Synthesis of Inversely-Fused Bicyclic β-Lactams

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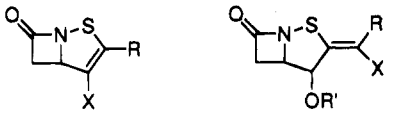
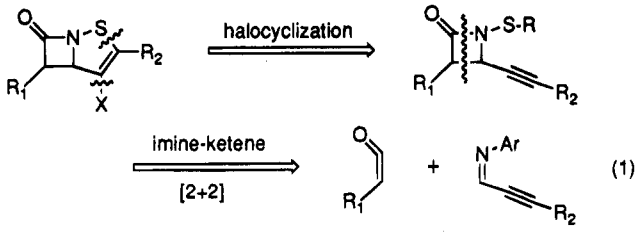
Our laboratory has become interested in the design and synthesis of bicyclic β-lactam ring systems whose novel structures might provide useful leads in the search for new antibacterial agents.[1] We recently described the synthesis of two such classes of structures related to the classical penam- or penem-ring systems in which the lactam is adjacent to, but not directly part of, the ring fusion.[2,3] In this paper, we report the synthesis of a second class of β-lactam core structures **1** and **2** that closely resemble those of the penems and clavulanic acids, except that the orientation of the lactam group has formally been *inverted* with respect to the thiazolidine ring, producing an effect that *enhances* the electrophilicity of the azetidinone ring.



1 **2**

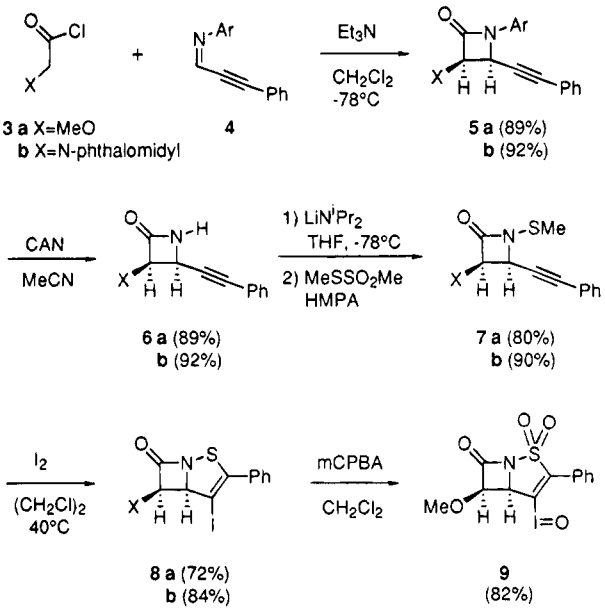
To construct the bicyclic core of these analogues, we decided to investigate the utility of our previously described "double annulation" procedure,[2] as illustrated retrosynthetically in eq 1. Thus, after formation of the



(1)

azetidinone intermediate by a [2 + 2]-imine–ketene cycloaddition,[4] we planned to fashion the thiazolidine ring by a regiospecific sulfide halocyclization process.[5] To our knowledge, the use of an *N*-acylsulfenamide in intramolecular additions to unsaturated centers has never been reported.

To test this strategy, we first set out to synthesize *isopenem* analogues **8**.[6] Alkenyl azetidinones **5** were prepared by [2 + 2]-reaction between methoxyacetyl chloride (**3a**) or phthalimidoacetyl chloride (**3b**) and unsaturated *N*-arylimine **4**.[7] The cycloadditions gave the



desired *cis*-disubstituted β-lactams **5** in about 90% yield. The cis stereochemistry of these rings was evident from the ^{1}H NMR spectrum which showed characteristic doublets with vicinal coupling constants of 4.8 Hz for the ring protons. The aryl nitrogen group of **5** was easily removed by oxidation with ceric ammonium nitrate,[8] and deprotonation of unprotected lactam **6** with LDA and trapping of the amide anion with methyl methanethiolsulfonate[9] provided *N*-(methylthio) β-lactams **7** in high overall yield. Iodocyclization of unsaturated compound **7** with I_2 gives a bicyclic β-lactam **8** as a single cycloadduct having a C=O stretching band near 1790 cm^{-1}. This ring closure was quite sluggish and required heating at elevated temperatures.[10] Attempts to convert sulfena-

(1) (a) *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, **1993**. (b) *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; Vols. 1–3. (c) Brown, A. G. *Pure Appl. Chem.* **1987**, *59*, 475.

