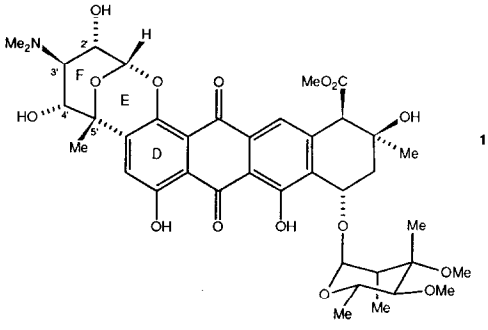
Tetrahedron Letters,Vol.27,No.40,pp 4885-4888,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

AN APPROACH TO THE ARYL-C-GLYCOSIDE DEF-RING SYSTEM OF NOGALAMYCIN

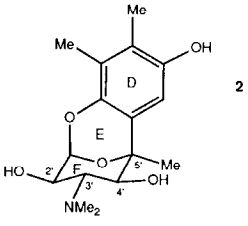
Richard P. Joyce, M. Parvez, and Steven M. Weinreb*
Department of Chemistry, The Pennsylvania State University
University Park, Pennsylvania 16802

ABSTRACT: Ketone **16**, a key intermediate in synthesis of the nogalamycin DEF-rings, has been efficiently and stereospecifically synthesized in nine steps using a strategy centered on an intramolecular N-sulfinyl dienophile Diels-Alder cycloaddition.

Nogalamycin (**1**) is a novel anthracycline antitumor antibiotic produced by *Streptomyces nogalater*.[1,2] The fact that a semisynthetic derivative of **1** (*ie* 7-*con*-O-methylnogarol) is a promising human cancer chemotherapy agent,[1] coupled with the interesting structures of nogalamycin and its congeners,[3] make it an



1

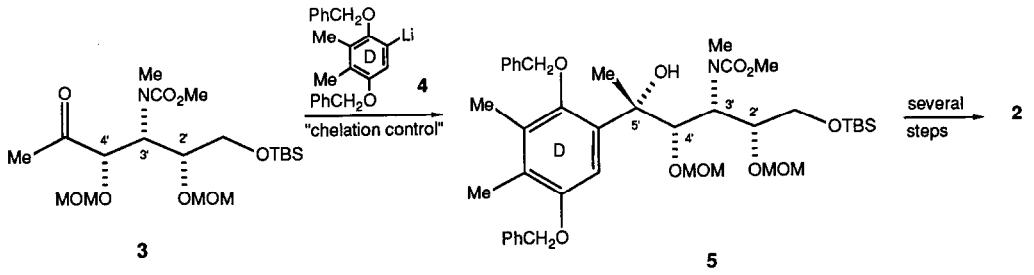


2

exciting synthetic target. In particular, the bridged amino sugar DEF moiety containing an aryl-C-glycosidic bond presents an especially interesting challenge. This structural fragment is exemplified by the nogalamycin model system **2**.

We have been involved in developing a synthesis of **2**, and we envisioned a strategy involving an important intermediate ketone such as **3** (Scheme 1), which bears three of the chiral centers of **2** (C-2',3',4' using nogalamycin numbering). It was hoped that a Cram "chelation controlled" addition of an aryl lithium reagent like **4** to ketone **3** would generate both the requisite C-5' chirality and

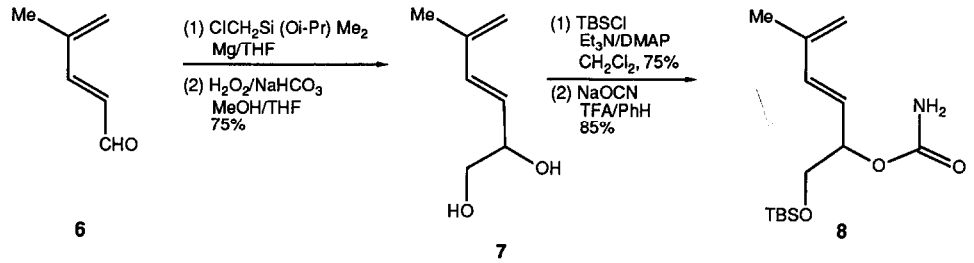
Scheme 1



the incipient C-glycosidic bond. During the early stages of our research, Terashima, et al. described the successful execution of this key transformation and subsequent conversion of 5 to nogalamycin model 2.[4,5] This group prepared ketone 3 by a multistep route from D-arabinose.

