*Tetrahedron* Vol 39, No 15, pp 2477 to 2484, 1983
Printed in Great Britain

0040-4020/83 $3.00 + 00
Pergamon Press Ltd

# STEREOSELECTIVE PREPARATION OF 6β-SUBSTITUTED PENICILLANATES

## TRI-ORGANOTIN HYDRIDE REDUCTION OF 6-ISOCYANO-, 6-PHENYLSELENENYL-, 6-HALO-, AND 6-ISOTHIOCYANATO-PENICILLANATES

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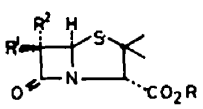
(*Received in UK* 12 *October* 1982)

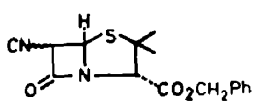
**Abstract**—6β-Benzyl-, 6β-(2-hydroxyprop-2-yl)-, 6β-methoxycarbonylmethyl-, 6β-methoxycarbonylethyl-, 6β-(t-butoxycarbonylmethyl)-, and 6β-methylthiopenicillanates **10–15** have been prepared stereoselectively by tri-n-butyltin hydride reduction of the corresponding 6β-isocyanopenicillanates **4–9**. A minor side-product (15%) isolated from the reduction of benzyl 6α-(2-hydroxyprop-2-yl)-6β-isocyanopenicillanate **5** was identified as (1*R*, 5*R*)-6-[(1*R*)-1-benzyloxycarbonyl-2-methylprop-1-yl]-1-(2-hydroxyprop-2-yl)-2,6-diaza-4-thiabicyclo [3,2,0]hept-2-en-7-one **18**, and small quantities of analogous thiazolines **19** and **20** were detected in the crude mixtures from the reductions of the 6α-benzyl- and 6α-methoxycarbonylmethyl-6β-isocyanopenicillanates **4** and **6**. Benzyl and methyl penicillanates **30** and **31** were obtained by tri-n-butyltin hydride reduction of the 6α-bromopenicillanates **28** and **29**, and reduction of benzyl 6,6-dibromopenicillanate **35** gave a mixture of products in which the 6β-bromopenicillanate **37** predominated. 6β-Chloro-, 6β-phenylselenenyl-, and 6β-allylpenicillanates **48, 49** and **52** were obtained by tri-n-butyltin hydride reduction of the corresponding 6-phenyl- selenenylpenicillanates **43, 45, 50** and **51**.

In contrast, tri-organotin hydride reduction of methyl 6β-isothiocyanatopenicillanate **53** was accompanied by sulphur-C(2) bond cleavage to give rearranged thiazoline–azetidinones **54** and **55**.

There has been considerable interest in the preparation of 6α- and 6β-alkylpenicillanates **1** and **2** because of the presence of an alkyl side-chain at C-6 in thienamycin and olivanic acid.[1] Until recently the most widely used procedure for the introduction of a 6β-alkyl group into a penam nucleus involved hydrogenation of the corresponding 6-alkylidenepenicillanate available via a Wittig reaction on the 6-oxo compound,[2] by dehydration of the corresponding 6-(1-hydroxyalkyl) compound,[3] or from the reaction between the 6-diazopenicillanate and suitable heterocycles.[4] 6-(1-Hydroxyalkyl) penicillanates can be prepared by halogen–metal exchange reactions of 6-halopenicillanates, followed by an aldol condensation.[3,5]



**1** $R^1$ = H, $R^2$ = alkyl
**2** $R^1$ = alkyl, $R^2$ = H



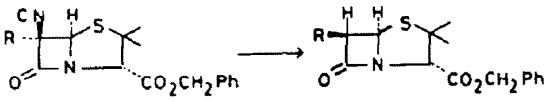
**3**

Since 6-alkyl-6-isocyanopenicillanates are available by alkylation of 6-isocyanopenicillanates,[6] the reductive removal of the isocyano substituent was considered as an alternative route to 6-alkylpenicillanates. Alkyl isocyanides have been reduced to alkanes using dissolving metal reductions,[7] but more attractive was the report that benzyl isocyanide could be reduced to toluene using tri-n-butyltin hydride[8] since it was felt that the tin hydride reagent would be compatible with the penicillanate nucleus. We here report that the reduction of 6-alkyl-6-isocyanopenicillanates by tri-n-butyltin hydride provides a stereoselective synthesis of 6β-alkylpenicillanates, and that the analogous reduction of 6-bromo- and 6-phenylselenenyl-penicillanates provides a useful preparation of other 6β-substituted penicillanates. In contrast tri-organotin hydride reduction of 6β-isothiocyanatopenicillanates is accompanied by sulphur–C(2) bond cleavage, to give rearranged thiazoline–azetidinones.

During the course of our work, 6β-halopenicillanates became of interest as potential β-lactamase inhibitors,[9] and several research groups have developed the tri-n-butyltin hydride reduction of 6,6 dihalopenams as a useful route to these compounds.[10] In addition Barton and his collaborators have developed the tri-n-butyltin hydride reduction of isonitriles as a method of deaminating amines and amino-acid derivatives.[11] Our results[12] complement those of these other workers.[10,11]

### RESULTS AND DISCUSSION

Benzyl 6α-benzyl-, 6α-(2-hydroxyprop-2-yl)-, 6α-methoxycarbonylmethyl-, and 6α-(2-methoxycar-



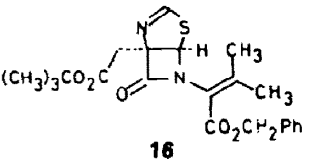
**4** R = $PhCH_2$–
**5** R = $(CH_3)_2C(OH)$–
**6** R = $CH_3O_2C{\cdot}CH_2$–
**7** R = $CH_3O_2C{\cdot}CH_2\ CH_2$–
**8** R = $(CH_3)_3CO_2C\ CH_2$–
**9** R = $CH_3S$–

**10** R = $PhCH_2$–
**11** R = $(CH_3)_2C(OH)$–
**12** R = $CH_3O_2C{\cdot}CH_2$–
**13** R = $CH_3O_2C\ CH_2\ CH_2$–
**14** R = $(CH_3)_3CO_2C\ CH_2$–
**15** R = $CH_3S$–

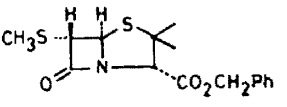
Scheme 1.

bonylethyl)-6$\beta$-isocyanopenicillanates **4**–**7** were prepared from benzyl 6$\alpha$-isocyanopenicillanate **3** according to the published procedures.[6] In addition benzyl 6$\alpha$-t-butoxycarbonylmethyl-6$\beta$-isocyanopenicillanate **8** was prepared (50%) by alkylation of isonitrile **3** with t-butyl bromoacetate in the presence of $K_2CO_3$ in anhydrous dimethylformamide; thiazoline **16** was a side product (14%) in this alkylation step. These 6$\alpha$-alkyl-6$\beta$-isocyanopenicillanates, together with 6$\beta$-isocyano-6$\alpha$-methylthiopenicillanate **9** were reduced using a small excess if tri-n-butyltin hydride in benzene, in the presence of a catalytic amount of azobisisobutyronitrile. A mildly exothermic reaction was usually observed, after which the mixture was heated under reflux for a further 0.5–1 h to ensure completion of the reaction. In all cases one major product was isolated (50–75%), and was identified as the corresponding 6$\beta$-alkylpenicillanate **10**–**15**.

