Tetrahedron Letters, Vol. 34, No. 3, pp. 385-388, 1993
Printed in Great Britain

0040-4039/93 $5.00 + .00
Pergamon Press Ltd

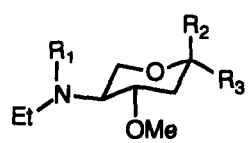
An Efficient Stereoconvergent Synthesis of the 4-Ethylamino-2,4-dideoxy-L-*threo*-pentopyranose Component of the Calicheamicins and Esperamicins

Eugene A. Mash* and Sandeep K. Nimkar

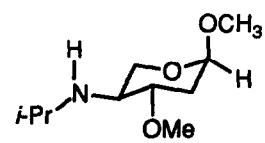
Department of Chemistry, The University of Arizona, Tucson, Arizona 85721

Abstract: A stereoconvergent synthesis of the 4-ethylamino-2,4-dideoxy-L-*threo*-pentopyranose component of calicheamicins γ_1^{Br}, γ_1^{I}, α_2^{I}, and esperamicin A_{1b} from methyl 2-deoxy-β-D-ribopyranoside is described. The synthesis requires eight steps in each branch. The overall yield is 54%. This synthesis should be adaptable for syntheses of the corresponding 4-methylamino-2,4-dideoxy-L-*threo*-pentopyranose and 4-isopropylamino-2,4-dideoxy-L-*threo*-pentopyranose components of other calicheamicin and esperamicin antibiotics.

The calicheamicins and esperamicins are structurally unusual enediyne-containing antitumor agents which function by DNA strand scission.[1] There has been much recent interest in syntheses of the oligosaccharide[2] portions of these molecules, which are likely responsible for DNA recognition and binding.[3] Synthetic approaches to the unusual 4-alkylaminopentopyranose components found in these molecules have been described, including syntheses of derivatives **1a-1d**[4,5] of the 4-ethylamino-2,4-dideoxy-L-*threo*-pentopyranose found in calicheamicins γ_1^{Br}, γ_1^{I}, α_2^{I}, and esperamicin A_{1b}, and of derivative **2**[6] of the 4-isopropylamino-2,4-dideoxy-L-*threo*-pentopyranose found in calicheamicins β_1^{I} and β_1^{Br} and esperamicins A_1 and A_2. These syntheses, of **1a-d** from L-serine and of **2** from 2-deoxy-D-ribose, have established the absolute configurations of these compounds as *3S, 4S*.[4-6] However, the syntheses reported to date suffer from one or more of the following shortcomings: excessive length, poor regioselectivity, and low overall yield. In the hope of developing a more compact, but versatile and efficient synthesis which might provide ready access to homologues and analogues of these unusual aminosugars, we have investigated several synthetic approaches to **1**,[7] and report herein an efficient, stereoconvergent synthesis of **1a** from commercially available 2-deoxy-D-ribose.

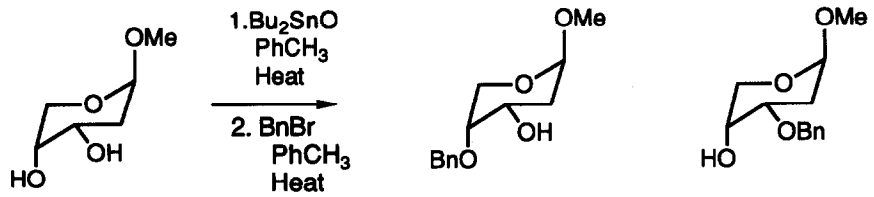


	R_1	R_2	R_3
1a	H	OMe	H
1b	H	H	OMe
1c	Ac	OMe	H
1d	Ac	H	OMe



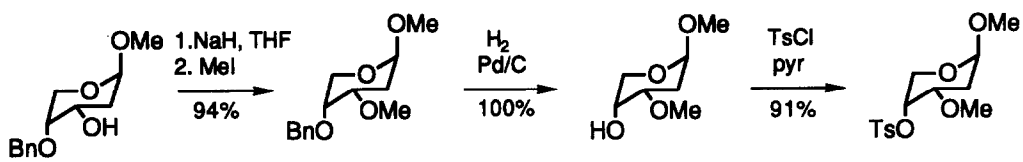
2

Methyl 2-deoxy-β-D-ribopyranoside 3[8,9] was reacted with dibutyltin oxide in refluxing toluene to produce the corresponding *O*-stannylene acetal,[10] which was not isolated. Alkylation with benzyl bromide provided the chromatographically separable (α=1.16, EtOAc) regioisomeric monobenzyl ethers **4a** and **4b** in 43% and 47% yields, respectively.



