Pergamon

Tetrahedron 56 (2000) 6053–6074

TETRAHEDRON

Syntheses of (6*S*)-Cephalosporins from 6-Aminopenicillanic Acid

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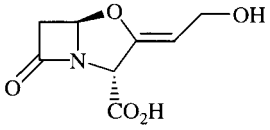
Received 20 April 2000; accepted 1 June 2000

Abstract—Two practical routes to (6*S*,7*S*)-cephalosporins from 6-aminopenicillanic acid (6-APA) are described. In the first, 6-APA was converted to (2*S*,4*S*,5*S*,6*S*)-penicillin sulfoxide **49**, which underwent Morin ring expansion to a protected (6*S*,7*S*)-cephem **50**. In the second, ester **15** was converted to (2*S*,4*S*,5*S*,6*R*)-penicillin sulfoxide **58**, which was then transformed into (6*S*,7*R*)-cephem **59**. Different methods for the epimerisation of the C-7 position of cephem **59** were examined.

Despite the continued threat of resistance, β-lactams remain the most important antibacterials in current clinical use. In addition to their exploitation as antibacterials and β-lactamase inhibitors, β-lactams are increasingly being used as inhibitors of other medicinally important targets, as exemplified by the pioneering Merck–Sharp & Dohme work on the inhibition of elastase.[1]

Penicillins and cephalosporins are biosynthesised with the (2*S*,5*R*,6*R*)- and (6*R*,7*R*)-stereochemistry, respectively,[2] which appear to be requisite for antibacterial activity mediated via inhibition of penicillin binding proteins.[3] It is of interest that clavulanic acid **1**, a potent β-lactamase inhibitor, possesses the same structural feature—the (*R*)-configuration at the carbon ring juncture. However, in the case of clavamycins, as exemplified by 2-hydroxy-methyl-clavam **2**, the ring juncture is (*S*)-configured.[4] Compounds of this family, although inactive as antibacterials, exhibit antifungal activity. Moreover, Pfaendler et al.[5] have recently reported the synthesis and activities of the 3-(*t*-butyl)-oxypenems **3** and *ent*-**3**. Interestingly, both enantiomers **3** and *ent*-**3** were apparently active as antibacterials, although it is unclear whether or not epimerisation of **3** to its (5*R*)-epimer **4** occurs under the assay conditions.



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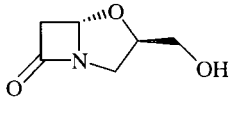

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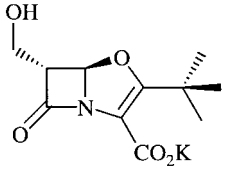

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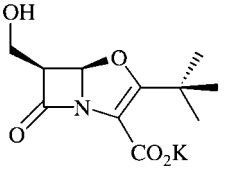

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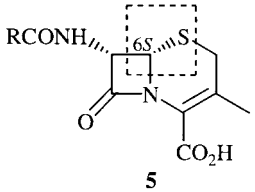
Woodward et al. were the first to report the total synthesis of a cephalosporin.[6] More recently, Oberhauser and Meduna have reported the synthesis of (±)-7-aminocephalosporanic acid and (±)-7-*epi*-aminocephalosporanic acid.[7] At the onset of our work, it seemed desirable to develop a general methodology for the synthesis of (6*S*)-cephems, with a view to investigate biological and chemical activities of such configured compounds (e.g. **5** and **6**).



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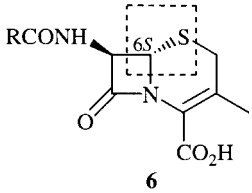

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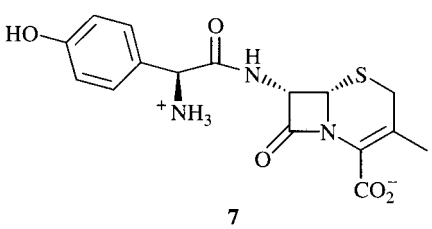

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Keywords: cephalosporins; penicillins; rearrangements; epimerisation.

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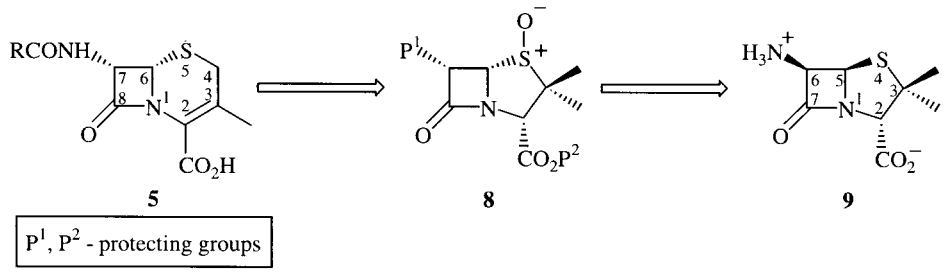
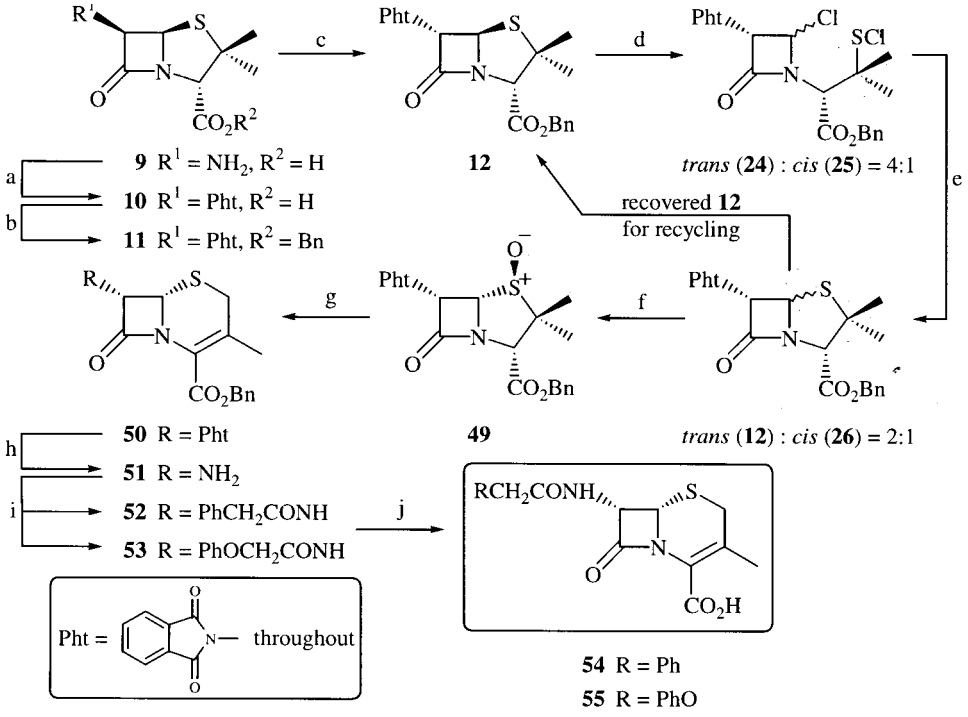


Scheme 1.