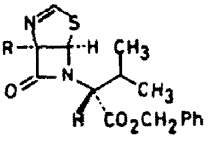
These reductions appeared to be extremely stereoselective; in only one case, reduction of 6$\beta$-isocyano-6$\alpha$-methylthiopenicillanate **9**, was any 6$\alpha$-substituted product isolated (3% in this case). The reduction of the 6$\alpha$-(2-hydroxyprop-2-yl)-6$\beta$-isocyanopenicillanate **5** was accompanied by the formation of a small amount (9–25%) of a side-product identified as the rearranged thiazoline–azetidinone **18**. Traces of analogous rearrangement products **19** and **20** were detected in the reductions of the



**16**



**17**

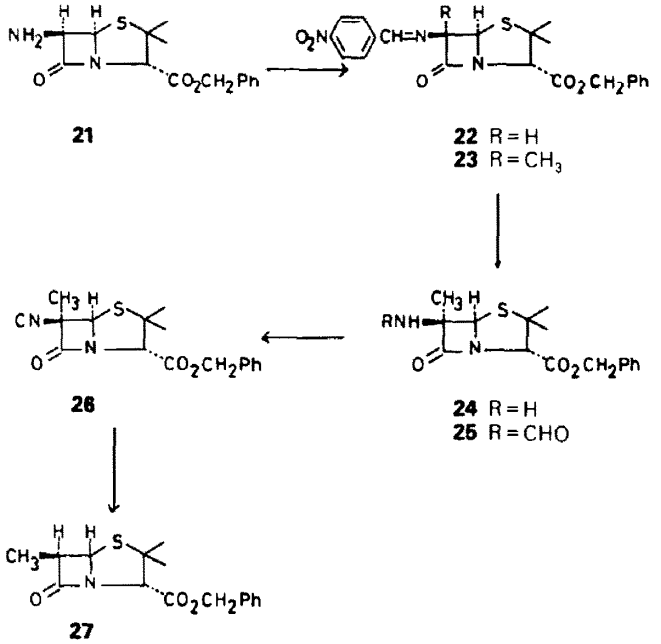


**18** R = $(CH_3)_2C(OH)$–
**19** R = $PhCH_2$–
**20** R = $CH_3O_2C{\cdot}CH_2$–

6$\alpha$-benzyl, and 6$\alpha$-methoxycarbonylmethyl-6$\beta$-isocyanopenicillanates **4** and **6**.

Structures were assigned to the products of these reactions on the basis of their spectroscopic data. In particular the H(5)–H(6) coupling constants for the alkylpenicillanate products were all in the region of 4.0–4.4 Hz consistent with the 6$\beta$-stereochemistry assigned.

Since the alkylation of 6-isocyanopenicillanates **3** is limited to reactive electrophiles, 6$\alpha$-methyl-6$\beta$-isocyanopenicillanate **26** was prepared from 6$\beta$-aminopenicillanate **21** by alkylation of the Schiff's base **22** as shown in Scheme 2.[13] Schiff's bases derived from 6$\beta$-aminopenicillanates have been reacted with a wide range of electrophiles,[13,14] and so reactions analogous to those in Scheme 2 should provide a wide range of 6$\alpha$-substituted-6$\beta$-isocyanopenicillanates.



**21**

**22** R = H
**23** R = $CH_3$

**24** R = H
**25** R = CHO

**26**

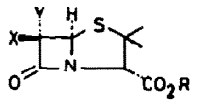
**27**

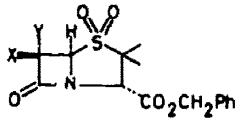
Scheme 2.

Reduction of 6β-isocyano-6α-methylpenicillanate **26** with tri-n-butyltin hydride gave 6β-methylpenicillanate **27**, 47%, not optimised, after chromatography.

The stereoselective tri-n-butyltin hydride reduction of isocyanopenicillanates **4–9** having been successful, attention was turned to the analogous reduction of other 6-substituted penicillanates. Thus benzyl and methyl 6α-bromopenicillanates **28** and **29** were cleanly reduced by tri-n-butyltin hydride, in the presence of a trace of ABIBN, to give benzyl and methyl penicillanates **30** and **31**,[15] respectively. The benzyl ester **30** was also obtained by reduction of benzyl 6-isocyanopenicillanate **3**. In this case, use of tri-n-butyltin deuteride gave a mixture of 6α- and 6β-deuteriated penicillanates **32** and **33**, ratio 7:1, respectively. Reduction, using tri-n-butyltin hydride, of methyl 6α-chloropenicillanate **34** was relatively slow, only 60% reduction was observed with excess hydride after 14 h reflux in benzene.[16]

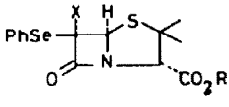
Reduction of benzyl 6,6-dibromopenicillanate **35** with tri-n-butyltin hydride in benzene under reflux proceeded smoothly to give a product mixture containing unchanged 6,6-dibromo-, 6α- and 6β-bromo-, and over-reduced 6,6-dihydropenicillanates **35–37** and **30**, ratio 18:8:43:28, respectively (judged by $^1$H NMR of the crude reaction mxiture), from which the pure 6β-isomer **37** was isolated by short column chromatography. This result is consistent with those of other workers who have studied the stereoselective reduction of various 6,6-dibromopenicillanates using tin hydride reagents because of the activity of 6β-bromopenicillanic acid as a β-lactamase inhibitor.[9,10] Finally the 6,6-dibromopenicillanate sulphone **38** available by per-acid oxidation of sulphide **35**, was reduced using tri-n-butyltin hydride in benzene (no free radical initiators were used in this case), to give a mixture of the 6,6-dibromo-, 6α-bromo-, 6β-bromo- and 6,6-dihydro-sulphones **38–41**, from which the 6β-bromo- and 6,6-dihydro-sulphones **40** and **41** were isolated by chromatography in 40 and 21% yields, respectively.

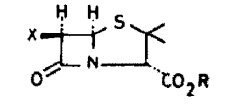




**28** X = H, Y = Br, R = $PhCH_2$
**29** X = H, Y = Br, R = $CH_3$
**30** X = Y = H, R = $PhCH_2$
**31** X = Y = H, R = $CH_3$
**32** X = H, Y = D, R = $PhCH_2$
**33** X = D, Y = H, R = $PhCH_2$
**34** X = H, Y = Cl, R = $CH_3$
**35** X = Y = Br, R = $PhCH_2$
**36** X = H, Y = Br, R = $PhCH_2$
**37** X = Br, Y = H, R = $PhCH_2$

**38** X = Y = Br
**39** X = H, Y = Br
**40** X = Br, Y = H
**41** X = Y = H



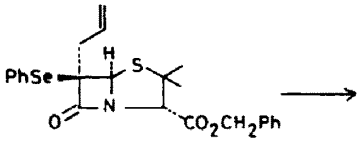


**42** X = Cl, R = $CCl_3CH_2$
**43** X = Cl, R = $PhCH_2$
**44** X = PhSe, R = $CCl_3CH_2$
**45** X = PhSe, R = $PhCH_2$

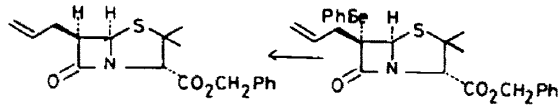
**46** X = Cl, R = $CCl_3CH_2$
**47** X = Cl, R = H
**48** X = Cl, R = $PhCH_2$
**49** X = PhSe, R = $PhCH_2$

As C–Se bonds are known to be cleaved by tin hydride reagents,[17] the ready availability of a range of 6-phenylselenenylpenicillanates[18] prompted an investigation into their reactions with tri-n-butyltin hydride. Thus 6-chloro-6-phenylselenenyl- and 6,6-bis(phenylselenenyl)-penicillanates **42–45** were prepared and reduced using tri-n-butyltin hydride. The reductions of the trichloroethyl esters **42** and **44** were found to be complicated by competing reduction of the trichloroethyl ester groups, e.g. the 6β-chloropenicillanate trichloroethyl ester **46** isolated was contaminated by about 10% of ester reduced products, although treatment of this mixture with Zn and acetic acid gave pure 6β-chloropenicillanic acid **47** (60%) as a white solid. However reduction of the benzyl esters **43** and **45** proceeded cleanly and gave good yields of the 6β-chloro- and 6-phenylselenenylpenicillanates **48** and **49**.

