

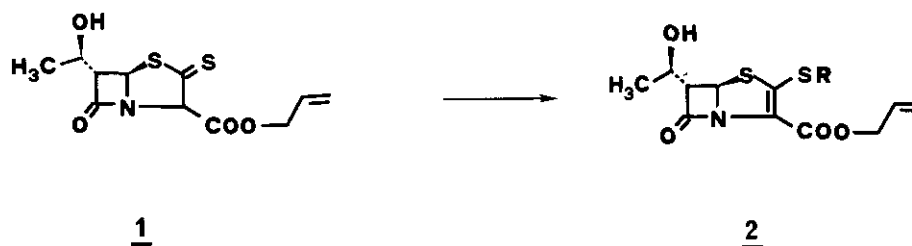
## A NOVEL SYNTHESIS OF A 2-THIOXOPENAM

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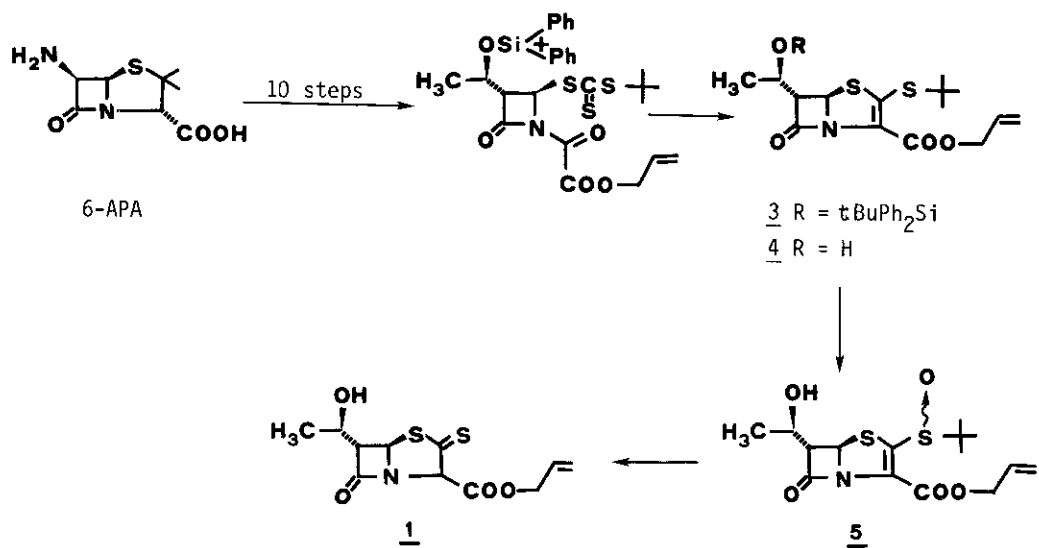
**Abstract** - The synthesis of an optically active 2-thioxopenam through thermal rearrangement of a 2-t-butylsulfinylpenem to a penemsulfenic acid intermediate and its in situ deoxygenation is described.

Penems are very potent  $\beta$ -lactam antibiotics with a broad antibacterial spectrum <sup>1</sup>. Biological activity and bioavailability can be influenced by variation of the side chain at C-2 of the penem skeleton. 2-Thioxopenams are convenient synthetic intermediates <sup>2,3</sup> in the multistep syntheses of penems: The C-2 sidechain can be easily introduced at this stage by alkylation <sup>2</sup> or by condensation with alcohols using triphenylphosphine-diethyl azodicarboxylate <sup>4</sup> (scheme 1).

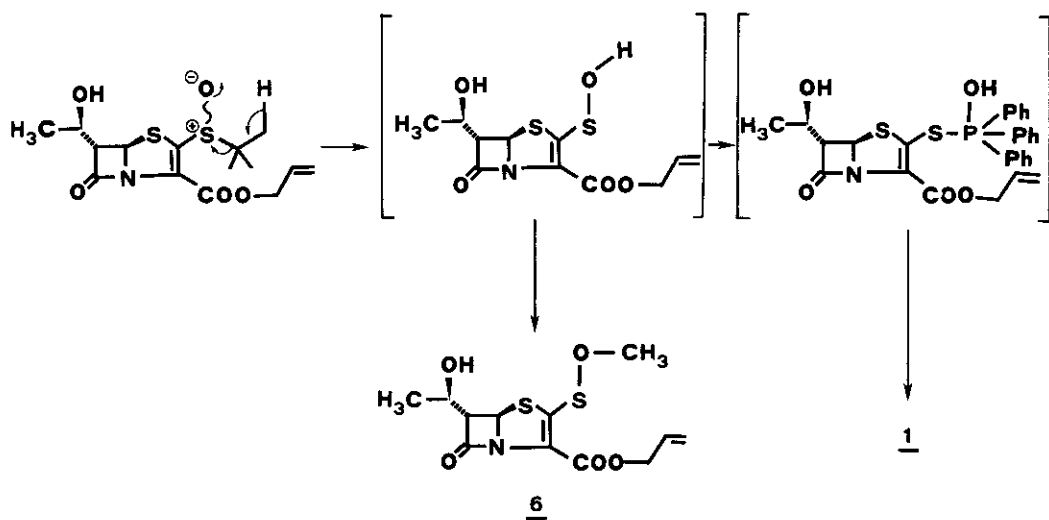


Scheme 1

There are only few syntheses of 2-thioxopenams <sup>2,3,5,6</sup> reported in the literature and most of these lead to the undesired *cis* product (5*S*,6*S* isomer) <sup>7</sup>. Our method which we present in this paper gives an enantiomerically pure *trans*-2-thioxopenam with 5*R*,6*S* configuration under very mild conditions. Our approach (see scheme 2) is based on the thermal rearrangement of tertiary sulfoxides to sulfenic acids <sup>8</sup> which can be deoxygenated by triphenylphosphine.