Scheme 2. *Reagents and conditions:* (a) $PhtCO_2Et$, Na_2CO_3, H_2O, rt, 2 h; 49%; (b) BnBr, Et_3N, DMF, rt, 6 h; 71%; (c) DBU (cat.), CH_2Cl_2, rt, 90 min; 98% or NaH (1 equiv.), THF, rt, 17 h; 85%; (d) Cl_2 (1 equiv.), CH_2Cl_2, CCl_4, rt, 30 min; (e) $SnCl_2$ (1.06 equiv.), THF, rt, 2 h; (f) O_3, Me_2CO, 0°C then chromatographic separation; 25% over three steps (64% if based on recovered **12**); (g) *p*TSA (cat.), DMF, 100°C, 90 min; 50%; (h) $N_2H_4{\cdot}H_2O$, DMF, −78°C→rt, 30 min; 47%; (i) RCO_2H, DCC, THF, rt, 2 h; 85% (R=$PhCH_2$) and 91% (R=$PhOCH_2$); (j) $AlCl_3$, PhOMe, CH_2Cl_2, $MeNO_2$, 0°C→rt, 6–8 h; 86% (R=$PhCH_2$) and 94% (R=$PhOCH_2$).

In this paper we report syntheses of (6*S*,7*R*)- and (6*S*,7*S*)-cephalosporins for analysis as enzyme inhibitors/antibacterials/antifungals and intermediates in the preparation of *ent*-Cefadroxil™ **7**.[‡8] A part of this work has been published in preliminary format.[9,10] De Angelis et al. have recently reported syntheses of phthalimido-protected *ent*-cephems using 7-aminodeacetoxycephalosporanic acid as the starting material.[11]

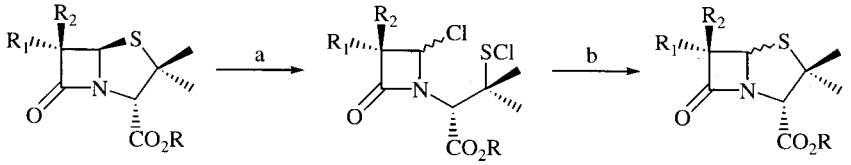
Results and Discussion

In the first successful approach to the (6*S*,7*S*)-cephem nucleus **5** (Scheme 1) we envisioned its formation via the well-established Morin rearrangement[12,13] of a suitable penicillin sulfoxide **8**, which in turn would be synthesised from readily available and inexpensive 6-aminopenicillanic acid **9** (6-APA).

Scheme 2 summarises our first successful synthesis. 6-APA **9** was protected as described by Vanderhaeghe and Busson.[14] Thus, the sodium salt of **9** was treated with Nefkens' reagent, *N*-carboethoxyphthalimide,[15] to give acid **10**[16] which was subsequently esterified with benzyl bromide in the presence of triethylamine to afford ester **11**.[§] The base-promoted epimerisation of the C-6 position

[‡] Cefadroxil™ exists in a number of different crystalline forms[8] and crystallisation studies of its enantiomer **7** were also undertaken. The results of the studies will be reported elsewhere.

[§] Although penam **11** has been prepared by others, its existence in two polymorphic forms has not been noted previously. Thus, the previously reported low-melting form (Form I, mp 136–138°C) is transformed into a higher-melting form (Form II, mp 153–154°C) either upon prolonged heating (ca. 20 min) at 110°C or during melting point determination when the temperature increase is slow (ca. 1°C min^{-1}, starting from 100°C). Form I, $C_{23}H_{20}N_2O_5S$, was shown not to be a hydrate or solvate by elemental analysis. The ^1H NMR (500 MHz) analysis confirmed that no decomposition occurred during the solid state transformation. The two forms are distinguished in solid state by FT IR and X-ray powder diffraction analyses (see Experimental).



Entry[a]			
1	**11** R_1 = H, R_2 = Pht, R = Bn [14]	*trans* (**13**) : *cis* (**14**) = 4:1	*trans* (**15**) : *cis* (**11**) > 20:1
2	**16** R_1 = H, R_2 = Pht, R = Me [22]	*trans* (**17**) : *cis* (**18**) = 4:1	only *trans* (**19**)
3	**20** R_1 = H, R_2 = Pht, R = Bzh [22]	*trans* (**21**) : *cis* (**22**) not reported	*trans* (**23**) : *cis* (**20**) = 10:1
4	**12** R_1 = Pht, R_2 = H, R = Bn	*trans* (**24**) : *cis* (**25**) = 4:1	*trans* (**12**) : *cis* (**26**) = 2:1
5	**27** R_1 = Pht, R_2 = H, R = Me[b]	*trans* (**28**) : *cis* (**29**) = 5:1	*trans* (**27**) : *cis* (**30**) = 1.5:1[b]
6	**31** R_1 = Pht, R_2 = H, R = Bzh	*trans* (**32**) : *cis* (**33**) = 9:1	*trans* (**31**) : *cis* (**34**) = 2.5:1
7	**35** R_1 = H, R_2 = H, R = Bn	**36** : **37** = 2:1[c]	(5*R*)-**35** : (5*S*)-**38** = 3:1
8	**39** R_1 = H, R_2 = H, R = Me	**40** : **41** = 2:1[c]	(5*R*)-**39** : (5*S*)-**42** = 4:1
9	**43** R_1 = H, R_2 = H, R = Bzh	**44** : **45** = 2.5:1[c]	(5*R*)-**43** : (5*S*)-**46** = 8:1

[a]Entries 1-3 are the results reported by others.[14,19] Entries 4-9 are the results of the work described herein.
[b]It was reported by Busson et al.[14] that the reaction resulted in recovery of the starting material **27**, only.
[c]Geometry of the products was not established.

