# Further Synthetic Studies in Penicillin C(6)-Substitution Including the Versatile 6α-Succinimidooxy Leaving Group

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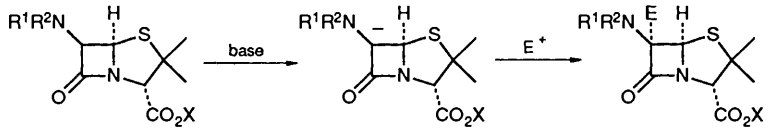
Treatment of benzyl 6α-dimethylamino-6β-phenoxyacetamidopenicillanate **3** with methyl iodide led, in the absence of added nucleophiles, to the oxygen-bridged dimer **8** *via* adventitious water present. Added methanol or water led to the 6α-methoxy or -hydroxy products **4** and **5**; similar reactions could be performed on an α-(acylureido)penicillin.

Much more generally useful was the 6α-succinimidooxy compound **11**, readily available from the 6α-methylthiopenicillin **2** *via* metal-catalysed displacement using *N*-hydroxysuccinimide. This product, which was stable on prolonged storage at 0 °C, readily underwent displacement by oxygen, nitrogen, carbon and sulphur nucleophiles. Many of the products were not accessible by direct displacement on **2** or by other methods of penicillin C(6)-substitution. The use of the even more stable 2,2,2-trichloroethoxycarbonyl protected compounds **28** and **31** permitted the introduction of biologically interesting 6β-side chains. The allyl ester series derived from intermediates **18** and **28** was important for 6α-substituents incompatible with the hydrogenolysis of benzyl esters. Final deprotection led to penicillin sodium salts **10**, **25**, **26**, **34**, **35** and **36** whose biological activities are summarised.

The isolation and characterisation of naturally occurring 7α-methoxycephalosporins (cephamycins) in 1971[1] ushered in a period of intense research directed towards the synthesis of 6α(7α)-substituted penicillins and cephalosporins and their biological evaluation.[2] Additional impetus came when in these laboratories we synthesised 6α(7α)-formamido-penicillins and -cephalosporins[3,4] having potent activity against Gram-negative bacteria. It was an unusual case in that the synthetic work bore fruit independently of the isolation of corresponding natural products (cephalosporins[5–7] and monocyclic β-lactams[8]).

Without attempting a comprehensive review of penicillin 6α-substitution here, we may conveniently divide methods of synthesis into two classes, shown in Schemes 1 and 2 (both assuming a 6β-amino substituent). In Scheme 1, electrophilic substitution is achieved by generation of a 6-anion (usually $R^1,R^2$ = arylidene, *viz.* a Schiff base) followed by reaction with an appropriate electrophile, *e.g.* alkyl halides,[9] formaldehyde.[10] By contrast, nucleophilic substitution (Scheme 2) is almost invariably achived *via* addition† to the putative acylimine intermediate **1** which has been derived in many ingenious ways.[2] These include the action of base on an *N*-acyl-*N*-(trifluoromethyl)sulphonamide,[11] oxidation–elimination of a 6α-(methylthio)derivative,[12] redox reaction of a hydroquinol Schiff base,[13] aza-Wittig reaction on a 6-oxopenicillin[14] and the early 6α-methoxylations using *tert*-butyl hypochlorite[15] ($Y^2$ = Cl) as illustrated in Scheme 2.[16]

One of the most frequently used procedures is also of this class, namely the displacement of a 6α-methylthio substituent ($Y^1$ = SMe) using heavy metal ($Hg^{II}$ or $Ag^{I}$) catalysis[17] or chlorination.[18] The 6α-methylthio group is itself introduced by a variant of Scheme 1. In preliminary communications on the present work[19,20] we pointed out certain limitations of this method and outlined attempts to define a 6α-substituent which could react under mild conditions with a wide variety of nucleophiles without heavy metal catalysis. Clearly this substituent would also have to provide sufficiently stable intermediates. We now give a fuller account of our work with experimental details, in particuar the selection of the 6α-succinimidooxy group and its worth in the preparation of 6α-substituted penicillins, including those not accessible by earlier methods.

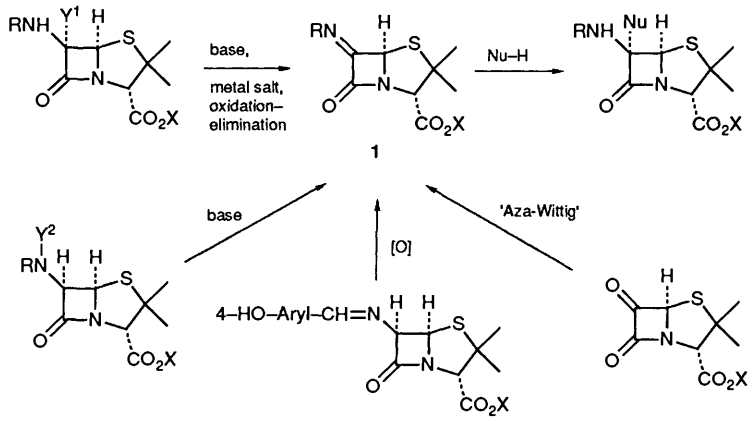



**Scheme 1** Penicillin C(6)-electrophilic substitution

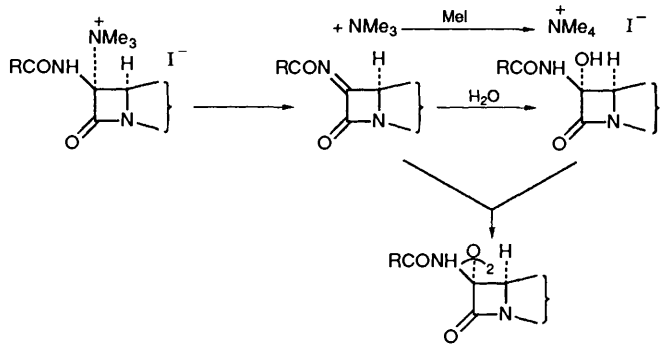
## Results and Discussion

As 6α-hydroxypenicillins[21] are themselves of limited chemical stability, there seemed little merit in attempts to prepare and use 6α-halogenopenicillins. However, a '6α-quaternary ammonium' penicillin (poorer leaving group) appeared feasible. To this end, the 6α-methylthiopenicillin V analogue **2**[3,17] was treated with alcoholic dimethylamine in dimethylformamide (DMF) using silver(I) acetate catalysis, affording the 6α-dimethylamino product **3**[22] in excellent yield. Attempted quaternisation of **3** with methyl iodide gave a reasonable rate of reaction only in polar organic solvents (acetonitrile or DMF). No trace of a quaternary ammonium penicillin resulted, however: instead a *less* polar material was produced (TLC) with concomitant deposition of a crystalline by-product, easily shown to be tetramethylammonium iodide. Work-up of the mother liquors afforded a crystallisable β-lactam product in 44% yield; $\delta_H$, *inter alia*, 1.28 (s) and 5.69 (s) ratio 6:1; *m/z* 894. The data were consistent with the oxygen-bridged penicillin dimer **8**. A plausible mechanism for its formation, based on

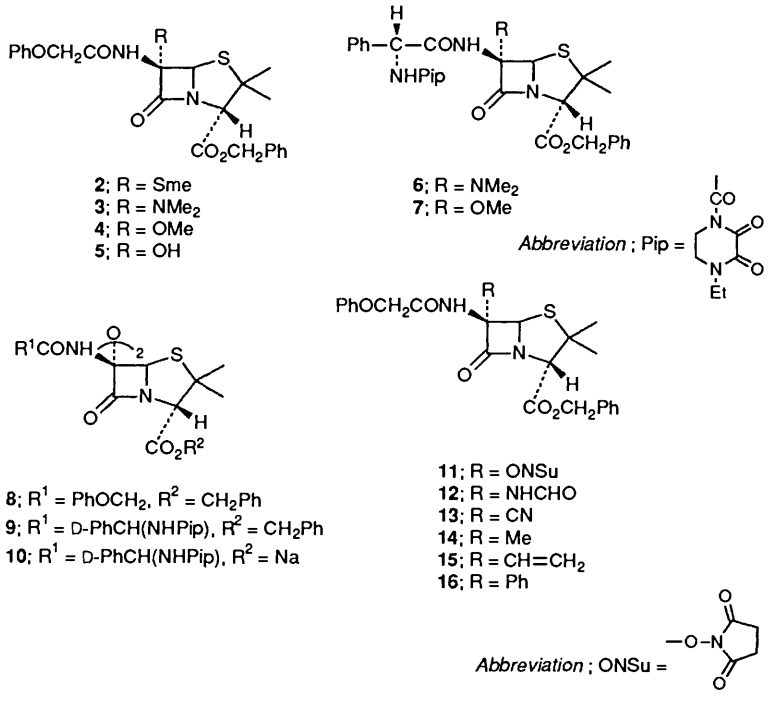
† Addition to the α-face is almost invariably observed in Schemes 1 and 2,[2] for steric reasons.



**Scheme 2** Penicillin C(6)-nucleophilic substitution



**Scheme 3** Postulated mechanism of oxygen-bridged dimer formation



addition of adventitious water to an acylimine intermediate, is given in Scheme 3.

Our intention of obtaining a reactive but isolable intermediate which could react with a variety of nucleophiles was thus thwarted; only nucleophiles which reacted very slowly with methyl iodide could be used. Thus, in the presence of added excess of methanol or water (better, acetic acid), the known [14,21] 6α-methoxy **4** or hydroxy **5** derivatives* resulted in fair yields.

These reactions were not confined to the 6β-phenoxyacetamido side-chain; thus the 6β-acylureido-6α-dimethylaminopenicillin **6** [21] on treatment with methyl iodide in acetonitrile similarly afforded the oxygen-bridged dimer **9** or, with methanol present, the 6α-methoxy derivative **7**.[21]

Various other 6α-'leaving groups' could be considered, always with the caveat that they should give penicillins sufficiently stable for isolation. The use of active esters, particularly of *N*-hydroxysuccinimide, in peptide synthesis [23] is well known; such esters combine stability with high reactivity towards nucleophiles. Derived penicillins therefore seemed likely candidates. Moreover, the 'α-effect' [24] imparts good nucleophilicity to *N*-

* The 6α-hydroxy compound here results from subsequent hydrolysis on silica gel chromatography.

hydroxysuccinimide. We found that treatment of the 6α-methylthiopenicillin ester **2** with *N*-hydroxysuccinimide and silver(I) acetate in DMF afforded a near-quantitative yield of the desired product **11**; $\delta_H$, *inter alia*, 2.65 (4 H, s); *m/z* 554. This material was non-crystalline, and silica-gel chromatography caused some decomposition; however, it could be stored for months at 0–5 °C without degradation.