Both of these reductions were fairly stereoselective, less than 10% of 6α-substituted products being detected in the crude product mixtures. The 6β-isomers were purified by chromatography, stereochemistry being assigned on the basis of H(5)–H(6) coupling constant of *ca.* 4 Hz. Finally since both C-6 epimers of benzyl 6-allyl-6-phenylselenenylpenicillanate **50** and **51** were available, the independence of product stereochemistry on the starting material configuration was established. Thus the 6-allyl-6-phenylselenenylpenicillanates **50** and **51** were reduced separately using tri-n-butyltin hydride; in both cases the 6β-allylpenicillanate **52** was the only product isolated.



**50**



**52** **51**

Finally the radical induced tri-n-butyltin hydride reduction of methyl 6β-isothiocyanatopenicillanate **53** was examined as alkyl isothiocyanates are known to be reduced under these conditions.[11] Rather unexpectedly these reactions did not proceed by simple reduction, instead rearranged thiazolines were the only products isolated. When methyl 6β-isothiocyanatopenicillanate **53** was treated with either tri-n-butyl- or triphenyltin hydride, the crude products were identified as the rearranged thiazoline–azetidinones **54** and **55**. These compounds were unstable to chromatography, repeated short column chromatography on silica causing loss of the tin moiety to give dithiourethane **56** in low yield (30%).[19] A more efficient cleavage of the tin moiety was achieved by treatment with tetra-n-butylammonium fluoride in dioxan,[20] thus triphenylstannylthiothiazoline **55** gave dithiourethane **56** in 68% yield using this procedure. In addition the triph-

enylstannylthiothiazoline **55** was converted into the crystalline methylthiothiazoline **57** (48%) on treatment with methyl iodide in benzene,[21] and tri-n-butylstannylthiothiazoline **54** gave disulphide **58** (59%) when treated with pyridinium perbromide.[21]

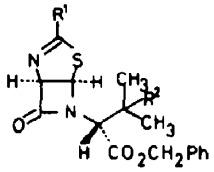
Structures were assigned to products **54–58** on the basis of spectroscopic data. The tautomeric structure shown was assigned to product **56**, and S-methyl rather than the N-methyl structure assigned to product **57**, on the basis of a comparison of their $^1$H NMR and IR spectra with the model systems **59–61**.

Thus the S-methyl thiazoline–azetidinone **57** had a methyl singlet in its $^1$H NMR spectrum at $\delta$ 2.61, and a C=N absorption in its IR spectrum at 1560 cm$^{-1}$ which compare favourable with the model S-methylthiazoline **59** (S–$CH_3$, $\delta$ 2.66; C=N, 1570 cm$^{-1}$), but not with the model N-methylthiazoline **60** (N–$CH_3$, $\delta$ 3.22; $\nu_{max}$ 1510 and 1045 cm$^{-1}$). Similarly the IR spectra of dithiourethane **56** showed bands at 1470 and 1030 cm$^{-1}$ which compare well with the model **61** ($\nu_{max}$ 1510 and 1045 cm$^{-1}$).

The stereoselectivity of the above tri-n-butyltin hydride reductions is consistent with a radical chain mechanism.[22] The formation of the 6$\beta$-substituted products is ascribed to the selective donation of a H atom by the bulky tin hydride reagent to the less hindered $\alpha$-face of the intermediate penicillanate radical **62**. Most of the reductions were extremely stereoselective, reduction of the 6,6-dibromopenicillanates **35** and **38**, and the 6$\beta$-isocyano-6$\alpha$-methylthiopenicillanate **9**, being the only cases where isolable quantities of the 6$\alpha$-products were obtained. During the reduction of the dibromopenicillanates, over-reduction to the 6,6-dihydropenicillanates **30** and **41** interfered; if the 6$\alpha$- and 6$\beta$-bromopenicillanates are reduced at different rates, then the ratio of 6$\alpha$- to 6$\beta$-bromo products isolated may not reflect the true stereoselectivity of the initial reduction.

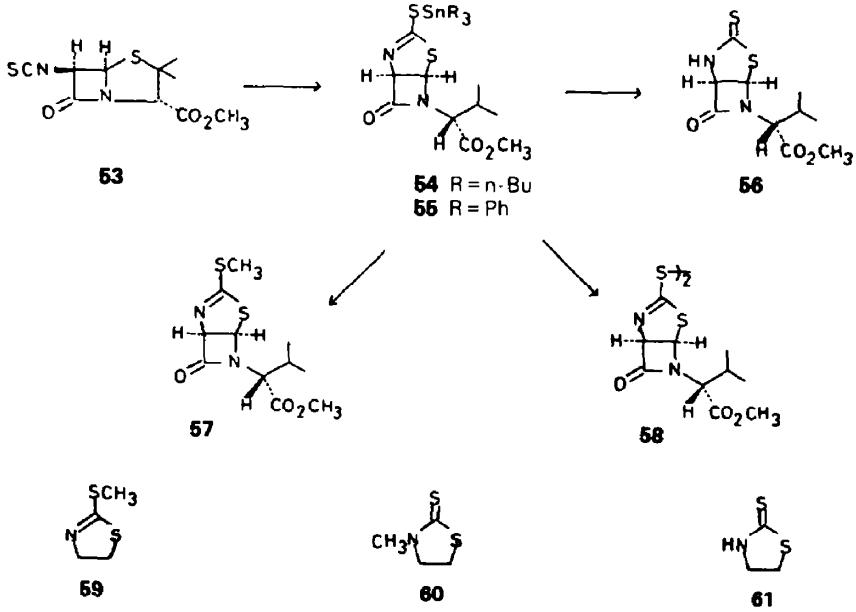
The thiazoline–azetidinone **18** isolated from reduction of the 6$\alpha$-(2-hydroxyprop-2-yl)-isonitrile **5** (10–25%) was of interest since its formation involves a radical induced S–C(2) bond cleavage, and tin hydride reagents do not usually cleave C–S bonds.[17,19] Preliminary evidence as to the mechanism of this rearrangement was provided by deuteriation. Thus use of tri-n-butyltin deuteride to reduce isonitrile **5** gave thiazoline–azetidinone **64** labelled at the valine $\beta$-position, and reduction using tri-n-butyltin hydride followed by treatment with silica and $D_2O$ gave thiazoline–azetidinone **65** labelled in the thiazoline ring. Use of tri-n-butyltin deuteride for reduction followed by treatment of the crude product with silica–$D_2O$, gave doubly deuteriated thiazoline–azetidinone **66**. Finally the $^1$H NMR spectrum of the crude product of reduction of isonitrile **5** with tri-n-butyltin hydride before chromatography, showed the imino-proton, H-3, to be absent; it only appears after short column chromatography of the product.

**62** **63**

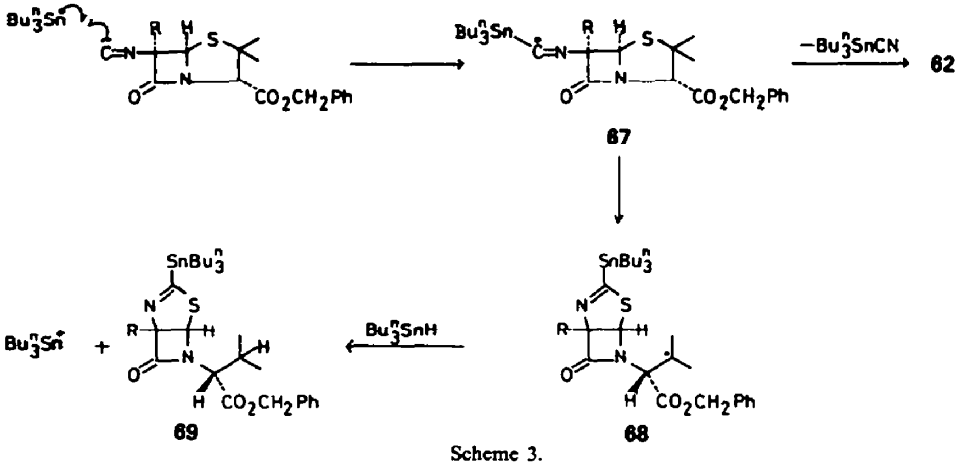


**64** $R^1$ = H, $R^2$ = D
**65** $R^1$ = D, $R^2$ = H
**66** $R^1$ = $R^2$ = D

These data support the mechanism outlined in Scheme 3 for the formation of rearranged thiazoline–azetidinone **18**. Addition of the tri-alkyltin radical to isonitrile **5** gives imino-radical **67**. This can either fragment to give penicillanate radical **62**, and hence the simple reduction product, or it can interact with the thiazolidine S to give alkyl radical **68** via S–C(2) cleavage. H-atom transfer from tri-n-butyltin