Scheme 3. *Reagents and conditions:* (a) Cl_2 (1 equiv.), CH_2Cl_2, CCl_4; (b) $SnCl_2$ (1 equiv.), THF, rt.

of penam **11** was accomplished readily in excellent yield using either a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or stoichiometric amount of NaH to give the (6*S*)-epimer **12**. As previously reported,[17] irrespective of the base used, the *cis*-penicillin **11** could not be detected in the crude reaction mixture by ^{1}H NMR (200 MHz) analysis.

In planning the synthesis of cephem **5**, we were cognisant that a pivotal step would involve epimerisation of the C-5 position of penam **12**. To our knowledge, only one method, that was developed by Kukolja, allows epimerisation of the C-5 position of penicillins bearing an imido substituent at C-6.[18,19] The reaction with 1 equiv. of chlorine or sulfuryl chloride as a source of electrophilic halogen, results in cleavage of the C_5–S bond of the penicillin thiazolidine ring.[18] Subsequent tin(II) chloride-mediated re-cyclisation (1 equiv. of anhydrous $SnCl_2$, THF, rt, 2 h) gives the desired fused bicyclic penam system.[19] Unfortunately, it has also been reported that the ring closure step is highly *trans*-selective. For example (Scheme 3, entry 1), when ester **11** was subjected to the Kukolja protocol, *cis*- and *trans*-penicillins **11** and **15** were obtained in a ca. 1:20 ratio, respectively.[14] Similarly, benzhydryl ester **20** gave a mixture of two diastereoisomers, **20** and **23**, in a ca. 1:10 ratio, respectively[19] (Scheme 3, entry 3). The most discouraging results reported involved subjecting methyl esters **16** and **27** to the Kukolja protocol. It was reported that the reactions resulted in clean formation of the *trans*-penam **19** from ester **16**[19] (Scheme 3, entry 2), and recovery of the starting material in the case of the *trans*-penam **27**, without any trace of the appropriate '*cis*-closure' product.[14] In the case of (6*R*)-phthalimidopenicillanates this high stereoselectivity can be attributed to the bulk of the phthalimido substituent that makes the *cis*-diastereoisomers kinetically and thermodynamically significantly less favoured cyclisation products than their *trans*-analogues. Moreover, it has been established, on the basis of base-catalysed equilibration experiments, that a sterically demanding ester substituent at C-2 prefers to occupy the *exo*- rather than *endo*-face of penicillins.[14] Thus, the literature precedent suggested that the *cis*-closure mode in the case of intermediates **24** and **25**, derived from penicillin **12**, may be even less probable than that of intermediates **13** and **14** corresponding to the favourably configured penam **11**.

To our delight, subjecting penicillin **12** to the Kukolja protocol furnished a mixture of two diastereoisomers, the requisite *cis*-penicillin **26** and the parent *trans*-penicillin **12** in a ratio of ca. 1:2. Earlier studies had indicated that the *trans*-selectivity of the ring closure step could be influenced by the presence of moisture or when the process was performed in boiling dioxane using tin(II) chloride dihydrate.[19] However, use of either of these conditions, whilst diminishing significantly the overall yield of penams **12** and **26**, did not result in bias of the product to the desired *cis*-isomer. Substitution of tin(II) chloride with other divalent tin halides ($SnBr_2$, SnF_2) was also not advantageous. Interestingly (Scheme 3), even when bulkier benzhydryl ester **31** was subjected to the Kukolja protocol, the *cis*-penicillin **34** was obtained along with the parent *trans*-penam **31** in a ratio of ca. 1:2.5. In this case, however, the overall yield of the penams was somewhat lower than in the case of its benzyl analogue, which may reflect the acid-sensitive nature of diphenylmethyl esters. Surprisingly and contrary to the aforementioned report,[14] in our hands *trans*-penam **27** afforded a mixture of two penicillins **27** and *cis*-**30** in a ratio of ca. 1.5:1 in excellent overall yield. Our results indicate that the *cis*-closure is enhanced slightly for the less sterically demanding esters within the series of (6*S*)-phthalimidopenicillanates.

To investigate factors affecting the stereochemical outcome of the Kukolja protocol, a series of penicillanates devoid of the phthalimido group at the C-6 position were prepared and subjected to the standard ring opening-cyclisation procedure (Scheme 3, entries 7–9). Thus, when benzyl ester **35** was subjected to the Kukolja protocol, its (5*S*)-epimer **38** and the starting material **35** were obtained in a ca. 1:3 ratio, respectively. Similarly, the methyl ester **39** gave its (5*S*)-epimer **42**, along with the recovered starting material **39**, in a ratio

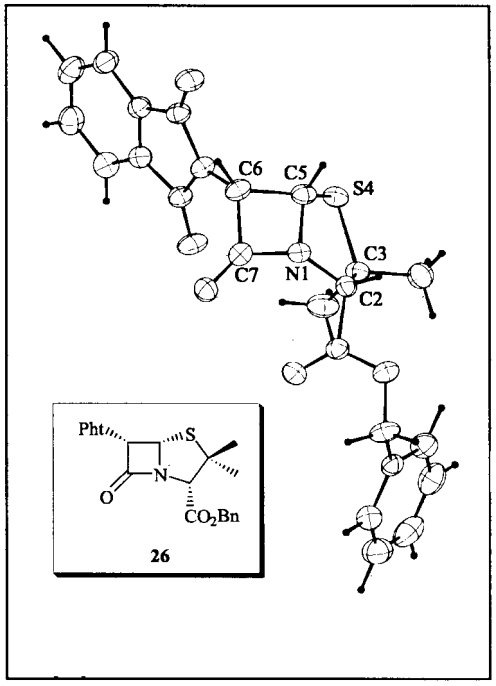
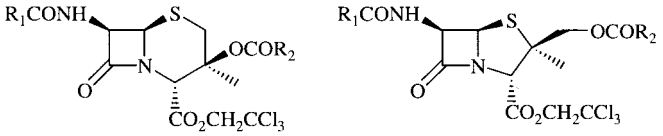


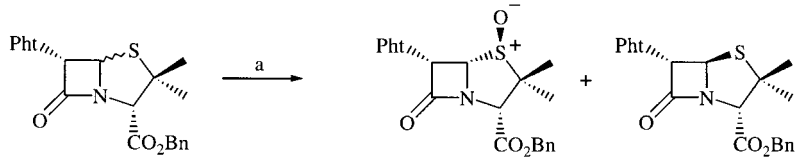
Figure 1.