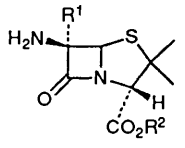
We were delighted to find that the 6α-succinimidooxypenicillin **11** showed excellent reactivity with a variety of nucleophiles, indeed proving significantly more versatile than the 6α-methylthio derivative **2** itself. From a large number of such reactions performed in these laboratories, we now give a selection to illustrate the scope of the method.

Treatment of **11** with triethylamine and methanol in tetrahydrofuran (THF) or with the same base and *N,N*-bis(trimethylsilyl)formamide[25] generated respectively the known compounds **4** and **12**[3b] in good yields. Turning to substituents not directly accessible from 6α-methylthio, we examined the synthesis of the 6α-cyano analogue **13**, previously prepared by Sheehan[14] *via* an aza-Wittig reaction on a 6-oxopenicillin followed by HCN addition. Treatment of **11** with cyanotrimethylsilane and triethylamine afforded an excellent yield of **13** having spectral data identical with literature values.

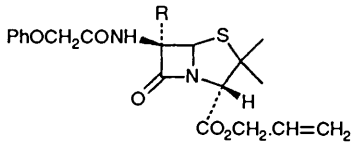
It was also of interest to see whether other carbon nucleophiles would react similarly. Grignard reagents proved very satisfactory for this purpose, acting both as bases (elimination of *N*-hydroxysuccinimide) and as nucleophiles, adding to give the final products. Thus reaction of **11** in THF with 3 mol $dm^{-3}$ ethereal methylmagnesium bromide (2 equiv.) produced the 6α-methylpenicillin **14** in 63% yield. This material is also available by alkylation of a Schiff base (Scheme 1),[9] but other Grignard reagents may be employed, leading to derivatives not available by the Scheme 1 procedure. Specifically, reaction of **11** with vinyl and phenyl Grignards afforded penicillin esters **15** and **16** in comparable yields.

To complete our quartet of nucleophilic atoms, we now move onto the introduction of the mercapto substituent. In view of catalyst poisoning by this substituent, benzyl esters (removed by catalytic hydrogenolysis) were now unsatisfactory. A solution to this problem was apparently offered by the use of allyl esters,[26] removable under neutral conditions using palladium(0) reagents. This technique was also valuable for deprotection of 6α-vinylpenicillins, since even brief hydrogenolysis of ester **15** led to reduction of the vinyl group. Combination of this technique with the use of temporary 2,2,2-trichloroethoxycarbonylamino protection, allowing the introduction of other 6β-substituents, led to more versatile synthetic procedures as demonstrated in the following section.

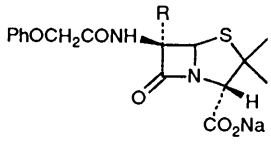
Transformation of the known allyl 6β-aminopenicillanate **17**[27] into the 6α-methylthio derivative **18** was achieved *via* the corresponding Schiff base.[17,18] Acylation of this material with phenoxyacetyl chloride afforded the penicillin V analogue **21**; nucleophilic displacement with *N*-hydroxysuccinimide as described above led to the product **22**. Without purification, this material was treated with triethylamine–$H_2S$, giving the 6α-mercapto compound **23** in 55% yield. Attempted deprotection of this ester using tetrakis(triphenylphosphinyl)palladium(0)[26] was disappointing, giving only a low yield of the *S*-allyl product **25**; this kind of *O*→*S*-allyl rearrangement has precedent.[28] However, a cognate synthesis of a 6α-vinylpenicillin V analogue proceeded smoothly. In this case, acylation of compound **18** with 2,2,2-trichloroethoxycarbonyl chloride gave the nicely crystalline urethane **27**. The standard displacement with *N*-hydroxysuccinimide afforded intermediate **28**, also crystalline: interestingly, this 6β-urethane proved even more stable than the 6β-amide **11**, being storable for years at 0–5 °C. Vinyl Grignard displacement as above gave a satisfactory (52%) yield of



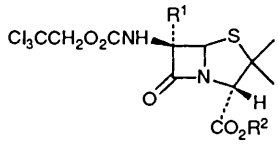
**17**; $R^1$ = H, $R^2$ = $CH_2CH{=}CH_2$
**18**; $R^1$ = SMe, $R^2$ = $CH_2CH{=}CH_2$
**19**; $R^1$ = $CH{=}CH_2$, $R^2$ = $CH_2CH{=}CH_2$
**20**; $R^1$ = Ph, $R^2$ = $CH_2Ph$



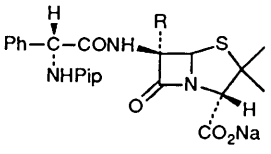
**21**; R = SMe
**22**; R = ONSu
**23**; R = SH
**24**; R = $CH{=}CH_2$



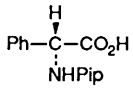
**25**; R = $SCH_2CH{=}CH_2$
**26**; R = $CH{=}CH_2$



**27**; $R^1$ = SMe, $R^2$ = $CH_2CH{=}CH_2$
**28**; $R^1$ = ONSu, $R^2$ = $CH_2CH{=}CH_2$
**29**; $R^1$ = $CH{=}CH_2$, $R^2$ = $CH_2CH{=}CH_2$
**30**; $R^1$ = SMe, $R^2$ = $CH_2Ph$
**31**; $R^1$ = ONSu, $R^2$ = $CH_2Ph$
**32**; $R^1$ = Ph, $R^2$ = $CH_2Ph$



**33**; R = H
**34**; R = Ph
**35**; R = $CH{=}CH_2$
**36**; R = SH
**37**; R = $SCH_2CH{=}CH_2$



**38**

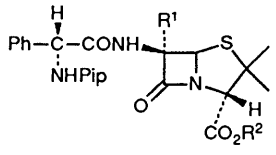
**Table 1** *In vitro* antibacterial activity

| Organism | MIC values[a] 10 | 33 |
|---|---|---|
| *Escherichia coli* ESS[b] | ≤0.06 | ≤0.06 |
| *E. coli* NCTC 10418 | 1.0 | 0.5 |
| *E. coli* JT425[c] | >128 | 10 |
| *Pseudomonas aeruginosa* NCTC 10662 | >128 | 5.0 |
| *Klebsiella aerogenes* A | 8.0 | 2.5 |
| *Enterobacter cloacae* N1 | 8.0 | 2.5 |
| *Proteus mirabilis* C977 | 2.0 | 0.1 |
| *Staphylococcus aureus* Oxford | 16 | 0.5 |
| *Streptococcus pyogenes* CN10 | ≤0.06 | ≤0.06 |

[a] Minimum inhibitory concentrations (MICs) are quoted in μg ml$^{-1}$ and were measured by serial dilution in nutrient agar, inoculum size *ca.* $10^6$ colony-forming units. [b] Outer cell-wall deficient mutant; see P. H. Bentley and A. V. Stachulski, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1187. [c] Non-plasmid mediated β-lactamse producing strain; both **10** and **33** were inactive at >100 μg ml$^{-1}$ against plasmid-mediated β-lactamase producing strains.

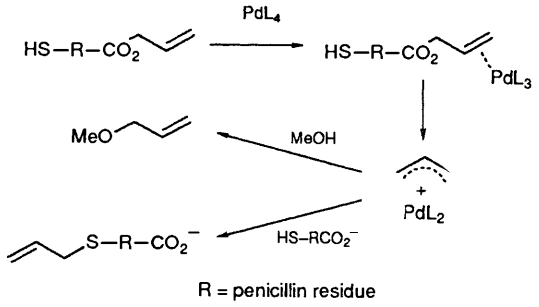
compound **29**. Deprotection of this and other 2,2,2-trichloroethoxycarbonyl protected derivatives was achieved using zinc in pH 4 buffer and THF;[29] the resulting versatile free amino compound **19** was acylated with phenoxyacetyl chloride. The resulting ester **24** (77%) was finally deprotected with $Pd(PPh_3)_4$ to give penicillin **26** in satisfactory yield.

While it is difficult to generalise about the structure–activity relationships of 6-substituted penicillins,[21,30] the α-acylureido series, in particular those related to piperacillin **33**,[31] generally show better activity than those bearing other side-chains. We naturally strove to prepare analogues of this type bearing the novel 6α-substituents above. Thus acylation of the 6α-vinylpenicillin ester **19** with the known acid **38**[21] afforded compound **39** which was again deprotected using the palladium(0) reagent to give penicillin **35** in good yield. In the case of the 6α-phenyl substituent, an allyl ester was unnecessary; this synthesis began with *N*-hydroxysuccinimide displacement on the known[3b] 6α-methylthio benzyl ester **30**. The resulting crystalline product **31** (79%), of comparable stability to **28**, was progressed *via* the previous sequence, *viz.* Grignard displacement to give 6α-phenyl compound **32**, zinc deprotection to free amino compound **20** and reacylation with acid **38** to give benzyl ester **40**. Another approach was successful in the 6α-mercapto series; thus acylation of amine **18** with acid **38** afforded the 6α-methyl-



**39**; $R^1$ = CH=$CH_2$, $R^2$ = $CH_2CH$=$CH_2$
**40**; $R^1$ = Ph, $R^2$ = $CH_2Ph$
**41**; $R^1$ = SMe, $R^2$ = $CH_2CH$=$CH_2$
**42**; $R^1$ = ONSu, $R^2$ = $CH_2CH$=$CH_2$
**43**; $R^1$ = SH, $R^2$ = $CH_2CH$=$CH_2$

thiopenicillin **41**. The usual displacement gave 6α-succinimidooxy compound **42**, which without purification was progressed by triethylamine–$H_2S$ treatment to the ester **43** in 51% yield.* It was found that palladium(0) deprotection of this ester could be effected satisfactorily in the presence of methanol as a competitive nucleophile, giving penicillin **36** in modest yield together with the *S*-allyl compound **37**. Apparently methanol is able to intercept a Pd π-allyl complex in competition with capture by SH (Scheme 4).




**Scheme 4** Palladium(0) catalysed deprotection of allyl esters in the presence of *O*- and *S*-nucleophiles

Finally, catalytic hydrogenolyses of benzyl ester **40** and diester **9** afforded free penicillins **10** and **34** in good yields.