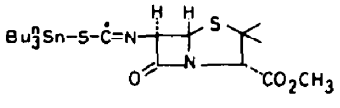


**53** **54** R = n-Bu **55** R = Ph **56** **57** **58** **59** **60** **61**



Scheme 3.

hydride then completes the cycle. The initial, unstable, product of the rearrangement **69** is then cleaved to give thiazoline **18** during the chromatographic purification step. The deuterium labelling results can all be accommodated by this scheme as can the rearrangement of 6β-isothiocyanatopenicillanate **53** on reduction with tri-alkyltin hydride. In this case the tri-alkyltin radical adduct **70** chooses to rearrange with S–C(2) cleavage rather than suffer reduction to the corresponding isonitrile, the expected intermediate in a tin hydride reduction of an isothiocyanate.[11]



**70**

## EXPERIMENTAL

M.ps were measured on a Koffler hot-stage apparatus and are uncorrected. $^1$H NMR spectra were obtained using a Bruker HFX-90 spectrometer and a Bruker WH250 spectrometer. IR spectra were recorded on a Perkin–Elmer 257 spectrophotometer and optical activity measurements on a Perkin–Elmer 141 polarimeter. Mass spectra were obtained on an AEI MS30 mass spectrometer.

Reactions were monitored using Merck silica-gel $GF_{254}$ pre-coated plates, and short column chromatography was used for preparative purposes using Hopkin and Williams silica gel for TLC (MFC without binder) eluted using EtOAc–light petroleum (60/80). All solvents were dried and distilled before use.

*Benzyl 6α - t - butoxycarbonylmethyl - 6β - isocyanopenicillanate* **8**. *t*-Butyl α-bromoacetate (0.85 g, 4.40 mmol) and $K_2CO_3$ (0.61 g, 4.40 mmol) were added to **3** (1.39 g, 4.40 mmol) in anhyd DMF (25 ml), and the mixture stirred for 24 hr at 20° before being poured into ice-water, and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo* to leave a semi-solid residue (1.7 g). Short-column chromatography gave two fractions. The first eluted fraction identified as **8** (0.94 g, 50%) was recrystallized from EtOAc/light petroleum, m.p. 153–154°; IR (KBr) $\nu_{max}$ 2130, 1800, 1740, 1735, 1309, 1187, 760 and 700 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 1.42 and 1.64 (each 3H, s, $CH_3$), 1.47 (9H, s, $C(CH_3)_3$), 2.96 and 3.09 (each 1H, d, $J$ = 16.5 Hz, $CH_2CO$), 4.55 (1H, s, H-3), 5.19 (2H, s, $CH_2Ph$), 5.50 (1H, s, H-5) and 7.37 (5H, s, Ar); MS *m/e* 430 ($M^+$) (Found: $M^+$ 430.1575. $C_{22}H_{26}N_2O_5S$ requires: 430.1562) (Found: C, 61.25; H, 6.11; N, 6.37. $C_{22}H_{26}N_2O_5S$ requires: C, 61.37; H, 6.09; N, 6.51%). The second eluted product was identified as thiazoline **16** (0.27 g, 14%), an oil; IR (film) $\nu_{max}$ 1770, 1720, 1365, 1210, 1155 and 695 cm$^{-1}$; $^1$H NMR ($CDCl_3$) 1.37 (9H, s, $C(CH_3)_3$), 1.89 and 2.26 (each 3H, s, $CH_3$), 2.78 and 3.18 (each 1H, d, $J$ = 16 Hz, $CH_2CO$), 5.17 (2H, s, $CH_2Ph$), 5.73 (1H, d, $J$ = 1.5 Hz, H-5), 7.34 (5H, m, Ar) and 7.91 (1H, d, $J$ = 1.5 Hz, H-3).

*Benzyl 6β - isocyano - 6α - methylpenicillanate* **26**. The *p*-TsOH salt of amine **24**[13] (2.49, 5.05 mmol) was dissolved in cold $NaHCO_3$aq. and the resulting soln extracted with EtOAc. Evaporation of the organic phase provided the free **24** which was dissolved in pyridine (20 ml) and the soln, cooled to −40°, then treated with excess formic-acetic anhydride (6 ml). After warming to 20° the pyridine was removed *in vacuo* and the residue redissolved in $CHCl_3$. Washing of the $CHCl_3$ soln with water, 1MHCl, $NaHCO_3$ and brine, followed by drying ($MgSO_4$) and removal of the solvent *in vacuo* provided **25** (1.58 g, 90%) as a partly crystalline oil. Recrystallization from EtOAc–light petroleum gave **25** m.p. 104–105°, $[\alpha]_D^{20}$ + 282° (*c* 0.64, $CHCl_3$); IR (KBr) $\nu_{max}$ 3310, 3250, 1775, 1740, 1670, 1515, 1310, 1210, 970, 755 and 700 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 1.37, 1.54 and 1.80 (each 3H, s, $CH_3$), 4.43 (1H, s, H-3), 5.20 (2H, s, $CH_2Ph$), 5.40 (1H, s, H-5), 6.55 (1H, br. s, NH), 7.37 (5H, m, Ar) and 8.15 (1H, s, CHO); MS *m/e* 348 ($M^+$) (Found: $M^+$ 348.1143. $C_{17}H_{20}N_2S$ requires: 348.1144).

$Et_3N$ (0.6 ml, 4.32 mmol) was added to **25** (0.75 g, 2.15 mmol) in $CH_2Cl_2$ (10 ml) at 0°, and the mixture cooled to −70° before the addition of phosgene (0.21 g, 2.15 mmol) in $CH_2Cl_2$. The mixture was then allowed to warm to 20°, filtered, and the filtrate washed with brine, dried ($MgSO_4$), and evaporated to give an oil which was crystallized from EtOAc–light petroleum to give **26** (0.54 g, 76%), m.p. 74–76°, $[\alpha]_D^{20}$ + 137° (*c* 0.6, $CHCl_3$); IR (film) $\nu_{max}$ 2130, 1790, 1740, 1300, 1200, 1180, 750 and 695 cm$^{-1}$; $^1$H NMR ($CHCl_3$) δ 1.41, 1.62 and 1.84 (each 3H, s, $CH_3$), 4.54 (1H, s, H-3), 5.19 (2H, s, $CH_2Ph$), 5.24 (1H, s, H-5) and 7.37 (5H, m, Ar); MS *m/e* 330 ($M^+$) (Found: $M^+$ 330.1038. $C_{17}H_{18}N_2O_3S$ requires: 330.1038).

*Benzyl 6α-bromopenicillanate* **28**. Benzyl 6β-aminopenicillanate *p*-toluenesulphonate salt (4.80 g, 10.0 mmol) was added to a mixture of water (20 ml), MeOH (70 ml) and 48% HBr (7.5 ml) at 0° and the stirred ice-cold soln treated with $NaNO_2$ (1.03 g, 15.0 mmol). After stirring for 1 hr without further cooling, $CHCl_3$ (50 ml) was added followed by $NaHCO_3$ until $CO_2$ evolution stopped. Dilution with water, separation, and washing with water and brine, gave after drying ($MgSO_4$), and concentration *in vacuo*, an oil (3.2 g). This was chromatographed to give **28**[3] (1.48 g, 40%); IR (film) $\nu_{max}$ 1785, 1740, 1290, 1200, 1180 and 695 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 1.35 and 1.53 (each 3H, s, $CH_3$), 4.57

(1H, s, H-3), 4.80 (1H, d, $J$ = 1.4 Hz, H-6), 5.15 (2H, s, $CH_2Ph$), 5.40 (1H, d, $J$ = 1.4 Hz, H-5), and 7.33 (5H, s, Ar); MS $m/e$ 369/371 ($M^+$).

