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SYNTHESIS OF 2-OXO-PENAMS AND PENEMS FROM PENICILLIN G†

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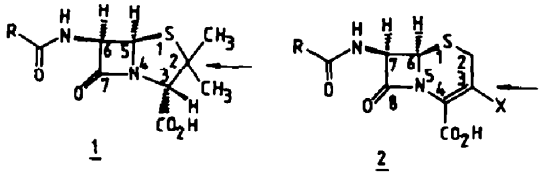
Abstract—Using Penicillin G as starting material, general methods of synthesis for the 2-oxo-penam skeleton have been established. Compounds **7** represent a new group of strained penicillin derivatives. They can be readily transformed into 2-alkoxy **17** or benzoyloxypenems **18**.

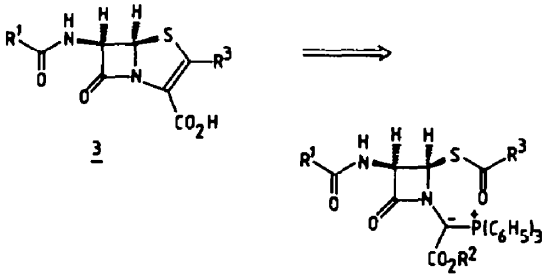
The search for more effective β-lactamase-resistant antibiotics has provided the incentive for continuing synthetic studies involving variations of the nuclei or substitution of penicillins **1** or cephalosporins **2** (Scheme 1). By far the most extensive investigations concern the modification of the side chain at C-6 (penicillins) or C-7 (cephalosporins). These studies have led to several products already in therapeutic use, or undergoing clinical trials. In the cephalosporin series, the importance of the substitution at C-3 has long been recognised and consequently, much work has been centred upon variations at that position. The related modification of substitution at C-2 in the penicillins is obviously a more difficult task requiring several steps involving cleavage and reconstruction of the 5-membered ring.



Scheme 1.

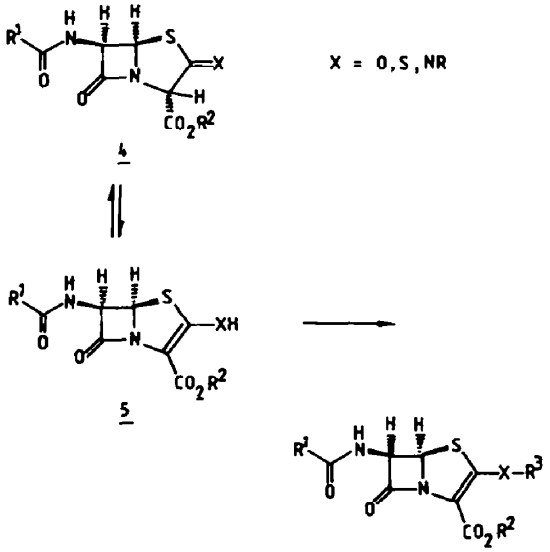
A major breach in these lines was made by Woodward *et al.*[2] who reported the first synthesis of penems **3**, a new class of β-lactam antibiotics in which carbons 2 and 3 of the penicillin nucleus are connected by a double bond (Scheme 2). The interest for this new type of nucleus was further increased by the isolation of potent antibiotics which possess a carbapenem nucleus.[3] In clavulanic acid,[4] a weak antibiotic but potent β-lactamase inhibitor, C-2 of the oxazolidine ring is part of an exocyclic double bond.

These discoveries stimulated many efforts toward the synthesis of analogs of these new structures.[5] Most syntheses of penem derivatives are based on Woodward's methodology, i.e. an intramolecular Wittig reaction which effects the closure of the 5-membered ring and simultaneously introduces the double bond (Scheme 2).



Scheme 2.

Our efforts in this area have concentrated on developing practical laboratory syntheses of penams bearing an exocyclic heterodouble bond at C-2 (Scheme 3). In our opinion the availability of mole-



Scheme 3.

†Some of these results have been presented in lectures or published in a preliminary form.[1]

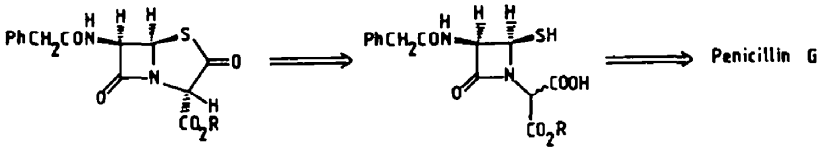
cules of the type **4** would offer several advantages. First the introduction of an sp^2 C atom into the penam nucleus was expected to increase the strain of the bicyclic system and, hence, the reactivity of the β-lactam. In addition, the unsaturated function at C-2 should be amenable to various chemical transformations. An attractive possibility would result from the equilibrium between 2-oxo-, thiono- or imino-penams **4** and the corresponding penems **5** which should readily be trapped by electrophilic reagents. Thus the availability of compounds of type **4** would also provide an easy access to 3-heterosubstituted penems **6**. In the present article, we report in detail[1] the successful realisation of the synthesis of 2-oxo-penams and penems derived therefrom.

For the synthesis of 2 - oxo - 6 - phenylacetamido–penam - 3 - carboxylic ester **7**, our plan was to build the 5-membered ring from a monocyclic β-lactam precursor **8** possessing all the stereochemical features of the final products (Scheme 4). One attractive possibility involved a thiolactonisation reaction as the 5-membered ring forming step. Penicillin G was considered as a cheap and optically active starting material for the formation of the key monocyclic β-lactam intermediate **8**.

RESULTS AND DISCUSSION

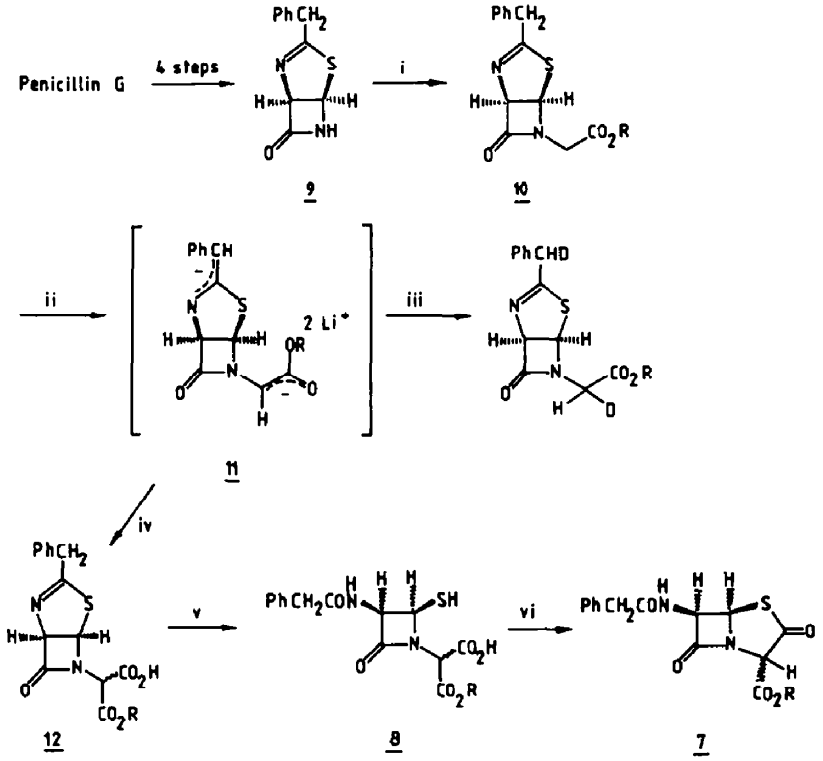
Penicillin G was readily converted, using known procedures,[6] into thiazoline–azetidinone **9** (35% overall yield).

To provide the 3-carbon unit in a form suitable for the final thiolactonisation, a two-step procedure was first adopted (Scheme 5). Compound **9** was readily



7 8

Scheme 4.



9 10 11 12 8 7

a R= CH_3- d R= $(C_6H_5)_2CH$-
b R= $(CH_3)_3C$- e R= $(CH_3)_3SiCH_2CH_2$-
c R= $C_6H_5CH_2$- f R= CH_2=CH-CH_2-

Reagents : i) $BrCH_2CO_2R$, Triton B or NaH; ii) $LiN(Si(CH_3)_3)_2$; iii) D_2SO_4-D_2O; iv) CO_2 and acidic work-up; v) H_3O^+; vi) iC_3H_7-N=C=N-iC_3H_7

Scheme 5.

alkylated[7] with methyl and t-butyl bromoacetate, in DMF, in the presence of Triton B to give **10a** (86%) or **10b** (90%). Introduction of the missing carboxyl group rested upon the possibility of acylating selectively the position α to the ester group. It was anticipated that, on treatment with strong bases, compounds **10** would be converted into the corresponding dianions **11**. The bridgehead situation of the proton α to the lactam group was expected to decrease its acidity in spite of a very favourable electronic environment. This was experimentally confirmed by submitting **10b** to excess (4 equiv) of lithium hexamethyldisilazide in THF at −60° and quenching the resulting mixture with D_2SO_4–D_2O. Deuterium was found at the benzylic C atom as well as the position α to the ester group. The reaction of dianions **11a** and **11b** with a large excess of carbon dioxide introduced the carboxyl group required for the cyclisation. It would not be surprising if both anionic centers in **11** had reacted with carbon dioxide. However, on acidification, decarboxylation at the imine N or at the benzylic position should have readily occurred. Both acids **12a** and **12b** were obtained (90–100% crude) as mixtures of diastereoisomers. In view of their low stability, they were used without purification in the following step. Mild acid hydrolysis[8] (1 N HCl, MeOH, 20°) quantitatively regenerated the amide side chain and the thiol group without giving rise to any significant decarboxylation.