However, the use of ozone as a selective oxidant circumvented the difficulty. Spry has demonstrated that ozone is a reagent of choice for the conversion of penicillins and cepham derivatives into sulfoxides; the sulfoxides are prepared in near quantitative yield, no overoxidation to sulfones occurs, and workup procedures are simple.[20,21] Moreover, the selective oxidation of bicyclic β-lactams with ozone had been clearly demonstrated by exclusive oxidation of cepham **47** in the presence of penam **48**.[21]



(*a*) $R_1 = PhOCH_2$, $R_2 = Me$
(*b*) $R_1 = PhOCH_2$, $R_2 = CH(CH_3)_2$
(*c*) $R_1 = PhCH_2$, $R_2 = Me$

Thus (Scheme 4), when a 1:2 mixture of esters **26** and **12** in cold acetone was carefully oxidised with ozone, selective formation of the desired sulfoxide **49** occurred.[‖] Only traces of the sulfoxides derived from penicillin **12** could be



trans (**12**) : *cis* (**26**) = 2:1
chromatographic separation difficult

49 **12**
readily separated by chromatography

Scheme 4. *Reagents and conditions:* (a) O_3, Me_2CO, 0°C.

of ca. 1:4. For the benzhydryl ester **43** the selectivity of the re-cyclisation step was markedly higher, and the (5*S*)-penam **46** was obtained, together with the starting material **43**, in a ratio of ca. 1:8, respectively. Note that for 6-unsubstituted penicillanates (e.g. **35**, **39**, and **43**) cyclisation of the corresponding intermediate sulfenyl chlorides takes place from the α-face less readily than for the intermediates derived from (6*S*)-phthalimidopenicillanates (e.g. **12**, **27**, and **31**). Thus, a factor(s) other than the presence and configuration of a 6-substituent must be involved in determining the stereochemical outcome of the ring closure reaction. However, since removal of the phthalimido group from the C-6 position of the penam molecule also changes electronic properties of the cyclisation step intermediates, it is difficult to single out a decisive factor.

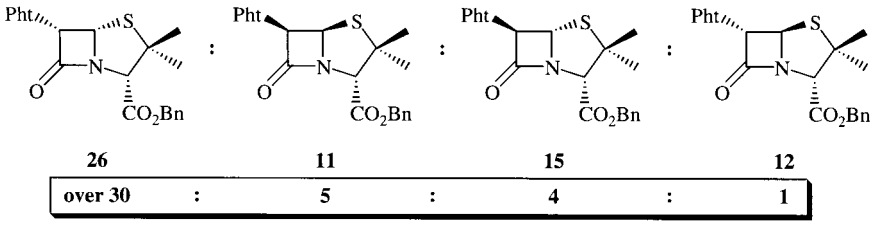
Structure of penam **26**, including the absolute configuration, was confirmed by single-crystal X-ray crystallographic analysis (Fig. 1).

Unfortunately, separation of diastereoisomers **12** and **26** (Scheme 2) by flash chromatography on a multi-gram scale proved to be inefficient and time-consuming. Furthermore, this obstacle precluded the recycling of penicillin **12**. detected by ^1H NMR (200 MHz) analysis. This operation not only differentiated polarities of the two diastereoisomers, making their separation easy, but also afforded the requisite sulfoxide **49** for subsequent penam-cephem rearrangement. Separation of sulfoxide **49** from sulfide **12** was, even on a multi-gram scale, easily accomplished by flash chromatography.[¶]

The scope of this oxidation was investigated by a series of competitive experiments involving four diastereoisomeric

[‖] The oxidation reaction was stereoselective giving a single isolated epimeric sulfoxide of penam **26**, whose configuration, initially assigned as (4*S*) on the ground of the well-documented steric control during sulfoxidation of naturally configured 6-phthalimidopenicillanates, was unambiguously confirmed by single crystal X-ray analysis. Baldwin, J. E.; Adlington, R. M.; Schofield, C. J.; Fekner, T. Unpublished work.

[¶] Selective chlorinolysis of penam **12** from its mixture with the requisite penam **26** was initially attempted. If successful, it would have enabled, by repeating the Kukolja protocol, to improve the *cis*/*trans* ratio of the products. Unfortunately, penam **26** undergoes the ring opening significantly faster than the epimer **12**. Presumably, due to the easily accessible *exo*-face of penam **26**, the sulfur atom, with its well-exposed *pro*-(*S*) lone electron pair, is preferentially attacked by electrophiles. This experiment suggested that selective sulfoxidation of penam **26** from its mixture with **12** might be feasible.



Scheme 5. Estimated relative reactivity of benzyl 6-phthalimidopenicillanates towards sulfoxidation with ozone in acetone.

benzyl 6-phthalimidopenicillanates. Scheme 5 summarises our results. Diastereoisomer **26** proved to be the most reactive of the compounds tested. The high reactivity of penam **26** may be attributed to the relative accessibility of the *pro*-(*S*) lone electron pair of the sulphur.

Cephem **50** was obtained in moderate yield via the Morin rearrangement[12,13]of sulfoxide **49** in hot DMF in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*TSA) (Scheme 2). The Ing-Manske[22,23] dephthaloylation using hydrazine hydrate furnished free amine **51** which was subsequently acylated with appropriate arylacetic acids using 1,3-dicyclohexylcarbodiimide (DCC) as a dehydrating agent to afford amides **52** and **53**, in both cases in excellent yield.[24] Finally, debenzylation with $AlCl_3$ as reported by Tsuji et al.,[25] produced free acids **54** and **55** in excellent yields.

The structures of cephem **50** (Fig. 2) and the corresponding amine **51** (Fig. 3) were confirmed by single-crystal X-ray crystallographic analyses.

Another successful approach to (6*S*,7*S*)-cephems (Scheme 6) relied on the observation that the target compound **5** might be easily obtained from its (7*R*)-epimer **56** by any of the methods devised to convert (6*R*,7*S*)-cephems, available from various total syntheses, to the naturally configured ones. (6*S*,7*R*)-Cephem **56** could be synthesised from the appropriate penicillin sulfoxide **57** via the Morin rearrangement[12,13] and 6-APA **9** would be again a suitable starting material.

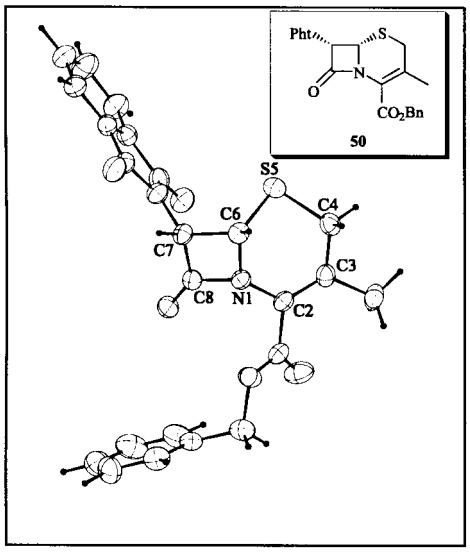


Figure 2.

