Synthesis of the First 2′,6 Bridged Penams

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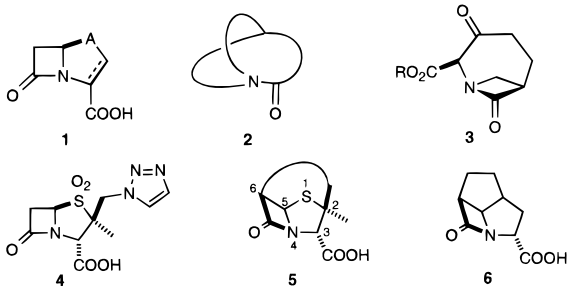
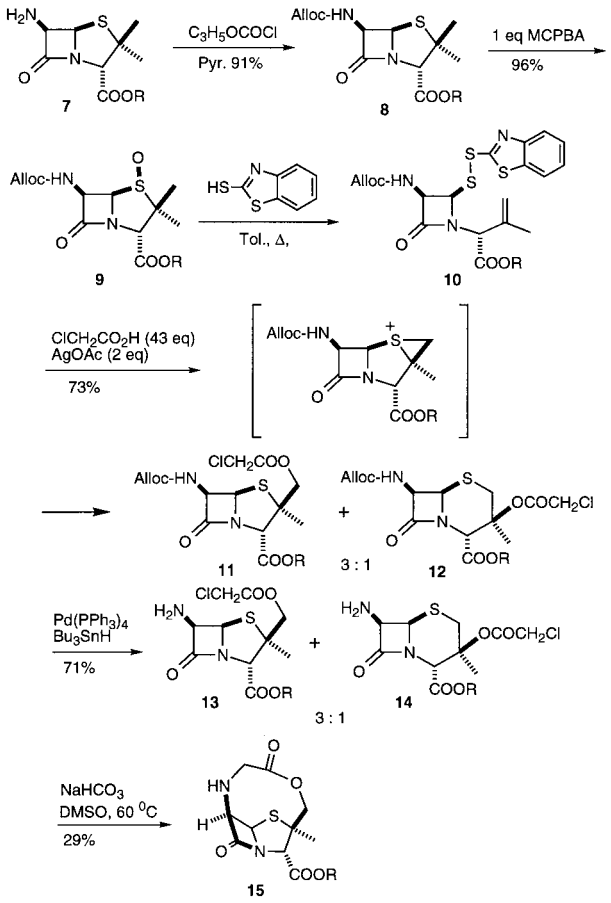
The reactivity of β-lactams toward nucleophiles in non-enzymological systems can be determined by a number of factors, including both the electronic and steric nature of substituents on the ring[1] as well as the pyrimidality of the β-lactam nitrogen. Particularly in the penam, penem, and carbapenem systems (**1**), the fusion of the β-lactam to a five-membered ring enhances the susceptibility of the β-lactam carbonyl toward nucleophiles by a factor of approximately 100.[1] A simultaneous increase in the



stretching frequency of the carbonyl group suggests that the added reactivity is caused by a partial pyrimidalization of the normally planar amide nitrogen. A more dramatic example of such pyrimidalization occurs in bridgehead lactams of type **2**, which have been referred to as "anti-Bredt", by analogy with the corresponding alkenes.[2] Williams and Lee have synthesized and examined the stability of 1,3-bridged-2-azetidinones (**3**).[3]

Recently 2′β-substituted penams, such as tazobactam (**4**),[4] have attracted attention as efficient inhibitors of class A β-lactamases, hydrolytic enzymes which are responsible for bacterial resistance to the β-lactam antibiotics. In our survey of the literature, we were surprised by the absence of any penam-type structures incorporating an additional bridge between the 2′β and the 6 positions, which are normally situated in close proximity on the concave face of this system (general structure **5**). Recent theoretical calculations on related hypothetical bridged tricyclic compounds such as **6**, suggested that the highly pyrimidal nitrogen might allow such compounds to serve as transition-state analogues for proteolytic processes.[5] We had recently reported the preparation and evaluation of a number of new penam- and cephem-derived inhibitors of β-lactamase[6] and elastase,[7] and we were interested in investigating the inhibitory potential of structures such as **5**. General structure **5** also provides a unique opportunity to explore the limits of strain in the penicillin series. We now report the synthesis of the first 2′,6 bridged penams.

Scheme 1



As shown in Scheme 1, benzhydryl and benzyl esters of 6-aminopenicillanic acid were protected by reaction with allyl chloroformate (R = Bhl or Bn, yields are shown for the benzhydryl series). The resultant urethanes were then oxidized to afford (>90%) the (*S*)-sulfoxide isomer (and a small amount of the opposite diastereomer). The directing effect of the 6-amido group in this oxidation has been noted previously.[8] Treatment of this sulfoxide with 2-mercaptobenzothiazole produced a quantitative yield of disulfide **10**.[9] Cyclization of **10** by treatment with silver acetate in the presence of excess chloroacetic acid[10] produced a 3:1 mixture of the 2′β-substituted penam (**11**) and 3β-substituted cephalosporin (**12**) as shown. Even when stored

