Tetrahedron Letters, Vol. 33, No 25, pp 3559-3562, 1992
Printed in Great Britain

0040-4039/92 $5.00 +
Pergamon Press Ltd

A NEW STRATEGY FOR THE CONVERSION OF PENAMS INTO CEPHEMS VIA ALLENE CHEMISTRY [a]

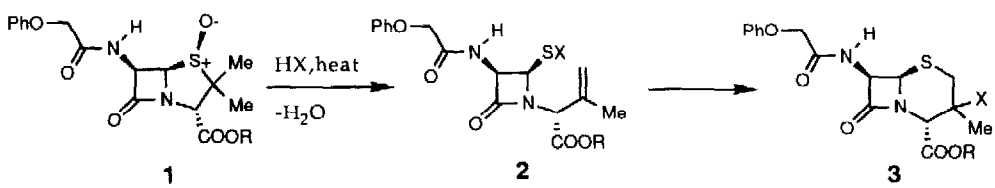
Vittorio Farina * and Joydeep Kant

Bristol-Myers Squibb Pharmaceutical Research Institute,
5 Research Parkway, P.O.Box 5100, Wallingford CT 06492-7660

Summary: *We describe an extension of the Morin rearrangement in which 3-norcephalosporins bearing sulfur substituents at C(3) are obtained directly from an allenic intermediate, which is efficiently prepared from penicillin V sulfoxide.*

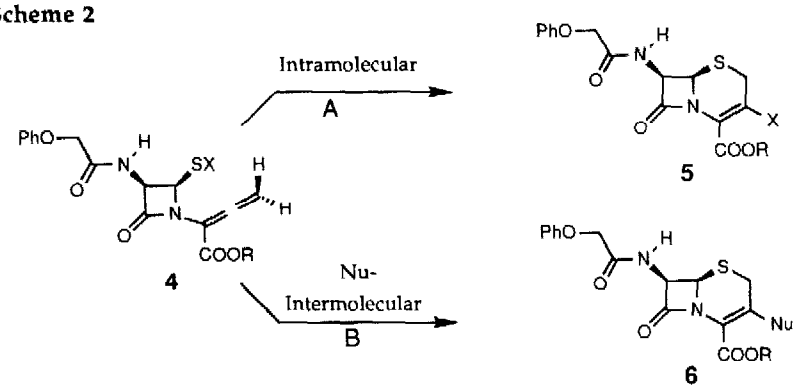
One of the key reactions in cephalosporin chemistry is the Morin ring expansion of penams into cephems (Scheme 1) [1] This rearrangement, in its several modifications, [2] has allowed the preparation of many semisynthetic cephalosporin antibiotics from very cheap starting materials, the penicillins.

Scheme 1



While the Morin rearrangement is ideal for the preparation of 3-methyl cephems, we have become interested in the efficient preparation of 3-substituted cephems bearing heteroatomic [3] or carbon-based [4] residues at C(3)

Scheme 2

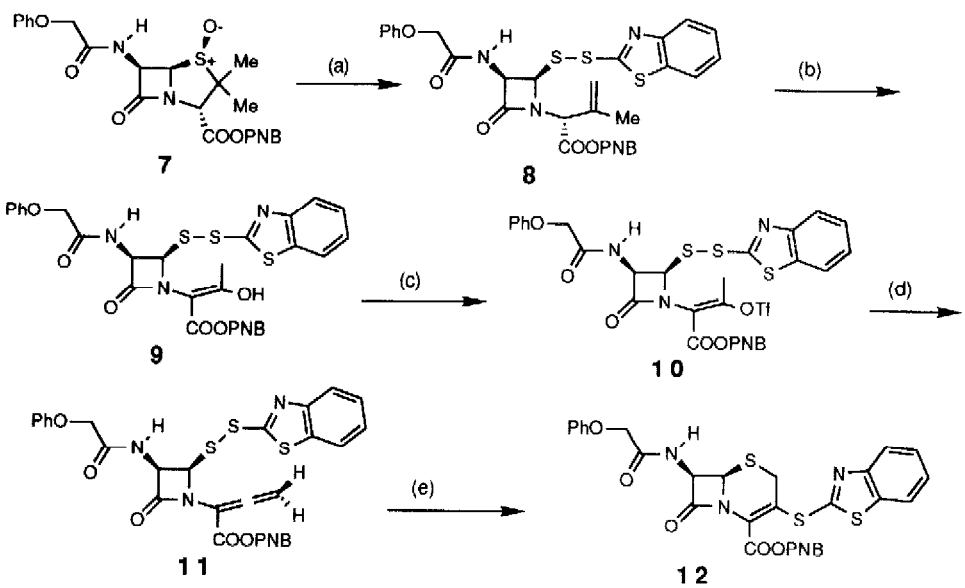


A strategy based on the above rearrangement that would ideally serve this purpose would entail an intramolecular sulfenylation of an allene, as opposed to the alkene moiety in **2**. Such a strategy is identified in Scheme 2 Allenyl ester **4** would undergo cyclization to yield directly 3-substituted cephem **5** via path A Addition of an exogenous nucleophile could lead, in conjunction with a "dummy" (non-nucleophilic) substituent at sulfenyl sulfur, to its incorporation at C(3) to yield **6** (path B)

We report in this Letter the preparation of allenes such as **4** and the reduction to practice of both strategies shown in Scheme 2.

