Bioorganic & Medicinal Chemistry Letters, Vol.3, No.11, pp. 2437-2438, 1993
Printed in Great Britain

0960-894X/93 $6.00 + .00

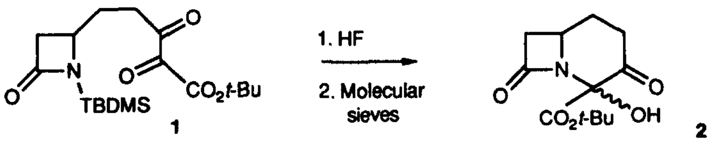
THE CHEMISTRY OF VICINAL TRICARBONYLS SYNTHESIS OF 3,4,7-TRISUBSTITUTED CARBACEPHAMS

Harry H. Wasserman* and Chuansheng Niu
Department of Chemistry, Yale University, New Haven, CT 06511 USA

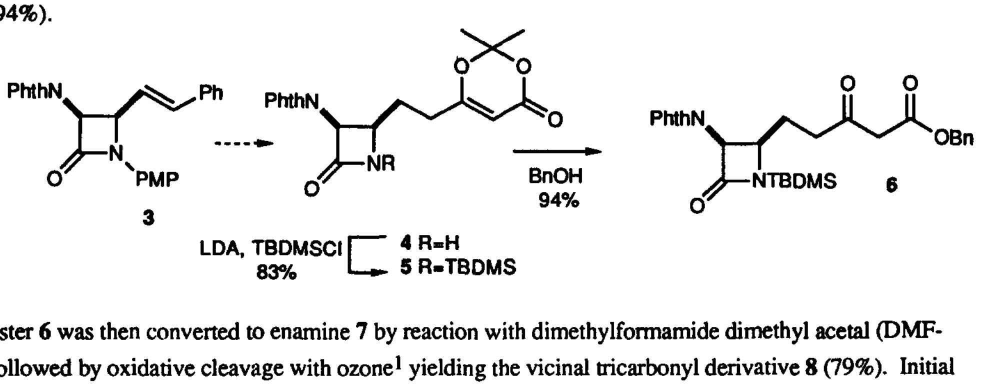
(*Received* 1 *April* 1993)

Abstract: Carbapenams substituted at the 3,4, and 7 positions have been prepared, starting with an intramolecular addition of a β-lactam to the central carbonyl of a tricarbonyl residue. The stereochemistry of the fused ring system was elucidated by X-ray analysis.

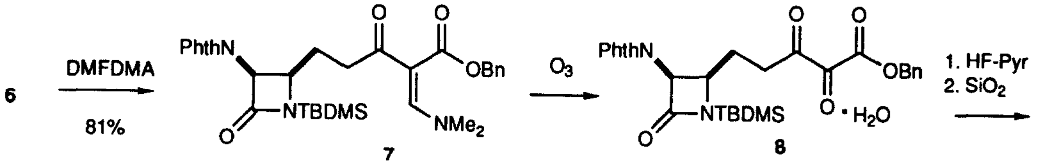
In earlier work,[1] we have explored the use of the highly electrophilic central carbonyl group of a tricarbonyl system to form carbapenam and carbacepham systems, as illustrated in the conversion of 1 to cepham 2 of undetermined stereochemistry.[1a] We now report further studies on the use of this methodology for the formation of cephams, in which substituents are incorporated at the 3,4 and 7 positions, and all stereochemical features are elucidated.

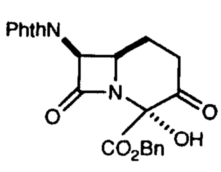


Our synthesis began with the dioxinone 4 previously prepared by Bodurow[2] from the β-lactam 3, with clearly established *cis*-stereochemistry. Treatment of 4 with LDA and TBDMSCl in THF at -78°C afforded the expected N-silylated product 5 (83%) which, on reaction with benzyl alcohol, provided the N-protected β-keto ester 6 (94%).