We were thus ready to effect the thiolactonisation forming the thiazolidinone ring and thus completing the synthesis of the desired 2-oxo-penam system. This was readily accomplished by slow addition of N,N-diisopropylcarbodiimide to the crude acids **8a** and **8b** at −60° and warming up at room temperature. Chromatography on silica gel and subsequent recrystallisation yielded the pure compounds **7a** (36%) and **7b** (65%) which were identified as 2-oxo-penam-3-carboxylates.† In spite of the presence of two diastereoisomers in the starting acids **8a** and **8b**, the thiolactonisation gave as the only isolable products the desired, more stable 2-oxo-penams with the ester groups *trans* with respect to the C–S bond.

These results had established the practicability of the proposed methodology but did not allow the preparation of the 2-oxo-penam-3-carboxylic acid **7g**. Indeed both **7a** and **7b** were found to be less stable than simple penams. Reagents like trimethylsilyl iodide,[12] trifluoroacetic acid or hydrogen bromide in dichloromethane induced decomposition of **7b**.

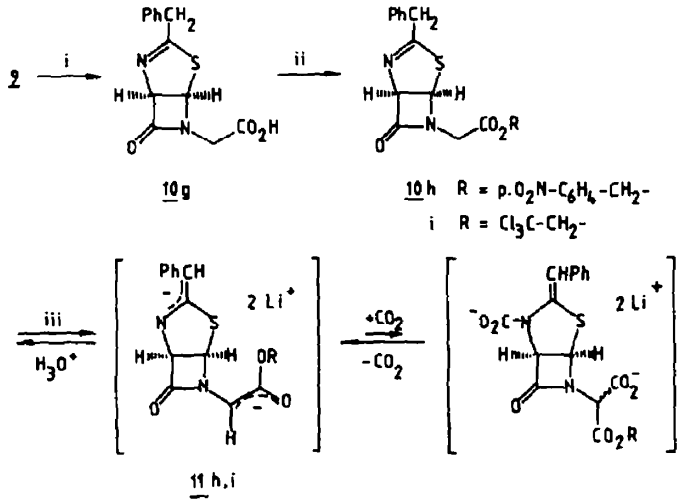
The same sequence was successfully applied to the preparation of a series of 2-oxo-penam-3-carboxylates **7c–f** bearing various ester protecting groups.[13] However none of these groups was found appropriate for the regeneration of the free acid or its salt without destruction of the β-lactam ring. Neither benzyl or benzhydryl esters **7c** and **7d** were hydrogenolysed under the usual conditions[14] (Pd–C, 20°, MeOH or EtOAc). Treatment of the β-trimethylsilyl ester **7e** with tetrabutylammonium fluoride[15] in acetonitrile led to the cleavage of the β-lactam ring. Finally, making use of the elegant procedure recently described by Jeffrey and McCombie[16] for the deprotection of allyl esters derived from penams and penems, compound **7f** was treated with potassium 2-ethylhexanoate in the presence of $Pd(PPh_3)_4$ in ethyl acetate at room temperature. Dissapointingly, these conditions also caused decomposition of **7f**.

On the basis of established precedent, the *p*-nitrobenzyl (PNB)[2] and trichloroethyl (TCE)[17] protecting groups appeared to be more appropriate for the liberation of the free carboxyl group under conditions which would not destroy the very reactive β-lactam of the 2-oxo-penam system. These new esters were also prepared using the same strategy based on the final thiolactonisation. However their preparation required some modifications of the sequence of reactions previously used for esters **7a–f** (Scheme 6). The direct alkylation of **9** with *p*-nitrobenzyl or trichloroethyl-α-bromoacetates gave complex mixtures of products under various conditions. Esters **10h** and **10i** were however conveniently prepared by alkylation of **9** with bromoacetic acid (2 eq of Triton B in DMF, yield **10g** 76%) followed by esterification (**10h**: 75%, *p*-nitrobenzylbromide and triethylamine; **10i**: 52%, trichloroethanol and N,N-(diethyl)amino-1-propyne). More surprising was the influence of the character of the ester group on the carboxylation reaction. Thus, *both PNB and TCE esters* **10h** *and* **10i** *were quantitatively recovered after being exposed to the conditions used successfully for the carbonatation of* **10a–f**. Deuteration experiments again confirmed the formation of dianions **11h, i**. Clearly, the presence of electron-withdrawing substituents in the alkyl part of the ester group displaces the equilibrium toward the decarboxylated form. This difficulty was avoided by using the sequence shown in Scheme 7. Acid **12b** which was readily available from **9** was esterified with *p*-nitrobenzylalcohol or trichloroethanol in the presence of N,N-diisopropylcarbodiimide to give **14h, i** respectively in 92% and 87% yield.‡ Attempts to prepare these esters by alkylation of **12b** with the corresponding halides in DMF in the presence of triethylamine led to decarboxylation of **12b** and quantitative recovery of **10b**.

The way was now open for the production of 2-oxo-penam-3-carboxylic acid. Selective cleavage of the butyl group in **14h, i** was readily effected with dry hydrogen bromide in dichloromethane at 0°. The crude acids **12h, i** were hydrolysed under mild conditions (1 N HCl, MeOH, 0°) to give the monocyclic β-lactams **8h, i**. The final lactonisation was accomplished by treatment of **8h, i** with N,N-diisopropylcarbodiimide. Chromatography on silica gel gave the pure *p*-nitrobenzyl 2-oxo-penam-3-carboxylate **7h** in 22% yield calculated from **14h**. Disappointingly this method gave no more than 9% yield of impure trichloroethyl 2-oxo-penam-3-carboxylate **7i**. The final deprotection of PNB ester **7h** (H_2, Pd–C, 20°, 2–3 atm, EtOAc) brought a happy end to the synthesis of 2-oxo-penicillin G **7g** which was obtained in 57% yield as an amorphous, highly hygroscopic material of limited stability.

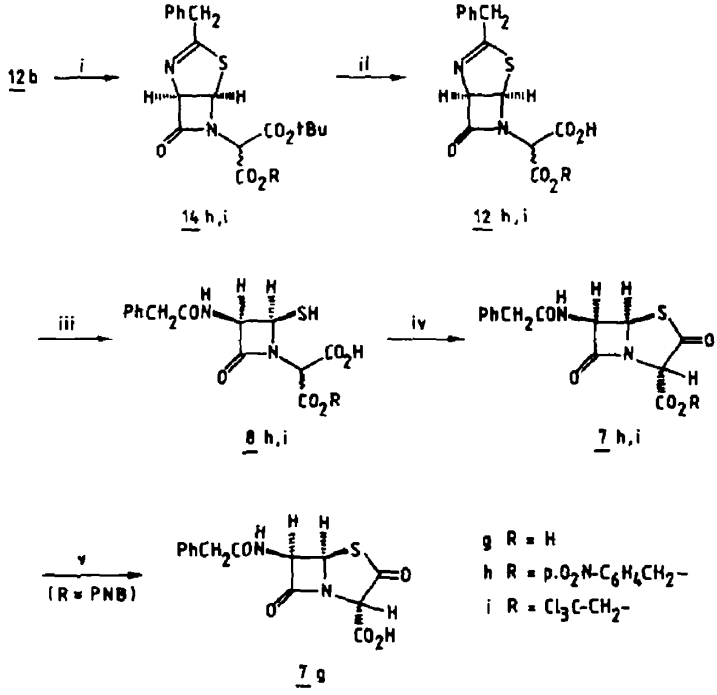
†Three independent reports on related systems have recently appeared in a patent[9] and in preliminary publications.[10,11]

‡An alternative route to esters **14h** and **14i**, involving the direct fixation of mixed bromomalonates has been investigated in detail and will be described in a subsequent paper.



Reagents : i) $BrCH_2CO_2H$, Triton B; ii) ROH, iC_3H_7-N=C=N-iC_3H_7 or CH_3-C≡C-$N(C_2H_5)_2$; iii) $LiN(Si(CH_3)_3)_2$

Scheme 6.

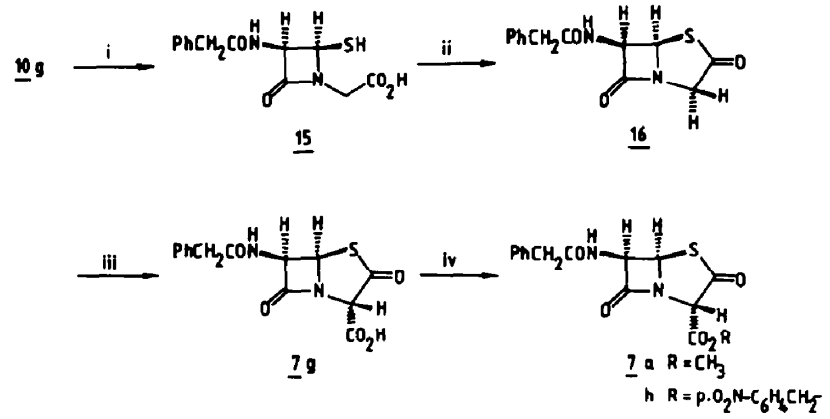


Reagents : i) ROH, iC_3H_7-N=C=N-iC_3H_7; ii) HBr; iii) H_3O^+ ; iv) iC_3H_7-N=C=N-iC_3H_7; v) H_2-Pd

Scheme 7.

At this point we were intrigued by the possibility of postponing the introduction of the carboxyl group till the last step of the synthesis. The main advantages of this modified route (Scheme 8) would be (a) a reduction in the number of steps, (b) the possibility of avoiding protecting groups, (c) the direct production of the free acid.

Hydrolysis of **10g** gave the monocyclic β-lactam **15** in 79% yield. The cyclisation to **16** was effected in high yield (81%) with N,N-diisopropylcarbodiimide.



Reagents : i) H_3O^+; ii) iC_3H_7-N=C=N-iC_3H_7; iii) $LiN(Si(CH_3)_3)_2$, CO_2; iv) CH_2N_2 or NO_2-C_6H_4-CHN_2

Scheme 8.