*Biological Results.*—The antibacterial activities of the ether-bridged dimer **10** and piperacillin **33**[31] against selected organisms are shown in Table 1. Clearly **10** was significantly less active, though interestingly it was comparable to the known 6α-hydroxypiperacillin.[21] The other penicillins **25**, **26**, **34**, **35** and **36** showed at best weak activity against the cell-wall deficient *E. coli* ESS mutant (MIC 16-32 μg ml$^{-1}$) but were otherwise antibacterially inactive.

## Experimental

Abbreviations used for common solvents are DCM (dichloromethane), DMF (*N*,*N*-dimethylformamide) and THF (tetrahydrofuran). Organic extracts were finally washed with saturated brine and dried over anhydrous magnesium sulphate prior to rotary evaporation at or below 30 °C under reduced pressure. M.p.s were determined in a Büchi oil-immersion apparatus and are uncorrected. Unless otherwise noted, IR spectra were recorded for KBr discs in a Perkin-Elmer 457 instrument. $^1$H NMR spectra were recorded on a Bruker WM 250 instrument at 250 MHz unless otherwise stated, using an appropriate internal standard in the solvent quoted; all δ values given are $\delta_H$ and coupling constants *J* are in hertz. Mass spectra were recorded using a VG 7070 instrument for the electron-impact mode (EI) or a VG ZAB instrument for the fast-atom bombardment mode (FAB) (positive ion mode, thioglycerol matrix unless otherwise stated). Homogeneity of products was assessed by TLC on Merck silica gel $60F_{254}$ plates, and by analytical HPLC on a Waters μBondapak™ $C_{18}$ reverse-phase column where appropriate. Preparative chromatography was performed on Merck silica gel 7729 (finer than 230 mesh ASTM).

*Benzyl 6α-Dimethylamino-6β-phenoxyacetamidopenicillanate* **3**.—A solution of benzyl 6α-methylthio-6β-phenoxyacetamidopenicillanate **2**[3a,b] (2.92 g, 6 mmol) in DMF (48 cm$^3$) was stirred under argon at −40 °C and treated sequentially with mercury(II) acetate (1.91 g, 6 mmol) and then a 33% (w/w) solution of dimethylamine in ethanol (1.17 cm$^3$). The mixture was allowed to regain ambient temperature over 1 h, after which it was poured into a mixture of water (100 cm$^3$) and ethyl acetate (100 cm$^3$). The organic phase was separated, washed further with water (4 × 100 cm$^3$) and evaporated to give the *title penicillin* (2.79 g, 96%) as a white foam which slowly crystallised with time at 0–5 °C, m.p. 97.5–98.5 °C (from ethyl acetate–hexane) (Found: C, 62.4; H, 6.2; N, 8.7. $C_{25}H_{29}N_3O_5S$ requires

* This more direct synthesis could not be employed for the 6α-vinylpenicillin **35**; treatment of intermediate **42** with vinylmagnesium bromide led to opening of the 2,3-dioxopiperazine ring as well as 6-substitution.

C, 62.1; H, 6.0; N, 8.7%); $\nu_{max}$/cm$^{-1}$ 1775, 1745, 1690, 1600, 1590sh, 1490 and 1455; $\delta_H$(90 MHz; $CDCl_3$) 1.34, 1.45 [6 H, 2 s, $(CH_3)_2C$], 2.40 ([6 H, s, $(CH_3)_2N$] , 4.40 (1 H, s, 3-H), 4.50 (2 H, s, $OCH_2CO$), 5.17 (2 H, s, $PhCH_2O$), 5.56 (1 H, s, 5-H) and 6.85–7.45 (11 H, m, ArH + NH).

*Dibenzyl 6α,6′α-Oxybis-6β-phenoxyacetamidopenicillanate* **8**.—Benzyl 6α-dimethylamino-6β-phenoxyacetamidopenicillanate **3** (0.48 g, 1 mmol) dissolved in DMF (2 cm$^3$)* was treated with iodomethane (0.71 g, 5 mmol) and kept first at ambient temperature for 6 h and then at 0–5 °C for 90 h without exclusion of moisture. Insoluble material was filtered off and the filtrate evaporated to dryness. The resulting dark red oil (*ca.* 0.5 g) was subjected to chromatography, eluting with chloroform. Appropriate fractions were pooled and evaporated to give the title *bis-ester* (0.197 g, 44%) as a colourless foam which crystallised on trituration with ether, m.p. 135–136 °C (from ethyl acetate–hexane) (Found: C, 61.7, H, 5.2; N, 6.2. $C_{46}H_{46}N_4O_{11}S_2$ requires C, 61.7; H, 5.1; N, 6.3%); $\nu_{max}$/cm$^{-1}$ 1780, 1740, 1710, 1595 and 1485br; $\delta_H$(90 MHz; $CDCl_3$) 1.28 [12 H, s, 2 × $(CH_3)_2C$], 4.36 (2 H, s, 2 × 3-H), 4.52 (4 H, ABq, 2 × $OCH_2CO$), 5.14 (4 H, ABq, 2 × $PhCH_2O$), 5.69 (2 H, s, 2 × 5-H), 6.85–7.50 (20 H, m, ArH) and 7.74 (2 H, br s, $D_2O$ exch., 2 × NH); *m/z* (positive FAB; Carbowax) MH$^+$, 895 (100%).

The solid filtered from the reaction mixture earlier was recrystallised from methanol-diethyl ether to afford *tetramethylammonium iodide*, m.p. > 300 °C (Found: C, 24.05; H, 5.95; N, 6.9; I, 63.0. $C_4H_{12}NI$ requires C, 23.9; H, 5.95; N, 6.95; I, 63.2%).

*Benzyl 6α-Methoxy-6β-phenoxyacetamidopenicillanate* **4**.—A solution of penicillin ester **3** (0.48 g, 1 mmol) in acetonitrile (2 cm$^3$) was treated with methanol (0.08 cm$^3$) and iodomethane (0.71 g, 5 mmol). The solution was set aside at ambient temperature for 21 h after which further methanol (0.04 cm$^3$) and iodomethane (0.23 g) were added. After a total of 40 h, the precipitated material was filtered off and washed with ethyl acetate (2 × 10 cm$^3$); the combined filtrate and washings were washed with 0.5 mol dm$^{-3}$ aqueous sodium thiosulphate and water. Evaporation gave crude product (0.44 g) which was crystallised from ethyl acetate–hexane to afford the title penicillin (0.18 g, 38%), m.p. 76–77.5 °C (lit.,[14] no m.p. quoted);† $\delta_H$(90 MHz; $CDCl_3$), *inter alia*, 3.46 (3 H, s, $CH_3O$) and 5.60 (1 H, s, 5-H).

*Benzyl 6α-Hydroxy-6β-phenoxyacetamidopenicillanate* **5**.—A solution of penicillin ester **3** (0.48 g, 1 mmol) in acetonitrile (2 cm$^3$) was treated with glacial acetic acid (0.2 cm$^3$) and iodomethane (1.42 g, 10 mmol). The solution was set aside at ambient temperature for 40 h and then worked up as for **4** with two additional washes with dil. aqueous sodium hydrogen carbonate. After evaporation, the crude product (0.47 g) was chromatographed, eluting with 2.5% methanol in chloroform. Appropriate fractions were pooled and evaporated, giving the title penicillin as a foam (0.117 g, 26%); $\nu_{max}(CHCl_3)$/cm$^{-1}$ 1780, 1740, 1690, 1600 and 1590; $\delta_H$(60 MHz; $CDCl_3$) 1.25, 1.35 [6 H, 2 s, $(CH_3)_2C$], 4.40 (1 H, s, 3-H), 4.45 (2 H, s, $OCH_2CO$), 5.10 (2 H, s, $PhCH_2O$), 5.40 (1 H, s, 5-H), 6.65–7.35 (10 H, m, ArH) and 7.90 (1 H, br s, NH). The spectral data were identical with those of material prepared from **3** in a standard procedure [mercury(II) acetate–$H_2O$].[21]

*Dibenzyl 6β-[(2R)-2-(4-Ethyl-2,3-dioxopiperazin-1-ylcarbonylamino)-2-phenylacetamido]-6α,6′α-oxybispenicillanate* **9**.—Benzyl 6α-dimethylamino-6β-[(2R)-2-(4-ethyl-2,3-dioxopiperazin-1-ylcarbonylamino)-2-phenylacetamido]penicillanate **6**[21] (0.400 g, 0.62 mmol) dissolved in acetonitrile (5 cm$^3$) was treated with iodomethane (0.35 g, 2.48 mmol) and set aside at ambient temperature without exclusion of moisture for 48 h. Work-up and chromatography as described for the isolation of **8** gave the title *bis-ester* (0.198 g, 51%), m.p. 165–170 °C (decomp.) (from acetone) (Found: C, 57.2; H, 5.4; N, 10.75. $C_{60}H_{64}N_{10}O_{15}S_2$·2-$H_2O$ requires C, 57.0; H, 5.4; N, 11.1%); $\nu_{max}$/cm$^{-1}$ 1780, 1745sh, 1710, 1685 and 1495br; $\delta_H[(CD_3)_2SO]$ 0.69, 1.12 [12 H, 2 s, 2 × $(CH_3)_2C$], 1.06 (6 H, t, *J* 7, 2 × $CH_3CH_2N$), 3.30–3.90 (12 H, 3 m, 6 × $CH_2N$), 4.54 (2 H, s, 2 × 3-H), 5.17 (4 H, ABq, 2 × $PhCH_2O$), 5.43 (2 H, s, 2 × 5-H), 5.61 (2 H, d, *J* 6, s on $D_2O$ exch., 2 × CHNH), 7.30–7.50 (20 H, br s, ArH), 8.96 (2 H, br s, $D_2O$ exch., 6-NH) and 10.00 (2 H, d, *J* 6, $D_2O$ exch., 2 × CHNH).

*Disodium 6β-[(2R)-2-(4-Ethyl-2,3-dioxopiperazin-1-ylcarbonylamino)-2-phenylacetamido]-6α,6′α-oxybispenicillanate* **10**.—The bis-ester **9** (0.120 g, 0.097 mmol) dissolved in THF (10 cm$^3$) was treated with 10% palladium on charcoal (0.090 g) and hydrogenated at ambient temperature and pressure. After 2 h, no starting material could be detected by TLC; the mixture was filtered, the precipitate washed with THF and the filtrate and washings were evaporated to dryness. The residue was redissolved in acetone containing a little THF and treated with 2 mol dm$^{-3}$ sodium 2-ethylhexanoate in isobutyl methyl ketone (0.097 cm$^3$); precipitation of solid was completed by addition of an equal volume of diethyl ether and cooling. The solid was filtered off, washed with acetone–diethyl ether (1:1), dried and reprecipitated from methanol–diethyl ether to give the title penicillin (0.069 g, 65%), $\nu_{max}$/cm$^{-1}$ 1771, 1710, 1683, 1610 and 1507; $\delta_H(D_2O)$ 0.77, 1.26 [12 H, 2 s, 2 × $(CH_3)_2C$], 1.17 (6 H, t, *J* 7, 2 × $CH_3CH_2N$), 3.40–4.10 (12 H, 4 m, 6 × $CH_2N$), 4.11 (2 H, s, 2 × 3-H), 5.58 [4 H, s, 2 × (5-H + CHNH)] and 7.30–7.60 (10 H, m, ArH); *m/z* (positive FAB) MH$^+$, 1093 (12%) and MNa$^+$, 1115 (25%).