The pathway, reagents, and conditions of the second approach are summarised in Schemes 7, 9 and 10. Ester **15** was obtained from its epimer **11** as previously described (Scheme 3). Oxidation with *m*-chloro-perbenzoic acid (*m*CPBA) afforded sulfoxide **58** (Scheme 7), which was identical to material obtained by epimerisation of the C-6 position of sulfoxide **49** with a catalytic amount of DBU. The assignment of the (4*S*)-configuration was confirmed by single-crystal X-ray crystallographic analysis of sulfoxide **58** (Fig. 4). It is the only one example in the series of benzyl 6-phthalimidopenicillanates studied (**11**, **12**, **15**, and **49**), where peracid (*m*CPBA) prefers to approach the molecule from the face occupied by bulky phthalimido substituent.[**]

Sulfoxide **58** underwent the acid-catalysed Morin rearrangement to give cephem **59**. Interestingly, this reaction was significantly slower than that of sulfoxide **49** (8 h and 90 min, respectively, under the standard reaction conditions[††]). Cooper has studied the penicillin sulfoxide–sulfenic acid equilibrium with naturally configured penam sulfoxides. He observed that, on heating in D_2O, the 6-phthalimido substituted penam sulfoxides incorporated deuterium into one of the geminal methyl groups significantly faster than their phenoxyacetamido (Penicillin V) analogues.[26] Amongst other possible explanations he postulated that the phthalimido substituent introduces significant steric strain into the molecule (its interaction with the β-methyl group seems to be the most important). This strain increases ground-state energy of the molecule, which results in a lower activation energy for the appropriate (pseudo)-pericyclic process leading to the sulfenic acid. Since the aforementioned sulfoxide–sulfenic acid equilibrium consists the very first stage of the Morin rearrangement, it seems reasonable to explain the difference in reactivity of *cis*- and *trans*-substituted 6-phthalimidopenicillanate-4-oxides under the Morin rearrangement conditions using a similar argument, i.e. there is a lower activation energy for reaction of the *cis*-penam sulfoxides (e.g. **49**) than for their

[**] Strictly speaking, the oxidant does not approach the molecule from the face occupied by the phthalimido group, but it is probably a side-on type approach in which the equatorial lone electron pair of sulfur reacts (it was established by n.O.e. studies that the thiazolidine ring of sulfoxide **58** adopts in chloroform solution the 'open' conformation, see: Experimental section).

[††] An appropriate sulfoxide (200 mg, 0.44 mmol) and anhydrous *p*TSA (20 mg, 0.12 mmol) in DMF (10 ml) were heated in a pre-equilibrated oil bath at 100±3°C until the sulfoxide had reacted (TLC analysis). Under these conditions *cis*-penam sulfoxide **64** and *trans*-penam sulfoxide **65** were consumed within 30 and 220 min, respectively.

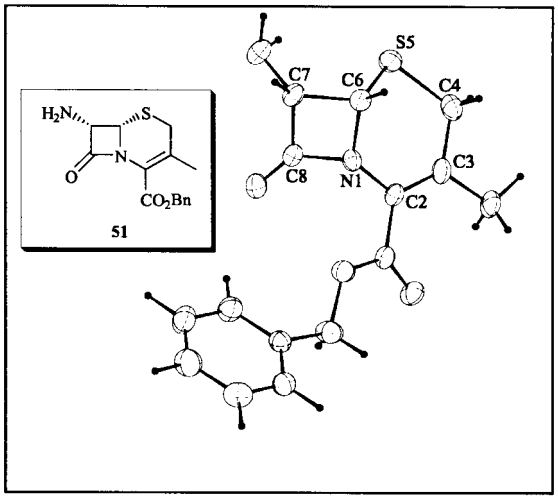
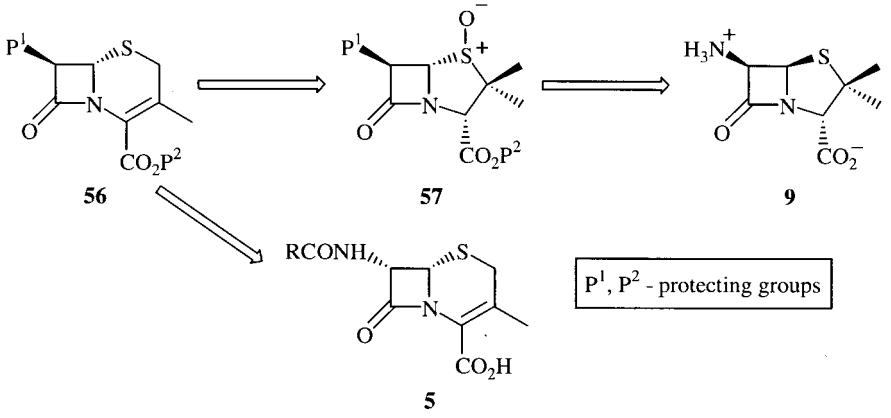


Figure 3.

As exemplified for a single deuterium incorporation into sulfoxide **58** (Scheme 8), its thermal rearrangement gives sulfenic acid **61**, which exchanges the acid proton with D_2O to form the deuterated analogue **62**.[26,27] After reversible ring closure, the deuterium is placed selectively in one of the geminal methyl groups (in this case β-CH_3) to give deuterated penam sulfoxide **63**.[26] The act of the ring opening can be then repeated resulting in incorporation of further deuterium atoms.[‡‡]

The results demonstrate that, as anticipated, the *cis*-penam sulfoxide **64** incorporates deuterium much faster than its *trans*-analogues **65** and **58** (Table 1). This outcome can be rationalised by assuming a very facile formation of the intermediate sulfenic acid from sulfoxide **64** for the reasons of steric strain discussed earlier. The results imply that, under the reaction conditions, formation of a sulfenic acid, and not its further transformations, may be the bottleneck in the Morin rearrangement of the *trans*-substituted 6-phthalimidopenicillanate-4-oxides tested (i.e. **58** and **65**). Interestingly,



Scheme 6.