*Methyl 6α-bromopenicillanate* **29**. 6-Aminopenicillanic acid (4.32 g, 20 mmol) was dissolved in a mixture of water (15 ml), MeOH (140 ml) and 48% HBr (15 ml) at 0° and the stirred ice-cold soln treated with $NaNO_2$ (2.06 g, 30 mmol). After stirring without further cooling for 1 hr, the soln was diluted with water and extracted with $CHCl_3$. Washing of the $CHCl_3$ extracts with water and brine followed by drying ($MgSO_4$) and concentration *in vacuo* gave 6α-bromopenicillanic acid (5.0 g) as a gum; IR (film) $\nu_{max}$ 3150 br, 1780 and 1735 $cm^{-1}$. Esterification using excess diazomethane gave **29**[15] (4.7 g, 80%) as an oil; IR (film) $\nu_{max}$ 1780, 1740, 1290, 1210, 1010, 820, 750 and 730 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.47 and 1.61 (each 3H, s, $CH_3$), 3.77 (3H, s, $CO_2CH_3$), 4.57 (1H, s, H-3) 4.88 (1H, d, $J$ = 1.5 Hz, H-6) and 5.43 (1H, d, $J$ = 1.5 Hz, H-5).

*Benzyl 6,6 - dibromo - 1,1 - dioxopenicillanate* **38**. A soln of **35** (0.32 g, 0.71 mmol) and *m*-chloroperbenzoic acid (0.31 g, 1.78 mmol) in $CHCl_3$ (5 ml) was stored for 96 hr at room temp. Filtration through celite, followed by washing with $Na_2SO_3$aq. and water, drying ($MgSO_4$), and removal of solvent *in vacuo* provided **38** (0.29 g, 86%). Recrystallization from EtOAc–light petroleum gave **38** m.p. 145–147°, $[\alpha]_D^{20}$ + 155° (*c* 1.62, $CHCl_3$); IR ($CHCl_3$) $\nu_{max}$ 1810, 1755 and 1330 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.26 and 1.56 (each 3H, s, $CH_3$), 4.54 (1H, s, H-3), 5.0 (1H, s, H-5), 5.20 and 5.30 (each 1H, d, $J$ = 12 Hz, $CH_2Ph$) and 7.37 (5H, m, Ar); MS $m/e$ 479/481/483 ($M^+$) (Found: C, 37.19; H, 3.13; N, 2.90; S, 6.74; Br, 32.84. $C_{15}H_{15}NO_5S\,Br_2$ requires: C, 37.44; H, 3.14; N, 2.91; S, 6.66; Br, 33.21%).

*General procedure for tri-n-butyltin hydride reductions.* Tri-n-butyltin hydride (10% excess) in anhyd benzene was added to the penicillanate dissolved in anhyd benzene under $N_2$. A trace of ABIBN was added, and the mixture heated gently under reflux. Usually a mildly exothermic reaction was observed causing the soln to boil fairly vigorously. After this had subsided the soln was heated gently under reflux for 0.5–1 hr. The benzene was removed *in vacuo*, and the product was then purified using short-column chromatography, eluted with EtOAc–light petroleum. Using this procedure the following compounds **10**, **12**, **13**, **14**, **15**, **27**, **30**, **31**, **48**, **49** and **52** were prepared: yields refer to chromatographed products.

*Benzyl 6β-benzylpenicillanate* **10**. Isonitrile **4** (0.39 g, 0.96 mmol) gave **10** (0.28 g, 77%) as an oil, IR (film) $\nu_{max}$ 1775, 1745, 1300, 1200, 1180 and 700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.38 and 1.65 (each 3H, s, $CH_3$), 3.10 (2H, d, J = 8 Hz, C–$CH_2Ph$), 3.86 (1H, dt, $J$ = 4.4 and 8 Hz, H-6), 4.45 (1H, s, H-3), 5.16 (2H, s, O·$CH_2Ph$), 5.37 (1H, d, $J$ = 4.4 Hz, H-5), 7.23 and 7.35 (each 5H, m, Ar); MS $m/e$ 381 ($M^+$) (Found: $M^+$ 381.1403. $C_{22}H_{23}NO_3S$ requires: 381.1396).

*Benzyl 6β-methoxycarbonylmethylpenicillanate* **12**. Isonitrile **6** (0.26 g, 0.66 mmol) gave **12** (0.15 g, 61%) as an oil; IR (film) $\nu_{max}$ 1775, 1735, 1295, 1205, 1175 and 700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.37 and 1.54 (each 3H, s, $CH_3$), 2.83 (2H, m, $CH_2CO$), 3.63 (3H, s, $OCH_3$), 3.95 (1H, m, H-6), 4.44 (1H, s, H-3), 5.15 (2H, s, $CH_2Ph$), 5.54 (1H, d, $J$ = 4.4 Hz, H-5) and 7.33 (5H, s, Ar); MS $m/e$ 363 ($M^+$) (Found: $M^+$ 363.1151. $C_{18}H_{21}NO_5S$ requires 363.1138). From this reduction there was also obtained (1*R*,5*R*) - 6 - [(1*R*) - 1 - *benzyloxycarbonyl* - 2 - *methylprop* - 1 - *yl*] - 1 - *methoxycarbonylmethyl* - 4 - *thia* - 2,6 - *diazabicyclo*[3,2,0]*hept* - 2 - *en* - 7 - *one* **20**. (12 mg, 5%) as an oil; IR (film) $\nu_{max}$ 1775, 1735, 1200 and 700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.93 (3H, d, $J$ = 5.6 Hz, $CH_3$), 0.99 (3H, d, $J$ = 6.8 Hz, $CH_3$), 2.35 (1H, m, $CHMe_2$) 3.09 and 3.47 (each 1H, d, $J$ = 17.5 Hz, $CH_2CO$), 3.65 (3H, s, $OCH_3$), 4.18 (1H, d, $J$ = 9 Hz, N–CHCO), 5.18 and 5.22 (each 1H, d, $J$ = 12.5 Hz, $CH_2Ph$), 5.78 (1H, d, $J$ = 1.3 Hz, H-5), 7.37 (5H, s, Ar) and 8.00 (1H, d, $J$ = 1.3 Hz, H-3); MS $m/e$ 391 ($M^+$ + 1) (Found: $M^+$ + 1 391.1334. $C_{19}H_{23}N_2O_5S$ requires 391.1325).

*Benzyl 6β-methoxycarbonylethylpenicillanate* **13**. Isonitrile **7** (0.20 g, 0.50 mmol) gave **13** (0.14 g, 75%) as an oil; IR (film) $\nu_{max}$ 1770, 1735, 1295, 1260, 1200, 1175, 755 and 700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.39 and 1.58 (each 3H, s, $CH_3$), 2.0–2.5 (4H, m, $CH_2CH_2$), 3.6 (1H, m, H-6), 3.64 (3H, s, $OCH_3$), 4.41 (1H, s, H-3), 5.16 (2H, s, $CH_2Ph$), 5.41 (1H, d, $J$ = 4.4 Hz, H-5) and 7.35 (5H, m, Ar); MS $m/e$ 377 ($M^+$) (Found: $M^+$ 377.1295. $C_{19}H_{23}NO_5S$ requires 377.1294).

