. An application of the method led to the synthesis of the esperamicin thiosugar, thereby establishing its absolute configuration.

The advent of the potent DNA cutting antibiotics esperamicin (**1**)[1] and calicheamicin[2] raises numerous issues in biology and chemistry. Not the least of the challenges and opportunities for organic synthesis in this area is that of the carbohydrate sector (cf. esperamicin trisaccharide type, **2**). While the enediyne carbocyclic region presumably serves as the source of the chemically destructive properties,[3] the carbohydrate ensemble may well play an important role as a recognition marker for the oligonucleotide.[4] In this paper we describe a synthesis of the hexose containing the thiomethyl group.[5]

While the methyl glycoside **3** was the focus of the effort, a more general objective was that of providing access to glycals bearing 3-axial alcohol derivatives, with a range of substituents at C4 (see allal and gulal structures **4** and **5**, respectively).[6] Glycals of this type might be useful intermediates for reaching **3** and might serve as glycosyl donors pursuant to a projected synthesis of the larger goal, i.e. system **2** (see Scheme I).

The concept is well illustrated by the conversion of the commercially available triacetylglucal (**6**) to the allal derivative **11**. Treatment of **6** with benzenethiol (BF_3·OEt_2–methylene chloride −78 °C) afforded, by Ferrier type rearrangement,[7a,b] the α-(phenylthio)pseudoglycal[7c] in 72% yield. There was also produced ca. 8% of the corresponding β-phenylthio anomer. Compound **7** was oxidized with *m*-chloroperoxybenzoic acid (mCPBA) in methylene chloride at 0 °C.[8] Exposure of resultant sulfoxide **8** to piperidine at room temperature afforded a 70% yield of **11**.[9] In a similar way L-rhamnal derivative **12** was converted to α-sulfide **13**[9] (71% yield) and thence to **17**[9] in 30% overall yield.[10]

The most obvious formulation of these results involves [2,3] sigmatropic rearrangement of **8** and **14**,[11,12] leading to sulfenates **9** and **15**, respectively (Scheme II). These intermediates are interdicted with piperidine to give **10** and **16**, which undergo acyl transfer to provide the observed products **11** and **17**. An alternate formulation, which avoids the need to invoke an acyl transfer, contemplates neighboring group participation by the trans-dis-

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

(2) (a) Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3464. (b) Lee, M. D.; Dunne, T. S.; Chang, C. C.; Ellestad, G. A.; Siegel, M. M.; Morton, G. O.; McGahren, W. J.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3466.

(3) For a review of the seminal experiments involving the generation of aromatic 1,4-diyls from cis-enediynes see: (a) Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25. For early applications of the generation of aromatic 1,4-diradicals to mimic the mode of action of the esperamicins and calicheamicins, see: (b) Magnus, P.; Lewis, R. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 6921. (c) Magnus, P.; Carter, P. A. *J. Am. Chem. Soc.* **1988**, *110*, 1626. (d) Nicolaou, K. C.; Zuccarello, G.; Ogawa, Y.; Schweiger, E. J.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4866. For examples of the use of related 1,4-diyls, such as that derived from esperamicin, in DNA cleavage, see: (e) Nicolaou, K. C.; Ogawa, Y.; Zuccarello, G.; Kataoka, H. *J. Am. Chem. Soc.* **1988**, *110*, 7247. (f) Mantlo, N. B.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 2781. (g) Zein, N.; McGahren, W. J.; Morton, G. O.; Ashcroft, J.; Ellestad, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 6888.

(4) (a) Hawley, R. C.; Kiessling, L. L.; Schreiber, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 1105. (b) Zein, N.; Poncin, M.; Nilakantan, R.; Ellestad, G. A. *Science* **1989**, *244*, 697. (c) Long, B. H.; Golik, J.; Forenza, S.; Ward, B.; Rehfuss, R.; Dabrowiak, J. C.; Catino, J. J.; Musial, S. T.; Brookshire, K. W.; Doyle, T. W. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 2. (d) Sugiura, Y.; Uesawa, Y.; Takahashi, Y.; Kuwahara, J.; Golik, J.; Doyle, T. W. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 7672.

(5) A nonselective synthesis of the thiol analogue of the methylthio monosaccharide was recently reported: Scharf, H.-D.; Laak, K. V. *Tetrahedron* **1989**, *34*, 4505.