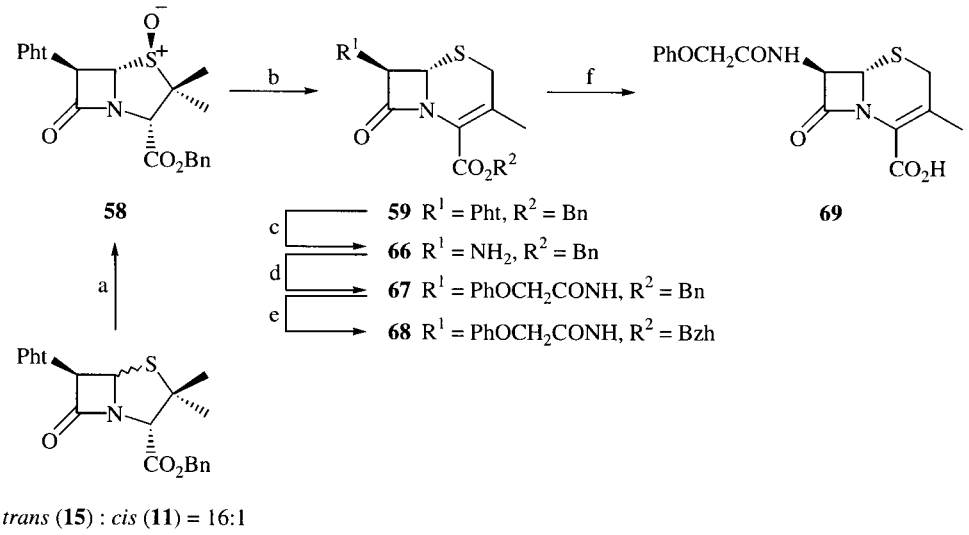
trans analogues (e.g. **58**). It is also possible that geometric constraints are responsible for the different observed rates of reaction.[27]

To further investigate, deuterium incorporation studies for various 6-phthalimidopenicillanate-4-oxides were conducted. Since the bulkiness of the phthalimido group seemed to be the dominant factor governing the ease of sulfenic acid formation, it was decided to include into these studies sulfoxide **60**, which is devoid of substituents at the C-6 position.

[‡‡] Deuterium incorporation was accomplished by heating the appropriate penam sulfoxide (0.13 mmol) in refluxing benzene (15 ml) for 150 min in the presence of a large excess of D_2O (300 μl, 15 mmol, 115 equiv.). Since penam sulfoxides give under mass spectrometry conditions strong peaks of dehydration products formed presumably via a sulfenic acid intermediate, it was necessary to preclude distortion of the results via label loss in the mass spectrometric analyses. Thus, prior to the mass spectrometry analysis, the deuterated sulfoxides were reduced to the corresponding penams (KI, AcCl, DMF, 0°C). The deuterium distribution in 6-phthalimidopenicillanates was calculated from the mass spectra using the well pronounced molecular ions (MNH_4^+, *m/z* 454–457) and peaks arising from a simple fission (with hydrogen transfer) of the β-lactam ring (MH^+−PhtCHCO, *m/z* 250–253). For the deuterated derivative of the 6-unsubstituted penam **60** the molecular peak was of no analytical value and, consequently, only the fission peak was used.

sulfoxide **60**, devoid of the phthalimido group at C-6, incorporates deuterium slightly faster than sulfoxide **58**. n.O.e. Studies implied that the thiazolidine ring of sulfoxides **58** and **60** adopts, at least in chloroform solution, the open conformation (see Experimental). Remarkably, sulfoxide **49** did not incorporate deuterium into either of the geminal methyl groups but, instead, the reaction delivered the corresponding sulfenic acid. This prompted us to investigate formation of unusually stable sulfenic acids from various (2*S*,5*S*,6*S*)-penicillanate-4-oxides in more detail. The results of the studies have been published elsewhere.[28]

As in the previous approach, dephthaloylation of cephem **59** using hydrazine hydrate[22,23] afforded amine **66** (Scheme 7). DCC-mediated coupling[24] with phenylacetic acid gave amide **67** in good yield. Debenzylation with $AlCl_3$[25] afforded contaminated acid **69** that was purified as its benzhydryl ester **68**. Final rapid deprotection with $AlCl_3$ under milder conditions gave pure acid **69**. As shown in Schemes 9 and 10, amine **66** was converted to (6*S*,7*S*)-cephem derivatives by two different methods. The first utilised, developed by Hiraoka and Kobayasi,[29] involves preparation and subsequent reduction of sulfenimines. Thus (Scheme 9), amine **66** upon treatment with *p*-nitrobenzenesulfenyl chloride in the presence of K_2CO_3 afforded sulfenamide



Scheme 7. *Reagents and conditions*: (a) *m*CPBA, $CHCl_3$, 0°C, 90 min; 85%; (b) *p*TSA, DMF, 100°C, 17 h; 33%; (c) $N_2H_4{\cdot}H_2O$, DMF,=−15°C, 30 min; 39%; (d) $PhOCH_2CO_2H$, DCC, THF, rt, 2 h; 89%; (e) $AlCl_3$, PhOMe, CH_2Cl_2, $MeNO_2$, rt, 8 h, then Ph_2CN_2, CH_2Cl_2, rt, 5 min; 52%; (f) $AlCl_3$, PhOMe, CH_2Cl_2, $MeNO_2$, 0°C, 30 min; 96%.

70 in good yield. Oxidation with active manganese dioxide furnished sulfenimine **71**, which was reduced with $NaBH_4$ to produce sulfenamide **72** as the major product, along with a small amount (<5%) of the parent sulfenamide **71**. Direct acylation of cephem **72** with phenoxyacetyl chloride afforded amide **53**, prepared in our first approach. It was also possible to cleave reductively (KI/AcOH/MeOH) the side chain of sulfenamide **72** with formation of free amine **51**.

Gordon's modification of the Hiraoka and Kobayashi's methodology allows preparation of sulfenimines from amines in one step.[30,31] In this case the appropriate sulfenyl chloride acts as oxidant converting the initially formed sulfenamide to thiooxime. When amine **66** was treated with three equivalents of freshly prepared *p*-toluenesulfenyl chloride[32] in the presence of propylene oxide and pulverised 4 Å molecular sieves, sulfenimine **73** was obtained in good yield. Subsequent reduction with $NaBH_4$ afforded *cis*-sulfenamide **74** which was directly acylated with phenoxyacetyl chloride to give amide **53** or reductively cleaved to afford amine **51**.

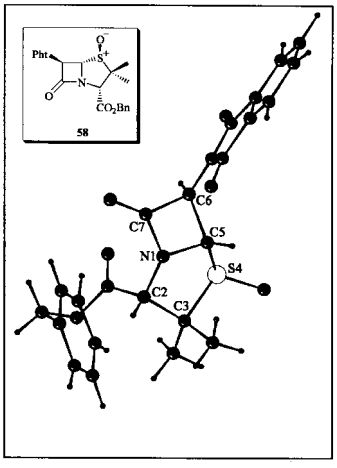


Figure 4.

