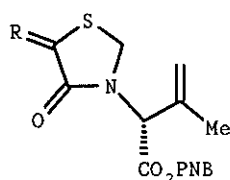




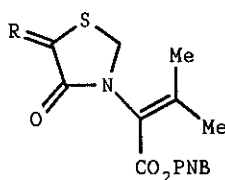
## RESULTS AND DISCUSSION

*p*-Nitrobenzyl 6 $\beta$ -aminopenicillanate<sup>12</sup> was smoothly converted ( $\text{Ph}_3\text{CCl}$  and  $\text{NEt}_3$  in  $\text{CH}_2\text{Cl}_2$ ) into the tritylamino derivative (**13**), whose oxidation with 3-chloroperbenzoic acid (MCPBA) gave the 1 $\beta$ -oxide (**1**), accompanied by a small amount of its  $\alpha$ -epimer (**15**). Treatment of the isolated  $\beta$ -sulfoxide (**1**) with an equimolecular amount of MBT in boiling toluene afforded a new product, whose molecular formula  $\text{C}_{34}\text{H}_{29}\text{N}_3\text{O}_5\text{S}$  (elemental analysis, FDms) indicated the loss of the elements of water without MBT incorporation. As evidenced by ir spectroscopy, the new entity did neither possess the  $\beta$ -lactam moiety nor the tritylamino proton present in the parent compound.  $^1\text{H-Nmr}$  spectroscopy showed an intact trityl group and typical signals of the *N*-butenoate appendage customarily generated upon thermal reaction of penam sulfoxides,<sup>1</sup> while the pattern characteristic of the  $\beta$ -lactam protons was absent and substituted by an AB system (two doublets at  $\delta$  4.22 and 4.74 ppm,  $J=9.4$  Hz) attributable to two diastereotopic protons. The presence of a methylene group was confirmed by  $^{13}\text{C-nmr}$  spectroscopy, which also evidenced, in addition to signals of the butenoate and trityl moieties, two carbons resonating at  $\delta$  151.0 and 162.8 ppm. These spectral data led us to formulate<sup>10</sup> the trityliminothiazolidinone structure (**8**). Concomitantly, Stoodley and co-workers<sup>13</sup> reported the crystallographic characterization of a related compound (**12**), obtained by thermolysis of a 3-tritylamino-4-*tert*-butylsulfinylazetidione.

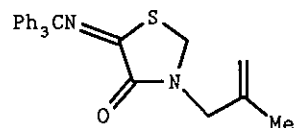
Chemical evidence of structure (**8**) was obtained as follows. Upon treatment with a catalytic amount of  $\text{NEt}_3$ , the optical activity of the compound ( $[\alpha]_D -72^\circ$ ) was lost, owing to isomerization of the chiral 3-butenoate moiety of **8** into the senecioate moiety of **10**. The presence of a tritylimino moiety in **8** and **10** was guaranteed by their conversion under mild hydrolytic conditions (*p*-toluenesulfonic acid, aqueous acetone) into the dioxo derivatives (**9**) and (**11**), respectively. To our knowledge 2-unsubstituted 4,5-dioxothiazolidines have not been reported previously. Mention was made in a literature precedent<sup>14</sup> to a derivative bearing a phenyl group at C-2, whose C-4 and C-5  $\delta_C$  assignments should be reversed in order to match those of **9** and **11**



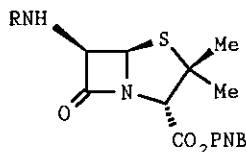
8 R =  $\text{Ph}_3\text{CN}$   
9 R = O



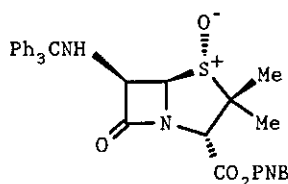
10 R =  $\text{Ph}_3\text{CN}$   
11 R = O