*Benzyl 6β-t-butoxycarbonylmethylpenicillanate* **14**. Isonitrile **8** (0.18 g, 0.42 mmol) gave **14** (0.09 g, 53%) as an oil; IR (film) $\nu_{max}$ 1780, 1750, 1730, 1370, 1160 and 700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.40 and 1.58 (each 3H, s, $CH_3$), 1.42 (9H, s, $C(CH_3)_3$), 2.75 (2H, m, $CH_2CO$), 3.9 (1H, m, H-6), 4.43 (1H, s, H-3), 5.18 (2H, s, $CH_2Ph$), 5.56 (1H, d, $J$ = 4.5 Hz, H-5) and 7.35 (5H, m, Ar); MS $m/e$ 405 ($M^+$) (Found: $M^+$ 405.1630. $C_{20}H_{27}NO_5S$ requires 405.1610).

*Benzyl 6β-methylthiopenicillanate* **15**. Isonitrile **9** (184 mg, 0.51 mmol) gave **15** (57 mg, 33%) as an oil; IR (film) $\nu_{max}$ 1770, 1740, 1295, 1200, 1180, 750 and 700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.40 and 1.65 (each 3H, s, $CH_3$), 2.29 (3H, s, $SCH_3$), 4.40 (1H, d, $J$ = 4.4 Hz, H-6), 4.47 (1H, s, H-3), 5.18 (2H, s, $CH_2Ph$) 5.53 (1H, d, $J$ = 4.4 Hz, H-5) and 7.37 (5H, m, Ar); MS $m/e$ 337 ($M^+$) (Found: $M^+$ 337.0813. $C_{16}H_{19}NO_3S_2$ requires 337.0804). From this reaction, after short column chromatography, as a fraction eluted just before **15**, was eluted benzyl 6α-methylthiopenicillanate **17** (5.3 mg, 3%), an oil; $^1H$ NMR (60 MHz, $CDCl_3$) $\delta$ 1.39 and 1.59 (each 3H, s, $CH_3$), 2.19 (3H, s, $SCH_3$), 4.17 (1H, d, $J$ = 1.6 Hz, H-6), 4.54 (1H, s, H-3), 5.18 (3H, m, $CH_2Ph$ and H-5) and 7.35 (5H, m, Ar).

*Benzyl 6β-methylpenicillanate* **27**. The isonitrile **26** (0.30 g, 0.91 mmol) gave **27** (0.13 g, 47%) as an oil, $[\alpha]_D^{20}$ + 159° (*c*, 0.42, $CHCl_3$); IR (film) $\nu_{max}$ 1770, 1740, 1290, 1200, 1170, 745 and 695 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.29 (3H, d, $J$ = 7.6 Hz, 6β-$CH_3$), 1.40 and 1.60 (each 3H, s, $CH_3$), 3.66 (1H, m, H-6) 4.41 (1H, s, H-3), 5.18 (2H, s, $CH_2Ph$), 5.43 (1H, d, $J$ = 4.5 Hz, H-5) and 7.36 (5H, m, Ar); MS $m/e$ 305 ($M^+$) (Found: $M^+$ 305.1087. $C_{16}H_{19}NO_3S$ requires: 305.1083).

*Benzyl penicillanate* **30**. Bromopenicillanate **28** (0.66 g, 1.78 mmol) gave **30** (0.33 g, 86%) as an oil; IR (film) $\nu_{max}$ 1775, 1745, 1295, 1205, 1175, 745 and 695 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.4 and 1.64 (each 3H, s, $CH_3$), 3.08 (1H, dd, $J$ = 1.9 and 15 Hz, H-6$_\beta$), 3.55 (1H, dd, $J$ = 4.1 and 15 Hz, H-6$_\alpha$), 4.49 (1H, s, H-3), 5.18 (2H, s, $CH_2Ph$), 5.30 (1H, dd, $J$ = 1.9 and 4.1 Hz, H-5) and 7.37 (5H, s, Ar); MS $m/e$ 291 ($M^+$) (Found: $M^+$ 291.0932. $C_{15}H_{17}NO_3S$ requires: 291.0935).

*Methyl penicillanate* **31**. Bromopenicillanate **29** (1.82 g, 6.19 mmol) gave **31**[15] (1.3 g) as an oil; IR (film) $\nu_{max}$ 1780, 1750, 1295 and 1010 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.45 and 1.65 (each 3H, s, $CH_3$), 3.0 (1H, dd, $J$ = 2 and 16 Hz, H-6$_\beta$), 3.6 (1H, dd, $J$ = 4.5 and 16 Hz, H-6$_\alpha$), 3.75 (3H, s, $OCH_3$), 4.46 (1H, s, H-3) and 5.30 (1H, dd, $J$ = 2 and 4.5 Hz, H-5), MS $m/e$ 215 ($M^+$) (Found: $M^+$ 215.0610. $C_9H_{13}NO_3S$ requires: 215.0614).

*Benzyl 6β-chloropenicillanate* **48**. Penicillanate **43** (0.90 g, 1.9 mmol) gave **48** (0.45 g, 74%) as a colourless oil, $[\alpha]_D^{20}$ + 249 (*c*, 1% $CHCl_3$); IR ($CHCl_3$) $\nu_{max}$ 1790, 1740, 1500, 1460, 1030 and 760 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.35 and 1.55 (each 3H, s, $CH_3$), 4.50 (1H, s, H-3), 5.15 (2H, s, $CH_2Ph$), 5.17 (1H, d, $J$ = 4 Hz, H-6), 5.55 (1H, d, $J$ = 4 Hz, H-5) and 7.30 (5H, m, Ar); MS $m/e$ 324/326 ($M^+$) (Found: $M^+$ 325.0513. $C_{15}H_{15}{}^{35}ClNO_3S$ requires: 325.0530).

*Benzyl 6β-phenylselenenylpenicillanate* **49**. Penicillanate **45** (0.25 g, 0.42 mmol) gave **49** (0.126 g, 70%) as an oil, $[\alpha]_D^{20}$ + 36° (*c*, 1%, $CHCl_3$); IR ($CHCl_3$) $\nu_{max}$ 1780, 1745, 1580, 1300, 1180 and 690 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.38 and 1.65 (each 3H, s, $CH_3$), 4.52 (1H, s, H-3), 4.76 (1H, d, $J$ = 4 Hz, H-6), 5.15 (2H, s, $CH_2Ph$), 5.55 (1H, d, $J$ = 4 Hz, H-5) and 7.45 (10H, m, Ar); MS $m/e$ 445/447/449 ($M^+$) (Found: $M^+$ 447.0417. $C_{21}H_{21}NO_3S^{78}Se$ requires: 447.0406).

*Benzyl 6β-allylpenicillanate* **52**. In separate reactions, the epimeric penicillanates **50** (0.20 g, 0.41 mmol) and **51** (0.11 g, 0.23 mmol) gave respectively (0.114 g, 84%) and

(0.06 g, 80%) of **52** as an oil, $[\alpha]_D^{20} + 262°$ (*c*, 1%, $CHCl_3$), IR ($CHCl_3$) $\nu_{max}$ 1760 br, 1640, 1500, 1200 and 760 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.39 and 1.61 (each 3H, s, $CH_3$), 2.54 (2H, m, $6_\beta$-$CH_2$–), 3.68 (1H, m, H-6), 4.40 (1H, s, H-3), 5.0 (2H, m, $CH_2$=C), 5.18 (2H, s, $CH_2Ph$), 5.43 (1H, d, $J$ = 4.4 Hz, H-5), 5.75 (1H, m, C=CH–) and 7.36 (5H, s, Ar); MS *m/e* 331 ($M^+$) (Found: $M^+$ 331.1245. $C_{18}H_{21}NO_3S$ requires: 331.1240).