*Benzyl 6β-[(2R)-2-(4-Ethyl-2,3-dioxopiperazin-1-ylcarbonylamino)-2-phenylacetamido]-6α-methoxypenicillanate* **7**.—The 6α-dimethylaminopenicillin ester **6**[21] (0.325 g, 0.5 mmol) dissolved in a mixture of acetonitrile (2 cm$^3$) and DMF (1 cm$^3$) was treated with iodomethane (0.35 g, 2.5 mmol) and methanol (0.04 cm$^3$) and set aside at ambient temperature for 22 h. The resulting dark solution was diluted with ethyl acetate, washed with 0.5 mol dm$^{-3}$ aqueous sodium thiosulphate (× 2) and water (× 4), and evaporated. Trituration of the residue with a little ethyl acetate caused deposition of a white solid to which diethyl ether was added; the mixture was cooled to complete crystallisation. The solid was filtered off, washed with diethyl ether and dried to give the *title penicillin* (0.234 g, 73%), m.p. 188–189 °C (prel. soft.) (from methanol–ethyl acetate–hexane) (Found: C, 57.6; H, 5.6; N, 10.8%. $C_{31}H_{35}N_5O_8S$. 0.5$H_2O$ requires C, 57.6; H, 5.6; N, 10.8%); $\nu_{max}$/cm$^{-1}$ 1770, 1750, 1710, 1690 and 1510; $\delta_H[(CD_3)_2SO]$ 0.83, 1.10 [6 H, 2 s, $(CH_3)_2C$], 1.07 (3 H, t, *J* 7, $CH_3CH_2N$), 3.33 (3 H, s, $CH_3O$), 3.30–3.95 (6 H, 3 m, 3 × $CH_2N$), 4.47 (1 H, s, 3-H), 5.16 (2 H, ABq, $PhCH_2O$), 5.32 (1 H, s, 5-H), 5.55 (1 H, d, *J* 6, CHNH), 7.20–7.50 (10 H, m, ArH), 9.82 (1 H, d, *J* 6, CHNH) and 9.96 (1 H, br s, 6-NH).

*Benzyl 6β-Phenoxyacetamido-6α-succinimidooxypenicillanate* **11**.—A solution of the 6α-methylthiopenicillin ester **2**[3] (0.97 g, 2 mmol) in DMF (16 cm$^3$) was stirred under argon at −40 °C and treated sequentially with silver(I) acetate (0.5 g, 3 mmol) and *N*-hydroxysuccinimide (0.34 g, 3 mmol). The mixture was allowed to regain ambient temperature and after 1.5 h was poured into

* Acetonitrile (2 cm$^3$) could be used with a similar result.

† Sheehan quotes correct microanalytical data but no m.p. for this compound; our microanalyses were also correct. The same is true of compound **13**.

water (50 $cm^3$) and extracted with ethyl acetate (50 $cm^3$). The organic phase was separated, washed further with water (4 × 50 $cm^3$), and evaporated to afford the title compound as a foam (1.10 g, quant.); $\nu_{max}/cm^{-1}$ 1786, 1734br, vs, 1598, 1589 and 1491; $\delta_H$[60 MHz; $(CD_3)_2CO$] 1.35, 1.40 [6 H, 2 s, $(CH_3)_2C$], 2.65 (4 H, s, 2 × $CH_2CO$), 4.50 (1 H, s, 3-H), 4.55 (2 H, s, $OCH_2CO$), 5.20 (2 H, s, $PhCH_2O$), 5.90 (1 H, s, 5-H), 6.70–7.50 (10 H, m, ArH) and 8.75 (1 H, br s, NH); *m/z* (positive FAB) $MH^+$, 554.

*Nucleophilic Substitution of the 6α-Succinimidooxy Group in* **11**: *General Procedure.*—The 6α-succinimidooxypenicillin ester **11** (0.55 g, 1 mmol) in anhydrous THF (5 $cm^3$) was stirred under argon at 0 °C and treated with the appropriate nucleophile and triethylamine (2 mmol). The resulting solution was allowed to regain ambient temperature and then stirred until complete reaction was indicated by TLC (1–3 h). Work-up was effected by dilution with ethyl acetate followed by washing with 0.5 mol $dm^{-3}$ hydrochloric acid, saturated aqueous sodium hydrogen carbonate and water. Following evaporation the products given below were isolated by crystallisation or chromatography, as appropriate, in the yields stated.

*Benzyl 6α-methoxy-6β-phenoxyacetamidopenicillanate* **4**. From methanol (0.5 $cm^3$), was obtained the crystalline ester (0.25 g, quant.), with spectral data identical with the material prepared from **3** (*v.s.*).

*Benzyl 6α-formamido-6β-phenoxyacetamidopenicillanate* **12**. From *N,N*-bis(trimethylsilyl)formamide[25] (0.48 $cm^3$, 2.5 mmol) was obtained after chromatography (5% methanol in chloroform elution) the known[3] ester (0.38 g, 78%) as a foam; $\delta_H(CDCl_3)$, neglecting formamido rotamers,[3b] *inter alia*, 5.73 (1 H, s, 5-H), 7.44 (1 H, br s, $D_2O$ exch., NH), 8.02 (1 H, br s, $D_2O$ exch., NH), and 8.22 (1 H, narrow d, s on $D_2O$ exch., NHC*H*O).

*Benzyl 6α-cyano-6β-phenoxyacetamidopenicillanate* **13**. On a 4 mmolar scale, from cyanotrimethylsilane (1.40 $cm^3$, 10 mmol) was obtained the crystalline ester (1.74 g, 96%), m.p. 73–76 °C (from ethyl acetate–cyclohexane; lit.,[14] no m.p. quoted);* $\delta_H(CDCl_3)$, *inter alia*, 5.90 (1 H, s).

*Reaction of* **11** *with Grignard Reagents: General Procedure.*—A solution of the 6α-succinimidooxypenicillin ester **11** (0.55 g, 1 mmol) in anhydrous THF (10 $cm^3$) was stirred at −70 °C under argon and treated with the appropriate Grignard reagent (2 mmol). The solution was allowed to regain ambient temperature over 1.5 h, and was then partitioned between ethyl acetate and 0.5 mol $dm^{-3}$ hydrochloric acid. The organic phase was separated, washed further with 0.5 mol $dm^{-3}$ hydrochloric acid, saturated aqueous sodium hydrogen carbonate (× 2) and water, and evaporated to give crude product, which was chromatographed, eluting with ethyl acetate–hexane mixtures. In this manner were obtained the products listed below in the yields cited.

*Benzyl 6α-methyl-6β-phenoxyacetamidopenicillanate* **14**. From 3 mol $dm^{-3}$ ethereal methylmagnesium bromide (0.67 $cm^3$) was obtained the *title compound*[9] (0.265 g, 63%) as a hard gum (Found: $M^+$, 454.1552. $C_{24}H_{26}N_2O_5S$ requires *M*, 454.1563); $\nu_{max}/cm^{-1}$ 1779, 1745, 1677, 1598, 1510 and 1493; $\delta_H$(90 MHz; $CDCl_3$) 1.33, 1.42 [6 H, 2 s, $(CH_3)_2C$], 1.80 (3 H, s, $CH_3CN$), 4.40 (1 H, s, 3-H), 4.45 (2 H, s, $OCH_2CO$), 5.15 (2 H, s, $PhCH_2O$), 5.40 (1 H, s, 5-H) and 6.80–7.40 (11 H, m, ArH + NH); *m/z* (E.I.) 454 ($M^+$, 2%), 250 (100).

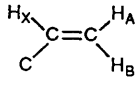
*Benzyl 6β-phenoxyacetamido-6α-vinylpenicillanate* **15**. From 1.1 mol $dm^{-3}$ vinylmagnesium bromide in THF (1.8 $cm^3$) was obtained the *title compound* (0.256 g, 55%), as a crystalline solid, m.p. 113–114 °C (from ethyl acetate–hexane) (Found: C, 64.2; H, 5.7; N, 6.05%; $M^+$, 466.1550. $C_{25}H_{26}N_2O_5S$ requires C, 64.5; H, 5.6; N, 6.0%; *M*, 466.1555); $\nu_{max}/cm^{-1}$ 1780, 1745, 1680sh, 1665, 1597, 1586, 1510 and 1488; $\delta_H(CDCl_3)$ 1.37, 1.47 [6 H, 2 s, $(CH_3)_2C$], 4.50 (1 H, s, 3-H), 4.54 (2 H, s, $OCH_2CO$), 5.20 (2 H, s, $PhCH_2O$), 5.38 (1 H, d, *J* 10, vinyl $H_A$†), 5.45 (1 H, d, *J* 17.5, vinyl $H_B$), 5.56 (1 H, s, 5-H), 6.18 (1 H, dd, *J* 17.5 and 10, vinyl $H_X$), 6.90–7.10 (3 H, m, ArH + NH) and 7.20–7.30 (8 H, m, ArH).

*Benzyl 6β-phenoxyacetamido-6α-phenylpenicillanate* **16**. On a 2 mmolar scale, from 2.0 mol $dm^{-3}$ phenylmagnesium chloride in THF (2.2 $cm^3$) was obtained the *title compound* as a foam (0.70 g, 68%) (Found: M, 516.1724. $C_{29}H_{28}N_2O_5S$ requires *M*, 516.1719); $\nu_{max}/cm^{-1}$ 1778, 1743, 1684, 1598, 1590sh and 1492; $\delta_H$(90 MHz; $CDCl_3$) 1.37, 1.50 [6 H, 2 s, $(CH_3)_2C$], 4.51 (3 H, s, $OCH_2CO$ + 3-H), 5.15 (2 H, s, $PhCH_2O$), 5.75 (1 H, s, 5-H) and 6.70–7.60 (16 H, m, ArH + NH).