12

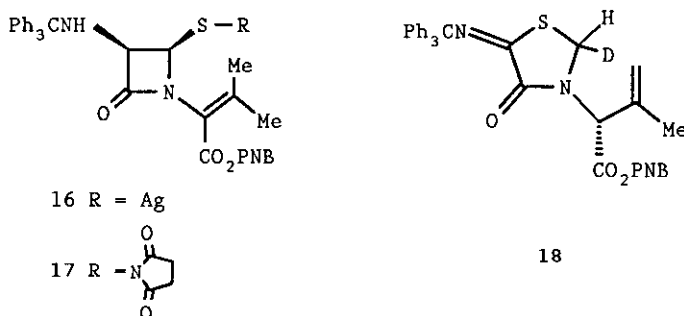


13 R =  $\text{Ph}_3\text{C}$   
14 R =  $\text{CH}_2=\text{CHCH}_2\text{OCO}$

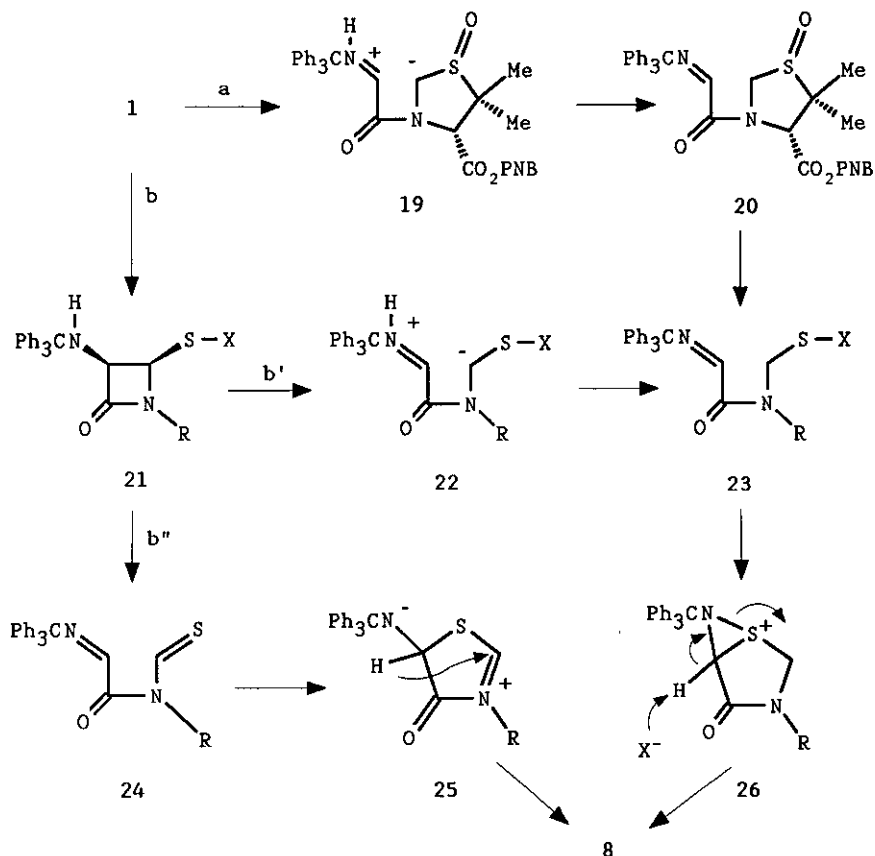


15

The first question essential to unravel the rearrangement pathway is whether  $\beta$ -lactam cleavage preceded or followed formation of 1,2-secopenicillanates from the original penam sulfoxide (paths *a* and *b* in Scheme 1). Since the reactions observed by Stoodley and us occurred under conditions wherein penam sulfoxides and the corresponding sulfenic acids are in equilibrium, we addressed this question by examining the thermal behaviour of the 4-succinimidosulphenylazetidinone (**17**), which possesses a leaving group at sulfur as sulfenic acids (**6**) and Kamiya disulfides (**7**), but cannot equilibrate to a penam sulfoxide. By applying an original methodology,<sup>15</sup> the tritylamino-1,2-secopenicillanate (**13**) was subjected to the action of silver nitrate and 1,5-diazabicyclo[4.3.0]non-5-ene affording the silver mercaptide (**16**), whose treatment with *N*-bromosuccinimide *in situ* gave the desired model compound (**17**). In refluxing toluene, the azetidinone (**17**) did rearrange to the iminothiazolidinone (**10**). Despite the low yield (11%), at least in part attributable to the substitution pattern at nitrogen and sulfur peculiar to **17**, this result proves that tritylamino-1,2-secopenicillanates can undergo the rearrangement without the necessary involvement of the parent penam nucleus. Further credit to the hypothesis that  $\beta$ -lactam cleavage occurred after opening of the thiazolidine ring of penam (**1**) was provided by considering the role played by MBT, that is not incorporated into **8**. Its amount could be drastically reduced, but not omitted, without reducing the reaction rate and yield. It could be inferred that MBT intercepts the thermally generated sulfenic acid (**21**, X = OH) to produce a disulfide (**21**, X = benzothiazolythio) more prone to rearrange (Scheme 1).



Given the fact that 3-tritylamino-4-sulphenylazetidinones (sulfenic acids (**6**), disulfides (**7**), sulfenimide (**17**)) are thermally unstable, further questions concern the mechanism of their structural reorganization to trityliminothiazolidinones (**8**, **10**, **12**). The involvement of a thiyl radical intermediate<sup>13</sup> seems unlikely, since in our hands the reaction was not affected by the presence of either the radical promoter 1,1'-bis(isobutyronitrile) or the inhibitor hydroquinone. According to another interpretation<sup>13</sup> (path *b*" in Scheme 1), the imine-thione (**24**) would be produced by Grob fragmentation<sup>16</sup> of the sulfenic acid (**21**); addition of the thione to the imine moiety would then lead to the cyclic dipolar intermediate (**25**). However, inspection of Dreiding molecular models reveals that a correct orientation of the nitrogen lone pair and the S-X bond in species (**21**), which must be disposed antiperiplanar in order that a Grob-like fragmentation can occur, is probably biased by the steric hindrance of the trityl group. Further, conversion of the proposed intermediate zwitterion (**25**) to the final product (**8**) would require an intramolecular [1,3]-hydride shift; on this hypothesis, rearrangement of a tritylamino-1,2-secopenicillanate sulfoxide deuteriated at C-6 would afford a thiazolidinone deuteriated at C-2.