Treatment of **16** with an excess of lithium hexamethyldisilazide at −78° followed by addition of dry-ice and acidification, introduced the carboxylic acid group to yield 2-oxo-penicillin G **7g** (67%), identical with the compound obtained by the route outlined in Scheme 7. The free acid could be readily converted into the corresponding methyl and *p*-nitrobenzyl esters **7a** and **7b** by reaction with diazomethane or *p*-nitrophenyldiazomethane (1 eq). This provides the shortest and most convenient synthesis of the 2-oxo-penam system.

The structure of the 2-oxo-penam 3-carboxylates **7** was firmly established by spectroscopic data and elemental analysis.† This is exemplified here for the t-butyl ester **7b**.

A high frequency stretching absorption of the β-lactam CO group at 1802 cm^{-1} in the IR spectrum is characteristic of strained β-lactam. In addition the spectrum shows three strong absorptions at 1745, 1730 and 1687 cm^{-1} which are respectively assigned to the ester, thioester and amide carbonyl stretching absorptions.

In the PMR spectrum, compound **7b** is characterised by a closely spaced multiplet, between 5.83 and 6.05δ, of the two β-lactam protons H-5 and H-6 and by a singlet at 4.82δ corresponding to the H atom H-3. By addition of D_2O, this singlet disappears and the multiplet for H-5 and H-6 is replaced by a sharp AB quartet with a coupling constant of 4 Hz.

The ^{13}C NMR spectrum of **7b** shows four signals which can be assigned to the four CO groups. The signal at 199.36 ppm is typical of a CO group which is part of a thioester.

In addition the UV spectrum does not show a long wavelength maximum at 300–310 nm typical of a penem structure.[2]

These data confirm that, as anticipated the thioester is more stable than its enol tautomer. However the 2-hydroxy-penem could be readily intercepted by alkylation or acylation (Scheme 9). Treatment of **7b** and **7f** with an excess of diazomethane at 20° (overnight, CH_2Cl_2–ether) yielded 2-methoxypenems[9,10] **17b** and **17f** which were isolated in 53% and 36% yields respectively after rapid chromatography on silica gel. The electron withdrawing PNB group accelerated the methylation reaction: using identical conditions, **7h** was converted in one hour into the corresponding 2-methoxy-penem **17h** (41% yield).

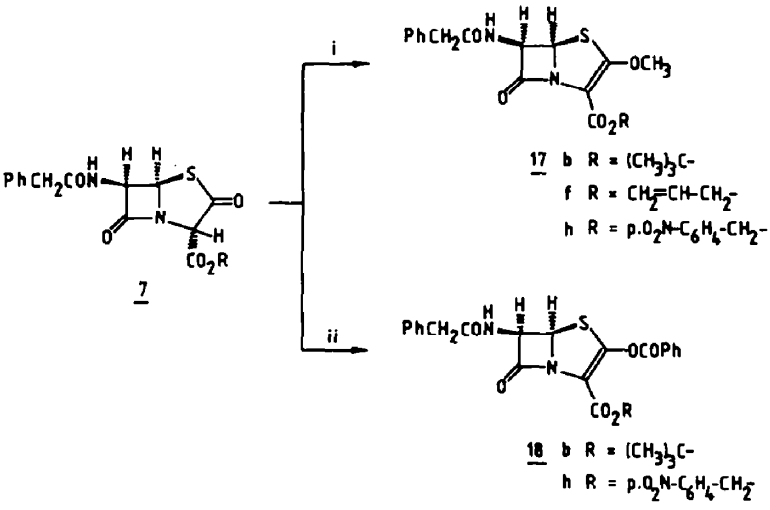
Compounds **17** represent new heterosubstituted penems characterised by a strong IR band at 1800–1805 cm^{-1} for the strained β-lactam CO and a broad band at ~1690–1700 cm^{-1} for the amide and conjugated ester CO. The penem structure is confirmed by the typical[2] UV absorption max at 300–310 nm. The PMR spectra display a singlet at 4.0 δ for the OMe group and a typical ABX pattern at 5.7–5.9 δ for the β-lactam protons H-5 and H-6. In the ^{13}C NMR spectrum (**17b**), the signal for a thioester C atom was no longer present but two other signals (158.75 and 106.94 ppm) indicate the presence of a heterosubstituted double bond.

Compounds **7b** and **7h** could also be acylated; the reaction with benzoyl chloride in the presence of triethylamine (−60 to 20°, CH_2Cl_2) gave the corresponding 2-benzoyloxypenems **18b** and **18h** which were too unstable for chromatographic purification. They were isolated by precipitation from the crude reaction mixture by addition of ether (**18b** 72%; **18h** 69%). Their spectral properties are quite similar to those of **17b** and **17h** and confirm the assigned structure.

Our final task was to convert the 2-methoxypenems **17** into the free acid **17g** or its salt. The reaction of **17f** with potassium 2-ethylhexanoate (or the free acid) in the presence of Pd $(PPh_3)_4$ gave rise to the disappearance of the β-lactam group.

More surprisingly, the catalytic hydrogenolysis of the PNB esters **17h** and **18h** also led to the destruction of the β-lactam ring.

†In the cases of **7f** and **16**, the structural assignment was further confirmed by X-ray diffraction analysis. Details of these results will be published separately.



Reagents : i)CH_2N_2; ii) PhCOCl, NEt_3

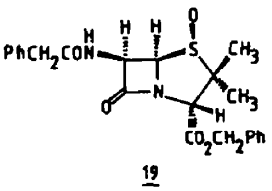
Scheme 9.

EXPERIMENTAL

M.ps (Leitz microscope) are uncorrected. All rotations (Perkin–Elmer 241 MC) were determined in $CHCl_3$ and all IR spectra (Perkin–Elmer 297 and 681, calibration with polystyrene) in CH_2Cl_2 as solvent, unless otherwise mentioned. The ^1H NMR spectra were recorded ($CDCl_3$ unless otherwise mentioned, with TMS as internal standard) on Varian T60 spectrometer or, if specified, on Varian XL 100 and XL 200 spectrometers. The ^{13}C NMR spectra were obtained ($CDCl_3$–TMS) with Varian CFT 20 or XL 200 spectrometers. The Mass spectra were determined with Varian MAT 44 spectrometer (EI 70 eV or DCI isobutane 200 μb 100 eV). The UV spectra were recorded in dioxane soln on an Unicam SP 1800 spectrophotometer. Column-chromatographies were performed with Merck silica gel 60 (70–230 mesh ASTM). CH_2Cl_2 and DMF were dried over P_2O_5 (reflux), then distilled. THF was dried over $LiAlH_4$ (reflux, argon) then distilled.

3 - *Benzyl* - 6 - *oxo* - 2 - *thia* - 4,7 - *diaza* - (1R,5R) - *bicyclo* - [3.2.0] - *hept* - 3 - *ene* **9**

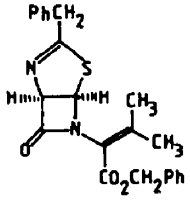
Compound **9** was prepared from the benzyl ester of penicillin G sulfoxide, using a procedure described in a Glaxo patent[6c] for the β-trichloroethyl ester, and well documented for penicillin V derivatives.[6a,b]



19

19: 6 - β - phenylacetamidopenicillanic acid-(1S)-oxide, prepared from the Na salt of penicillin G and aqueous $NaIO_4$ (90% yield-lit[18]: 83%), was esterified with benzyl bromide (NEt_3, DMF, 20°) following known[18,19] procedures (83% yield).

20: A mixture of **19** (50 g, 0.113 mol), $MgSO_4$ anh (22.5 g, 0.187 mol) and $(CH_3O)_3P$ (67 ml, 0.57 mol) in benzene (400 ml) was refluxed with stirring for 40 hr. Filtration and evaporation gave an oil which was dissolved in CH_2Cl_2



20

(80 ml) and stirred for 30 min with NEt_3 (3 ml). Chromatography (silica gel, CH_2Cl_2–EtOAc 9:1) yielded pure **20** (30 g, 65%; IR (KBr) 1750, 1720, 1610 cm^{-1}; ^1H NMR δ 1.58 (s, 3), 2.15 (s, 3), 3.80 (s, 2), 5.12 (br s, 2), 5.70 (d, 1, J = 4 Hz), 5.88 (d, 1 J = 4 Hz), 7.18 (s, 5), 7.28 (s, 5).

Oxidative cleavage of **20**. A soln of $KMnO_4$ (8.3 g, 0.0525 mol) and $MgSO_4$ (5.8 g, 0.0482 mol) in water (400 ml) was added dropwise with vigorous stirring and at controlled temp (15–20°) to a soln of **20** (25 g, 0.061 mol) in EtOH (400 ml). One hr after complete addition, five portions of solid $KMnO_4$ (2.5 g, 0.016 mol) were added one every 30 min. After evaporation, EtOAc (1.25 l.) and water (400 ml) were added and the mixture was stirred overnight. The inorganic salts were filtered off and washed with water (3 × 50 ml) then EtOAc (3 × 50 ml), and the aqueous phases extracted with EtOAc (3 × 150 ml). Drying ($MgSO_4$) and concentration furnished a yellow solid which was triturated in hot ether (~ 15 ml) then filtered to give **9** (10 g, 74%; IR (KBr) 3210, 1745 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.91 (s, 2), 5.6 (d, 1, J = 4.5 Hz), 5.88–6.15 (m, 1), 7.30 (s, 5), 8.9 (m, 1).