*Allyl 6β-Amino-6α-methylthiopenicillanate* **18**.—The toluene-*p*-sulphonate of allyl 6β-aminopenicillanate **17**[27] was converted into its 4-nitrobenzylidene Schiff base using a known procedure.[9] This material (6.74 g, 17 mmol) dissolved in DMF (50 $cm^3$) was stirred at 0 °C with anhydrous potassium carbonate (4.78 g, 34 mmol) and methyl methanethiosulphonate (2.36 g, 18.7 mmol) was added. The reaction mixture was stirred for 1.5 h at 0 °C, then for 1 h at ambient temperature, poured into ethyl acetate and washed with water (× 5). Following evaporation, the crude Schiff base was redissolved in chloroform (110 $cm^3$) and added to a solution of 2,4-dinitrophenylhydrazine (3.36 g, 17 mmol) and toluene-*p*-sulphonic acid (3.23 g, 17 mmol) in ethanol (150 $cm^3$); then the mixture was stirred at ambient temperature for 1 h. Insoluble material was filtered off and the filtrate was evaporated to dryness; the residue was then redissolved in ethyl acetate and the solution washed with saturated aqueous sodium hydrogen carbonate (× 2). Evaporation gave a red–brown oil (4.80 g) which was purified by chromatography, eluting with ethyl acetate–hexane (1:4), to afford the *title compound* (1.21 g, 24%), which crystallised on trituration with diethyl ether, m.p. 52–53 °C (from ethyl acetate–hexane) (Found: C, 47.9; H, 6.2; N, 9.2; S, 20.8%; M, 302.0764. $C_{12}H_{18}N_2O_3S_2$ requires C, 47.7; H, 6.0; N, 9.3; S, 21.2%; *M*, 302.0759); $\nu_{max}/cm^{-1}$ 1764, 1731 and 1607w; $\delta_H$(90 MHz; $CDCl_3$) 1.48, 1.60 [6 H, 2 s, $(CH_3)_2C$], 2.25 (3 H, s, $CH_3S$), 4.44 (1 H, s, 3-H), 4.64 (2 H, d, *J* 6, $OCH_2CH$), 5.15–5.45 (2 H, m, $CH{=}CH_2$), 5.36 (1 H, s, 5-H) and 5.60–6.10 (1 H, m, $CH{=}CH_2$); *m/z* (EI) 302 ($M^+$, 17%), 287 ($M - CH_3^+$, 6) and 250 (100).

*Allyl 6α-Methylthio-6β-phenoxyacetamidopenicillanate* **21**.—The aminopenicillin ester **18** (1.00 g, 3.3 mmol) dissolved in DCM (20 $cm^3$) and pyridine (0.39 g, 5 mmol) was stirred at 0 °C and a solution of phenoxyacetyl chloride (0.56 g, 3.3 mmol) in DCM (5 $cm^3$) was added dropwise. The mixture was subsequently stirred at ambient temperature for 2 h, evaporated to dryness and the residue redissolved in ethyl acetate. The solution was washed with 0.5 mol $dm^{-3}$ hydrochloric acid (× 3) and half-saturated aqueous sodium hydrogen carbonate (× 3) and evaporated to give a brown oil which was subjected to chromatography, eluting with ethyl acetate–hexane (1:4) to afford the *title penicillin* as a foam (1.17 g, 81%) (Found: M, 436.1123. $C_{20}H_{24}N_2O_5S_2$ requires *M*, 436.1126); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1785, 1745, 1690, 1600w, 1590w and 1490; $\delta_H(CDCl_3)$ 1.44, 1.48 [6 H, 2 s, $(CH_3)_2C$], 2.29 (3 H, s, $CH_3S$), 4.46 (1 H, s, 3-H), 4.57 (2 H, s, $OCH_2CO$), 4.61–4.75 (2 H, m, $CHCH_2O$), 5.26–5.45 (2 H, m, $CH_2{=}CHCH_2$), 5.62 (1 H, s, 5-H), 5.84–6.00 (1 H, m, $CH_2{=}CHCH_2$), 6.90–7.08, 7.27–7.38 (5 H, 2 m, ArH)

* See footnote to compound **4**.

† Denoting the 6α-vinyl group as 

and 7.47 (1 H, s, NH); *m/z* (EI) 436 ($M^+$, 15%), 421 ($M - CH_3^+$, 3) and 200 (100).

*Allyl 6β-Phenoxyacetamido-6α-succinimidoxypenicillanate* **22**.—A solution of the 6α-methylthiopenicillin **21** (1.00 g, 2.3 mmol) in anhydrous DMF (20 $cm^3$) was treated sequentially with *N*-hydroxysuccinimide (0.39 g, 3.4 mmol) and then silver(I) acetate (0.57 g, 3.4 mmol) and the reaction mixture stirred at ambient temperature for 1 h. It was then filtered through Celite and the precipitate was washed with a little DMF; the combined filtrate and washings were then diluted with ethyl acetate, washed with water (×6), and evaporated to give the title penicillin as a yellow solid (1.03 g, 89%), which was sufficiently pure to be used without further purification; $\nu_{max}/cm^{-1}$ 1785, 1733, 1597w and 1490; $\delta_H$(60 MHz; $CDCl_3$) 1.38, 1.42 [6 H, 2 s, $(CH_3)_2C$], 2.80 (4 H, s, 2 × $CH_2CO$), 4.46 (1 H, s, 3-H), 4.50–4.80 (4 H, 2 m, $CHCH_2O$ + $CH_2$=$CHCH_2$), 5.15–5.50 (1 H, m, $CH_2$=$CHCH_2$), 6.03 (1 H, s, 5-H), 6.80–7.45 (5 H, 2 m, ArH) and 8.00 (1 H, s, NH).

*Allyl 6α-Mercapto-6β-phenoxyacetamidopenicillanate* **23**.—A solution of the 6α-succinimidooxypenicillin ester **22** (0.253 g, 0.5 mmol) in anhydrous DCM (15 $cm^3$) was stirred at 0 °C whilst $H_2S$ gas was bubbled through for 0.17 h; triethylamine (0.111 g, 1.1 mmol) was then added and passage of $H_2S$ continued for a further 0.17 h. The solution was stirred at 0–5 °C for 1 h after which solvent was removed by a stream of argon. The residue was dissolved in DCM (20 $cm^3$) and the solution washed with 0.5 mol $dm^{-3}$ hydrochloric acid and then evaporated. The residue was chromatographed, eluting with ethyl acetate–hexane (2:1) to afford the *title compound* (0.118 g, 55%) as a foam (Found: M, 422.0970. $C_{19}H_{22}N_2O_5S_2$ requires *M*, 422.0971); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1785, 1745, 1690 and 1490; $\delta_H(CDCl_3)$ 1.44, 1.46 [6 H, 2 s, $(CH_3)_2C$], 3.67 (1 H, s, $D_2O$ exch., SH), 4.48 (1 H, s, 3-H), 4.56 (2 H, ABq, $OCH_2CO$), 4.60–4.75 (2 H, m, $CHCH_2O$), 5.25–5.45 (2 H, m, $CH_2$=CH), 5.67 (1 H, s, 5-H), 5.85–6.05 (1 H, m, $CH_2$=$CHCH_2$), 6.90–7.10, 7.25–7.40 (5 H, 2 m, ArH) and 7.53 (1 H, br s, $D_2O$ exch., NH).

*Deprotection of allyl ester* **23**. The penicillin allyl ester **23** (0.090 g, 0.21 mmol) in DCM (2 $cm^3$) and ethyl acetate (1 $cm^3$) was stirred with 2 mol $dm^{-3}$ sodium 2-ethylhexanoate in isobutyl methyl ketone (0.12 $cm^3$, 0.24 mmol) and a mixture of tetrakis(triphenylphosphinyl)palladium(0)[26] (0.007 g) and triphenylphosphine (0.002 g). Further triphenylphosphine (0.005 g) was added after 0.25 h; after a total of 0.75 h little starting material was visible by TLC. The solution was evaporated and the residue triturated with diethyl ether to give a solid which was filtered off, washed with diethyl ether and redissolved in water. This solution was washed with ethyl acetate and then freeze-dried to afford a yellow solid (*ca.* 0.030 g) which was chromatographed, eluting with 20% ethanol–ethyl acetate, to give a colourless glass that was again dissolved in water and freeze-dried to yield a fluffy white solid (0.007 g). This material had spectral data corresponding to sodium 6α-allylthio-6β-phenoxyacetamidopenicillanate **25**; $\nu_{max}/cm^{-1}$ 1766, 1675, 1598 and 1490; $\delta_H(D_2O)$ 1.42, 1.43 [6 H, 2 s, $(CH_3)_2C$], 3.47 (2 H, approx. d, $CH_2S$), 4.26 (1 H, s, 3-H), 5.05–5.30 (2 H, m, $CH_2$=CH), 5.52 (1 H, s, 5-H), 5.75–5.95 (1 H, m, $CH_2$=$CHCH_2$), 7.00–7.15 and 7.30–7.45 (5 H, 2 m, ArH); *m/z* (positive FAB; 3-nitrobenzyl alcohol/$Na^+$) 467 ($MNa^+$, 100%) and 445 ($MH^+$, 35).

*Allyl 6α-Methylthio-6β-(2,2,2-trichloroethoxycarbonylamino)penicillanate* **27**.—A solution of 2,2,2-trichloroethoxycarbonyl chloride (2.12 g, 10 mmol) in DCM (15 ml) was added dropwise to a stirred solution of aminopenicillin ester **18** (3.02 g, 10 mmol) and pyridine (1.19 g, 15 mmol) in DCM (40 $cm^3$) at 0 °C. The resulting solution was further stirred first at 0 °C for 0.5 h and then at ambient temperature for 0.75 h; it was then evaporated to dryness. The residue was partitioned between ethyl acetate and water after which the organic phase was further washed with 0.5 mol $dm^{-3}$ hydrochloric acid. Evaporation of the organic phase gave the crude product which was chromatographed, eluting with ethyl acetate–hexane (1:4), to afford the title *urethane* (3.21 g, 67%) as a syrup which crystallised with time at 0 °C, m.p. 90–91 °C (from ethyl acetate–hexane) (Found: C, 37.9; H, 4.1; Cl, 22.0; N, 5.9; S, 13.6%; M, 475.9808. $C_{15}H_{19}Cl_3N_2O_5S_2$ requires C, 37.7; H, 4.0; Cl, 22.3; N, 5.9; S, 13.4%; *M*, 475.9801); $\nu_{max}$ ($CH_2Cl_2$)/$cm^{-1}$ 1780, 1745 and 1490; $\delta_H$(90 MHz; $CDCl_3$) 1.43, 1.56 [6 H, 2 s, $(CH_3)_2C$], 2.31 (3 H, s, $CH_3S$), 4.44 (1 H, s, 3-H), 4.61 (2 H, d, *J* 6.5, $CHCH_2O$), 4.65, 4.81 (2 H, AB qt, *J* 11, $CH_2CCl_3$), 5.17–5.45 (2 H, m, $CH_2$=CH), 5.48 (1 H, s, 5-H), 5.65–6.10 (1 H, m, $CH$=$CH_2$) and 6.12 (1 H, s, NH).