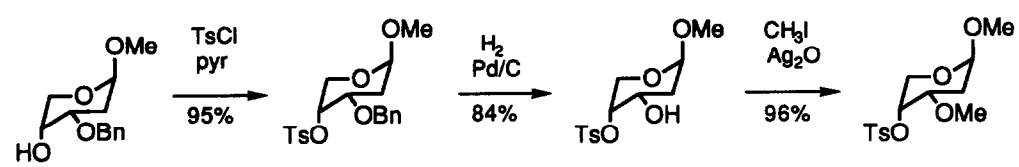
3 **4a** **4b**

The less polar regioisomeric alcohol **4a**, m.p 37-39 °C, was deprotonated and alkylated to give methyl ether **5** in 94% yield. Following debenzylation, alcohol **6** was tosylated to give in 91% yield pyranoside **7**, $[\alpha]_D^{26}$ -137.6° (*c* 4.45, CH_3OH).



4a **5** **6** **7**

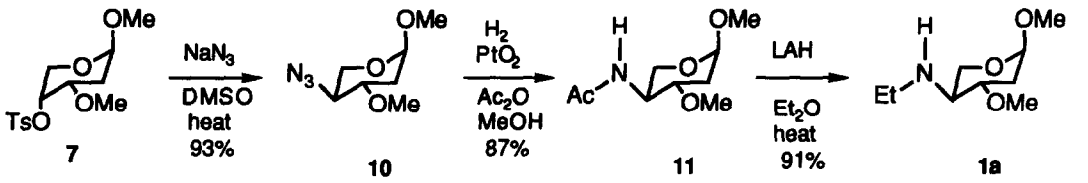
Regioisomeric monobenzyl ether **4b**, an oil, could also be converted to tosylate **7** by changing the step order. Tosylation of **4b** produced **8**, m.p. 115-116 °C, in 95% yield. Debenzylation using hydrogen and palladium-on-carbon gave alcohol **9** in 84% yield, and methylation of **9** at room temperature using methyl iodide and silver oxide[11] in DMF provided pyranoside **7** in 96% yield. The combined yield of tosylate **7** from methyl 2-deoxy-β-D-ribopyranoside **3** was 73%.



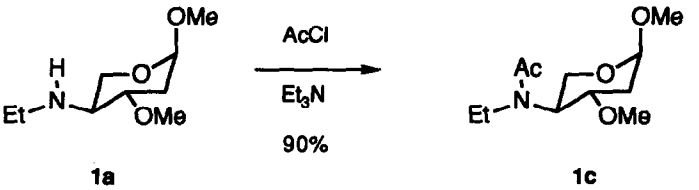
4b **8** **9** **7**

Attempts at direct displacement of the tosylate group of **7** using ethylamine were unsatisfactory. However, the tosylate was cleanly displaced by the use of sodium azide in DMSO[12] at 120-130 °C, providing **10** as an oil, $[\alpha]_D^{26}$ -12.5° (*c* 0.4, $CHCl_3$), in 93% yield after chromatography. Azide reduction and

concomitant *N*-acetylation[13] produced in 87% yield pyranoside **11**, m.p. 105-106 °C, which was subsequently reduced using $LiAlH_4$ to give in 91% yield 4-ethylamino sugar **1a**, $[\alpha]_D^{26}$ -56.8° (*c* 1.4, $CHCl_3$), lit.[5] $[\alpha]_D^{23}$ -56.7° (*c* 1.0, $CHCl_3$). The proton NMR spectrum obtained for compound **1a** was consistent with the previously published data.[5] The overall yield of **1a** from **3** was 54%.



Further confirmation of the structure and purity of **1a** was obtained by its conversion to *N*-acetyl derivative **1c** in 90% yield, $[\alpha]_D^{25}$ -98° (*c* 0.4, $CHCl_3$), lit.[5] $[\alpha]_D^{25}$ -99.0° (*c* 0.96, $CHCl_3$), lit.[4] $[\alpha]_D^{20}$ -96.0° (*c* 0.9, $CHCl_3$). Proton and carbon NMR spectra obtained for **1c** were in accord with those kindly supplied by Professor Daniel Kahne of Princeton University.



The above synthesis provides a relatively short and efficient route to the novel 4-ethylamino-2,4-dideoxy-L-*threo*-pentopyranose found in calicheamicins γ_1^{Br}, γ_1^{I}, α_2^{I}, and esperamicin A_{1b}. We are currently adapting this synthetic approach in order to prepare the 4-methylamino- and 4-isopropylaminopentose sugars which are components of other members of the calicheamicin and esperamicin antibiotic families, as well as unnatural *N*-substituted analogues for use in structure-activity studies.

Acknowledgement. Support of this research by the Elsa U. Pardee Foundation is gratefully acknowledged.