**SCHEME 1** (X= OH or 2-benzothiazolythio, R= CH(CO<sub>2</sub>PNB)C(Me)=CH<sub>2</sub>)

This possibility was actually tested. The amino-protected penam sulfoxide (**3**) was selected as a suitable substrate for the incorporation of deuterium at C-6 by applying the methodology developed by Vanderhaeghe.<sup>17</sup> Acylation of *p*-nitrobenzyl 6-amino-penicillanate with allyl chloroformate provided the penam (**14**), whose oxidation with stoichiometric MCPBA gave the single 1 $\beta$ -oxide (**3**). Exposure of this compound to triethylamine in D<sub>2</sub>O-CH<sub>3</sub>CN overnight provided the desired 6 $\alpha$ -deuterio derivative (**4**) and its C-6 epimer (**5**) in about 2:1 ratio. Deallylation of the former compound with tetrakis(triphenylphosphine)palladium(0) in the presence of acetic acid, followed by tritylation of the crude amino product, gave the 6 $\alpha$ -deuterio-6 $\beta$ -tritylamino-penicillanate (**2**) in low unoptimized yield. Thermolysis of this product in toluene in the presence of MBT led to the undeuteriated trityliminothiazolidinone (**8**). Instead, the C-2 deuteriated thiazolidinone (**18**) was obtained, as epimeric mixture at C-2 (3:2 ratio), upon heating a D<sub>2</sub>O-toluene solution of the unlabelled penam (**1**) and MBT.

Following these observations, we propose species (**23**) as the key intermediate of the rearrangement process (Scheme 1). Compared to classical 6-amidopenicillins and 3-amidoazetidinones, the corresponding tritylamino derivatives feature a more nucleophilic nitrogen lone pair. Shielded from the attack of external electrophiles by the cumbersome trityl group, it could trigger the C-3,C-4 bond cleavage (azetidinone numbering), providing

stabilized zwitterionic species (**19** or **22**) by path *a* or *b'*. Both compounds can in principle evolve to **23**, but involvement of **19** is much less likely since, as discussed above, circumstantial evidence argues for azetidinone intermediates (path *b*) even when the rearranging substrate is the penam sulfoxide (**1**). In the proposed intermediate (**23**), intramolecular addition of the sulfenyl moiety to the imine double bond may provide the thiaziridinium ion (**26**), wherein everything is set up for a particularly favourable conversion to the thiazolidinone (**8**).

In summary, conventional exploitation of penicillin sulfoxide chemistry<sup>1</sup> is not possible on 6-tritylamino penam derivatives, the corresponding 1,2-secopenicillanates (sulfenic acids, disulfides, sulfenimides) undergoing rearrangement to 5-trityliminothiazolidinones through the unusual scission of the C-3,C-4 azetidinone bond. The formal transfer of the penam C-6 hydrogen atom to the thiazolidine C-2 methylene is a protomeric process rather than an intramolecular [1,3]-hydride shift, as originally proposed. Mercaptobenzothiazole in virtually catalytic amount is a very efficient promoter of this reaction on the penam sulfoxide (**1**). Conventional deblocking of the trityl moiety from obtained products (**8**) and (**10**) provides a simple entry to representatives (**9**, **11**) of the unvisited 2-unsubstituted 4,5-dioxothiazolidine structure.

## EXPERIMENTAL

Melting points were determined in a Büchi apparatus and are uncorrected. Spectral data were recorded on the following spectrometers: ir - Perkin Elmer 1420; <sup>1</sup>H-nmr - Varian EM390 and VXR-200; <sup>13</sup>C-nmr - Varian VXR-400S. FD mass spectra were recorded on a Varian Mat 311/A instrument. Elemental analyses were performed on a Carlo Erba NA 1005 analyzer. Flash chromatography was carried out with silica gel Merck 60 (230-400 mesh) eluting with hexane:ethyl acetate mixtures (ratio between brackets) unless otherwise stated.

*p*-Nitrobenzyl 6 $\beta$ -tritylamino penicillanate (**13**). - *p*-Nitrobenzyl 6 $\beta$ -aminopenicillanate was obtained as a syrup by treatment of its *p*-toluenesulfonic acid salt in EtOAc-aqueous NaHCO<sub>3</sub>, drying of the organic phase over Na<sub>2</sub>SO<sub>4</sub> and removal of the solvent. The compound (6.3 g, 17.9 mmol) was dissolved in dry dichloromethane (100 ml) and treated with trityl chloride (5.6 g, 20.1 mmol) and triethylamine (3.0 ml, 21.5 mmol). After stirring for 1 h at room temperature, the solution was washed with water, dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness. Crystallization of the residue from dichloromethane-ethyl ether provided **13** as a white powder (8.7 g, 82%), mp 161-163 °C. Ir (KBr)  $\nu_{\max}$  3320 (NH), 1780 ( $\beta$ -lactam) and 1735 (ester) cm<sup>-1</sup>; <sup>1</sup>H nmr (200 MHz; CDCl<sub>3</sub>)  $\delta$  1.26 (3H, s, 2 $\alpha$ -Me), 1.56 (3H, s, 2 $\beta$ -Me), 3.18 (1H, d, *J* = 11.4, NH, D<sub>2</sub>O exch.), 4.39 (1H, d, *J* = 3.9, 5-H), 4.43 (1H, s, 3-H), 4.50 (1H, dd, *J* = 3.9 and 11.4, 6-H), 5.17 (2H, ABq, *J* = 13.0, ArCH<sub>2</sub>), 7.2-7.6 (17H, m, CPh<sub>3</sub> + PNB AA'), 8.21 ppm (2H, d, *J* = 8.5, PNB BB'). Anal. Calcd for C<sub>34</sub>H<sub>31</sub>N<sub>3</sub>O<sub>5</sub>S: C, 68.78; H, 5.3; N, 7.1. Found: C, 68.77; H, 5.3; N, 7.0.