2 - [3 - *Benzyl* - 6 - *oxo* - 2 - *thia* - 4,7 - *diaza* - (1R,5R) - *bicyclo* - [3.2.0] - *hept* - 3 - *en* - 7 - *yl*] - *alkyl acetates* **10**

Methyl ester **10a**. To a soln of 2.18 g (0.01 mol) of **9** in 40 ml of DMF, stirred at −30° under argon, 4.5 ml of triton B (40% methanolic soln, 0.01 mol) were added dropwise. After 15 min at −30° and a further 15 min at 0°, the dark-red soln of the anion was cooled at −30° and 1.7 g (0.01 mol) of methyl bromoacetate in 5 ml of DMF was introduced dropwise. Stirring was continued for 15 min at −30°, 1 hr at 0° and 2 hr at room temp. The mixture was poured into cold water (~200 ml) and extracted with EtOAc (3 × 75 ml). The organic layers were washed (2 ×) with brine, dried ($CaCl_2$) and concentrated. Chromatography of

the residue (silica gel, benzene–EtOAc, 4:1) gave 2.5 g (86%) of **10a** as an oil which crystallised slowly from ether: m.p. 50–52°; $[\alpha]_D$ (±0.5) −59° (*c* = 0.505%); IR 1760 (broad) cm^{-1}; ^1H NMR δ 3.66 (d, 1, J = 18 Hz), 3.71 (s, 3), 3.88 (br s, 2), 4.26 (d, 1, J = 18 Hz), 5.73 (d, 1, J = 4 Hz), 6.03 (br d, 1, J = 4 Hz), 7.28 (s, 5). (Found: C, 57.76; H, 4.95; N, 9.64. Calc for $C_{14}H_{14}N_2O_3S$ (290.27): C, 57.93; H, 4.86; N, 9.65%.)

t-Butyl ester **10b**. **10b** was prepared in the same way, from 2.18 g (0.01 mol) of **9** in 40 ml DMF, 4.5 ml triton B (40% methanolic soln, 0.01 mol) and 1.5 ml (0.01 mol) t-butyl bromoacetate in 5 ml DMF. Crystallisation of the crude product from ether (0°), gave 3.0 g (90%) of **10b**: m.p. 125–127.5°; $[\alpha]_D$ (±0.5) −61.4° (*c* = 0.63%); IR 1770, 1735 cm $^{-1}$; ^1H NMR δ 1.46 (s, 9), 3.60 (d, 1, J = 18 Hz), 3.93 (br s, 2), 4.23 (d, 1, J = 18 Hz), 5.83 (d, 1, J = 4 Hz), 6.10 (br d, 1, J = 4 Hz), 7.33 (s, 5). (Found: C, 61.80; H, 5.70. Calc for $C_{17}H_{20}N_2O_3S$ (332.35): C, 61.43; H, 6.07%.)

Benzyl ester **10c**. To a suspension of 480 mg NaH (50% on oil, 0.01 mol) in 20 ml DMF, stirred at −30° under argon, 2.18 g (0.01 mol) of **9** in 20 ml DMF were added. Stirring was continued at 0° until complete dissolution of NaH(± 30 min). 2.5 g (0.01 mol) benzyl bromoacetate in 10 ml DMF were then introduced dropwise at −20°. After 1 hr at 0° and 2 hr at room temp, the mixture was worked up as described for **10a**. Chromatography (silica gel, benzene–EtOAc, 4:1) followed by crystallisation from CH_2Cl_2–ether (0°) yielded 1.72 g (47%) of **10c**: m.p. 110–113.5°; $[\alpha]_D$ (±0.5) −49.6° (*c* = 0.6%); IR 1775, 1745 cm^{-1}; ^1H NMR δ 3.70 (d, 1, J = 18 Hz); 3.86 (br s, 2), 4.30 (d, 1, J = 18 Hz), 5.15 (s, 2), 5.73 (d, 1, J = 4 Hz), 6.01 (br d, 1, J = 4 Hz), 7.26 (s, 5), 7.33 (s, 5). (Found: C, 65.52; H, 4.77. Calc for $C_{20}H_{18}N_2O_3S$ (366.36): C, 65.56; H, 4.95%.)

Benzhydryl ester **10d**. **10d** was prepared (see procedure for **10a**) from 436 mg (2 mmol) of **9** in 10 ml DMF, 0.9 ml triton B (40% methanolic soln, 2 mmol) and 0.7 g (2 mmol) benzhydryl bromoacetate in 5 ml DMF. Chromatography (silica gel, benzene–EtOAc, 4:1) followed by crystallisation from ether, yielded 0.31 g (35%) of **10d**: m.p. 145–146°; $[\alpha]_D$ (±0.4) −62.8° (*c* = 0.49%); IR 1772, 1750 cm $^{-1}$; ^1H NMR δ 3.75 (d, 1, J = 18 Hz), 3.85 (sharp AB print, 2), 4.38 (d, 1, J = 18 Hz), 5.71 (d, 1, J = 4 Hz), 6.00 (br d, 1, J = 4 Hz), 6.90 (s, 1), 7.28 (s, 5), 7.33 (s, 10). (Found: C, 70.31; H, 5.12; N, 6.28. Calc for $C_{26}H_{22}O_3NS$ (442.45): C, 70.58; H, 5.01; N, 6.33%.)

β-(Trimethylsilyl)-ethyl ester **10e**. **10e** was prepared (see procedure for **10a**) from 436 mg (2 mmol) of **9** in 10 ml DMF, 0.9 ml triton B (40% methanolic soln, 2 mmol) and 500 mg (2.2 mmol) β-(trimethylsilyl)-ethyl bromoacetate in 5 ml DMF. Chromatography of the crude product (silica gel, benzene–EtOAc, 4:1) yielded 500 mg (66%) of **10e**: m.p. 55–56.5°; $[\alpha]_D$ (±0.4) −57.5° (*c* = 0.48%); IR 1772, 1740 cm $^{-1}$; ^1H NMR δ 0.60 (br s, 9), 0.86–1.20 (m, 2), 3.66 (d, 1, J = 18 Hz), 3.86 (br s, 2), 4.23 (d, 1, J = 18 Hz), 4.06–4.43 (m, 2), 5.74 (d, 1, J = 4 Hz), 6.02 (br d, 1, J = 4 Hz), 7.30 (s, 5). (Found: C, 57.03; H, 6.39; N, 7.44. Calc for $C_{18}H_{24}O_3N_2SSi$ (376.45): C, 57.42; H, 6.42; N, 7.44%.)

Allyl ester **10f**. **10f** was prepared, according to the procedure used for **10c**, from a mixture of 500 mg NaH (50% on oil, 0.01 mol) and 2.18 g (0.01 mol) of **9** in 40 ml DMF, and 1.8 g (0.01 mol) allyl bromoacetate in 5 ml DMF. Chromatography (silica gel, benzene–EtOAc, 4:1) and precipitation from hexane gave 1.5 g (47%) of **10f**: m.p. 92–92.5°; $[\alpha]_D$ (±0.7) −59.6° (*c* = 0.985%); IR 1775, 1748 cm $^{-1}$; ^1H NMR δ 3.76 (d, 2, J = 18 Hz), 3.93 (s, 2), 4.33 (d, 2, J = 18 Hz), 4.66 (br d, 2, J = 5 Hz), 5.16–5.56 (m, 2), 5.83 (m + d, 2, J = 4 Hz), 6.10 (br d, 1, J = 4 Hz), 7.31 (s, 5). (Found: C, 61.15; H, 5.17. Calc for $C_{16}H_{16}O_3N_2S$ (316.2): C, 60.75; H, 5.10%.)

2 - [3 - *Benzyl* - 6 - *oxo* - 2 - *thia* - 4,7 - *diaza* - (1R,5R) - *bicyclo* - [3.2.0] - *hept* - 3 - *en* - 7 - *yl*] - *acetic acid* **10g**

The acid **10g** was prepared according to the procedure used for **10a**, from 21.8 g (0.1 mol) of **9** in 180 ml DMF, 112.5 ml triton B (40% methanolic soln, 0.225 mol) and 17.4 g (0.125 mol) bromoacetic acid in 25 ml DMF. The crude soln (dark-red) was diluted with EtOAc (500 ml) and poured into ice–water (1 l.) containing 7 ml AcOH. The pH was adjusted at 2.5 by addition of 1N HCl. After extraction with EtOAc (2 × 250 ml), drying ($MgSO_4$) and concentration of the organic layers ($T° \leq 20°$), the crude mixture was triturated with dry ether. Filtration yielded 21 g (76%) of **10g** as a white powder: IR (KBr) 3700–2200, 1760, 1720 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.78 (d, 1, J = 17 Hz), 3.87 (s, 2), 4.16 (d, 1, J = 17 Hz), 5.70 (d, 1, J = 4 Hz), 5.99 (d, 1, J = 4 Hz), 7.26 (s, 5).

p-*Nitrobenzyl ester* **10h**. A soln of **10g** (276 mg, 1 mmol), Et_3N (0.140 ml, 1 mmol) and *p*-nitrobenzyl bromide (216 mg, 1 mmol) in DMF (5 ml) was stirred for 24 hr at room temp. The crude soln was poured into cold water (25 ml, slightly acidified) and extracted with EtOAc (3 × 25 ml). The organic layers were washed with brine, dried ($CaCl_2$) and evaporated. Precipitation from dry ether gave 310 mg (75%) of **10h**: m.p. 182°; $[\alpha]_D$ (±0.4) −56.2° (*c* = 0.535%), IR 1770, 1750 cm^{-1}; ^1H NMR δ 3.80 (d, 1, J = 19 Hz), 3.90 (br s, 2), 4.38 (d, 1, J = 19 Hz), 5.26 (s, 2), 5.78 (d, 1, J = 4 Hz), 6.10 (br d, 1, J = 4 Hz), 7.33 (s, 5), 7.53 (d, 2, J = 9 Hz), 8.26 (d, 2, J = 9 Hz). (Found: C, 57.92; H, 4.11; N, 10.20. Calc for $C_{20}H_{17}O_5N_3S$ (411.36): C, 58.30; H, 4.17; N, 10.22%.)