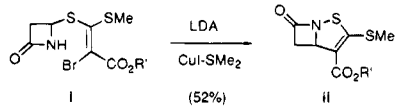
(2) Ren, X.-F.; Turos, E. *J. Org. Chem.* **1994**, *59*, 5858.

(3) Bicyclic azetidinones having the lactam group *adjacent* to the ring fusion have been reported; however, the biological properties of these compounds have apparently not been investigated. See: (a) Woodward, R. B.; Heusler, K.; Gosteli, J.; Naegeli, P.; Oppolzer, W.; Ramage, R.; Ranganathan, S.; Vorbruggen, H. *J. Am. Chem. Soc.* **1966**, *88*, 852. (b) Baldwin, J. E.; Christie, M. A.; Haber, S. B.; Kruse, L. I. *J. Am. Chem. Soc.* **1976**, *98*, 3045. (c) Nakatsuka, S.-i.; Tanino, H.; Kishi, Y. *J. Am. Chem. Soc.* **1975**, *97*, 5008. (d) Nakatsuka, S.-i.; Tanino, H.; Kishi, Y. *J. Am. Chem. Soc.* **1975**, *97*, 5010. (e) Spitzer, W. A.; Goodson, T.; Lammert, S. R.; Kukolja, S. *J. Org. Chem.* **1981**, *46*, 3568. (f) Cooper; R. D. G.; Jose, F. L. *J. Am. Chem. Soc.* **1970**, *92*, 2576. (g) Barton, D. H. R.; Comer, F.; Sammes, P. G. *J. Am. Chem. Soc.* **1969**, *91*, 1529.

(4) (a) Staudinger, M. *Liebigs Ann. Chem.* **1907**, *356*, 51. (b) Georg, G. I.; Ravikumar, V. T. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; Verlag Chemie: New York, 1993; pp 295–368.

(5) (a) Ren, X.-F.; Turos, E.; Lake, C. H.; Churchill, M. R. *J. Org. Chem.*, in press. (b) Ren, X.-F.; Turos, E. *Tetrahedron Lett.* **1993**, 1575.

(6) To our knowledge, only one other example of a β-lactam ring system having this type of structural motif has been described in the literature. In 1980, a Japanese group reported the isolation and X-ray crystal structure of compound **ii** from the cyclization of seco-lactam **i** (Oida, S.; Yoshida, A.; Hayashi, T.; Nakayama E.; Sato, S.; Ohki, E. *Tetrahedron Lett.* **1980**, *21*, 619). These investigators demonstrated that the procedure previously described by workers at Merck (DeNinno, F.; Linek, E. V.; Christensen, B. C. *J. Am. Chem. Soc.* **1979**, *101*, 2210) to close the five-membered ring of **i** to give a penam derivative unexpectedly results in the formation of isopenem **ii**.