*Oxidation of the penam (13) with 3-chloroperbenzoic acid.* - 80% MCPBA (1.85 g, 8.58 mmol) dissolved in dichloromethane (35 ml) was added dropwise to a solution of penicillanate (**13**) (5.0 g, 8.42 mmol) in dichloromethane (70 ml) cooled to -20 °C. After stirring for 15 min at -20 °C, the precipitate was filtered off and the solution was washed in sequence with an aqueous solution of NaHCO<sub>3</sub> (1.45 g) and Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub> (0.8 g), then with 4% aqueous NaHCO<sub>3</sub>. The dried (MgSO<sub>4</sub>) organic phase was evaporated and the residual solid was suspended in ether. Filtration afforded *p*-nitrobenzyl 6 $\beta$ -tritylamino penicillanate 1 $\beta$ -oxide (**1**) as a white powder (4.1 g, 80%), mp 187 °C (decomp.). Ir (KBr)  $\nu_{\max}$  3330 (NH), 1785 ( $\beta$ -lactam) and 1735 cm<sup>-1</sup>

(ester);  $^1\text{H}$  nmr (200 MHz,  $\text{CDCl}_3$ )  $\delta$  0.81 (3H, s, 2 $\alpha$ -Me), 1.51 (3H, s, 2 $\beta$ -Me), 3.71 (1H, d,  $J$  = 4.0, 5-H), 3.96 (1H, d,  $J$  = 12.8, NH,  $\text{D}_2\text{O}$  exch.), 4.58 (1H, s, 3-H), 4.70 (1H, dd,  $J$  = 4.0 and 12.8, 6-H), 5.23 (2H, ABq,  $J$  = 13.0,  $\text{ArCH}_2$ ), 7.2-7.8 (17H, m,  $\text{CPh}_3$  + PNB AA'), 8.22 ppm (2H, d,  $J$  = 8.5, PNB BB'). Anal. Calcd for  $\text{C}_{34}\text{H}_{31}\text{N}_3\text{O}_5\text{S}$ : C, 68.78; H, 5.3; N, 7.1. Found: C, 68.77; H, 5.3, N, 7.0.

Evaporation of the ethereal filtrate and purification of the residue by flash chromatography (2:1) gave a second crop (200 mg, 4%) of the  $\beta$ -oxide (1) as the first eluted material. The second eluted material was *p*-nitrobenzyl 6 $\beta$ -tritylamino-penicillanate 1 $\alpha$ -oxide (15) as an amorphous solid (95 mg, 2%). Ir (KBr)  $\nu_{\text{max}}$  3330 (NH), 1790 ( $\beta$ -lactam) and 1740  $\text{cm}^{-1}$  (ester);  $^1\text{H}$  nmr (200 MHz;  $\text{CDCl}_3$ )  $\delta$  1.17 (3H, s, 2 $\alpha$ -Me), 1.56 (3H, s, 2 $\beta$ -Me), 2.94 (1H, d,  $J$  = 8.5, NH,  $\text{D}_2\text{O}$  exch.), 4.04 (1H, d,  $J$  = 4.0, 5-H), 4.31 (1H, s, 3-H), 4.68 (1H, dd,  $J$  = 4.0 and 8.5, 6-H), 5.22 (2H, s,  $\text{ArCH}_2$ ), 7.2-7.6 (17H, m,  $\text{CPh}_3$  + PNB AA'), 8.22 ppm (2H, d,  $J$  8.5, PNB BB').