β-Trichloroethyl ester **10i**. To a soln of **10g** (552 mg, 2 mmol) and trichloroethanol (298 mg, 2 mmol) in CH_2Cl_2 (25 ml), stirred at −60°, N,N-(diethyl)-amino-1-propyne (0.276 ml, 2 mmol) was added dropwise (with a syringe through a rubber stopper). The mixture was allowed to come slowly at room temp and stirring was continued for 2 hr. Evaporation, chromatography (silica gel, benzene–EtOAc, 4:1) and crystallisation from ether, furnished 850 mg (52%) of **10i**: m.p. 115–116°; $[\alpha]_D$ (±0.5) −46.1° (*c* = 0.505%); IR 1780, 1768 cm^{-1}; ^1H NMR δ 3.85 (d, 1, J = 18 Hz), 3.89 (br s, 2), 4.41 (d, 1, J = 18 Hz), 4.75 (s, 2), 5.76 (d, 1, J = 4 Hz), 6.03 (br d, 1, J = 4 Hz), 7.27 (s, 5). (Found: C, 43.82; H, 3.29; N, 6.80. Calc for $C_{15}H_{13}O_3N_2SCl_3$ (407.64): C, 44.16; H, 3.21; N, 6.87%.)

2 - [3 - *Benzyl* - 6 - *oxo* - 2 - *thia* - 4,7 - *diaza* - (1R,5R) - *bicyclo* - [3.2.0] - *hept* - 3 - *en* - 7 - *yl*] - *mono-alkyl malonates* **12**

Mono-methyl malonate **12a**. To a soln of 4.2 g (0.017 mol, 4 equiv) lithium hexamethyldisilazide–ether (1:1 complex) in 40 ml dry THF, stirred at −60° under argon, 1.16 g (0.004 mol) of **10a** in 5 ml THF was added dropwise. Stirring was continued for 30 min at low temp. Then, a stream of dry CO_2 was passed through the soln for 30 min at −60° and for 1 hr without cooling. The soln was poured in ice-cooled 0.5 N HCl (75 ml, 0.037 mol, 9 equiv) and extracted with EtOAc (3 × 75 ml). The organic layers were dried ($CaCl_2$) and evaporated under vacuum ($T° \leq 20°$), to give 1.07 g (80%) of crude **12a** (mixture of two diastereoisomers): IR ($CHCl_3$) 1750 (broad) cm^{-1}; ^1H NMR δ 3.63 and 3.76 (two s, 3), 3.90 (br s, 2), 5.05 and 5.11 (two s, 1), 5.96 (br s, 2), 7.30 (s, 5).

Mono-t-butyl malonate **12b**. The acid **12b** was prepared in the same way (see **12a**), from 10.5 g (0.0435 mol, 4 equiv) base in 50 ml THF and 3.6 g (0.0108 mol) of **10b** in 20 ml THF. After work-up (100 ml 1N HCl, ~9 equiv), the crude product was precipitated from dry ether to give 3.65 g (90%) of **12b** as a white powder: IR (KBr) 1770 (broad), 1740 (broad) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.43 and 1.45 (two s, 9), 3.90 (br s, 2), 4.93 (s, 1), 5.80–6.16 (m, 2 + 1), 7.30 (s, 5); ($CDCl_3$ + 10% DMSO-d_6) 1.43 (br s, 9), 3.90 (s, 2), 4.90 and 4.93 (two s, 1), 6.01 (br s, 2), 7.33 (s, 5).

Mono-benzyl malonate **12c**. The acid **12c** was prepared (as described for **12a**) from 4.66 g (0.019 mol, ~4 equiv) base in 40 ml THF and 1.58 g (0.0043 mol) of **10c** in 20 ml THF. After work-up (80 ml 0.5 N HCl, 0.04 mol, ~9 equiv), 1.65 g (92%) crude **12c** was obtained: IR 1755 (broad) cm^{-1};

^{1}H NMR (DMSO-d_6) δ 3.80 (br s, 2), 5.10 (br s, 3), 5.63–6.10 (m, 2 + 1), 7.20 (s, 5), 7.30 (s, 5).

Mono-benzhydryl malonate **12d**. The acid **12d** was prepared (as described for **12a**) from 1.35 g (5.6 mmol, ~4 equiv) base in 20 ml THF and 620 mg (1.4 mmol) of **10d** in 10 ml THF. After work-up (25 ml 0.5N HCl, 12.5 mmol, ~8 equiv), 695 mg (~100%) crude **12d** were obtained: IR 1775 (broad), 1750 (broad) cm^{-1}; ^{1}H NMR δ 3.63–3.86 (m, 2), 5.11 and 5.20 (two s, 1), 5.83 (broad s, 2), 6.86 (s, 1), ~7.26 (br s, 15).

Mono-β-(trimethylsilyl)ethyl malonate **12e**. The acid **12e** was prepared (as described for **12a**) from 7 g (0.029 mol, ~4 equiv) base in 60 ml THF and 2.4 g (0.0064 mol) of **10e** in 25 ml THF. After work-up (120 ml 0.5 N HCl, 0.06 mol, ~9 equiv), 2.22 g (82%) crude **12e** were obtained: IR 1773, 1740 (broad) cm^{-1}; ^{1}H NMR δ ~0.03 (s, 9), 0.8–1.2 (m, 2), 3.91 (br s, 2), 4.03–4.56 (m, 2), 5.05 and 5.10 (two s, 1), 6.02 (br s, 2), 7.33 (s, 5).

Mono-allyl malonate **12f**. The acid **12f** was prepared (as described for **12a**) from 2.1 g (8.7 mmol, ~4 equiv) base in 20 ml THF and 632 mg (2 mmol) of **10f** in 10 ml THF. After work-up (40 ml 0.5N HCl, 20 mmol, 10 equiv), 690 mg (96%) crude **12f** were obtained: IR 1780 (broad), 1753 (broad) cm^{-1}; ^{1}H NMR δ 3.93 (br s, 2), 4.60 and 4.73 (two br d, 2), 5.10–5.56 (m, 3), ~5.80 (m, 1), 6.03 (br s, 2), 7.30 (s, 5).

Deuteration experiments

Di-deuterated **10b**. A soln of **11b** was prepared (according to the procedure described in **12b**) from 332 mg (1 mmol) of **10b** in 5 ml THF and 964 mg (4 mmol) lithium hexamethyldisilazide in 10 ml THF. After 30 min at −60°, 2.8 ml of 3.6N D_2SO_4 in D_2O (~10 equiv) were added rapidly. The cooling-bath was removed and, after 15 min (vigorous stirring), CH_2Cl_2 (~20 ml) was added and the mixture washed with cold water. Drying ($CaCl_2$) and evaporation of the solvent left 330 mg (99%) of **10b**-d_2 as a solid: ^{1}H NMR δ 1.46 (s, 9), 3.56–4.03 (m, 2), 5.83 (d, 1, J = 4 Hz), 6.10 (br d, 1, J = 4 Hz), 7.33 (s, 5); Mass (DCI) 335 ($M^+ + 1$).

Di-deuterated **10h**. The dianion **11h** was similarly prepared from 50 mg (0.12 mmol) of **10h** and 120 mg (0.5 mmol) base in 10 ml THF. Quenching with 0.6 ml 2N D_2SO_4 in D_2O and work-up gave 46 mg (92%) of **10h**-d_2 as a solid: ^{1}H NMR δ ~3.9 (m, 2) 5.28 (s, 2), 5.78 (d, 1, J = 4 Hz), 6.11 (br d, 1, J = 4 Hz), 7.33 (s, 5), 7.53 (d, 2, J = 9 Hz), 8.27 (d, 2, J = 9 Hz).

Di-deuterated **10i**. The dianion **11i** was prepared in the same way from 100 mg (0.25 mmol) of **10i** and 250 mg (1.04 mmol) base in 20 ml THF. Quenching with 0.7 ml 3.6N D_2SO_4 in D_2O and work-up yielded 94 mg (93%) of **10i**-d_2 as a solid: ^{1}H NMR δ ~3.91 (m, 2), 4.78 (s, 2), 5.77 (d, 1, J = 4 Hz), 6.05 (br d, 1, J = 4 Hz), 7.28 (s, 5).

2 - [3 - *Benzyl* - 6 - *oxo* - 2 - *thia* - 4,7 - *diaza* - (1R,5R) - *bicyclo* - [3.2.0] - *hept* - 3 - *en* - 7 - *yl*] - *t* - *butyl and alkyl malonates* **14**

p-*Nitrobenzyl malonate* **14h**. To a mixture of crude **12b** (574 mg, 1.52 mmol), *p*-nitrobenzyl alcohol (215 mg, 1.40 mmol) and dimethylaminopyridine (10–15 mg) in CH_2Cl_2 (20 ml), a soln of N,N-diisopropylcarbodiimide (0.235 ml, 1.5 mmol) in CH_2Cl_2 (5 ml) was added dropwise at 0°. The mixture was stirred for 1 hr at 0° and 2 hr at room temp, then filtered, washed with cold 0.5 N HCl (~25 ml), dried ($CaCl_2$) and evaporated. Chromatography (silica gel, benzene–EtOAc 4:1) yielded 660 mg (92%) of **14h** as a pale yellow syrup (mixture of two diastereoisomers): $[\alpha]_D$ (±0.5) − 105.3° (c = 0.318%); IR 1778, 1750 (broad) cm^{-1}; ^{1}H NMR δ 1.40 and 1.45 (two s, 9), 3.81 and 3.86 (two br s, 2), 5.03 and 5.06 (two s, 1), 5.15 and 5.28 (two sharp ABq, 2), 5.97 (sharp ABq, 2), 7.26 (s, 5), 7.43 and 7.46 (two d, 2, J = 9 Hz), 8.18 (d, 2, J = 9 Hz). (Found: C, 58.48; H, 5.05; N, 8.04. Calc for $C_{25}H_{25}O_7N_3S$ (511.47): C, 58.70; H, 4.93; N, 8.22%.)