The second methodology utilised, devised by Firestone et al.,[33] was based on kinetically controlled protonation of anions derived from the appropriate Schiff base (Scheme 10). Thus, condensation of amine **66** with *p*-nitrobenzaldehyde in the presence of $MgSO_4$ furnished imine **75** in good yield. Treatment with PhLi followed by DMF generated the free anion, which was quenched with acetic acid giving a mixture of two imines **77** and **76** in the ratio of ca. 2.5:1. Hydrolysis of the mixture with *p*TSA in wet EtOAc,[34] followed by spontaneous crystallisation, gave pure salt **77**, not contaminated with its 7-epimer. It was also possible to acylate the mixture of the Schiff bases[35] and obtain, after chromatographic separation, the requisite amide **53**.

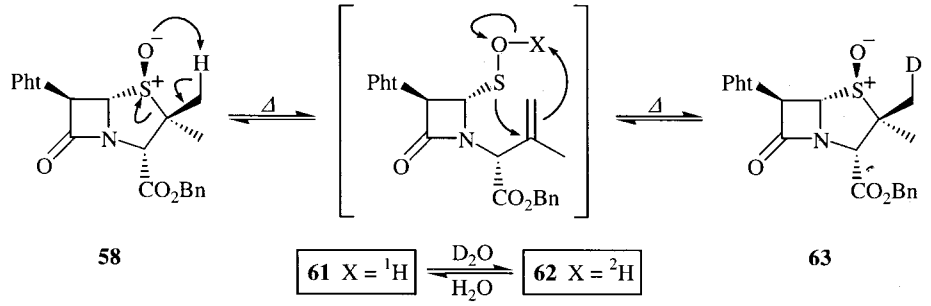
Conclusions

Two approaches for the synthesis of the enantiomers of naturally configured cephalosporins have been developed. Mechanistic observations have been made involving stereoselectivity in the Kukolja reaction and use of ozone as a highly selective oxidant of diastereoisomeric penicillins. The Morin penam sulfoxide-cephem rearrangement has also been shown to be a practical method for preparation of various cephalosporins with unnatural configurations.

Experimental

General experimental techniques

Melting points (mp) were recorded using a Gallenkamp or a Büchi 510 capillary melting point apparatus. Values are given to the nearest 1°C, followed by the crystallisation solvent(s) in parentheses. Optical rotations $\{[\alpha]_D^t\}$ were taken using a Perkin–Elmer 241 polarimeter at 589 nm (Na D-line) and the defined temperature '*t*' with a

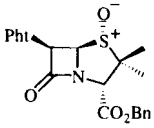
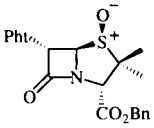
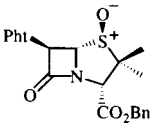
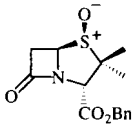


58 61 62 63

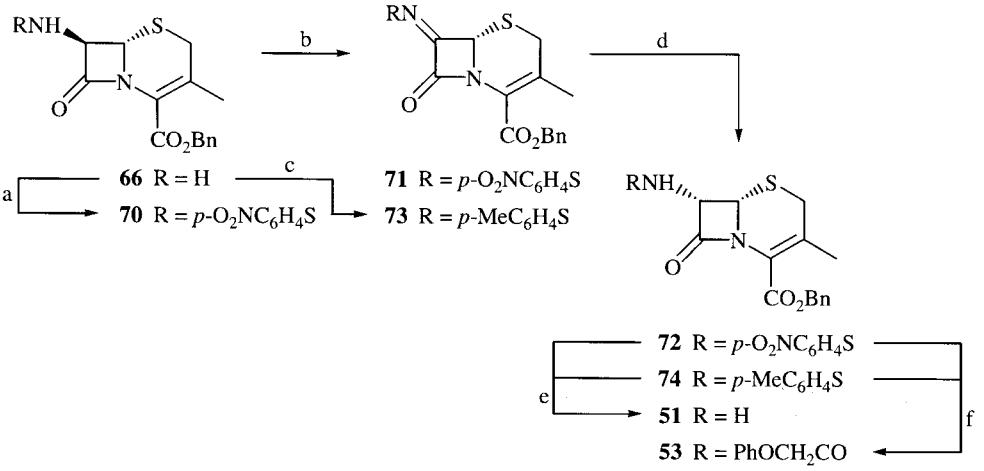
Scheme 8.

pathlength of 10.0 cm. Values are given in 10^{-1} deg cm^2 g with concentrations given in 10^{-2} g cm^{-3}. Combustion microanalyses were performed in-house by Mrs V. Lamburn. Fourier Transform Infrared (FT IR) spectra were recorded on a Perkin–Elmer 1750 Fourier Transform Spectrometer as either KBr discs or $CHCl_3$ solutions. Absorbtions (ν_{max}) are reported in wavenumbers (cm^{-1}) and only main features of each spectrum are given. Abbreviations used are as follows: 's' strong, 'm' medium, 'w' weak, 'sh' shoulder, and 'br' broad. Proton Nuclear Magnetic Resonance (^{1}H NMR) spectra were recorded at 200 and 500 MHz on a Varian Gemini 200 and Brüker AMX500 spectrometers, respectively. Chemical shifts (δ_H) are given in ppm relative to tetramethylsilane and referenced to the residual solvent peak. Coupling constants (J) are recorded in Hertz and quoted to the nearest 0.5 Hz. The following abbreviations are used: 's' singlet, 'd' doublet, 'dd' double doublet, 't' triplet, 'q' quartet, 'm' multiplet, 'AB' AB system, and 'br' broad. Carbon Nuclear Magnetic Resonance (^{13}C NMR) spectra were recorded at 50.31 and at 125.77 MHz on a Varian Gemini 200 and Brüker AMX500 spectrometers, respectively. Chemical shifts (δ_C) are given in ppm and referenced to the residual solvent peak, unless otherwise stated. Distortionless Enhancement by Polarisation Transfer (DEPT) editing was used for spectra recorded at 50.31 MHz, and in this context the following abbreviations were used: 's'=CH$_0$, 'd'=CH$_1$, 't'=CH$_2$, and 'q'=CH$_3$. Low Resolution Mass

Table 1.