Described in this paper is a short, stereospecific synthesis of a molecule closely related to 3 using an approach based upon an intramolecular N-sulfinyl dienophile Diels-Alder reation.[6] The precursor required for the cycloaddition was prepared from diene aldehyde 6, which was homologated to diol 7 using the method of Tamao and Ishida[7] (Scheme 2). The primary alcohol group of 7 could be selectively silylated, and the secondary alcohol was converted to the carbamate[8] affording 8 in good overall yield.

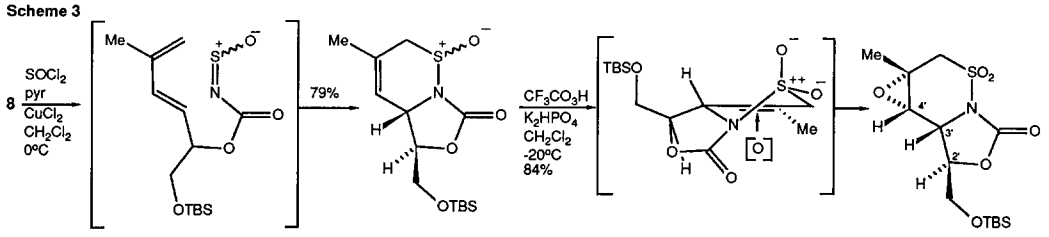
Scheme 2



Treatment of carbamate 8 with thionyl chloride/pyridine produced a transient N-sulfinyl carbamate 9, which cyclized to give the desired trans-bicyclic dihydrothiazine oxide 10 in 63% yield as a 2.5:1 mixture of sulfur epimers. Interestingly, when the reaction was catalyzed with $CuCl_2$•pyridine complex, a 78:1 mixture of sulfur epimers was obtained in 79% yield. In neither case was any compound having the undesired cis-relationship at the chiral carbons produced. This stereochemical outcome has precedent in some related all carbon[9] and hetero[10] Diels-Alder cycloadditions, and the mechanistic rationale offered

for these examples is applicable to our case. Since we have not established the configuration at sulfur, we cannot now satisfactorily explain the affect of the Lewis acid catalyst upon the reaction.

Scheme 3

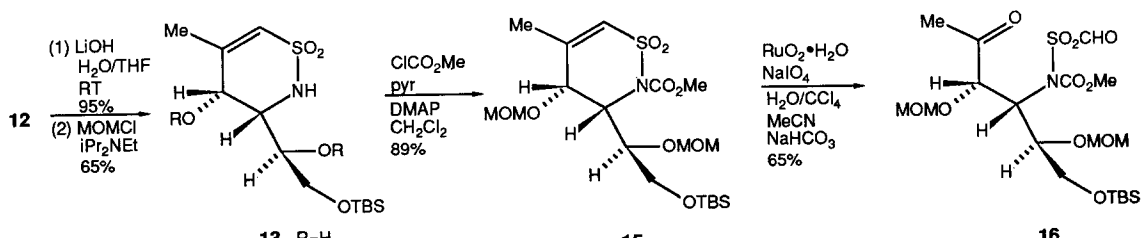


9 10 11 12

Oxidation of the mixture of adducts **10** with trifluoroperacetic acid afforded a single epoxysultam which was found by X-ray crystallography to have the α-configuration shown in **12**. This compound contains the desired stereochemistry at C-2',3',4' for nogalamycin intermediate **3**. We believe the epoxidation occurs via initially formed sultam **11**, which probably exists in the half chair conformation shown in the drawing. Thus, in order to obtain the α-epoxide **12**, peracid attack on the double bond must occur from the more hindered concave face of **11**. The best explanation we can offer for this observation is that a dipole-dipole replusion between the quasi-axial sultam oxygen and the incoming peracid directs the epoxidation anti. Such an effect is precedented for alkenes containing electronegative, non-hydrogen bearing substituents.[11,12]