*Allyl 6α-(Succinimidooxy)-6β-[(2,2,2-trichloroethoxy)carbonylamino]penicillanate* **28**.—The 6α-(methylthio)penicillin ester **27** (0.478 g, 1 mmol) was dissolved with *N*-hydroxysuccinimide (0.173 g, 1.5 mmol) in anhydrous DMF (10 $cm^3$). This solution was stirred under argon at −40 °C and mercury(II) acetate (0.320 g, 1 mmol) was added; the temperature was allowed to rise to 10 °C over 1 h, when reaction appeared complete by TLC. The reaction mixture was poured into ethyl acetate–water, the organic phase was separated and washed further with water (×4). Evaporation afforded a white solid (*ca.* 0.55 g) which was recrystallised from ethyl acetate–hexane to afford the *title compound* (0.370 g, 67%), m.p. 98–102 °C (prel. soft.) (Found: C, 40.1; H, 3.7; N, 7.4; Cl, 19.6; S, 5.8. $C_{18}H_{20}Cl_3N_3O_8S$ requires C, 39.7; H, 3.7; Cl, 19.6; N, 7.7; S, 5.9%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1790, 1740 and 1495; $\delta_H$(90 MHz; $CDCl_3$) 1.41, 1.48 [6 H, 2 s, $(CH_3)_2C$], 2.70 (4 H, s, 2 × $CH_2CO$), 4.48 (1 H, s, 3-H), 4.64 (2 H, d, *J* 7, $CHCH_2O$), 4.67, 4.86 (2 H, ABq, *J* 11, $CH_2CCl_3$), 5.05–5.50 (2 H, m, $CH_2$=CH), 5.69–6.10 (1 H, m, $CH$=$CH_2$), 5.87 (1 H, s, 5-H) and 6.57 (1 H, s, NH); *m/z* (positive FAB) 561 ($MNH_4^+$, 3%) and 544 ($MH^+$, 8).

*Allyl 6β-(2,2,2-Trichloroethoxycarbonylamino)-6α-vinylpenicillanate* **29**.—A solution of the 6α-succinimidooxypenicillin ester **28** (0.100 g, 0.184 mmol) in anhydrous THF (10 $cm^3$) was stirred under argon at −70 °C and treated with a solution of 1.0 mol $dm^{-3}$ vinylmagnesium bromide in THF (0.37 $cm^3$). The reaction mixture was worked up as for compounds **14**–**16** above giving, after chromatography, the title *vinylpenicillin* as an oil (0.044 g, 52%) (Found: M, 456.0093. $C_{16}H_{19}Cl_3N_2O_5S$ requires *M*, 456.0080); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1785, 1745 and 1495; $\delta_H$($CDCl_3$) 1.49, 1.61 [6 H, 2 s, $(CH_3)_2C$], 4.53 (1 H, s, 3-H), 4.69 (2 H, m, $CHCH_2O$), 4.77 (2 H, br s, $CH_2CCl_3$), 5.31 (1 H, dd, *J* 10 and 1, $CH_2$=$CHCH_2$), 5.39 (1 H, dd, *J* 17 and 1, $CH_2$=$CHCH_2$), 5.42 (1 H, d, *J* 10.5, 6-CH=$CH_2$), 5.49 (1 H, s, 5-H), 5.53 (1 H, d, *J* 17, 6-CH=$CH_2$), 5.92 (2 H, m, $CH_2$=$CHCH_2$ + NH) and 6.16 (1 H, dd, *J* 17 and 10.5, 6-$CH$=$CH_2$).

*Allyl 6β-Amino-6α-vinylpenicillanate* **19**.—A solution of the 6α-vinylpenicillin ester **29** (0.120 g, 0.26 mmol) in THF (5 $cm^3$) was stirred with 1 mol $dm^{-3}$ potassium dihydrogen phosphate (1 $cm^3$)[29] at ambient temperature, and freshly acid-washed zinc powder (0.120 g) was added. The pH of the mixture was maintained at 4.0 by dropwise addition of 2 mol $dm^{-3}$ hydrochloric acid; more zinc (0.120 g) was added after 0.5 h. No starting material was visible by TLC after 3.25 h; the mixture was diluted with ethyl acetate and filtered through Celite and the precipitate was washed with a little ethyl acetate. The combined filtrate and washings were washed with brine and evaporated to give a crude product which was chromatographed, eluting with ethyl acetate–hexane (1:2), to afford the aminopenicillin as a foam (0.047 g, 64%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1775 and 1745;

$\delta_H(CDCl_3)$ 1.51, 1.65 [6 H, 2 s, $(CH_3)_2C$], 1.94 (2 H, br s, $NH_2$), 4.49 (1 H, s, 3-H), 4.67 (2 H, d, *J* 6.5, $CHCH_2O$), 5.25–5.45 (3 H, m, $CH_2$=CHCH$_2$ + one of 6-CH=C$H_2$), 5.36 (1 H, s, 5-H), 5.54 (1 H, d, *J* 17, 6-CH=C$H_2$), 5.85–6.00 (1 H, m, $CH_2$=C$H$CH$_2$) and 6.08 (1 H, dd, *J* 17 and 10.5, 6-C$H$=CH$_2$); *m/z* (positive FAB; 3-nitrobenzyl alcohol/$Na^+$) 305 ($MNa^+$, 35%).

*Allyl* 6β-*Phenoxyacetamido*-6α-*vinylpenicillanate* **24**.—A solution of the 6α-aminopenicillin **19** (0.043 g, 0.15 mmol) in anhydrous DCM (5 $cm^3$) was stirred at 0 °C and treated sequentially by dropwise addition of pyridine (0.018 g, 0.23 mmol) in DCM (1 $cm^3$) and then phenoxyacetyl chloride (0.026 g, 0.015 mmol) in DCM (1 $cm^3$). After the mixture had been stirred first at 0 °C for 0.25 h and then at ambient temperature for 0.5 h, TLC indicated complete reaction. The solution was evaporated to dryness, the residue redissolved in ethyl acetate and the solution washed with 0.5 mol $dm^{-3}$ hydrochloric acid. After evaporation, the crude product was chromatographed, eluting with ethyl acetate–hexane (1:3) to afford the *title penicillin* (0.048 g, 77%) as a foam (Found: M, 416.1413. $C_{21}H_{24}N_2O_5S$ requires *M*, 416.1407); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1785, 1745, 1690, 1495 and 1205; $\delta_H(CDCl_3)$ 1.46, 1.50 [6 H, 2 s, $(CH_3)_2C$], 4.49 (1 H, s, 3-H), 4.55 (2 H, s, $OCH_2CO$), 4.67 (2 H, m, $CHCH_2O$), 5.30 (1 H, dd, *J* 10.5 and 1, C$H_2$=CHCH$_2$), 5.38 (1 H, dd, *J* 17 and 1, C$H_2$=CHCH$_2$), 5.39 (1 H, d, *J* 10.5, 6-CH=C$H_2$), 5.47 (1 H, d, *J* 17, 6-CH=C$H_2$), 5.57 (1 H, s, 5-H), 5.91 (1 H, m, $CH_2$=C$H$CH$_2$), 6.20 (1 H, dd, *J* 17 and 10.5, 6-C$H$=CH$_2$), 6.90–7.10 (3 H, m, ArH) and 7.20–7.40 (3 H, m, ArH + NH).

*Sodium* 6β-*Phenoxyacetamido*-6α-*vinylpenicillanate* **26**.—A solution of the penicillin allyl ester **24** (0.040 g, 0.1 mmol) in DCM (1 $cm^3$) and ethyl acetate (0.5 $cm^3$) was treated with 2 mol $dm^{-3}$ sodium 2-ethylhexanoate in isobutyl methyl ketone (0.05 $cm^3$), triphenylphosphine (0.005 g) and tetrakis(triphenylphosphinyl)palladium(0)[26] (0.005 g) and the mixture stirred at ambient temperature for 1 h, when no starting material was visible by TLC. Solvents were evaporated and the residue triturated with diethyl ether to give a gummy solid, which (after decantation of the solvent) was dissolved in water. The solution was washed with ethyl acetate and then lyophilised. The crude product (0.036 g) was subjected to chromatography, eluting with ethanol–ethyl acetate (1:9 to 1:4), to afford a colourless glass which was redissolved in water and lyophilised to give the sodium salt (0.018 g, 45%); $\nu_{max}/cm^{-1}$ 1769, 1674, 1598 and 1491; $\delta(D_2O)$ 1.43, 1.45 [6 H, 2 s, $(CH_3)_2C$], 4.27 (1 H, s, 3-H), 4.76 (2 H, s, $OCH_2CO$), 5.40 (1 H, d, *J* 17, 6-CH=C$H_2$), 5.39 (1 H, d, *J* 10, 6-CH=C$H_2$), 5.52 (1 H, s, 5-H), 6.13 (1 H, dd, *J* 17 and 10.5, 6-C$H$=CH$_2$), 7.07 and 7.38 (5 H, 2 m, ArH); no molecular ion seen by FAB-MS.