β-Trichloroethyl malonate **14i**. **14i** was prepared in the same way from 1.5 g (3.98 mmol) crude **12b**, 0.35 ml (3.7 mmol) β-trichloroethanol and 0.618 ml (3.96 mmol) N,N-diisopropylcarbodiimide (DMAP catalysis) in 50 ml CH_2Cl_2. Chromatography (silica gel, benzene–EtOAc 9:1) yielded 1.64 g (87%) of **14i** as an oil (mixture of two diastereoisomers) which crystallised slowly: m.p. 82–85°; $[\alpha]_D$ (±0.5) − 96° (c = 0.505%); IR 1780, 1770, 1745 cm^{-1}; ^{1}H NMR δ 1.45 and 1.50 (two s, 9), 3.90 (br s, 2), 4.66 and 4.83 (two br s, 2), 5.15 (s, 1), 6.01 (br s, 2), 7.30 (s, 5). (Found: C, 47.49; H, 4.32. Calc for $C_{20}H_{21}O_5N_2SCl_3$ (507.7): C, 47.30; H, 4.17%.)

Selective cleavage of the t-butyl ester in **14**

Mono-p-nitrobenzyl malonate **12h**. To a soln of 800 mg (1.56 mmol) of **14h** in 10 ml CH_2Cl_2, stirred at 0°, a cold (−20°) soln of HBr in CH_2Cl_2 (0.9N, 20 ml, 18 mmol) was added rapidly. Stirring was continued for 2 hr at 0° and 1 hr at 15° (formation of an insoluble oil). After evaporation under reduced pressure (T° ≤ 20°), the residue was triturated with ice-cold water (50 ml) and a 4:1 mixture of CH_2Cl_2 and EtOAc. The organic layer was separated and the water extracted twice with EtOAc (~25 ml). Drying ($CaCl_2$) and concentration (T° ≤ 20°) yielded 696 mg (98%) crude **12h** as a gum: IR 1780, 1755 (broad) cm^{-1}; ^{1}H NMR δ 3.80 (br s, 2), ~5.15 (sharp m, 2 + 1), 5.93 (br, s, 2), 7.20 (s, 5), 7.40 (br d, 2, J = 9 Hz), 8.10 (d, 2, J = 9 Hz).

Mono-β-trichloroethyl malonate **12i**. The acid **12i** was prepared in the same way from 980 mg (1.93 mmol) of **14i** in 20 ml CH_2Cl_2 and 25 ml 1N HBr in CH_2Cl_2 (25 mmol). After work-up, 890 mg (~100%) crude **12i** (gum) were obtained: IR 1780 (broad) cm^{-1}; ^{1}H NMR ($CDCl_3$ + 5% EtOAc) δ 3.91 (br s, 2), 4.71 and 4.83 (two br s, 2), 5.26 (br s, 1), 6.02 (br s, 2), 7.30 (s, 5).

2 - *Oxo* - *bisnorpenicillin G* - 3 - *carboxylates* **7**

Methyl ester **7a**. An aqueous soln of HCl (1.2 N, 6 ml, 7.2 mmol) was added dropwise, at 10° and with stirring, to a soln of 1.6 g (4.79 mmol) of **12a** in 25 ml MeOH. After 30 min at room temp, the soln was concentrated (T° ≤ 20°) to a volume of ~10 ml, then treated with cold water (~30 ml). Extraction with CH_2Cl_2 (30 ml) and EtOAc (30 ml), drying ($CaCl_2$) and evaporation (T° ≤ 20°) yielded 1.6 g (95%) crude **8a** (amorphous solid): IR 1770, 1745, 1725, 1680–1650 cm^{-1}; ^{1}H NMR δ ~2.23 (m, 1, SH), 3.65 (br s, 2), 3.75 (s, 3), 5.01 (br s, 1), ~5.40 (m, 2), ~7.26 (s + m, 6), ~8.93 (m, 1, COOH). To a suspension of **8a** (1.6 g, 4.5 mmol) in 50 ml CH_2Cl_2, 0.702 ml (4.5 mmol) N,N-diisopropylcarbodiimide in 5 ml CH_2Cl_2 was added dropwise, at −60° with stirring. The soln was allowed to reach 20° in about 5 hr. After evaporation of the solvent, the urea was precipitated by addition of EtOAc (~30 ml, 0°). Filtration, concentration (1.53 g) and chromatography (silica gel, benzene–EtOAc 4:1) gave 550 mg (36%) of **7a** (recrystallisation from ether): m.p. 148.5°; $[\alpha]_D$ (±0.4) + 308.2° (c = 0.28%); IR 3400, 1800, 1755, 1727, 1690 cm^{-1}; ^{1}H NMR δ 3.60 (s, 2), 3.82 (s, 3), 4.91 (s, 1), 5.76–6.00 (m, 2), ~6.33 (m, NH), 7.30 (s, 5); D_2O exchange (100 MHz) 3.60 (s, 2), 3.82 (s, 3), 5.82 (s, 2), 7.13–7.40 (m, 5); Mass (EI) 334 (M^+, 43%), 274 (M-COS, 15%), 160 (M–GCH=C=O, 100%), 175 (50%). (Found: C, 54.18; H, 4.24; N, 8.26. Calc for $C_{15}H_{14}O_5N_2S$ (334.28): C, 53.89; H, 4.22; N, 8.38%.)

t-Butyl ester **7b**. 1.34 g (3.56 mmol) of **12b** in 6 ml EtOAc and 40 ml MeOH was hydrolysed (procedure for **8a**) with 6 ml 1.2 N HCl (7.2 mmol) to give 1.45 g (~100%) crude **8b** (amorphous solid): IR 1775, 1745 (broad), 1690–1650 cm^{-1}; ^{1}H NMR δ 1.48 (br s, 9), ~2.13 (m, 1, SH), 3.63 (br s, 2), 4.81 and 4.91 (two s, 1), ~5.36 (m, 2), 7.23 (s, 5), ~7.50 (m, 1, NH), ~9.2 (m, 1, COOH).

Compound **8b** (1.45 g, 3.56 mmol) in 40 ml CH_2Cl_2 was treated (procedure for **7a**) with N,N-diisopropylcarbodiimide (453 mg, 3.6 mmol) in 5 ml CH_2Cl_2. Chromatography (silica gel, benzene–EtOAc 4:1) yielded 870 mg (65%) of **7b** (recrystallisation from CH_2Cl_2–ether): m.p.

120–123°; $[\alpha]_D$ (± 0.5) + 276.4° (c = 0.53%); IR 3400, 1802, 1745, 1730, 1687 cm^{-1}; ^1H NMR δ 1.5 (s, 9), 3.63 (s, 2), 4.82 (s, 1), 5.83–6.05 (m, 2), ~6.35 (m, NH), 7.33 (sharp m, 5); D_2O exchange (100 MHz) 1.5 (s, 9), 3.63 (s, 2), ~5.83 (sharp ABq, 2, J = 4 Hz), 7.15–7.40 (m, 5); ^{13}C NMR (decoupl) ppm 27.71, 42.68, 62.34, 66.87, 68.03, 84.73, 127.45, 128.89, 129.23, 133.92, 162.25, 170.77, 171.32, 199.36; UV λ_m 243 nm (ϵ = 2889); Mass (EI) 376 (M^+, 63%), 316 (M-COS, 2%), 202 (M–GCH=C=O, 49%), 175 (53%). (Found: C, 57.80; H, 5.41; N, 7.40. Calc for $C_{18}H_{20}O_5N_2S$ (376.36): C, 57.44; H, 5.35; N, 7.44%.)

Benzyl ester **7c**. 1.55 g (3.7 mmol) of **12c** in 10 ml CH_2Cl_2 and 40 ml MeOH was hydrolysed (procedure for **8a**) with 9 ml 1 N HCl (9 mmol) to give 1.5 g (94%) crude **8c** (amorphous solid): IR 1760, 1740, 1680 – 1640 cm^{-1}; ^1H NMR δ ~ 2.36 (m, 1, SH), ~3.60 (sharp m, 2), 4.93–5.53 (m, ~5), ~7.26 (m, 11), ~8.3 (m, 1, COOH).

Compound **8c** (1.5 g, 3.5 mmol) in 50 ml CH_2Cl_2 was treated (procedure for **7a**) with N,N-diisopropylcarbodiimide (440 mg, 3.5 mmol) in 2 ml CH_2Cl_2. Chromatography (silica gel, benzene–EtOAc 4:1) yielded 470 mg (31%) of **7c** (recrystallisation from CH_2Cl_2–ether): m.p. 107°; $[\alpha]_D$ (± 0.5) + 265.4° (c = 0.59%); IR 3400, 1802, 1752, 1728, 1690 cm^{-1}; ^1H NMR δ 3.61 (s, 2), 4.95 (s, 1), 5.23 (s, 2), 5.76–6.06 (m, 2), ~6.4 (m, NH), ~7.30 (br s, 10); Mass (EI) 410 (M^+, 31%), 350 (M-COS, 9%), 236 (M–GCH–C=O, 58%), 175 (62%). (Found: C, 61.74; H, 4.53; N, 6.87. Calc for $C_{21}H_{18}O_5N_2S$ (410.37): C, 61.46; H, 4.42; N, 6.83%.)

Benzhydryl ester **7d**. 695 mg (1.4 mmol) of **12d** in 10 ml CH_2Cl_2 and 15 ml MeOH were hydrolysed with 5.5 ml 35% $HClO_4$ (procedure for **8a**) to give 635 mg (90%) crude **8d** (amorphous solid): IR 1770, 1745 (br), 1680–1650 cm^{-1}; ^1H NMR δ ~ 2.00 (m, 1, SH), 3.56 (br s, 2), 5.03 and 5.08 (two s, 1), ~5.35 (m, 2), ~6 (m, 1, NH), 6.90 (s, 1), ~7.30 (m, ~15), ~9.16 (m, 1, COOH).