Scheme 2



Scheme 3

The 2-t-butylthiopenerm 4 which we needed as starting material was prepared from 6-aminopenicillanic acid (6-APA) in analogy to already established methods <sup>9</sup>. The ring closure to the 2-t-butylthiopenerm 3 was performed via the corresponding trithiocarbonate using the oxalimide cyclisation reaction <sup>10</sup>. Desyllilation gave starting material 4 (3 equiv. n-Bu<sub>4</sub>NF, 6 equiv. CH<sub>3</sub>COOH, THF, 48 h, 75 % after chromatography)<sup>11</sup>.

The exocyclic sulfur atom of 4 could be selectively oxidized to an 8:3 mixture of the epimeric sulfoxides 5 <sup>12</sup> (1 equiv. MCPBA, CH<sub>2</sub>Cl<sub>2</sub>, -30°C, 40 % after chromatography, plus 30 % unreacted 4 recovered). Rearrangement and deoxygenation were performed by refluxing 5 with 1 equiv. triphenylphosphine in CH<sub>2</sub>Cl<sub>2</sub> for 4 h. The isolated 2-thioxopenerm 1 <sup>13</sup> (85 % after chromatography) was the pure trans isomer (5R,6S) and existed in CDCl<sub>3</sub> solution exclusively in the thioxo form. This is in good agreement with the literature <sup>2,3</sup>. For further structure proof we alkylated 1 to 2 (R = C<sub>2</sub>H<sub>5</sub>) (10 equiv. C<sub>2</sub>H<sub>5</sub>Br, 1 equiv. (iPr)<sub>2</sub>EtN, -20°C, 16 h, 60 % after chromatography). 2 (R = C<sub>2</sub>H<sub>5</sub>) was in all spectroscopical data identical with a sample prepared by a different way <sup>10</sup>.

The existence of an azetidionesulfenic acid intermediate during the rearrangement of penicillin sulfoxides<sup>14</sup> is well documented in the literature<sup>15</sup> but to our knowledge a penemsulfenic acid which we postulate as intermediate (scheme 3) has never been reported. Therefore we did further investigation to prove the intermediacy of a penemsulfenic acid during the thermal rearrangement of 5. When we kept a freshly prepared sample of 5 in a CDCl<sub>3</sub> solution at 50° C for 0.5 h in an NMR test tube the formation of a new compound (40 % of total material) was observed in the NMR spectrum<sup>16</sup>. These new signals could be attributed to the mixture of the postulated penemsulfenic acid and 2-methylpropene. For further structure proof we prepared the more stable methyl ester of the sulfenic acid by treating a solution of 5 in CH<sub>2</sub>Cl<sub>2</sub> with diazomethane (room temperature, 16 h, 27 % after chromatography). All spectroscopic data <sup>17</sup> were in good agreement with the proposed structure of 6. These results show that the penemsulfenic acid is generated under very mild conditions during the t-butylsulfoxide rearrangement.

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11. Spectroscopical data identical with those given in lit. cit. 10b.
12. IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 1788 (β-lactam), 1708 (ester).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250 MHz, δ) a) 5.71 (d, J = 1.5 Hz, H-C<sub>5</sub>), 4.20 (m, H-C<sub>8</sub>), 3.92 (dd, J<sub>1</sub> = 7 Hz, J<sub>2</sub> = 1.5 Hz, H-C<sub>6</sub>), b) 5.86 (d, J = 1.5 Hz, H-C<sub>5</sub>), 4.20 (m, H-C<sub>8</sub>), 3.87 (dd, J<sub>1</sub> = 7 Hz, J<sub>2</sub> = 1.5 Hz, H-C<sub>6</sub>).
13. IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 1790 (β-lactam), 1742 (ester).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 90 MHz, δ) 5.90 (d, J = 1.5 Hz, H-C<sub>5</sub>), 5.38 (s, H-C<sub>3</sub>), 4.38 (quintet, J = 7 Hz, H-C<sub>8</sub>), 3.69 (dd, J<sub>1</sub> = 7 Hz, J<sub>2</sub> = 1.5 Hz, H-C<sub>6</sub>), 1.41 (d, J = 6.5 Hz, CH<sub>3</sub>).
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16. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250 MHz, δ) 5.71 (d, J = 1.5 Hz, H-C<sub>5</sub>), 4.20 (m, H-C<sub>8</sub>), 3.79 (dd, J<sub>1</sub> = 7 Hz, J<sub>2</sub> = 1.5 Hz, H-C<sub>6</sub>).
17. IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 1787 (β-lactam).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250 MHz, δ) 5.81 (d, J = 1.5 Hz, H-C<sub>5</sub>), 4.26 (quintet, J = 7 Hz, H-C<sub>8</sub>), 3.81 (s, OCH<sub>3</sub>), 3.78 (dd, J<sub>1</sub> = 1.5 Hz, J<sub>2</sub> = 7 Hz, H-C<sub>6</sub>), 1.38 (d, J = 7 Hz, CH<sub>3</sub>).  
 MS (m/z) 317 (M<sup>+</sup>), 231 (M<sup>+</sup> - CH<sub>3</sub>CHOH-CH=C=O), 200 (231-OCH<sub>3</sub>).

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