*Allyl* 6β-[(2R)-2-(4-*Ethyl*-2,3-*dioxopiperazin*-1-*ylcarbonylamino*)-2-*phenylacetamido*]-6α-*vinylpenicillanate* **39**.—A solution of acid **38**[21] (0.113 g, 0.35 mmol) in DCM (5 $cm^3$) was stirred at ambient temperature with a few drops of DMF and oxalyl chloride (0.087 g, 0.70 mmol) was added. After 1 h the yellow solution was evaporated to dryness and re-evaporated from DCM (5 $cm^3$). This residue was dissolved in DCM (5 $cm^3$) and added dropwise to a stirred solution of the aminopenicillin **19** (0.100 g, 0.35 mmol) and pyridine (0.041 g, 0.53 mmol) in DCM (5 $cm^3$) at 0 °C. The mixture was allowed to regain ambient temperature over 2 h, when no amine component was visible by TLC; following evaporation to dryness, the product was redissolved in ethyl acetate and the solution washed with 0.5 mol $dm^{-3}$ hydrochloric acid (× 3) and half-saturated aqueous sodium hydrogen carbonate (× 3) and evaporated. The crude product, a yellow oil, was chromatographed, eluting with ethyl acetate–hexane (1:3) to afford the penicillin ester as a foam (0.120 g, 59%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1780, 1745, 1718 and 1692; $\delta_H(CDCl_3)$ 1.06, 1.32 [6 H, 2 s, $(CH_3)_2C$], 1.20 (3 H, t, *J* 7, C$H_3$CH$_2$N), 3.43–4.19 (6 H, 3 m, 3 × $CH_2$N), 4.34 (1 H, s, 3-H), 4.58–4.71 (2 H, m, $CHCH_2O$), 5.27–5.40 (2 H, m, C$H_2$=CH-CH$_2$), 5.33 (1 H, d, *J* 10.5, 6-CH=C$H_2$), 5.45 (1 H, d, *J* 17, 6-CH=C$H_2$), 5.47 (1 H, s, 5-H), 5.54 (1 H, d, *J* 7, PhC$H$NH), 5.82 (1 H, m, $CH_2$=C$H$CH$_2$), 6.13 (1 H, dd, *J* 17 and 10.5, 6-C$H$=CH$_2$), 6.73 (1 H, s, 6-NH), 7.30–7.57 (5 H, m, ArH) and 10.00 (1 H, d, *J* 7, CHN$H$): *m/z* (positive FAB; 3-nitrobenzyl alcohol/$Na^+$) 606 ($MNa^+$, 20%) and 584 ($MH^+$, 100).

*Sodium* 6β-[(2R)-2-(4-*Ethyl*-2,3-*dioxopiperazin*-1-*ylcarbonylamino*)-2-*phenylacetamido*]-6α-*vinylpenicillanate* **35**.—The penicillin ester **39** (0.100 g, 0.17 mmol) in DCM (2 $cm^3$) and ethyl acetate (1 $cm^3$) was treated with triphenylphosphine (0.009 g), 2 mol $dm^{-3}$ sodium 2-ethylhexanoate in isobutyl methyl ketone (0.09 $cm^3$) and tetrakis(triphenylphosphinyl)-palladium(0) (0.009 g) and stirred at ambient temperature for 0.5 h. The resulting suspension, which showed no ester by TLC, was concentrated to low volume and diluted with diethyl ether. The diethyl ether was decanted and, after a further ether washing, the residue was redissolved in water and the solution washed with ethyl acetate and lyophilised to give the sodium salt (0.096 g, 99%); $\nu_{max}/cm^{-1}$ 1761, 1712, 1675 and 1608; $\delta_H(D_2O)$ 1.00, 1.28 [6 H, 2 s, $(CH_3)_2C$], 1.17 (3 H, t, *J* 7, C$H_3$CH$_2$N), 3.49 (2 H, q, *J* 7, CH$_3$C$H_2$N), 3.58–4.11 (4 H, 2 m, 2 × $CH_2$N), 4.14 (1 H, s, 3-H), 5.39 (1 H, d, *J* 10.5, 6-CH=C$H_2$ *cis*), 5.45 (1 H, s, 5-H), 5.49 (1 H, d, *J* 17, 6-CH=C$H_2$ *trans*), 5.51 (1 H, s, Ph C$H$NH), 6.12 (1 H, dd, *J* 17 and 10.5, 6-C$H$=CH$_2$) and 7.42–7.51 (5 H, m, ArH); *m/z* (positive FAB; 3-nitrobenzyl alcohol/$Na^+$) 588 ($MNa^+$, 55%) and 566 ($MH^+$, 100). The NMR also showed *ca.* 6% (w/w) contamination by 2-ethylhexanoic acid.

*Benzyl* 6α-*Succinimidooxy*-6β-(2,2,2-*trichloroethoxycarbonylamino*)*penicillanate* **31**.—A solution of benzyl 6α-(methylthio)-6β-(2,2,2-trichloroethoxycarbonylamino)penicillanate **30**[3b] (1.58 g, 3 mmol) in anhydrous DMF (24 $cm^3$) was stirred at −40 °C under argon and treated sequentially with silver(I) acetate (0.75 g, 4.5 mmol) and *N*-hydroxysuccinimide (0.51 g, 4.5 mmol). The mixture was allowed to regain ambient temperature after which it was stirred for 2 h and worked up as for **28**. Evaporation gave a semi-solid which was triturated with hexane, filtered, and dried to give the practically pure *penicillin ester* (1.41 g, 79%), m.p. 98–100 °C (from ethyl acetate–hexane) (Found: C, 44.1; H, 3.7; N, 6.8; S, 5.3. $C_{22}H_{22}Cl_3N_3O_8S$ requires C, 44.4; H, 3.7; N, 7.1; S, 5.4%); $\nu_{max}/cm^{-1}$ 1786, 1734, 1512m, 1453w and 1429w; $\delta_H$(90 MHz; $CDCl_3$) 1.45, 1.57 [6 H, 2 s, $(CH_3)_2C$], 2.70 (4 H, 2 s, 2 × $CH_2CO$), 4.51 (1 H, s, 3-H), 4.78 (2 H, ABq, $CH_2CCl_3$), 5.19 (2 H, s, PhC$H_2O$), 5.88 (1 H, s, 5-H), 6.63 (1 H, br s, NH) and 7.35 (5 H, s, ArH); *m/z* (positive FAB) 613 ($MNH_4^+$, 42%) and 596 ($MH^+$, 7).

*Benzyl* 6α-*Phenyl*-6β-(2,2,2-*trichloroethoxycarbonylamino*)-*penicillanate* **32**.—The 6α-succinimidooxypenicillin ester **31** (1.11 g, 2 mmol) in anhydrous THF (20 $cm^3$) was stirred under argon at −70 °C and treated with 2 mol $dm^{-3}$ phenylmagnesium chloride in diethyl ether (2.0 $cm^3$). The reaction was completed and worked up as for compounds **14**–**16**, to give after chromatography, eluting with ethyl acetate–hexane (2:3), the *title penicillin* as a foam (0.38 g, 34%) (Found: M, 556.0404. $C_{24}H_{23}Cl_3N_2O_5S$ requires *M*, 556.0393); $\nu_{max}/cm^{-1}$ 1782, 1740, 1640w and 1496; $\delta_H$(90 MHz; $CDCl_3$) 1.40, 1.60 [6 H, 2 s, $(CH_3)_2C$], 4.56 (1 H, s, 3-H), 4.65 (2 H, s, $CH_2CCl_3$), 5.16 (2 H, s, PhC$H_2O$), 5.66 (1 H, s, 5-H), 6.04 (1 H, br s, NH) and 7.20–7.50 (10 H, m, ArH).

*Benzyl* 6α-*Amino*-6β-*phenylpenicillanate* **20**.—A solution of

the 6α-phenylpenicillin ester **32** (0.670 g, 1.20 mmol) in THF (15 $cm^3$) was stirred vigorously at ambient temperature with 1 mol $dm^{-3}$ aqueous potassium dihydrogen phosphate (3 $cm^3$) and freshly acid-washed zinc (0.8 g). The pH was maintained at *ca.* 4 using 2 mol $dm^{-3}$ hydrochloric acid; when no starting material was visible by TLC (*ca.* 3 h), the reaction was worked up as for **19** to afford after chromatography (ethyl acetate–hexane, 1:2) the title *aminopenicillin* as a white solid after trituration with hexane, filtration, and drying (0.205 g, 45%), m.p. 120–122 °C (prel. soft.) (Found: C, 66.0; H, 5.9; N, 7.15%; M, 382.1357. $C_{21}H_{22}N_2O_3S$ requires C, 66.0; H, 5.8; N, 7.3%; *M*, 382.1351); $\nu_{max}/cm^{-1}$ 1772, 1751, 1600w, 1576w and 1495; $\delta_H(CDCl_3)$ 1.43, 1.67 [6 H, 2 s, $(CH_3)_2C$], 2.05 (2 H, br s, $NH_2$), 4.57 (1 H, s, 3-H), 5.19 (2 H, s, PhC$H_2$O), 5.47 (1 H, s, 5-H) and 7.30–7.60 (10 H, m, ArH).

*Benzyl* 6β-[(2R)-2-(4-*Ethyl*-2,3-*dioxopiperazin*-1-*ylcarbonyl*-*amino*)-2-*phenylacetamido*]-6α-*phenylpenicillanate* **40**.—A solution of the aminopenicillin **20** (0.191 g, 0.5 mmol) and *N*,*N*′-dicyclohexylcarbodiimide (0.103 g, 0.5 mmol) in ethyl acetate (3 $cm^3$) was stirred at 0 °C and treated with a solution of acid **38**[21] (0.160 g, 0.5 mmol) in THF (3 $cm^3$), added over 0.25 h. The mixture was allowed to regain ambient temperature when it was stirred for 3.5 h and then stored at 5 °C. for 16 h. The precipitate was filtered off and washed with ethyl acetate and the combined filtrate and washings were washed with 0.5 mol $dm^{-3}$ hydrochloric acid ( × 2), saturated aqueous sodium hydrogen carbonate ( × 2) and water. Evaporation followed by chromatography, eluting with 3% methanol in chloroform, afforded the product which was reprecipitated from ethyl acetate–diethyl ether to give the title penicillin as an amorphous solid (0.161 g, 47%); $\nu_{max}/cm^{-1}$ 1779, 1740sh, 1715, 1684, 1609w, 1585w and 1496; $\delta_H[(CD_3)_2CO]$ 1.09, 1.24 [6 H, 2 s, $(CH_3)_2C$], 1.16 (3 H, t, *J* 7, C$H_3$CH$_2$N), 3.40–4.10 (6 H, 3 m, 3 × $CH_2$N), 4.47 (1 H, s, 3-H), 5.23 (2 H, s, PhC$H_2$O), 5.73 (1 H, s, 5-H), 5.78 (1 H, d, *J* 7, PhC*H*NH), 7.25–7.70 (15 H, m, ArH), 8.69 (1 H, br s, 6-NH) and 9.96 (1 H, d, *J* 7, CHN*H*); *m*/*z* (positive FAB) 684 ($MH^+$, 17%).