Our route (Scheme 3) uses penicillin V sulfoxide *p*-nitrobenzyl ester, which upon fragmentation and trapping with 2-mercaptobenzothiazole gave **8** in high yield; ozonolytic cleavage [5] then afforded enol **9**. This was converted in high yield to triflate **10** (single isomer, geometry unknown), which underwent elimination under mild conditions, in analogy with the literature, [6] to afford allene **11** as an amorphous solid. Especially diagnostic were the NMR absorptions of the allenic protons (δ 5.65 and 5.38, J = 15 5 Hz) [7] and the IR spectrum (doublet at 1950 and 1910 cm $^{-1}$, typical of terminal allenes [8]). Although fairly stable, allene **11** was used *in situ*: it was found that addition of lithium chloride in THF at low temperature brought about smooth cyclization to cephem **12**. [9]

Scheme 3

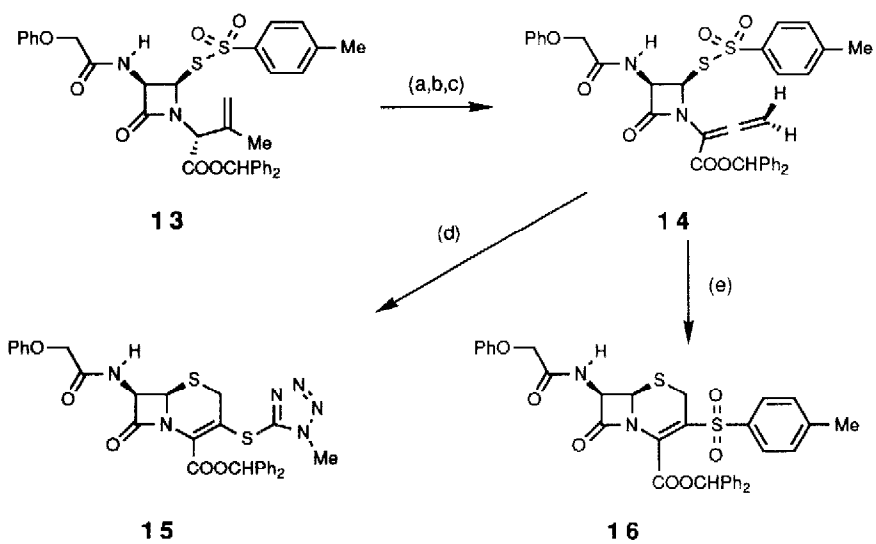


Reaction conditions (a) 1 eq. 2-Mercaptobenzothiazole, toluene, reflux, 85%. (b) O_3, MeOAc, -78°C, the Me_2S, 95%. (c) Tf_2O, iPr_2NEt, CH_2Cl_2, -78°C, 87% (d) NEt_3, 1 eq , THF, 1h, RT, 100% (e) LiCl, 2 eq , -40°C to 0°C, 2h, 65%. PNB=*p*-nitrobenzyl.

The value of this novel ring closure would be, of course, much greater if exogenous nucleophiles could be directly incorporated at C(3) in an intermolecular fashion. In order to demonstrate this strategy (Scheme 2, path B), we selected as "dummy" substituent at sulfur the rather poorly nucleophilic (but excellent leaving group) sulfinate This leaving group has been used recently by Torii in his elegant approach to 3-hydroxycephems [10]

Our synthetic approach [11] is shown in Scheme 4 The known azetidinone **13** [5] was smoothly ozonized and converted to allene **14** via the corresponding enol triflate as before. Somewhat unexpectedly, allene **14** was also capable of undergoing the formally intramolecular cyclization In this case it was found advantageous to isolate the allene by simple aqueous work-up. Treatment with lithium bromide in a more polar solvent (NMP) at room temperature was required to induce reaction. Under these modified conditions, sulfone **16** was obtained in good yield (yellow solid, m p. 192-3°C, with decomp ; IR 1325, 1150 cm $^{-1}$). If the allene was not isolated, the yields were lower (10-20%), the major side-products apparently resulting from attack of the sulfinate on the allene without subsequent ring closure (NMR and mass spectroscopy evidence). The effect of external nucleophiles was investigated by adding sodium 1-methyl-2-mercapto tetrazolate.