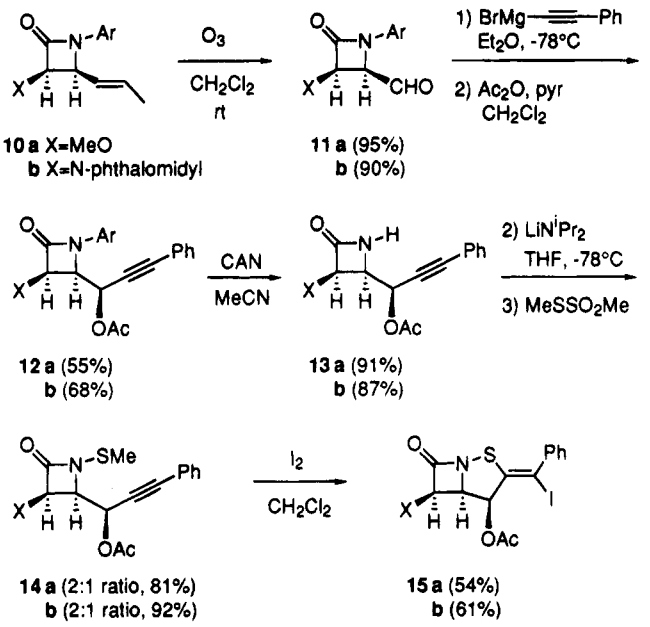
i ii

(7) The unsaturated imines were prepared by refluxing 1.0 equivalent of *p*-anisidine and 1.1 equiv of the aldehyde in benzene under Dean–Stark conditions. The imines were purified by filtering the crude solution through a pad of SiO_2 (to remove residual *p*-anisidine) and evaporating *in vacuo*.

(8) Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765.

0022-3263/95/1960-4980$09.00/0

Scheme 1



10a X=MeO
b X=N-phthalomidyl

11a (95%)
b (90%)

12a (55%)
b (68%)

13a (91%)
b (87%)

14a (2:1 ratio, 81%)
b (2:1 ratio, 92%)

15a (54%)
b (61%)

mide **8** to its sulfone derivative by peracid oxidation afforded a highly crystalline compound that showed an infrared absorption band above 1800 cm^{-1}, confirming the survival of the β-lactam ring. However, the highly polar nature of this material and the observance of an M + 16 signal in its mass spectrum allows us to tentatively assign this compound to be structure **9**, in which oxidation of the vinyl iodide to the iodoso group occurs. This compound proved to be surprisingly stable to aqueous bicarbonate and bisulfite workup (buffered to pH 7.2) and to purification by flash chromatography on silica gel.[11]

For the synthesis of clavulanic acid analogues **15**, we decided to utilize alkenylazetidinone **10**[12] as the starting material. Ozonolysis of **10** at room temperature provided *cis*-aldehydes **11** in high yield without any noticeable epimerization. Grignard addition of the magnesium phenylacetylide to **11** gave the alcohol adducts, which following acetylation afforded acetates **12**. After flash chromatography, **12a** and **12a** were obtained as a single diastereomers in 55% and 68% overall yields, respectively. The compounds are tentatively assigned to be the β-acetates based on the delivery of the Grignard reagent via a chelation-controlled approach to the aldehyde. To construct the remaining five-membered ring, it was necessary at this point to replace the *N*-aryl protecting group of the azetidinone with the *N*-(methylthio) moiety. The removal of the *N*-aryl group was accomplished in high yield by treatment with ceric ammonium nitrate to give unprotected lactam **13**, which upon deprotonation with LDA at low temperature and subsequent anion trapping gave N-methylthio derivative **14** in excellent overall yield.[13] With alkynyl azetidinones **14a** and **14b** in hand, the iodocyclization procedure was attempted using I_2 at room temperature. In each case, the 2:1 mixture was found to yield bicycloadducts **15** as a *single* regio- and stereoisomer in high yield. The structures of **15a** and **15b** are tentatively assigned to have the acetate group *anti* to the ring protons.[14] The olefinic moiety of adducts **15** is presumed to have the *E*-geometry arising from stereospecific trans addition to the triple bond and to be exocyclic to the ring based on our previous studies that demonstrate the overwhelming preference of alkynylsulfides to undergo *5-exo-dig* ring closures in halocyclization reactions.[5]