*p*-Nitrobenzyl (2R)-3-Methyl-2-(4-oxo-5-tritylimino-3-thiazolidinyl)-3-butenolate (8). - A solution of *p*-nitrobenzyl 6 $\beta$ -tritylamino-penicillanate 1 $\beta$ -oxide (1) (366 mg, 0.6 mmol) and 2-mercaptobenzothiazole (17 mg, 0.1 mmol) in toluene (25 ml) was heated at reflux for 4.5 h. After evaporation to dryness, the residue was purified by flash chromatography (3:1) to provide 8 as a white powder (178 mg, 50%), mp 205-207 °C (decomp.).  $[\alpha]_{\text{D}} - 72^\circ$  (c 0.1,  $\text{CHCl}_3$ ); ir (KBr)  $\nu_{\text{max}}$  1750, 1700sh, 1690, 1620, 1605, 1530, 1350, 1240 and 1170  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (200 MHz,  $\text{CDCl}_3$ )  $\delta$  1.82 (3H, m,  $\text{CH}_3\text{C}=\text{CH}_2$ ), 4.22 and 4.74 (2H, 2 x d,  $J$  = 9.4,  $\text{NCH}_2\text{S}$ ), 4.92 and 5.24 (2H, 2 x m,  $\text{CH}_3\text{C}=\text{CH}_2$ ), 5.29 (2H, s,  $\text{ArCH}_2$ ), 5.72 (1H, s,  $\text{NCHCO}_2$ ), 7.2-8.2 ppm (19H, m,  $\text{CPh}_3$  + PNB);  $^{13}\text{C}$  nmr (50 MHz,  $\text{CDCl}_3$ )  $\delta$  21.7 (q,  $\text{CH}_3\text{C}=\text{C}$ ), 43.4 (t,  $\text{NCH}_2\text{S}$ ), 61.6 (d,  $\text{NCHCO}$ ), 65.9 (t,  $\text{ArCH}_2$ ), 77.6 (s,  $\text{NCPH}_3$ ), 118.3 (t,  $\text{C}=\text{CH}_2$ ), 123.9, 127.3, 128.0, 128.7, 130.0, 136.8 (s,  $\text{C}=\text{CH}_2$ ), 142.0, 143.8, 147.9, 151.0 (s,  $\text{NC}=\text{O}$ ), 162.8 (s,  $\text{SC}=\text{N}$ ), 168.8 ppm (s,  $\text{CO}_2$ ). Anal. Calcd for  $\text{C}_{34}\text{H}_{29}\text{N}_3\text{O}_5\text{S}$ : C, 69.02; H, 4.9; N, 7.1, S, 5.4. Found: C, 68.89; H, 5.0; N, 7.1, S, 5.4.

*p*-Nitrobenzyl (2R)-2-(4,5-Dioxo-3-thiazolidinyl)-3-methyl-3-butenolate (9). - *p*-Toluenesulfonic acid monohydrate (59 mg, 0.31 mmol) was added to a solution of the tritylimine (8) (183 mg, 0.31 mmol) in acetone (12 ml). After stirring for 15 h at room temperature, evaporation to dryness and flash chromatography (1:1) provided 9 (86 mg, 79%) as a colourless oil that solidified on standing, mp 93-95 °C  $[\alpha]_{\text{D}} + 104^\circ$  (c 0.1,  $\text{CHCl}_3$ ); ir (KBr)  $\nu_{\text{max}}$  1755, 1710 and 1695  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (90 MHz;  $\text{CDCl}_3$ )  $\delta$  1.85 (3H, m,  $\text{CH}_3\text{C}=\text{CH}_2$ ), 4.62 and 5.15 (2H, 2 x d,  $J$  = 10.5,  $\text{NCH}_2\text{S}$ ), 4.97 and 5.35 (2H, 2 x m,  $\text{C}=\text{CH}_2$ ), 5.31 (2H, s,  $\text{ArCH}_2$ ), 5.60 (1H, s,  $\text{NCHCO}$ ), 7.55 (2H, d,  $J$  = 8.5, PNB AA'), 8.23 (2H, d,  $J$  = 8.5, PNB BB');  $^{13}\text{C}$  nmr (50 MHz;  $\text{C}_6\text{D}_6$  +  $\text{CDCl}_3$ )  $\delta$  21.2 (q,  $\text{CH}_3\text{C}=\text{C}$ ), 41.3 (t,  $\text{NCH}_2\text{S}$ ), 62.4 (d,  $\text{NCHCO}$ ), 66.0 (t,  $\text{ArCH}_2$ ), 118.7 (t,  $\text{C}=\text{CH}_2$ ), 123.8, 136.6 (s,  $\text{C}=\text{CH}_2$ ), 141.6, 148.2, 158.2 (s,  $\text{NC}=\text{O}$ ), 168.8 (s,  $\text{CO}_2$ ), 184.0 ppm (s,  $\text{SC}=\text{O}$ ); addition of chromium(III) acetylacetonate as a relaxant was required to detect the signal at  $\delta_{\text{C}}$  184.0 ppm; resonances between  $\delta_{\text{C}}$  127-129 ppm (Ar) were obscured by the solvent. Anal. Calcd for  $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_6\text{S}$ : C, 51.42; H, 4.0; N, 8.0; S, 9.1. Found: C, 51.44; H, 4.1; N, 8.0, S 9.1.