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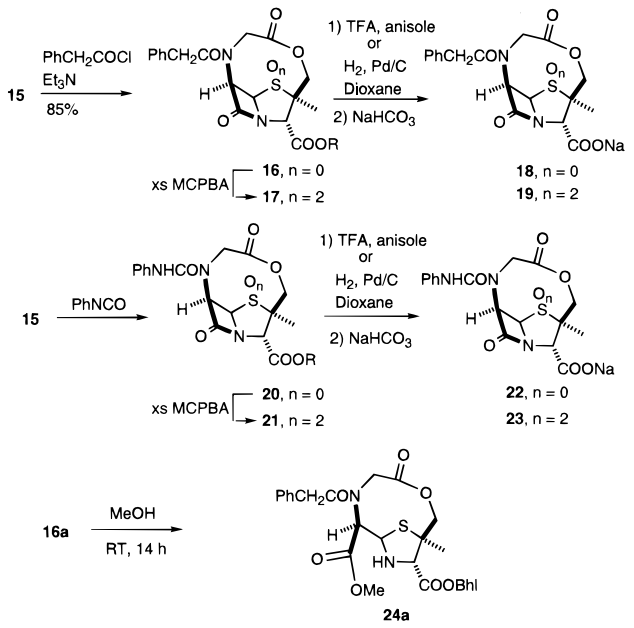
Scheme 2



at −20 °C, this mixture gradually equilibrated to the cephalosporin. This transformation is believed to involve the episulfonium ion shown.[11]

The mixture was thus immediately deprotected by treatment with Pd° in the presence of tributyltin hydride, and the mixture of resultant amines was heated in DMSO to produce the desired cyclized compound **15** in 29% yield. Attempts to perform a similar cyclization on the corresponding sulfoxide failed. To further demonstrate the thermal stability of this unusual tricyclic system, **15** (R = Bhl) was heated to 100 °C in DMSO-d_6 for 12 h with no detectable change in the ^{1}H NMR spectrum.

This secondary amine could be functionalized in a number of ways (Scheme 2). In particular, it was treated with phenylacetyl chloride to produce the corresponding tertiary amide (**16**) and deprotected or, alternatively, oxidized to the corresponding sulfone and deprotected. Similarly, reactions with phenyl isocyanate produced the urea which could also be deprotected as either the sulfide or sulfone. Although these carboxylate salts were stable in aqueous solution, when the benzhydryl ester **16** was stirred in methanol at room temperature for 14 h, cleavage of the β-lactam occurred to produce **24**.

An X-ray crystal structure of compound **16** was obtained,[12] verifying the tricyclic nature of these compounds (Figure 1).

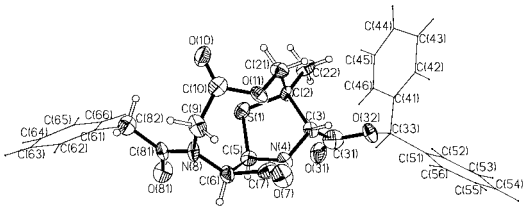


Figure 1. Perspective view of **16** showing the atom-numbering scheme with thermal ellipsoids drawn at the 40% probability level. For clarity, all H atoms, as well as the carbons of the aromatic residues, are drawn with circles of arbitrary radii.

These compounds are 1,3-bridged-2-azetidinones similar to **3**, with an extra link between the bridge and the 4-position of the azetidinone (this link being represented by the 1-position sulfur of the penam). Relative to other 1,3-bridged-2-azetidinones, this additional linkage may actually stabilize the β-lactam carbonyl toward reaction with nucleophiles by increasing the planarity of the azetidinone nitrogen. In support of this, it should be noted that an attempt to remove the sulfur by heating **15** (R = Bn) with tributyltin hydride in the presence of AIBN was unsuccessful, resulting in only decomposition of the starting material.

Unfortunately, these compounds did not display appreciable activity as inhibitors of representative class A (TEM-1) or class C (P99) serine-based β-lactamases.[13] Biological screening as inhibitors of other proteases is in progress. A wide variety of substituted bridged penams should be available using this synthetic methodology.

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Supporting Information Available: Tables of positional and thermal parameters, selected bond distances and angles, anisotropic displacement factors, and H atom coordinates and isotropic displacement parameters for **16** and experimental procedures for the transformations of **10** to **15** (7 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(12) $[C_{31}H_{28}N_2O_6S]\cdot[C_6H_6]$, formula weight 634.7, crystallized in an orthorhombic system, $P2_12_12_1$, $a = 6.215(3)$, $b = 17.174(5)$, and $c = 31.074(10)$ Å, $v = 3317(2)$ Å^3, $Z = 4$, $d = 1.271$ Mg/m^3, $\mu = 0.146$ mm^{-1}. Data were collected on a Siemens P4 diffractometer at −45°, Mo Kα, 2θ 3.0−42.0°; 2058 reflections were collected. Data were corrected for Lorentz and polarization effects, but not for absorption. The structure was solved with direct methods and refined on F^2 (G. M. Sheldrick, *SHELX93*, University of Göttengen, Germany, 1993). All non H atoms were anisotropically refined, while H atoms were located on a "riding model". The final refinement converged at $R = 0.068$, $wR_2 = 0.135$, GOF = 1.02 for 1742 observed reflections ($I > 2.0\sigma(I)$].

(13) In each case, the IC50 values of these bridged analogues were evaluated as greater than 1 mM, relative to a measured value for tazobactam of 0.3 μM for TEM-1 and 50 μM for P99.