(6) All attempted reductions of the corresponding ketones lead to equatorial alcohols: (a) Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 15. Attempts to directly invert the equatorial 3-OH using Mitsunobu conditions or by displacing equatorial leaving groups led only to S_n2' reactivity. For some previous preparations of allal and gulal derivatives, see: (b) Sharma, M.; Brown, R. K. *Can. J. Chem.* **1966**, *44*, 2825. (c) Lemieux, R. U.; Fraga, E.; Watanabe, K. A. *Can. J. Chem.* **1968**, *46*, 61.

(7) (a) Ferrier, R. J.; Prasad, N. *J. Chem. Soc. C* **1969**, 570. (b) Ferrier, R. J. *Adv. Carbohydr. Chem. Biochem.* **1969**, *24*, 199. (c) Valverde, S.; Garcia-Ochoa, S.; Martin-Lomas, M. *J. Chem. Soc., Chem. Commun.* **1987**, 383.

(8) The sulfoxides were isolated but were not characterized. They were immediately treated with piperidine without any attempt to isolate their corresponding sulfenates. For a striking demonstration of the lability of anomeric sulfoxides, see: Kahne, D.; Walker, S.; Cheng, Y.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881.

(9) All new compounds were characterized by IR and NMR spectroscopy, HRMS, and optical rotation.

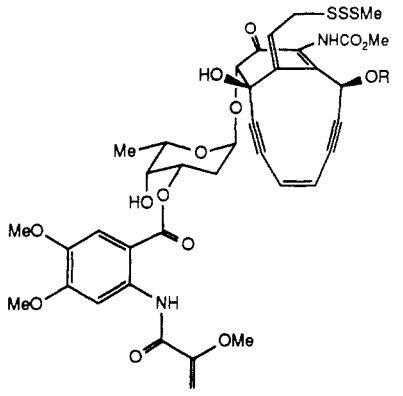
(10) Complications arising from the votalility of glycal **17** rather than differences in chemistry are responsible for the decreased yields in this case.

(11) (a) Bickart, P.; Carson, F. W.; Jacobus, J.; Miller, E. G.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4869. (b) Tang, R.; Mislow, K. *J. Am. Chem. Soc.* **1970**, *92*, 2100.

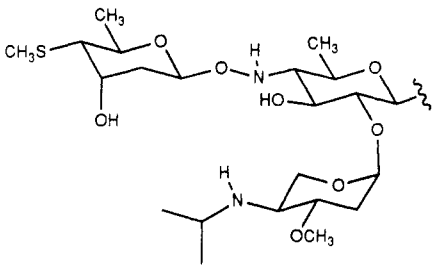
(12) (a) Evans, D. A.; Andrews, G. C.; Sims, C. L. *J. Am. Chem. Soc.* **1971**, *93*, 4956. (b) Evans, D. A.; Bryan, C. A.; Sims, C. L. *J. Am. Chem. Soc.* **1972**, *94*, 2891. (c) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147.

0022-3263/90/1955-1979$02.50/0

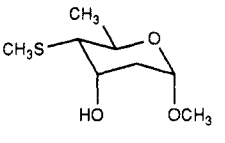
Scheme I



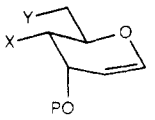
1 esperamicin
R = esperamicin trisaccharide