Compound **8d** (635 mg, 1.35 mmol) in 20 ml CH_2Cl_2 was treated (procedure for **7a**) with N,N-diisopropylcarbodiimide (170 mg, 1.35 mmol) in 5 ml CH_2Cl_2. Chromatography (silica gel, benzene–EtOAc 4:1) furnished 165 mg (25%) of **7d** (recrystallisation from ether): m.p. 115–118°; $[\alpha]_D$ (± 0.6) + 230.7° (c = 0.335%); IR 3400, 1801, 1750, 1728, 1687 cm^{-1}; ^1H NMR δ 3.55 (s, 2), 4.98 (s, 1), 5.70–5.90 (m, 2), ~5.95 (m, NH), 6.87 (s, 1), ~7.30 (m, 15); Mass (EI) 442 (M-CO_2, 10%), 425 (M-COS, 20%), 409 (M-C_6H_5, 18%), 268 (M–CO_2–GCH=C=O, 48%), 175 (27%), 167 (80%). (Found, C, 66.78; H, 4.57; N, 5.66. Calc for $C_{27}H_{22}O_5N_2S$ (486.46): C, 66.66; H, 4.56; N, 5.76%.)

β-(Trimethylsilyl)-ethyl ester **7e**. 2.2 g (5.23 mmol) of **12e** in 50 ml MeOH were hydrolysed with 15 ml 35% $HClO_4$ (procedure for **8a**) to give 2.21 g (97%) crude **8e** (amorphous solid): IR 1770, 1740 (broad), 1680–1640 cm^{-1}; ^1H NMR δ ~ 0.03 (s, 9), 0.83–1.33 (m, 2), ~2.13 (m, 1, SH), 3.66 (br s, 2), 4.06–4.53 (m, 2), 4.93 and 5.00 (two s, 1), ~5.40 (m, 2), ~7.30 (m, ~6), ~8.06 (m, COOH).

Compound **8e** (2.2 g, 5 mmol) in 50 ml CH_2Cl_2 was treated (procedure for **7a**) with N,N-diisopropylcarbodiimide (630 mg, 5 mmol) in 10 ml CH_2Cl_2. Chromatography (silica gel, benzene–EtOAc 4:1) yielded 840 mg (40%) of **7e** (recrystallisation from ether): m.p. 109–110°; $[\alpha]_D$ (± 0.6) + 241.7° (c = 0.295%); IR 3400, 1800, 1735 (broad), 1690 cm^{-1}; ^1H NMR δ ~ 0.03 (s, 9), 0.83–1.23 (m, 2), 3.60 (s, 2), 4.13–4.50 (m, 2), 4.86 (s, 1), 5.73–6.00 (m, 2), ~6.56 (m, NH), ~7.30 (br s, 5); Mass (EI) 420 (M^+, 50%), 360 (M-COS, 5%), 246 (M–GCH=C=O, 12%), 175 (50%). (Found: C, 54.43; H, 5.61; N, 6.55. Calc for $C_{19}H_{24}O_5N_2$ SSi (420.55): C, 54.26; H, 5.75; N, 6.66%.)

Allyl ester **7f**. 687 mg (1.91 mmol) of **12f** in 12 ml MeOH were hydrolysed with 4 ml 1 N HCl (4 mmol) (procedure for **8a**) to give 713 mg (99%) crude **8f** (amorphous solid): IR 1775, 1750 (broad), 1685–1650 cm^{-1}; ^1H NMR δ ~ 2.20 (m, SH), 3.66 (br s, 2), 4.73 (br d, 2), 5.00–5.66 (m, ~6), 7.30 (m, ~6).

Compound **8f** (713 mg, 1.9 mmol) in 20 ml CH_2Cl_2 was treated (procedure for **7a**) with N,N-diisopropylcarbodiimide (0.312 ml, 2 mmol) in 5 ml CH_2Cl_2. Chromatography (silica gel, CH_2Cl_2–EtOAc 9:1) afforded 340 mg (49%) of **7f** (recrystallisation from ether–hexane): m.p. 102–103°; $[\alpha]_D$ (± 0.6) + 260° (c = 0.12%); IR 3420, 1804, 1760, 1735, 1690 cm^{-1}; ^1H NMR δ 3.65 (s, 2), 4.73 (br d, 2, J = 5 Hz), 4.96 (s, 1), 5.16–5.60 (m, 2), 5.66–6.10 (m, 2 + 1), 6.43 (m, NH), ~7.33 (br s, 5). (Found: C, 56.61; H, 4.48; N, 7.90. Calc for $C_{17}H_{16}O_5N_2S$ (360.31): C, 56.67; H, 4.47; N, 7.78%.)

p-Nitrobenzyl ester **7h**. 690 mg (1.51 mmol) of **12h** in 20 ml MeOH and 2 ml EtOAc were hydrolysed with 3.5 ml 1.2 N HCl (4.2 mmol) (procedure for **8a**) to give 720 mg (100%) crude **8h** (amorphous solid): IR 1780, 1760 (broad), 1660 (broad) cm^{-1}; ^1H NMR (CD_3COCD_3) δ ~ 3.65 (br s, 2), 5.18–5.68 (m + s, 5), ~7.33 (m, 5), 7.73 (d, 2), 8.24 (d, 2).

Compound **8h** (720 mg, 1.51 mmol) in 45 ml CH_2Cl_2 was treated (procedure for **7a**) with N,N-diisopropylcarbodiimide (0.250 ml, 1.6 mmol) in 5 ml CH_2Cl_2. Chromatography (silica gel, CH_2Cl_2–EtOAc 4:1) yielded 400 mg impure oily product. Addition of dry ether gave 152 mg (22%) of **7h** (white solid): m.p. 170–172°; $[\alpha]_D$ (± 0.7) + 255.9° (c = 0.22%); IR (KBr) 3330, 1798, 1730 (broad), 1655 cm^{-1}; ^1H NMR ($CDCl_3$ + 20% DMSO-d_6) δ 3.61 (s, 2), 5.11 (s, 1), 5.38 (br s, 2), 5.76–6.00 (m, 2), 7.30 (s, 5), 7.56 (d, 2, J = 9 Hz), 8.26 (d, 2, J = 9 Hz), ~8.86 (NH); Mass (EI) 411 (M-CO_2), 395 (M-COS), 281 (M–GCH=C=O), 175; UV λ_m 260 nm (ϵ = 10204). (Found: C, 55.18; H, 3.73; N, 9.04. Calc for $C_{21}H_{17}O_7N_3S$ (455.37): C, 55.39; H, 3.76; N, 9.23%.)

β-(Trichloro)-ethyl ester **7i**. 100 mg (0.22 mmol) crude **12i** in 3 ml isopropanol and 0.5 ml EtOAc were hydrolysed (procedure for **8a**) with 0.5 ml 1.2 N HCl (0.06 mmol) to give 90 mg (86%) crude **8i** (IR 1770 (broad), 1670 (broad) cm^{-1}) which was dissolved in 10 ml CH_2Cl_2 and treated (procedure for **7a**) with N,N-diisopropylcarbodiimide (0.03 ml, 0.19 mmol). Chromatography (silica gel, benzene–EtOAc 4:1) gave ~9 mg (~10%) impure **7i** (IR 3430, 1807, 1778, 1735, 1690 cm^{-1}).

6 - *β - Phenylacetamido - 2 - oxo - penam* **16**

In 500 ml MeOH, 21 g (0.076 mol) of **10g** were hydrolysed with 125 ml 1.2 N HCl (0.15 mol), as described for **8a**, to give, after work-up and precipitation from dry ether, 17.6 g (79%) of **15** as an amorphous solid: IR (KBr) 3700–2200, 3275, 2540, 1760, 1715, 1660, 1540 cm^{-1}; ^1H NMR (CD_3OD) δ 3.62 (s, 2), 3.87 (br d, 1, J ≃ 17 Hz), 4.15 (d, 1, J ≃ 17 Hz), 4.77 (s, 3), 5.18 (br d, 1, J ≃ 4.5 Hz), 5.32 (br d, 1, J ≃ 4.5 Hz), 7.19 (s, 5). To a suspension of **15** (17.6 g, 0.06 mol) in dry CH_2Cl_2 (2.5 l.), cooled at −30°, a soln of N,N-diisopropylcarbodiimide (9.4 ml, 0.06 mol) in CH_2Cl_2 (250 ml) was added at such a rate as to maintain the temp below −25°. After complete addition, the soln was allowed to warm up to 20° during ~4 hr. Concentration to ~200 ml allowed the filtration of most of the urea. Chromatography (silica gel, CH_2Cl_2–EtOAc 7:1) and crystallisation from $CHCl_3$–ether, yielded pure **16** (13.4 g, 81%): m.p. 135° $[\alpha]_D$ (± 0.9) + 277.1° (c = 0.345%); IR ($CDCl_3$) 3425, 1800, 1735, 1690 cm^{-1}; ^1H NMR δ 3.36 (d × d × d, 1, J = 16.5, 1.25 and 1 Hz), 3.54 (s, 2), 4.16 (d, 1, J = 16.5 Hz), 5.60 (d × d, J = 4 and 1 Hz), 5.76 (d × d × d, 1, J = 8, 4 and 1.25 Hz), 6.82 (d, 1, J = 8 Hz), 7.15–7.40 (m, 5); ^{13}C NMR (decoupl) ppm 42.92, 53.19, 62.35, 68.14, 127.57, 129.01, 129.31, 133.85, 171.16, 172.05, 203.60. (Found: C, 56.55; H, 4.40; N, 10.15. Calc for $C_{13}H_{12}O_3N_2S$ (276.32): C, 56.51; H, 4.38; N, 10.14%.)