Epoxide **12** could be elaborated into nogalamycin synthon **16** as shown in Scheme 4. Treatment of **12** with lithium hydroxide caused carbamate hydrolysis and epoxide β-elimination to diol **13**. This compound was protected as bis-MOM ether **14**

Scheme 4



13 R=H
14 R=MOM

15 16

which was N-acylated to afford 15. Cleavage of the double bond of 15 with ruthenium tetroxide generated *in situ* by the Sharpless procedure,[13] yielded ketone 16. This compound differs from the Terashima ketone 3 only in the presence of an interesting formyl sulfonamide group rather than a N-methyl substituent. It might be noted that this functional array is essentially unknown,[14] and we hope to further explore its chemistry. We have thus prepared this key intermediate stereospecifically in nine steps from diene aldehyde 6 and intend to use it in approaches to nogalamycin.

Acknowledgement. We are grateful to the National Science Foundation for financial support (CHE-84-02127).

References and Notes

1. Wiley, P. F. in "Anthracycline Antibiotics," El Khadem, H. S., Ed.; Academic Press, New York: 1982; p. 97-117, and references cited therein.
2. Arora, S. K. J. Am. Chem. Soc. 1983, 105, 1328, for the X-ray crystal structure of nogalamycin.
3. Arugomycin is a closely related metabolite: (a) Kawai, H.; Hayakawa, Y.; Nakagawa, M.; Furihata, K.; Seto, H.; Otake, N. Tetrahedron Lett. 1984, 25, 1937. (b) Kawai, H.; Hayakawa, Y.; Nakagawa, M.; Imamura, K.; Tanabe, K.; Shimazu, A.; Seto, H.; Otake, N. J. Antibiotics 1983, 30, 1569.
4. Kawasaki, M.; Matsuda, F.; Terashima, S. Tetrahedron Lett. 1985, 26, 2693. Idem., Ibid. 1986, 27, 2145.
5. For a different route to a compound similar to 2 see: Bates, M. A.; Sammes, P. G. J. Chem. Soc., Chem. Commun. 1983, 896.
6. For some other applications of intramolecular N-sulfinyl Diels-Alder cycloadditions see: (a) Garigipati, R. S.; Freyer, A. J.; Whittle, R. R.; Weinreb, S. M. J. Am. Chem. Soc. 1984, 106, 7861. (b) Remiszewski, S. W.; Stouch, T. R.; Weinreb, S. M. Tetrahedron 1985, 41, 1173.
7. Tamao, K.; Ishida, N. Tetrahedron Lett. 1984, 25, 4245.
8. Loev, B.; Kormendy, M. R. J. Org. Chem. 1963, 28, 3421.
9. Nicolaou, K. C.; Magolda, R. L. J. Org. Chem. 1981, 46, 1506. Roush, W. R.; Myers, A. G. Ibid. 1981, 46, 1509.
10. Gobao, R. A.; Bremmer, M. L.; Weinreb, S. M. J. Am. Chem. Soc. 1982, 104, 7065. Nader, B.; Bailey, T. R.; Franck, R. W.; Weinreb, S. M. Ibid. 1981, 103, 7573.
11. For a review see: Berti, G. Top Stereochem. 1973, 7, 93.
12. Symmes, C.; Quinn, L. D. Tetrahedron Lett. 1976, 22, 1853.
13. Carlsen, P.; Katsuki, T.; Sharpless, K. B. J. Org. Chem. 1981, 46, 3936.
14. Based upon a Chemical Abstracts partial structure search.

(Received in USA 7 July 1986)