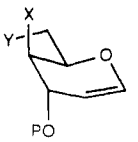
2 = esperamicin trisaccharide



3

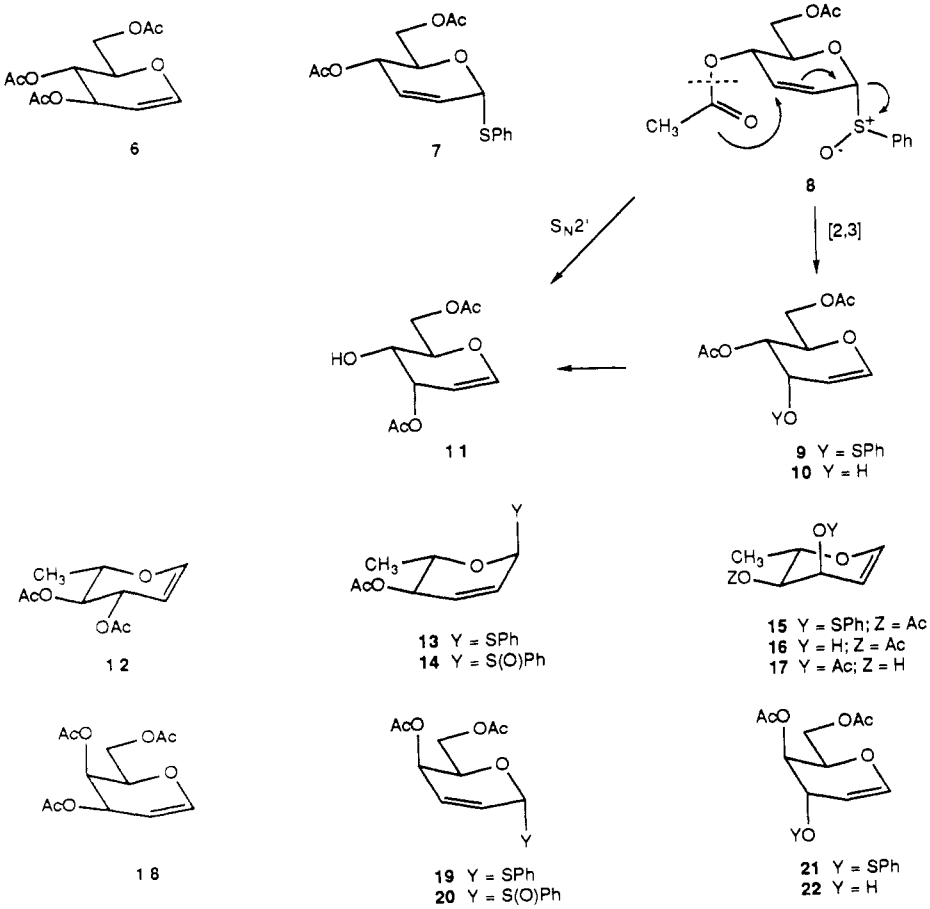


4 (allal derivatives)



5 (gulal derivatives)

Scheme II



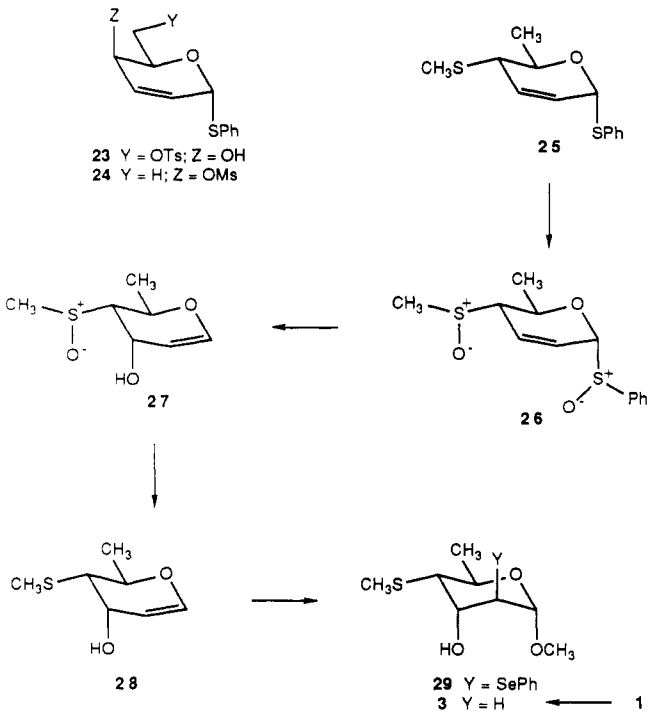
6 7 8 9 Y = SPh; 10 Y = H 11 12 13 Y = SPh; 14 Y = S(O)Ph 15 Y = SPh; Z = Ac; 16 Y = H; Z = Ac; 17 Y = Ac; Z = H 18 19 Y = SPh; 20 Y = S(O)Ph 21 Y = SPh; 22 Y = H

posed acetoxyl functions in **8** and **14** followed by solvolysis of the respective acetoxonium species.[13]

That the [2,3]-rearrangement mechanism is viable in other cases is seen from the transformation of D-galactal triacetate **18** to **22**[9] (60% overall) via sulfide **19**.[9] In this instance no acyl transfer is observed and the process is well accommodated by proposing rearrangement of sulfoxide **20** and interdiction of sulfenate **21**.

(13) A problem with the simple acetoxonium mechanism is that glycal formation is not noted until thiophile[12] (either secondary amine or phosphite) is added.

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

Mark D. Wittman, Randall L. Halcomb, and Samuel J. Danishefsky*
Department of Chemistry, Yale University, New Haven, Connecticut 06511
Received December 7, 1989

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