*Sodium* 6β-[(2R)-2-(4-*Ethyl*-2,3-*dioxopiperazin*-1-*ylcarbonyl*-*amino*)-2-*phenylacetamido*]-6α-*phenylpenicillanate* **34**.—The penicillin ester **40** (0.125 g, 0.18 mmol) dissolved in THF (10 $cm^3$) was treated with 10% palladium on charcoal (0.075 g) and hydrogenated at ambient temperature and pressure. Further catalyst (0.050 g) was added after 1.5 h; after 2 h in all, when no ester was visible by TLC, the catalyst was filtered off and washed with THF. The combined filtrate and washings were evaporated to dryness, the residue redissolved in acetone (2 $cm^3$) and the solution treated with 2 mol $dm^{-3}$ sodium 2-ethylhexanoate in isobutyl methyl ketone (0.09 $cm^3$). Precipitation was completed by addition of diethyl ether (10 $cm^3$); the precipitate was filtered off, washed first with acetone–diethyl ether (1:1), and then diethyl ether, and finally dried and reprecipitated from methanol–diethyl ether to give the sodium salt (0.070 g, 62%); $\nu_{max}/cm^{-1}$ 1761, 1713, 1675, 1611, 1510sh and 1496; $\delta_H[(CD_3)_2SO]$ 0.94, 1.24 [6 H, 2 s, $(CH_3)_2C$], 1.07 (3 H, t, *J* 7, C$H_3$CH$_2$N), 3.30–3.90 (6 H, 3 m, 3 × $CH_2$N), 3.81 (1 H, s, 3-H), 5.55 (1 H, s, 5-H), 5.70 (1 H, d, *J* 7, s on $D_2O$ exch., PhC*H*NH), 7.25–7.55 (10 H, m, ArH), 9.66 (1 H, s, $D_2O$ exch., 6-NH) and 9.81 (1 H, d, *J* 7, $D_2O$ exch., CHN*H*); *m*/*z* (positive FAB; $H_2O$–glycerol) 638 ($MNa^+$, 100%) and 616 ($MH^+$, 62).

*Allyl* 6β-[(2R)-2-(4-*Ethyl*-2,3-*dioxopiperazin*-1-*ylcarbonyl*-*amino*)-2-*phenylacetamido*]-6α-*methylthiopenicillanate* **41**.—The acid **38**[21] (3.18 g, 10.00 mmol) was converted into its acid chloride using oxalyl chloride–DMF as described for the preparation of **39**. A solution of this product in DCM (50 $cm^3$) was added dropwise to a solution of the aminopenicillin **18** (3.52 g, 10.0 mmol) in DCM (100 $cm^3$) and pyridine (1.17 g, 15 mmol) stirred at 0 °C. The resulting mixture was stirred at ambient temperature for 2 h and then worked up as described for **39**. Chromatography of the yellow crude product, eluting with ethyl acetate–hexane (4:1 to 5:1), afforded the title penicillin as a yellowish foam (2.91 g, 45%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1780, 1752, 1717 and 1690; $\delta_H(CDCl_3)$ 0.98, 1.29 [6 H, 2 s, $(CH_3)_2C$], 1.20 (3 H, t, *J* 7, C$H_3$CH$_2$N), 2.29 (3 H, s, $CH_3S$), 3.45–3.60, 3.94–4.21 (6 H, 2 m, 3 × $CH_2$N), 4.30 (1 H, s, 3-H), 4.57–4.65 (2 H, m, CHC$H_2$O), 5.25–5.39 (2 H, m, C$H_2$=CHCH$_2$), 5.53 (1 H, s, 5-H), 5.62 (1 H, d, *J* 7, PhC*H*NH), 5.81–5.94 (1 H, m, CH$_2$=C*H*CH$_2$), 7.14–7.56 (6 H, m, ArH + 6-NH) and 10.04 (1 H, d, *J* 7, CHN*H*); *m*/*z* (positive FAB) 604 ($MH^+$, 15%).

*Allyl* 6β-[(2R)-2-(4-*Ethyl*-2,3-*dioxopiperazin*-1-*ylcarbonyl*-*amino*)-2-*phenylacetamido*]-6α-*succinimidooxypenicillanate* **42**.—A solution of the 6α-methylthiopenicillin ester **41** (0.227 g, 0.38 mmol) in anhydrous DMF (20 $cm^3$) was stirred under argon at ambient temperature and treated with *N*-hydroxysuccinimide (0.065 g, 0.56 mmol) and silver(I) acetate (0.064 g, 0.38 mmol). After being stirred for 1 h the mixture was poured into water and extracted with ethyl acetate ( × 3); the combined organic extracts were washed with water ( × 6) and evaporated to afford a yellow foam (0.170 g). Since NMR showed that this material still contained DMF, it was redissolved in ethyl acetate, and the solution washed with water ( × 5) and re-evaporated to give the title penicillin (0.110 g, 44%) as a pale yellow foam sufficiently pure for further use; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1785, 1735, 1718 and 1690; $\delta_H(CDCl_3)$ 0.73, 1.04–1.35 [9 H, s + m, $(CH_3)_2C$ + C$H_3$CH$_2$N], 2.72 (4 H, s, 2 × $CH_2CO$), 3.32–3.69, 3.98–4.51 (6 H, 2 m, 3 × $CH_2$N), 4.31 (1 H, s, 3-H), 4.52–4.78 (2 H, m, CHC$H_2$O), 5.22–5.50 (2 H, m, C$H_2$=CHCH$_2$), 5.58, 5.78 (1 H, 2 d, both *J* 6, PhC*H*NH), 5.80–6.00 (1 H, m, CH$_2$=C*H*CH$_2$), 6.20 (1 H, s, 5-H), 7.15–7.60 (5 H, m, ArH), 8.00, 8.37 (1 H, 2 s, 2 × 6-NH), 10.06 and 10.28 (1 H, 2 d, both *J* 6, CHN*H*); *m*/*z* (positive FAB) 671 ($MH^+$, 4%). The doubling of certain peaks in the NMR spectrum is thought to be due to some restricted rotation phenomenon, possibly about the N–O bond, not to isomerisation at the α-CH, since only one isomer is seen again after the next step.

*Allyl* 6β-[(2R)-2-(4-*Ethyl*-2,3-*dioxopiperazin*-1-*ylcarbonyl*-*amino*)-2-*phenylacetamido*]-6α-*mercaptopenicillanate* **43**.—A solution of the 6α-succinimidooxypenicillin **42** (0.670 g, 1.0 mmol) in DCM (30 $cm^3$) was stirred at 0 °C whilst $H_2S$ gas was bubbled through it for 0.17 h; triethylamine (0.222 g, 2.2 mmol) was then added and the passage of $H_2S$ continued for 0.17 h. The resulting solution was stirred at 0–5 °C for 1 h after which it was evaporated to dryness, and worked up as for compound **23**. Chromatography, eluting with ethyl acetate, afforded the title penicillin as a foam (0.301 g, 51%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1785, 1740sh, 1715 and 1690; $\delta_H(CDCl_3)$ 0.98, 1.28 [6 H, 2 s, $(CH_3)_2C$], 1.21 (3 H, t, *J* 7, C$H_3$CH$_2$N), 3.40–3.70, 3.90–4.25 (6 H, 2 m, 3 × $CH_2$N), 4.32 (1 H, s, 3-H), 4.50–4.70 (2 H, m, CHC$H_2$O), 5.25–5.45 (2 H, m, C$H_2$=CHCH$_2$), 5.60 (1 H, s, 5-H), 5.63 (1 H, d, *J* 7, PhC*H*NH), 5.80–6.00 (1 H, m, CH$_2$=C*H*CH$_2$), 7.25–7.55 (5 H, m, ArH) and 10.11 (1 H, d, *J* 7, CHN*H*); *m*/*z* (positive FAB; 3-nitrobenzyl alcohol) 590 ($MH^+$, 19%).

*Sodium* 6β-[(2R)-2-(4-*Ethyl*-2,3-*dioxopiperazin*-1-*ylcarbonyl*-*amino*)-2-*phenylacetamido*]-6α-*mercaptopenicillanate* **36**.—A solution of the 6α-mercaptopenicillin ester **43** (0.100 g, 0.17 mmol) in DCM (2 $cm^3$), ethyl acetate (2 $cm^3$) and methanol (1 $cm^3$) containing 2 mol $dm^{-3}$ sodium 2-ethylhexanoate in isobutyl methyl ketone (0.008 $cm^3$) was treated with triphenylphosphine (0.007 g) and tetrakis(triphenylphosphinyl)palladium(0) (0.007 g) and stirred under argon at ambient temperature. No ester was visible by TLC after 0.5 h; the solution was

evaporated to dryness and the residue was partitioned between ethyl acetate and water and the aqueous phase was separated, washed again with ethyl acetate and then lyophilised to give crude product (0.058 g). Purification was effected by chromatography on HP20SS resin ('Diaion'), eluting with water–THF mixtures containing up to 20% THF. Early column fractions, assayed by HPLC, were combined and lyophilised to give the title penicillin (0.012 g, 12%); $\nu_{max}/cm^{-1}$ 1749, 1710, 1675, 1605 and 1515; $\delta_H(D_2O)$ 0.97, 1.25 [6 H, 2 s, $(CH_3)_2C$], 1.17 (3 H, t, *J* 7, $CH_3CH_2N$), 3.48 (2 H, q, *J* 7, $CH_3CH_2N$), 3.66, 3.97 (4 H, 2 m, 2 × $CH_2N$), 4.02 (1 H, s, 3-H), 5.31 (1 H, s, 5-H), 5.45 (1 H, s, PhCHNH) and 7.30–7.58 (5 H, m, ArH); *m/z* (positive FAB) 594 ($MNa^+$, 100%) and 572 ($MH^+$, 45). Later-eluting column fractions (HPLC) were combined and lyophilised to give *sodium 6α-allylthio-6β-[(2R)-2-(4-ethyl-2,3-dioxopiperazin-1-ylcarbonylamino)-2-phenylacetamido]penicillanate* **37** (0.011 g, 11%); $\nu_{max}/cm^{-1}$ 1764, 1713, 1674, 1609 and 1506; $\delta_H(D_2O)$ 0.95, 1.25 [6 H, 2 s, $(CH_3)_2$], 1.17 (3 H, t, *J* 7, $CH_3CH_2N$), 3.45–3.60, 3.65–3.75 (6 H, 2 m, 3 × $CH_2N$), 3.90–4.10 (2 H, m, $CHCH_2S$), 4.12 (1 H, s, 3-H), 5.00–5.40 (2 H, m, $CH_2$=$CHCH_2$), 5.43, 5.44 (2 H, 2 s, 5-H and PhCHNH), 5.80–6.00 (1 H, m, $CH_2$=$CHCH_2$) and 7.35–7.55 (5 H, m, ArH); *m/z* (positive FAB) 634 ($MNa^+$, 100%) and 612 ($MH^+$, 33).

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