2 - *Oxo - bisnorpenicillin G* - 3 - *carboxylic acid* **7g**

Method A: hydrogenolysis of **7h**. Compound **7h** (130 mg, 0.28 mmol) in EtOAc (15 ml) was hydrogenolysed (T° = 20°, p = 40 psi) in the presence of 10% Pd-C (100 mg), during 2 hr. Fresh catalyst was added (100 mg) and hydrogenolysis continued for a further 2 hr. Filtration, washing with EtOAc (2 × 10 ml), evaporation and precipitation from dry ether

(−20°), furnished crude **7g** (52 mg, 57%) as an amorphous white solid. The acid is unstable (neat or in soln) and must be stored at low temp (dry-ice): IR ($CDCl_3$) 3700–2200, 3425, 1790, 1740–1710 (broad), 1680-(KBr) 3700–2200, 3300, 1785, 1730–1700 (broad), 1660 cm^{-1}; ^1H NMR δ 3.63 (s, 2), 4.85 (s, 1), ~5.80 (m, 2), ~6.80 (NH), 7.24 (s, 5), ~8.3 (COOH).

Method B: Carbonatation of **16**. To a soln of lithium hexamethyldisilazide (1.928 g, 8 mmol) in dry THF (10 ml), stirred at −78° under argon, a cold (−78°) soln of **16** (0.552 g, 2 mmol) in THF (10 ml) was added within 10 min. After another 10 min stirring, the soln was cooled in liquid air and an excess of dry CO_2 gas was solidified in the reaction flask. Then the soln was kept at −60° until evolution of CO_2 ceased (1–2 hr), and poured into a vigorously stirred cold (−5°) mixture of 0.4 N HCl (50 ml) and $CHCl_3$–EtOAc 2:1 (50 ml). The organic layer was separated and the aqueous layer extracted with cold $CHCl_3$–EtOAc 2:1 (2 × 15 ml). The combined organic phases were washed with cold water (2 × 25 ml), dried ($MgSO_4$, 0°) and concentrated under reduced pressure (−20°–0°) to give crude **7g** (0.43 g, 67%) as an amorphous solid.

Esterification of acid **7g**

Methyl ester **7a**. **7g** was prepared, as previously described, from 241 mg (1 mmol) of base in 2.5 ml THF and 69 mg (0.25 mmol) of **16** in 2.5 ml THF. The crude soln obtained after work-up was concentrated to a volume of ~2 ml and directly treated with a soln of CH_2N_2 in ether (~2 equiv) at −20°. The mixture was allowed to attain room temp within 1 hr. Concentration and chromatography (silica gel, CH_2Cl_2–EtOAc 4:1) afforded 38 mg (46%) of **7a** identical with an authentic sample.

p-*Nitrobenzyl ester* **7h**. A soln of **7g** (prepared as before from 0.25 mmol of **16**) in $CHCl_3$ (2 ml) was treated at −20° with *p*-nitrophenyl-diazomethane (41 mg, 0.25 mmol, in 2 ml CH_2Cl_2). The mixture was allowed to warm up slowly to room temp. One drop of AcOH was added, and the solvent removed. Chromatography of the residue (silica gel, CH_2Cl_2–EtOAc 4:1) and precipitation from $CHCl_3$–ether yielded **7h** (34 mg, 30%) identical with an authentic sample.

(6R) - *Phenylacetamido* - 2 - *methoxy* - (5R) - *penem* - 3 - *carboxylates* **17**

t-Butyl ester **17b**. An excess CH_2N_2 (20 ml of ~0.66 M ethereal soln, 13.2 mmol) was added to **7b** (500 mg, 1.32 mmol) in CH_2Cl_2 (10 ml). After 24 hr at room temp, the soln was concentrated and chromatographed (silica gel, CH_2Cl_2–AcOEt 4:1) to give **17b** (283 mg, 55%—precipitation from ether–petroleum ether, 210 mg, 40%): m.p. 53.5–55.5° (dec); $[\alpha]_D$ (± 5) + 162° (c = 0.325%); IR 3405, 1798, 1690 (broad) cm^{-1}; ^1H NMR (XL 200) δ 1.47 (s, 9), 3.63 (s, 2), 3.96 (s, 3), 5.70 (d × d, 1, J = 8 and 4 Hz), 5.79 (d, 1, J = 4 Hz), 6.61 (br d, J = 8 Hz), 7.24–7.40 (m, 5); ^{13}C NMR (decoupl) ppm 28.06, 42.79, 62.29, 63.20, 67.88, 81.36, 106.94, 127.37, 128.83, 129.20, 133.82, 158.75, 171.11, 171.53, 173.53; Mass (EI) 390 (M^+), 334, 290, 257 (M-G), 215 (M–GCH=C=O), 175; UV λ_m 268 nm (ϵ = 4822), 304 nm (ϵ = 5166). (Found: C, 58.51; H, 5.74; N, 7.20. Calc for $C_{19}H_{22}O_5N_2S$ (390.38): C, 58.45; H, 5.68; N, 7.18%.)

Allyl ester **17f**. **7f** (150 mg, 0.41 mmol) in CH_2Cl_2 (5 ml) was treated with excess CH_2N_2 (5 ml ~0.66 M ethereal soln, 3.3 mmol) during 24 hr at room temp. Concentration under reduced pressure, chromatography (silica gel, CH_2Cl_2–EtOAc 4:1) and precipitation from ether–petroleum ether, furnished **17f** (56 mg, 36%): m.p. 118–121° (dec); $[\alpha]_D$ (± 5) + 220° (c = 0.18%); IR 3410, 1805, 1700 (broad band) cm^{-1}-(KBr) 3300, 1793, 1708, 1650 cm^{-1}; ^1H NMR δ 3.65 (s, 2), 4.00 (s, 3), ~4.70 (br d, 2, J = 5 Hz), 5.10–6.00 (m, 5), ~6.63 (m, 1), ~7.33 (s, 5). (Found: C, 57.36; H, 4.83. Calc for $C_{18}H_{18}O_5N_2S$ (374.34); C, 57.75; H, 4.85%.)

p-*Nitrobenzyl ester* **17h**. **7h** (200 mg, 0.44 mmol) in CH_2Cl_2 (5 ml) was treated with excess CH_2N_2 (5 ml of ~0.66 M ethereal soln, 3.3 mmol). After 1 hr at room temp, the soln was concentrated under reduced pressure. Chromatography (silica gel, CH_2Cl_2–EtOAc 4:1) and precipitation from ether yielded **17h** (85 mg, 41%): m.p. 154.5–156.5° (dec); $[\alpha]_D$ (± 5) + 154° (c = 0.19%); IR 3415, 1803, ~1700 (broad band) cm^{-1}-(KBr) 3300, 1793, 1693, 1650 cm^{-1}; ^1H NMR δ 3.62 (s, 2), 4.00 (s, 3), 5.26 (br s, 2), 5.66–5.93 (m, 2), 7.30 (m, 6), 7.50 (d, 2, J = 9 Hz), 8.16 (d, 2, J = 9 Hz); UV λ_m 279 nm (ϵ = 13291), 310 nm (ϵ = 9382). (Found: C, 56.02; H, 4.13; N, 8.87. Calc for $C_{22}H_{19}O_7N_3S$ (469.40): C, 56.29; H, 4.08; N, 8.95%.)

(6R) - *Phenylacetamido* - 2 - *benzoyloxy* - (5R) - *penem* - 3 - *carboxylates* **18**

t-Butyl ester **18b**. To a soln of **7b** (228 mg, 0.6 mmol) in CH_2Cl_2 (5 ml), stirred at −60°, PhCOCl (70 μl, 0.6 mmol) and NEt_3 (84 μl, 0.6 mmol) were added with a syringe. The mixture was allowed to warm up slowly at room temp and stirring was continued for 2 hr. Washing with cold water, drying ($CaCl_2$) and concentration under reduced pressure (T° ≤ 20°) yielded crude **18b** (290 mg, ~100%). Precipitation from CH_2Cl_2–ether (0°) afforded ~pure product (207 mg, 72%): m.p. 114.4–115.5° (dec); $[\alpha]_D$ (± 2) + 143° (c = 2.05%); IR 3410, 1804, 1752, ~1700 (broad) cm^{-1}; ^1H NMR (XL 200) δ 1.42 (s, 9), 3.66 (s, 2), 5.80–5.98 (m, 2-after irradiation on NH, ABq, J = 4 Hz), 6.71 (br d, 1, NH), 7.26–7.73 (m, 8), 8.13–8.23 (m, 2); ^{13}C NMR (decoupl) ppm 27.97, 42.86, 62.83, 68.42, 82.57, 116.42, 126.92, 127.44, 128.73, 128.91, 129.26, 130.67, 133.70, 134.69, 157.48, 157.60, 161.34, 171.10, 173.66; Mass (DCI) 306, (M + 1-GCH=C=O), 250, 176, 105; UV λ_m 240 nm (ϵ = 19555), 313 nm (ϵ = 5777). (Found: C, 61.86; H, 5.16; N, 6.08. Calc for $C_{25}H_{24}O_6N_2S$ (480.46): C, 62.49; H, 5.04; N, 5.83%.)

p-*Nitrobenzyl ester* **18h**. **7h** (68 mg, 0.15 mmol) in CH_2Cl_2 (3 ml) was treated with PhCOCl (17 μl, 0.15 mmol) and NEt_3 (21 μl, 0.15 mmol), as described for **18b**. The crude product (80 mg, 96%) was precipitated from CH_2Cl_2–ether (0°) to give ~pure **18h** (58 mg, 69%): m.p. 150–153.5° (dec); $[\alpha]_D$ (± 2) + 124° (c = 0.51%); IR (KBr) 3350, 1802, 1768, 1720–1680 (broad) cm^{-1}; ^1H NMR δ 3.66 (s, 2), ~5.30 (br s, 2), 5.77–6.05 (m, 2), 6.8 (m, NH), 7.26–7.76 (m, ~10), 7.96–8.26 (m, 4). (Found: C, 59.55; H, 3.79; N, 7.35. Calc for $C_{28}H_{21}O_8N_3S$ (559.47): C, 60.11; H, 3.78; N, 7.51%.)

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