As anticipated, reorganization of the azetidinone ring so that the lactam moiety is attached to the thiazolidine sulfur center produces a noticeable effect on the electrophilicity of the azetidinone carbonyl group. The infrared stretching frequency for the carbonyl group for these analogues ($\nu_{C=O}$ 1790 cm^{-1}) appears at a considerably higher wavenumber than that observed for our previously described C-fused analogues ($\nu_{C=O}$ 1750–1760 cm^{-1}) and are comparable to those of the biologically active penems.[15] We are presently attempting to develop efficient protocols for derivatizing these rings with appropriate recognition and binding domains and to investigate their biological capabilities.[16]

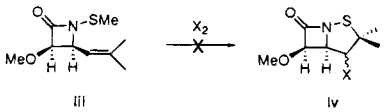
Acknowledgment. We wish to thank the donors of the Petroleum Research Fund, administered by the ACS, for financial support and to express our gratitude to Professor Jiali Gao and Mr. Joseph Pavelites for assistance in carrying out the molecular modelling experiments.

Supporting Information Available: Experimental procedures, ^1H and ^{13}C NMR, infrared, and mass spectral data, and photoreduced copies of the ^1H and ^{13}C NMR spectra for compounds **5-15** (32 pages).

JO942173A

(9) Shah, N. V.; Cama, L. D. *Heterocycles* **1987**, *25*, 221.

(10) For reasons which remain unclear, the corresponding halocyclizations of *alkenyl* azetidinone **iii** fail to give the desired penicillin analogues **iv**. This is in contrast to the *5-endo-trig* cyclizations wereported earlier[2] for azetidinones in which the thioether substituent resides α to the carbonyl (rather than on the lactam nitrogen). We are trying to investigate what causes *N*-(methylthio)azetidinones to be more resistant to halocyclization and to provide rationale for why certain reactions within this series proceed while others fail.



iii iv

(11) We have found that under slightly different conditions, or use of only 1 equiv of *m*-CPBA in this reaction, a yet unidentified monooxygenated species is produced that is unstable to aqueous workup or flash chromatography.

(12) This adduct was prepared by [2 + 2] reaction of acetyl chlorides **3a,b** with the imine derived from crotonaldehyde.

(13) Although only one isomer of **13** was used in this reaction, 2:1 mixtures of adducts **14** were produced. A reviewer has suggested that this 2:1 mixture may be due to the existence of conformational isomers having restricted rotation around the N–S bond. Sulfenamides are reported to have barriers to rotation around the S–N bond in the range of 9–23 kcal/mol (Raban, M. *Tetrahedron* **1984**, *40*, 3345.) Similar behavior has been observed for the monocyclic thiamazins, which molecular modeling studies show have a barrier to S–N bond rotation as high as 12 kcal/mol (Boyd, D. B.; Eigenbrot, C.; Indelicato, J. M.; Miller, M. J.; Pasini, C. E.; Woulfe, S. R. *J. Med. Chem.* **1987**, *30*, 528). Variable temperature NMR studies, semiemperical calculation, and X-ray crystallography analysis of *N*-(methylthio) compounds **7** and **14** are being carried out in an attempt to understand this behavior more fully. A full discussion of this data will be presented at a later time.

(14) We are presently attempting to obtain X-ray crystallographic data to confirm the structure of these adducts.

(15) For β-lactams within the same family, qualitative correlations exist between the reactivity of the azetidinone (as measured by its rate of base hydrolysis) and antimicrobial activity. However, in comparing *different* classes of β-lactams, no direct correlations exist between reactivity and antimicrobial activity. For references and a discussion, see: Blaszczak, L. C.; Brown, R. F.; Cook, G.K.; Hornback, W. J.; Hoying, R. C.; Indelicato, J. M.; Jordon, C. L.; Katner, A. S.; Kinnick, M. D.; McDonald, J. H., III; Morin, J. M., Jr.; Munroe, J. E.; Pasini, C. E. *J. Med. Chem.* **1990**, *33*, 1656.

(16) For discussion on the bioactivation of bicyclic β-lactam antibiotics, see: Rando, R. *Acc. Chem. Res.* **1975**, *8*, 281.