Scheme 4



Reaction conditions: O_3, MeOAc, -78°C, then Me_2S, 91%. (b) iPr_2NEt, Tf_2O, CH_2Cl_2, -78°C, 86%. (c) NEt_3, CH_2Cl_2, RT, 1h,100%. (d) LiBr, 2 eq., THF, sodium 1-methyl-2-mercaptotetrazolate, 1 5 eq , 0°C, 31% (e) LiBr, 3.8 eq., NMP, RT, 16h, 61%.

In this case, only traces of **16** were detected: the major product, **15**, features incorporation of the thiolate at C(3) of the cephem. Even though the above yields are not fully optimized, it is obvious that this novel ring expansion holds considerable synthetic potential

The current approach to 3-substituted cephems bears resemblance to the Woodward synthesis of 3-alkoxycephems [12] and related methodologies, [13] but it is clearly milder and more efficient. The cyclization proceeds essentially under neutral conditions, and the typical problem that afflicts the other methods, i.e. base-induced formation of Δ^2 cephems, is not observed here.

In continuation of this work, we have been able to introduce carbon-based nucleophiles directly at C(3) of the cephem nucleus by using allenes **4** in conjunction with organocuprates Our results in this area form the subject of the next Letter in this issue.[14]

REFERENCES AND NOTES:

(a) Part I in the series. See following paper in this issue for Part II. This work was carried cut at the Chemical Process Development Dept , Bristol-Myers Company, Syracuse NY.

1. Morin, R.B.; Jackson, B G ; Mueller, R.A , Lavagnino, E R.; Scanlon, W.B.; Andrews, S L. *J.Am.Chem.Soc.* **1963,** *85,* 1896.
2. Cooper, R.D.G.; Koppel, G.A. in *"Chemistry and Biology of β-Lactam Antibiotics"*. Morin, R.B.; Gorman, M. Eds., Academic Press: New York, **1982,** Vol I, 1
3. Farina, V.; Baker, S.R.; Hauck, S.I. *J.Org.Chem.* **1989,** *54,* 4962.
4. Farina, V.; Baker, S.; Benigni, D.A.; Hauck, S.I., Sapino, C. *J.Org Chem.* **1990,** *55,* 5833.
5. Scartazzini, R.; Bickel, H *Heterocycles* **1977,** *7,* 1165 Also: Woodward, R.B.; Bickel, H. *US Patent* 4,255,328.
6. Stang, P.J ; Hargrove, R.J *J Org Chem.* **1975,** *40,* 657 For an application of this reaction to the synthesis of 2-oxacephems, see: Conway, T.T et al *Can.J.Chem* **1978,** *56,* 1335. For a recent application of similar allenes to the synthesis of penams, see· Tanaka, H ; Kameyama, Y., Kosaka, A.; Yamauchi, T ; Torii, S. *Tetrahedron Lett.* **1991,** *50,* 7445.
7. This coupling constant is typical of cumulene systems, see : Allred, E.L.; Grant, D.M.; Goodlett,W. *J.Am Chem Soc.* **1965,** *87,* 673.
8. Wotiz, J.H.; Mancuso, D.E. *J.Org.Chem.* **1957,** *22,* 207.
9. All new compounds were characterized by NMR spectroscopy and combustion analyses and/or high resolution mass spectroscopy. The ring closure reaction is triggered by many halide salts, and is mainly an *intermolecular* process, as evidenced by crossover experiments We favor halide attack at sulfenyl sulfur as the event that initiates ring closure Further details will be given in a full account
10. Tanaka, H ; Taniguchi, M.; Kameyama, Y ; Monnin, M ; Sasaoka, M.; Shiroi, T.; Nagao, S.; Torii, S *Chem Lett.* **1990,** 1867.
11. Typical procedure for a ring closure reaction: Triflate 10 (143 5 mg, 0.183 mmol) was stirred in dry THF (3 mL) in the presence of triethylamine (0.026 mL, 1 eq.) at RT. After 1h, the solution was cooled to -40°C and solid LiCl (15.5 mg, 2 eq) was added quickly. The suspension was allowed to reach 0°C (external temp.) over 2h, then was worked up with water and EtOAc. Chromatography gave **12** as a foam (75.2 mg, 65%).
12. Scartazzini, R ; Schneider, P.; Bickel, H *Helv Chim.Acta* **1975,** *58,* 2437
13. Gosteli, J. *Chimia,* **1976,** *30,* 13. Also· Hamashima, Y ; Kubota, T.; Ishikura, K ; Minami, K ; Takura, K., Nagata, W. *Heterocycles* **1976,** *5,* 419
14. After the completion of our work, a paper describing similar chemistry has appeared, see: Tanaka, H ; Kameyama, Y.; Sumida, S., Yamada, T ; Tokumaru, Y.; Shiroi, T ; Sasaoka, M.; Taniguchi, M.; Torii, S *Synlett* **1991,** 888.

(Received in USA 18 February 1992)