*Reduction of benzyl 6β-(2-hydroxyprop-2-yl)-6α-isocyano penicillanate* **5**. Isonitrile **5** (0.46 g, 1.23 mmol) was reduced using tri-n-butyltin hydride (0.38 g, 1.29 mmol) in benzene (10 ml) containing ABIBN (40 mg) as described above to give a crude product which was chromatographed on silica (eluted with EtOAc–light petroleum). The first eluted product was benzyl *6β-(2-hydroxyprop-2-yl)penicillanate* **11** (0.27 g, 63%); IR (film) $\nu_{max}$ 3460, 1775, 1740, 1200, 960, 750 and 700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.29 and 1.67 (each 3H, s, $CH_3$), 1.42 (6H, s, 2 × $CH_3$), 3.38 (1H, br.s, exch. with $D_2O$, OH), 3.64 (1H, d, $J$ = 4.4 Hz, H-6), 4.50 (1H, s, H-3), 5.18 (2H, s, $CH_2Ph$), 5.46 (1H, d, $J$ = 4.4 Hz, H-5) and 7.37 (5H, m, Ar); MS *m/e* 349 ($M^+$) (Found: $M^+$ 349.1358. $C_{18}H_{23}NO_4S$ requires: 349.1345). The second eluted product was (1R,5R) - 6 - [(1R) - 1 - *benzyloxycarbonyl* - 2 - *methylprop* - 1 - *yl*] - 1 - (2 - *hydroxyprop* - 2 - *yl*) - 4 - *thia* - 2,6 - *diazabicyclo*[3,2,0]*hept* - 2 - *en* - 7 - *one* **18** (83 mg, 18%), recrystallized from EtOAc–light petroleum, m.p. 102.5–103.5°; $[\alpha]_D^{20} - 43°$ (*c*, 1.43, $CHCl_3$); IR (KBr) $\nu_{max}$ 3500, 1745, 1735, 1205, 1145 and 700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.90 and 0.98 (each 3H, d, $J$ = 6.8 Hz, $CH(CH_3)_2$), 1.19 and 1.51 (each 3H, s, 2 × $CH_3$), 2.17 (1H, br.s, exch. with $D_2O$, OH), 2.25 (1H, m, $CHMe_2$), 4.12 (1H, d, $J$ = 9.1 Hz, CHCO), 5.10 and 5.25 (each 1H, d, $J$ = 11 Hz, $CH_2Ph$), 5.78 (1H, d, $J$ = 1.5 Hz, H-5), 7.36 (5H, m, Ar) and 8.03 (1H, d, $J$ = 1.5 Hz, H-3); MS *m/e* 377 ($M^+ + 1$) (Found: C, 60.57; H, 6.31; N, 7.36; S, 8.43. $C_{19}H_{24}N_2O_4S$ requires: C, 60.62; H, 6.43; N, 7.44; S, 8.52). Use of tri-n-butyltin deuteride in this reduction gave **11** (54%) deuteriated at C-6, $^1H$ NMR showing a singlet at $\delta$ 5.46 and no peak at $\delta$ 3.64; MS *m/e* 350 ($M^+$); together with thiazoline **64** (14%), $^1H$ NMR showing $\delta$ 0.88 and 0.96 (each 3H, s, $CD(CH_3)_2$, 4.12 (1H, s, CHCO), and no peak at 2.25, MS *m/e* 378 ($M^+ + 1$).

Reduction of **5** with tri-n-butyltin hydride as above, followed by treatment of the crude product with $D_2O$ and oven-dried silica-gel in $CHCl_3$ for 24 hr at 20°, and then with $D_2O$ and silica-gel in acetone for 24 hr at 20° gave, after chromatography, **11**, together with *thiazoline* **65** (7%); $^1H$ NMR showing $\delta$ 5.79 (1H, s, H-5) and 8.06 (0.13H, d, $J$ = 1.5 Hz, H-3 of unlabelled thiazoline), MS *m/e* 378 ($M^+ + 1$).

Reduction of 6-hydroxyalkyl isonitrile **5** (0.25 g, 0.67 mmol) with tri-n-butyltin deuteride (0.6 g) gave a crude product which was dissolved in dry acetone (5 ml) to which was added oven-dried silica-gel (0.4 g) and $D_2O$ (0.5 ml), and the mixture stirred at 20° for 24 hr. Short column chromatography gave **11** (79 mg, 34%) deuteriated at C-6, together with *thiazoline* **66** (28 mg, 11%) $^1H$ NMR ($CDCl_3$) $\delta$ 0.90 and 0.98 (each 3H, s, $CD(CH_3)_2$), 1.20 and 1.52 (each 3H, s, 2 × $CH_3$), 1.91 (1H, s, OH), 4.15 (1H, s, CHCO), 5.14 and 5.23 (each 1H, d, $J$ = 12 Hz, $CH_2Ph$), 5.79 (1H, s, H-5), 7.37 (5H, m, Ar) and 8.06 (0.1H, d, $J$ = 1.5 Hz, H-3 of monolabelled thiazoline); MS *m/e* 379 ($M^+ + 1$).

*Reduction of benzyl 6,6-dibromopenicillanate* **35**. Reduction of **35** (0.29 g, 0.65 mmol)[3] using tri-n-butyltin hydride (0.19 g, 65 mmol) in benzene (5 ml) containing ABIBN (trace) as above gave an oil shown by $^1H$ NMR to contain unchanged **35**, 6α-bromo-**36**, 6β-bromo-**37** and **30**, ratio 18:8:43:28, respectively. Short column chromatography gave a mixture of **35** and **36** (40 mg), followed by *benzyl 6β-bromopenicillanate* **37** (0.1 g, 40%) as an oil; IR (film) $\nu_{max}$ 1785, 1740, 1295, 1200, 1180 and 700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.40 and 1.63 (each 3H, s, $CH_3$), 4.54 (1H, s, H-3), 5.19 (2H, s, $CH_2Ph$), 5.30 (1H, d, $J$ = 4.0 Hz, H-6), 5.57 (1H, d, $J$ = 4.0 Hz, H-5) and 7.36 (5H, s, Ar); MS *m/e* 369/371 ($M^+$) (Found: $M^+$ 369.0044. $C_{15}H_{16}NO_3S^{79}Br$ requires: 369.0032). Finally penicillanate **30** (54 mg), was eluted.

*Reduction of benzyl 6,6-dibromo-1,1-dioxopenicillanate* **38**. Reduction of **38** (89 mg, 0.19 mmol) with tri-n-butyltin hydride 64 mg, 0.22 mmol) gave, after chromatography, a mixture of unchanged **38** and **39** (23 mg), followed by *benzyl 6β-bromo-1,1-dioxopenicillanate* **40** (30 mg, 40%), as an oil; IR (film) $\nu_{max}$ 1810, 1755, 1335, 1200, 1120, 955 and 700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.25 and 1.55 (each 3H, s, $CH_3$), 4.53 (1H, s, H-3) 4.75 (1H, d, $J$ = 5 Hz, H-5), 5.20 and 5.30 (each 1H, d, $J$ = 12 Hz, $CH_2Ph$), 5.35 (1H, d, $J$ = 5 Hz, H-6) and 7.37 (5H, m, Ar); MS *m/e* 402 ($M^+ + 1$) (Found: $M^+ + 1$: 401.9989. $C_{15}H_{17}NO_5S^{79}Br$ requires: 402.0010). Finally benzyl 1,1-dioxopenicillanate **41** (12 mg, 21%) was eluted.

(1R,5R) - 6 - [(1R) - 1 - *Methoxycarbonyl* - 2 - *methylprop* - 1 - *yl*] - 3 - (*tri* - *n* - *butylstannylthio*) - 2,6 - *diaza* - 4 - *thiabicyclo*[3,2,0]*hept* - 2 - *en* - 7 - *one* **54**. Compound **53** (0.50 g, 1.83 mmol) was reduced using tri-n-butyltin hydride (0.55 g, 1.83 mmol) in benzene (5 ml) containing ABIBN (60 mg) heated under reflux for 0.25 hr. Concentration *in vacuo* gave *thiazoline* **54** which could not be purified because of its instability, IR (film) $\nu_{max}$ 1780, 1745, 1540, 1340 and 970 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 0.7–1.7 (33H, m, 3 × ($CH_3CH_2CH_2CH_2$) + 2 × $CH_3$), 2.1 (1H, m, $CHMe_2$), 3.74 (3H, s, $OCH_3$), 4.15 (1H, d, $J$ = 8.8 Hz, CHCO) and 5.65 and 5.96 (each 1H, d, $J$ = 4.2 Hz, H-1 and H-5).