*p*-Nitrobenzyl 3-Methyl-2-(4-oxo-5-tritylimino-3-thiazolidinyl)-2-butenolate (10). - A solution of the 3-butenolate (8) (41 mg, 0.07 mmol) in dichloromethane (8 ml) was treated with triethylamine (0.04 ml, 0.28 mmol) and let stand at room temperature for 1.5 h. The solution was washed with 2% hydrochloric acid and brine, then dried over  $\text{Na}_2\text{SO}_4$  and evaporated to provide 10 as a gum (35 mg, 85%). Ir ( $\text{CHCl}_3$ )  $\nu_{\text{max}}$  (*inter alia*) 1720sh and 1710  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (200 MHz;  $\text{CDCl}_3$ )  $\delta$  1.92 (3H, s, Me), 2.36 (3H, s, Me), 4.36 (2H, s,  $\text{NCH}_2\text{S}$ ), 5.24 (2H, s,  $\text{ArCH}_2$ ), 7.2-7.5 (17H, m,  $\text{CPh}_3$  + PNB AA'), 8.12 ppm (2H, d,  $J$  = 8.7, PNB BB'); FDms,  $m/z$  591  $[\text{M}]^+$ , base peak.

*p*-Nitrobenzyl 2-(4,5-Dioxo-3-thiazolidinyl)-3-methyl-2-butenolate (**11**).- A solution of *p*-toluenesulfonic acid monohydrate (114 mg, 0.6 mmol) and the trityliminothiazolidinone (**10**) (120 mg, 0.2 mmol) in acetone (10 ml) was stirred at room temperature for 2 h. Removal of the solvent and flash chromatography (1:1) of the residue gave **11** as a gum (50 mg, 68%). Ir (CHCl<sub>3</sub>)  $\nu_{\max}$  (*inter alia*) 1730 cm<sup>-1</sup>; <sup>1</sup>H nmr (60 MHz; CDCl<sub>3</sub>)  $\delta$  1.99 (3H, s, Me), 2.44 (3H, s, Me), 4.84 (2H, s, NCH<sub>2</sub>S), 5.32 (2H, s, ArCH<sub>2</sub>), 7.48 (2H, d, *J* = 8.5, PNB AA'), 8.07 ppm (2H, d, *J* = 8.5, PNB BB'); FDms, *m/z* 360 [M]<sup>+</sup>, base peak.

*p*-Nitrobenzyl 2-[(3R,4R)-3-(2,5-Dioxo-1-pyrrolidinyl)sulfenyl-4-tritylamino-2-oxo-1-azetidiny]-3-methyl-3-butenolate (**17**).- A mixture of silver chloride (0.3 g, 2.8 mmol) and 1,5-diazabicyclo[4.3.0]non-5-ene (0.2 ml, 1.6 mmol) in dry acetonitrile (10 ml) was stirred under nitrogen for 5 min before addition of the tritylaminopenam (**13**) (594 mg, 1.0 mmol). When the starting material had disappeared (tlc monitoring; 3 h), *N*-bromosuccinimide (356 mg, 2 mmol) was added. After 15 min, the reaction mixture was partitioned between EtOAc and water, and the dried (Na<sub>2</sub>SO<sub>4</sub>) organic phase was evaporated to dryness. Flash chromatography (1:1) of the residue afforded **17** as an amorphous solid (310 mg, 45%), mp 110-117 °C. Ir (KBr)  $\nu_{\max}$  3340 (NH), 1775 ( $\beta$ -lactam) and 1725vs cm<sup>-1</sup> (ester and imide); <sup>1</sup>H nmr (90 MHz; CDCl<sub>3</sub>)  $\delta$  2.07 (3H, s, Me), 2.13 (3H, s, Me), 2.63 (4H, s, COCH<sub>2</sub>CH<sub>2</sub>CO), 3.12 (1H, d, *J* = 8.0, NH, D<sub>2</sub>O exch.), 4.57 (1H, dd, *J* = 4.5 and 8.0, 3-H), 5.12 (2H, s, ArCH<sub>2</sub>), 5.42 (1H, d, *J* = 4.5, 4-H), 7.2-7.6 (17H, m, CPh<sub>3</sub> + PNB AA'), 8.18 ppm (2H, d, *J* = 8.5, PNB BB'). Anal. Calcd for C<sub>38</sub>H<sub>34</sub>N<sub>4</sub>O<sub>7</sub>S · 0.5 H<sub>2</sub>O: C, 65.22; H, 5.0; N, 8.0. Found: C, 65.38, H, 5.1; N, 7.9.

*Thermolysis of the azetidione (17)*.- A solution of the imidosulfenylazetidione (**17**) (50 mg, 0.075 mmol) in toluene (15 ml) was heated at reflux for 5 h under nitrogen. Concentration to dryness and flash chromatography (3:1) afforded a sample (5 mg, 11%) of *p*-nitrobenzyl (2R)-3-methyl-2-(4-oxo-5-tritylimino-3-thiazolidinyl)-2-butenolate (**10**), identical to the one obtained from penam sulfoxide (**1**) (*vide supra*).