Ester 6 was then converted to enamine 7 by reaction with dimethylformamide dimethyl acetal (DMF-DMA), followed by oxidative cleavage with ozone[1] yielding the vicinal tricarbonyl derivative 8 (79%). Initial attempts to effect desilylation with TBAF resulted in substantial decomposition along with a small amount of the fused ring product (16%). However, desilylation with HF-pyridine complex[3] followed by treatment with silica gel afforded the cyclized product 9 in 54% yield. The structure of 9 was confirmed by X-ray crystallographic analysis (Figure 1),[4] showing the α-orientation of the hydroxyl group at C_4.





9

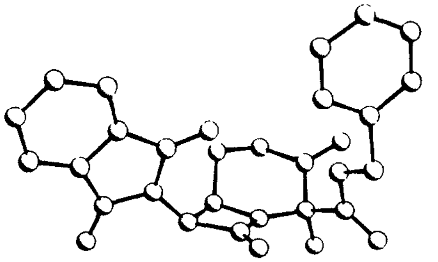
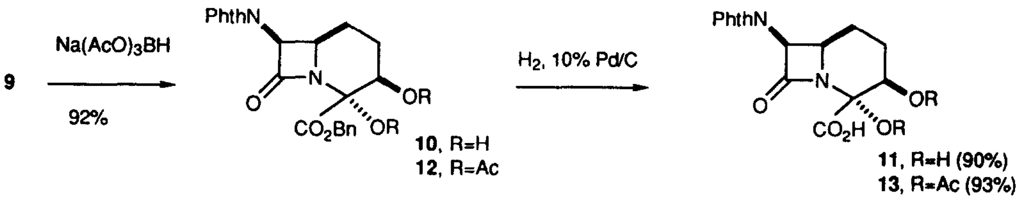


Figure 1. ORTEP drawing of cepham **9**.

Reduction of **9** with sodium triacetoxyborohydride in glacial acetic acid gave, exclusively, diol **10** (92%), which underwent hydrogenolysis over palladium on activated carbon to provide the free acid **11** (90%).[5] Acetylation of diol **10** yielded diacetate **12** (91%) convertible to carboxylic acid **13** (93%) on hydrogenolysis.



Acknowledgment. This work was supported by the General Medical Sciences Institute of the National Institutes of Health. C. Niu expresses his appreciation to the Fogarty International Center of the NIH for a postdoctoral fellowship. We also thank Mr. Dan Pentek for determing HRMS spectra and Ms. Gayle Schulte for the X-ray crystallographic data.

References.

(1) (a) Wasserman, H. H.; Han, W. T. *Tetrahedron Lett.* **1984**, *25*, 3743 and 3747. (b) Wasserman, H.H.; Han, W. T. *J. Am. Chem. Soc.* **1985**, *107*, 1444. (c) Wasserman, H. H.; Henke, S. L.; Luce, P.; Nakanishi, E. *J. Org. Chem.* **1990**, *55*, 5821.

(2) (a) Bodurow, C.; Carr, M. A. *Tetrahedron Lett.* **1989**, *30*, 4081. (b) Bodurow, C.; Carr, M. A.; Moore, L. L. *Org. Prep. Proced. Int.* **1990**, *22*, 109.

(3) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *J. Am. Chem. Soc.* **1981**, *103*, 1222.

(4) For compound 9: $C_{23}H_{18}O_7N_2$, MW 434, monoclinic, colorless crystals, space group with a = 10.092 (1) Å, b = 17.013 (2) Å, c = 12.3911 (9) Å, b = 104.529 (7)°, V = 2059.5 (3)Å^3, z = 4, p = 1.401 g/cm^3. Data were collected at 23°C and the diffraction measurements were made on a four-circle Rigaku AFC5S fully automated diffractometer using graphite monochromated CuKa(λ = 1.54178 Å).

(5) Assignment of the diaxial *trans*-relationship of the alcohol residues at the 3- and 4-positions is in accord with the expected mode of hydride delivery to the C-3 ketone from the reducing agent complexed with the C-4 hydroxyl.[6]

(6) (a) Saksena, A. K.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, *24*, 273. (b) Turnbull, M. D.; Hatter, G.; Ledgerwood, D. E. *Tetrahedron Lett.* **1984**, *25*, 5449.