(1R,5R) - 6 - [(1R) - 1 - *Methoxycarbonyl* - 2 - *methylprop* - 1 - *yl*] - 3 - (*triphenylstannylthio*) - 2,6 - *diaza* - 4 - *thiabicyclo*[3,2,0]*hept* - 2 - *en* - 7 - *one* **55**. Compound **53** (50 mg, 1.84 mmol) was reduced using triphenyltin hydride (67 mg, 1.91 mmol) as above. Concentration *in vacuo* gave an oil identified as the unstable *thiazoline* **55**; IR (film) $\nu_{max}$ 1780, 1740, 1540, 1430, 1340, 1215, 970, 735 and 700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.85 and 0.87 (each 3H, d, $J$ = 7 Hz, $C(CH_3)_2$), 2.2 (1H, m, $CHMe_2$) 3.71 (3H, s, $OCH_3$), 4.09 (1H, d, $J$ = 8.8 Hz, CHCO), 5.47 and 5.88 (each 1H, d, $J$ = 4.1 Hz, H-1 and H-5), 7.45 (9H, m, Ar) and 7.65 (6H, m, Ar).

(1R,5R) - 6 - [(1R) - 1 - *Methoxycarbonyl* - 2 - *methylprop* - 1 - *yl*] - 2,6 - *diaza* - 4 - *thia* - 3 - *thionobicyclo*[3,2,0]*heptan* - 7 - *one* **56**. Compound **54** (0.64 g, 1.13 mmol) in anhyd dioxan (10 ml) was treated with tetra-n-butylammonium fluoride in THF (1M, 4.5 ml), and the mixture stirred for 17 hr at 20°. The red soln was concentrated *in vacuo*, and the residue dissolved in EtOAc (15 ml). Addition of water gave a white ppt which was filtered off using a filter aid. Separation of the organic layer, drying ($MgSO_4$), and concentration *in vacuo* gave an oil chromatographed on silica, being eluted with 50% EtOAc–light petroleum, to give **56** (0.21 g, 68%), $[\alpha]_D^{20} - 205°$ (*c*, 0.84, $CHCl_3$); IR (film) 3040, 1775, 1735, 1480, 1280 and 1030 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.99 and 1.09 (each 3H, d, $J$ = 6.9 Hz, $C(CH_3)_2$) 2.35 (1H, m, $CHMe_2$), 3.78 (3H, s, $OCH_3$), 4.22 (1H, d, $J$ = 8.7 Hz, CHCO), 5.35 (1H, d, $J$ = 5.5 Hz, H-1), 6.13 (1H, d, $J$ = 5.5 Hz, H-5) and 7.9 (1H, br.s, NH); MS *m/e* 274 ($M^+$) (Found: $M^+$ 274.0454. $C_{10}H_{14}N_2O_3S_2$ requires: 274.0444).

(1R,5R) - 6 - [(1R) - 1 - *Methoxycarbonyl* - 2 - *methylprop* - 1 - *yl*] - 3 - *methylthio* - 2,6 - *diaza* - 4 - *thiabicyclo*[3,2,0]*hept* - 2 - *en* - 7 - *one* **57**. Compound **53** (0.10 g, 0.37 mmol) was reduced using triphenyltin hydride (0.13 g, 0.38 mmol) in benzene (5 ml) containing ABIBN (trace). After heating under reflux for 10 min, excess MeI was added, and the mixture stirred at 20° for 5 days. The mixture was then diluted with $CHCl_3$, and tin residues precipitated by the addition of KFaq. Filtration, and concentration *in vacuo* gave an oil which was chromatographed to give *thiazoline* **57** (48 mg, 45%), recrystallized from EtOAc–light petroleum, m.p. 84–86°, $[\alpha]_D^{20} - 229°$ (*c*, 0.65, $CHCl_3$); IR (KBr) $\nu_{max}$ 1760, 1730, 1560, 1340, 1215, 1165, 990, 957 and 755 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.95 (3H, d, $J$ = 7.0 Hz, $CH_3$), 1.02 (3H, d, $J$ = 6.6 Hz, $CH_3$), 2.3 (1H, m, $CHMe_2$), 2.61 (3H, s, $CH_3$), 3.76 (3H, s, $OCH_3$), 4.17 (1H,

d, 9.2 Hz; CHCO), 5.91 (1H, d, $J = 4.0$ Hz, H-1) and 6.04 (1H, d, $J = 4.0$ Hz, H-5); MS $m/e$ 288 ($M^+$) (Found: $M^+$ 288.0598. $C_{11}H_{16}N_2O_3S_2$ requires: 288.0600).

*Di - (1R,5R) - 6 - [(1R) - 1 - methoxycarbonyl - 2 - methylprop - 1 - yl] - 7 - oxo - 2,6 - diaza - 4 - thiabicyclo[3,2,0]hept - 2 - en - 3 - yl disulphide* **58**. N-Methylpyridinium perbromide (0.26 g, 0.78 mmol) was added to **54** (0.40 g, 0.71 mmol) in $CH_2Cl_2$ (5 ml) at 0°, and the mixture stirred for 10 min before being diluted with more $CH_2Cl_2$ (15 ml), and stirred overnight with KFaq. Little precipitation was observed, so the $CH_2Cl_2$ was removed *in vacuo*, and the residue treated with EtOAc. This gave a thick white ppt which was filtered off, and the filtrate washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica, eluted with EtOAc–light petroleum to give **58** (0.11 g, 59%) as a glass, $[\alpha]_D^{20} + 3°$ (*c*, 0.48, $CHCl_3$); IR (KBr) $\nu_{max}$ 1765, 1735, 1555, 1340, 1215, 1163, 985, 965 and 755 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.96 (3H, d, $J = 7.0$ Hz, $CH_3$), 1.03 (3H, d, $J = 6.6$ Hz, $CH_3$), 2.25 (1H, m, $CHMe_2$), 3.76 (1H, s, $OCH_3$), 4.18 (1H, d, $J = 8.8$ Hz, CHCO), 6.02 and 6.06 (each 1H, d, $J = 4.2$ Hz, H-1 and H-6).

*Tri-n-butyltin deuteride reduction of benzyl 6-isocyanopenicillanate* **3**. Excess tri-n-butyltin deuteride (120 mg) was added to **3** (58 mg, 0.18 mmol) in dry benzene (5 ml) and the mixture, after addition of ABIBN (trace), heated under reflux for 10 min. After concentration *in vacuo*, the residual oil on examination by $^1H$ NMR showed an epimeric mixture of benzyl 6α- and 6β-*deuteriopenicillanates* **32** and **33**, ratio 7:1, respectively. Chromatography on silica-gel, eluted with EtOAc–light petroleum, provided the mixture of **32** and **33** (40 mg, 75%), free from organotin residue; IR (film) $\nu_{max}$ 2960, 2925, 1760, 1745, 1455, 1295, 1200, 1160, 745 and 695 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.40 and 1.53 (each 3H, s, $CH_3$), 3.04 (0.88H, br. unresolved, H-6$_\beta$), 3.53 (0.12H, br. unresolved, H-6α), 4.49 (1H, s, H-3), 5.19 (2H, s, $CH_2Ph$), 5.28 (1H, d, unresolved, H-5) and 7.37 (5H, s, Ar).

*Acknowledgements*—We thank the S.E.R.C. for a CASE award (to N.D.T.) and Beecham Pharmaceuticals for their generous support. We should also like to thank Dr. P. J. Giddings for carrying out the reductions of the 6-phenylselenylpenicillanates and Dr. P. H. Bentley for helpful discussions and exchange of information prior to publication.

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