*p*-Nitrobenzyl 6 $\beta$ -Allyloxycarbonylaminopenicillanate (**14**).- *p*-Nitrobenzyl 6 $\beta$ -amino-penicillanate *p*-toluenesulfonic acid salt (7.83 g, 15 mmol) was dissolved in a cold (0 °C) dichloromethane solution (100 ml) containing triethylamine (2.2 ml, 15.8 mmol), then allyl chloroformate (2.4 ml, 22.6 mmol) and a second portion of triethylamine (3.15 ml, 22.6 mmol) were added simultaneously under stirring. After 15 min at room temperature, the reaction mixture was washed twice with brine and evaporated to dryness. The resultant thick oil was passed through a short pad of silica gel (hexane-EtOAc 1:2) to provide reagent-grade **14** as a syrup (5.5 g, 85%). Ir (CHCl<sub>3</sub>)  $\nu_{\max}$  3400 (NH), 1785 ( $\beta$ -lactam) and 1725 cm<sup>-1</sup> (ester); <sup>1</sup>H nmr (90 MHz; CDCl<sub>3</sub>)  $\delta$  1.47 (3H, s, Me), 1.67 (3H, s, Me), 4.52 (1H, s, 3-H), 4.5-4.7 (2H, m, CH<sub>2</sub>=CHCH<sub>2</sub>), 5.2-5.6 (5H, m, NH + 5-H + 6-H + CH<sub>2</sub>=CHCH<sub>2</sub>), 5.7-6.1 (1H, m, CH<sub>2</sub>=CHCH<sub>2</sub>), 7.58 (2H, d, *J* = 8.7, PNB AA'), 8.28 ppm (2H, d, *J* = 8.7, PNB BB').

*p*-Nitrobenzyl 6 $\beta$ -Allyloxycarbonylaminopenicillanate 1 $\beta$ -oxide (**3**).- A solution of the penam (**14**) (5.07 g, 11.7 mmol) in dichloromethane (100 ml) was cooled to -20 °C and treated with 80% MCPBA (2.55 g, 11.8 mmol). After 5 min the solution was sequentially washed with 1M aqueous NaHSO<sub>3</sub>, saturated aqueous NaHCO<sub>3</sub> and water. Evaporation to dryness provided crude **3** as a foam (5.2 g, 98%), which was used as such in the deuteration experiment below. <sup>1</sup>H Nmr (90 MHz; CDCl<sub>3</sub>)  $\delta$  1.15 (3H, s, 2 $\alpha$ -Me), 1.69 (3H, s, 2 $\beta$ -Me), 4.58 (2H, m, CH<sub>2</sub>=CHCH<sub>2</sub>), 4.70 (1H, s, 3-H), 5.05 (1H, d, *J* = 4, 5-H), 5.1-5.5 (2H, m, CH<sub>2</sub>=CHCH<sub>2</sub>), 5.32 (2H, s, ArCH<sub>2</sub>), 5.75 (1H, dd, *J* = 4 and 10, 6-H), 5.7-6.2 (1H, m, CH<sub>2</sub>=CHCH<sub>2</sub>), 6.31 (1H, d, *J* = 10, NH, D<sub>2</sub>O exch.), 7.60 (2H, d, *J* = 9, PNB AA'), 8.26 ppm (2H, d, *J* = 9, PNB BB'); FDms, *m/z* (% rel. int.) 451 (100, [M]<sup>+</sup>), 452 (83, [MH]<sup>+</sup>).

*Deuteration of the penam sulfoxide (3).*- A solution of the penam (3) (2 g, 4.4 mmol) and triethylamine (0.62 ml, 4.4 mmol) in acetonitrile (20 ml) and deuterium oxide (2 ml) was let stand at room temperature for 15 h. After cooling to 0 °C, acetic acid-*d* (CH<sub>3</sub>CO<sub>2</sub>D) (0.5 ml) was added. The reaction mixture was partitioned between water and EtOAc, and the organic layer was evaporated to a syrup. Flash chromatography (2:1) afforded the two deuteriated penam sulfoxides (4 and 5) in the order below.

*p*-Nitrobenzyl 6β-Allyloxycarbonylamino-6α-deuteriopenicillanate 1β-oxide (4) was obtained as a gum (1.05 g, 52%). Ir (KBr)  $\nu_{\max}$  3400, 1800, 1750sh and 1730 cm<sup>-1</sup>; <sup>1</sup>H nmr (90 MHz; CDCl<sub>3</sub>)  $\delta$  1.10 (3H, s, 2α-Me), 1.64 (3H, s, 2β-Me), 4.53 (2H, m, CH<sub>2</sub>=CHCH<sub>2</sub>), 4.70 (1H, s, 3-H), 5.01 (1H, s, 5-H), 5.1-5.4 (2H, m, CH<sub>2</sub>=CHCH<sub>2</sub>), 5.29 (2H, s, ArCH<sub>2</sub>), 5.6-6.1 (1H, m, CH<sub>2</sub>=CHCH<sub>2</sub>), 6.28 (1H, s, NH, D<sub>2</sub>O exch.), 7.52 (2H, d, *J* = 8.5, PNB AA'), 8.22 ppm (2H, d, *J* = 8.5, PNB BB'); FDms, *m/z* (% rel. int.) 452 (100, [M]<sup>+</sup>), 453 (78, [MH]<sup>+</sup>).