References

1. (a) Zein, N.; Sinha, A. M.; McGahren, W. J.; Ellestad, G. A. *Science* **1988**, *240*, 1198-1201. (b) Sugiura, Y.; Uesawa, Y.; Takahashi, Y.; Kuwahara, J.; Golik, J.; Doyle, T. W. *Proc. Natl. Acad. Sci. U. S. A.* **1989**, *86*, 7672-7676. (c) Kishikawa, H.; Jiang, Y-P.; Goodisman, J.; Dabrowiak, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 5434-5440. (d) Lee, M. D.; Ellestad, G. A.; Borders, D. B. *Acc. Chem. Res.* **1991**, *24*, 235-243. (e) Lu, M.; Guo, Q.; Krishnan, B.; Golik, J.; Rosenberg, I. E.; Doyle

T. W.; Kallenbach, N. R. *J. Biomol. Struct. Dyn.* **1991**, *9*, 285-298. (f) Walker, S.; Landovitz, R.; Ding, W. D.; Ellestad, G. A.; Kahne, D. *Proc. Natl. Acad. Sci. U. S. A.* **1992**, *89*, 4608-4612. (g) Lee, M. D.; Dunne, T. S.; Chang, C. C.; Siegel, M. M.; Morton, G. O.; Ellestad, G. A.; McGahren, W. J.; Borders, D. B. *J. Am. Chem. Soc.* **1992**, *114*, 985-997.

2. (a) Nicolaou, K. C.; Groneberg, R. D.; Miyazaki, T.; Stylianides, N. A.; Schulze, T. J.; Stahl, W. *J. Am. Chem. Soc.* **1990**, *112*, 8193-8195. (b) Van Laak, K.; Rainer, H.; Scharf, H. D. *Tetrahedron Lett.* **1990**, *31*, 4113-4116. (c) Nicolaou, K. C.; Caulfield, T. J.; Groneberg, R. D. *Pure Appl. Chem.*, **1991**, *63*, 555-560. (d) Yang, D.; Kim, S-H.; Kahne, D. *J. Am. Chem. Soc.* **1991**, *113*, 4715-4716. (e) Halcomb, R. L.; Wittman, M. D.; Olson, S. H.; Danishefsky, S. J.; Golik, J.; Wong, H.; Vyas, D. *J. Am. Chem Soc.* **1991**, *113*, 5080-5082.
3. (a) Zein, N.; Poncin, M.; Nilakantan, R.; Ellestad, G. A. *Science* **1989**, *244*, 697-699. (b) 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*, 2-6. (c) Walker, S.; Valentine, K. G.; Kahne, D. *J. Am. Chem. Soc.* **1990**, *112*, 6428-6429. (d) DeVoss, J. J.; Townsend, C. A.; Ding, W. D.; Morton, G. O.; Ellestad, G. A.; Zein, N.; Tabor, A. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 9669-9670. (e) Ding, W.-D.; Ellestad, G. A. *J. Am. Chem. Soc.* **1991**, *113*, 6617-6620.
4. Kahne, D.; Yang, D.; Lee, M. D. *Tetrahedron Lett.* **1990**, *31*, 21-22.
5. Nicolaou, K. C.; Groneberg, R. D.; Stylianides, N. A.; Miyazaki, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1275-1277.
6. Golik, J.; Wong, H.; Vyas, D. M.; Doyle, T. W. *Tetrahedron Lett.* **1989**, *30*, 2497-2500.
7. Mash, E. A. *Synlett*, **1991**, 529-538.
8. Prepared from commercially available 2-deoxy-D-ribose by the method of Deriaz, *et al.*: Deriaz, R. E.; Overend, W. G.; Stacey, M.; Wiggins, L. F. *J. Chem. Soc.* **1949**, 2836-2841. See also: Inokawa, S.; Mitsuyoshi, T.; Kawamoto, H.; Yamamoto, H.; Yamashita, M. *Carbohydrate Res.* **1985**, *142*, 321-323.
9. Commercially available from Aldrich Chemical Company.
10. (a) David, S.; Hanessian, S. *Tetrahedron*, **1985**, *41*, 643-663. (b) Nagashima, N.; Ohno, M. *Chemistry Lett.*, **1987**, 141-144.
11. Purdie, T.; Irvine, J. C. *J. Chem. Soc.* **1903**, *83*, 1021-1037.
12. Cheung, T.-M.; Horton, D.; Weckerle, W. *Carbohydrate Res.* **1979**, *74*, 93-103.
13. Brimacombe, J. S.; Hanna, R.; Tucker, L. C. N. *Carbohydrate Res.* **1985**, *136*, 419-425.

(Received in USA 15 September 1992; accepted 19 October 1992)