*p*-Nitrobenzyl 6α-Allyloxycarbonylamino-6β-deuteriopenicillanate 1β-oxide (5) was obtained as a white solid (0.5 g, 25%), mp 148-150 °C. Ir (KBr)  $\nu_{\max}$  3360, 1803, 1778, 1755 and 1730 cm<sup>-1</sup>; <sup>1</sup>H nmr (90 MHz; CDCl<sub>3</sub>)  $\delta$  1.13 (3H, s, 2α-Me), 1.58 (3H, s, 2β-Me), 4.50 (1H, s, 3-H), 4.53 (2H, m, CH<sub>2</sub>=CHCH<sub>2</sub>), 5.12 (1H, s, 5-H), 5.0-5.5 (4H, m, CH<sub>2</sub>=CHCH<sub>2</sub> + ArCH<sub>2</sub>), 5.7-6.1 (1H, m, CH<sub>2</sub>=CHCH<sub>2</sub>), 6.40 (1H, s, NH, D<sub>2</sub>O exch.), 7.55 (2 H,d, *J* = 8.5, PNB AA'), 8.19 ppm (2H, d, *J* = 8.5, PNB BB'); FDms, *m/z* (% rel. int.) 452 (80, [M]<sup>+</sup>), 453 (100, [MH]<sup>+</sup>) Anal. Calcd for C<sub>19</sub>H<sub>20</sub>DN<sub>3</sub>O<sub>8</sub>S: C, 50.44; H, 4.5, N, 9.3. Found: C, 50.24; H, 4.6; N, 9.2.

*p*-Nitrobenzyl 6α-Deuterio-6β-tritylaminoopenicillanate 1β-oxide (2).- Triphenylphosphine (0.3 g, 1.14 mmol) and tetrakis(triphenylphosphine)palladium(0) (300 mg, 0.26 mmol) were added to a solution of the penam (4) (1 g, 2.2 mmol) in dichloromethane (12 ml) and acetic acid (0.5 ml). After 2 h at room temperature, the solvent was removed and the residue was washed with ether. The obtained tan solid was dried *under vacuum*, then dissolved in dichloromethane (20 ml) and treated with trityl chloride (560 mg, 2.0 mmol) and triethylamine (0.35 ml, 2.5 mmol). After stirring for 3 h, the reaction mixture was washed with water, dried and evaporated. Flash chromatography of the residue provided 2 as a pale yellow syrup (100 mg, 7.5%). <sup>1</sup>H Nmr (200 MHz; CDCl<sub>3</sub>)  $\delta$  0.81 (3H, s, 2α-Me), 1.51 (3H, s, 2β-Me), 3.71 (1H, s, 3-H), 3.95 (1H, s, NH, D<sub>2</sub>O exch.), 4.57 (1H, s, 5-H), 5.23 (2H, ABq, *J* = 13.0, ArCH<sub>2</sub>), 7.2-7.7 (17H, m, CPh<sub>3</sub> + PNB AA'), 8.22 ppm (2H, d, *J* = 8.6, PNB BB'); FDms, *m/z* (% rel. int.) 610 (100, [M]<sup>+</sup>), 611 (71, [MH]<sup>+</sup>).

*Thermolysis of the 6α-deuteriopenicillanate (2).*- A solution of 2 (37 mg, 0.06 mmol) and 2-mercaptobenzothiazole (17 mg, 0.1 mmol) in toluene (15 ml) was heated at reflux for 5 h under nitrogen. Concentration to dryness and flash chromatography (eluting with benzene-EtOAc 3:1) afforded a sample of *p*-nitrobenzyl (2R)-3-methyl-2-(4-oxo-5-tritylimino-3-thiazolidinyl)-3-butenolate (8) (16 mg; 45%), identical by <sup>1</sup>H nmr spectroscopy and FD mass spectrometry to the one obtained from the undeuteriated penam sulfoxide (1) (*vide supra*)

*Thermolysis of the penicillanate (1) in toluene-deuterium oxide.*- Deuterium oxide (0.6 ml) was added to a solution of the tritylaminoopenam(1)(370 mg, 0.6 mmol) and 2-mercaptobenzothiazole (20 mg, 0.12 mmol) in toluene (25 ml). After stirring overnight at room temperature, the mixture was heated at reflux for 6 h. Evaporation to dryness gave a syrup which was purified by flash chromatography (1:2), affording *p*-nitrobenzyl (2R)-2-(2-deuterio-4-oxo-5-tritylimino-3-thiazolidinyl)-3-methyl-3-butenolate (18) (95 mg, 27%) as an epimeric mixture at C-2 (3:2 ratio). <sup>1</sup>H Nmr (200 MHz; CDCl<sub>3</sub>)  $\delta$  1.78 (3H, s, Me), 4.15 (0.4H, s, NCHDS), 4.70 (0.6H, s, NCDHS), 4.89 and 5.21 (2H, 2 x m, C=CH<sub>2</sub>) 5.28 (2H, s, ArCH<sub>2</sub>), 5.65 (1H, s, NCHCO), 7.2-7.4 (15H, m, CPh<sub>3</sub>), 7.50 (2H, d, *J* = 8.6, PNB AA'), 8.21 ppm (2H, d, *J* = 8.6, PNB BB'); FDms, *m/z* 592 [M]<sup>+</sup>, base peak.



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