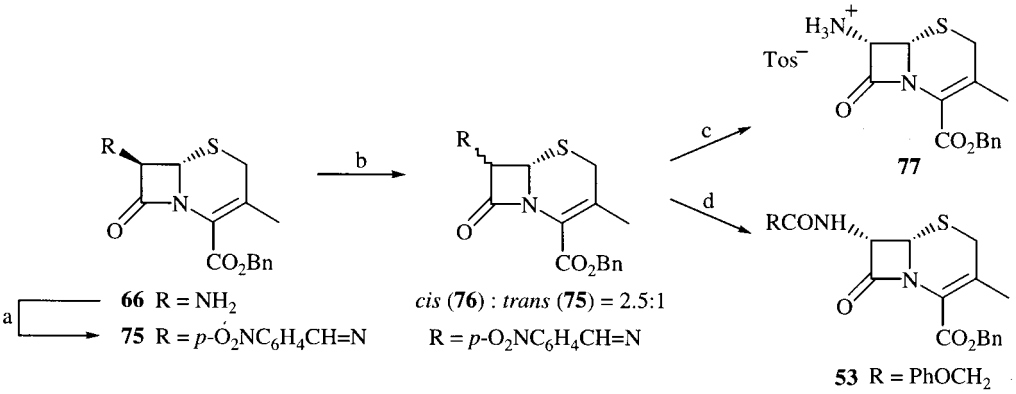
Sulfoxide[a]	Deuterium incorporation site[b]	Average number of deuterium atoms incorporated	Deuterium distribution (%)[c]			
			D_0	D_1	D_2	D_3
 **64**	α-CH_3	2.10[c] (1.9)[d]	7	15	39	39
 **65**	β-CH_3	0.88 (0.8)	38	40	18	4
 **58**	β-CH_3	0.24	83	11.5	4.5	1
 **60**	β-CH_3	0.31 (0.3)	72	25	3	0

[a] The geometry of the sulfoxide bond was established by single-crystal X-ray crystallographic analyses, chemical correlation, and/or ^{13}C NMR studies.[9] For every sulfoxide tested, the configuration at sulfur remained unchanged after the deuterium incorporation.
[b] Established by n.O.e. studies.
[c] Determined by mass spectrometry.
[d] Determined by ^{1}H NMR (500 MHz) analysis.



Scheme 9. *Reagents and conditions:* (a) *p*-$O_2NC_6H_4SCl$, K_2CO_3, CH_2Cl_2, 0°C, 1 h; 83% or *p*-$O_2NC_6H_4SCl$, Et_3N, THF, 0°C, 3 h; 63%; (b) active MnO_2, PhH, rt, 1 h; 48% (**70** to **71**); (c) *p*-MeC_6H_4SCl (3 equiv.), propylene oxide, 4 Å molecular sieves, CH_2Cl_2, 0°C→rt, 3 h; 75% (**66** to **73**); (d) $NaBH_4$, THF, DMSO, 0°C, 10 min; 53% (**71** to **72**) and 40 min, 50% (**73** to **74**); (e) KI, $Na_2S_2O_3$, CH_2Cl_2, MeOH, AcOH, 0°C, 2 h; 99% (**72** to **51**) and ~100% (**74** to **51**); (f) $PhOCH_2COCl$, CH_2Cl_2, 0°C, 120 min; 85% (**72** to **53**) and 73% (**74** to **53**).

Spectrometry (LRMS) was performed on a V.G. Micromass ZAB 1F (FAB/CI/DCI), a V.G. Masslab 20-250 (CI/DCI/EI), or a V.G. BIO-Q (electrospray) spectrometer. Modes of ionisation are described as Direct Chemical Ionisation (DCI), Probe Chemical Ionisation (CI), Probe or In Beam Chemical Impact (EI), or Fast Atom Bombardment (FAB). Only molecular ions (M^+) and major peaks, as the mass-to-charge ratio (*m/z*), are reported with intensities given as percentages of the base peak. High Resolution Mass Spectrometry (HRMS) was performed by the staff of EPSRC Mass Spectrometry Service Centre, Chemistry Department, University of Wales, Swansea. The accurate mass measurements are valid to ±10 ppm. Flash chromatography was carried out using Merck Kiesegel 60 F_{254} (230–400 mesh) or Janssen (35–70 μm) silica gel according to the method described by Still et al.[36] Only distilled solvents were used as eluents. Thin layer chromatography (TLC) was performed on Merck DC-Alufolien or glass plates precoated with silica gel 60 F_{254} which were visualised either by quenching of ultraviolet fluorescence (λ_{max} 254 nm), by staining with iodine vapour, or by charring with 5% w/v phosphomolybdic acid in 95% EtOH, 10% w/v ammonium molybdate in 1 M H_2SO_4, 5% w/v ninhydrin in absolute EtOH, or 10% $KMnO_4$ in 1 M H_2SO_4. Eluents are given in parentheses. Observed retention factors (R_f) are quoted to the nearest 0.05 unless ΔR_f for the compounds separated was less than 0.1. All reaction solvents were distilled before use and stored over activated 4 Å molecular sieves, unless otherwise indicated. Anhydrous dichloromethane, benzene, triethylamine, and nitromethane were obtained by refluxing over calcium hydride followed by distillation under an inert atmosphere of argon. Anhydrous carbon tetrachloride was obtained by distillation from phosphorus pentoxide. Anhydrous tetrahydrofuran was obtained by distillation, immediately before use, from sodium/benzophenone ketyl under an inert atmosphere of nitrogen. Anhydrous *N*,*N*-dimethylformamide was obtained by distillation from calcium hydride under reduced pressure. Anhydrous 1,4-dioxane was obtained by distillation from sodium. Petroleum ether refers to the fractions of light petroleum boiling between either 30–40°C or 40–60°C. Low boiling solvents were evaporated under reduced pressure on a Büchi RE111 Rotavapor at 30°C, unless otherwise stated. High boiling solvents were evaporated under reduced pressure on a Büchi RE111 Rotavapor fitted with a dry ice condenser at $p \leq 2$ mmHg. All reactions were performed under anhydrous conditions and an inert atmosphere of argon in the flame-dried glassware with dry, freshly distilled



Scheme 10. *Reagents and conditions*: (a) *p*-$O_2NC_6H_4CHO$, $MgSO_4$, CH_2Cl_2, rt, 10 h; 83%; (b) PhLi, THF, DMF, then AcOH, and H_2O,=−78°C; (c) *p*TSA, H_2O, EtOAc, rt, 30 min, 45% over two steps; (d) $PhOCH_2COCl$, CH_2Cl_2, rt, 20 h; 51% over two steps.

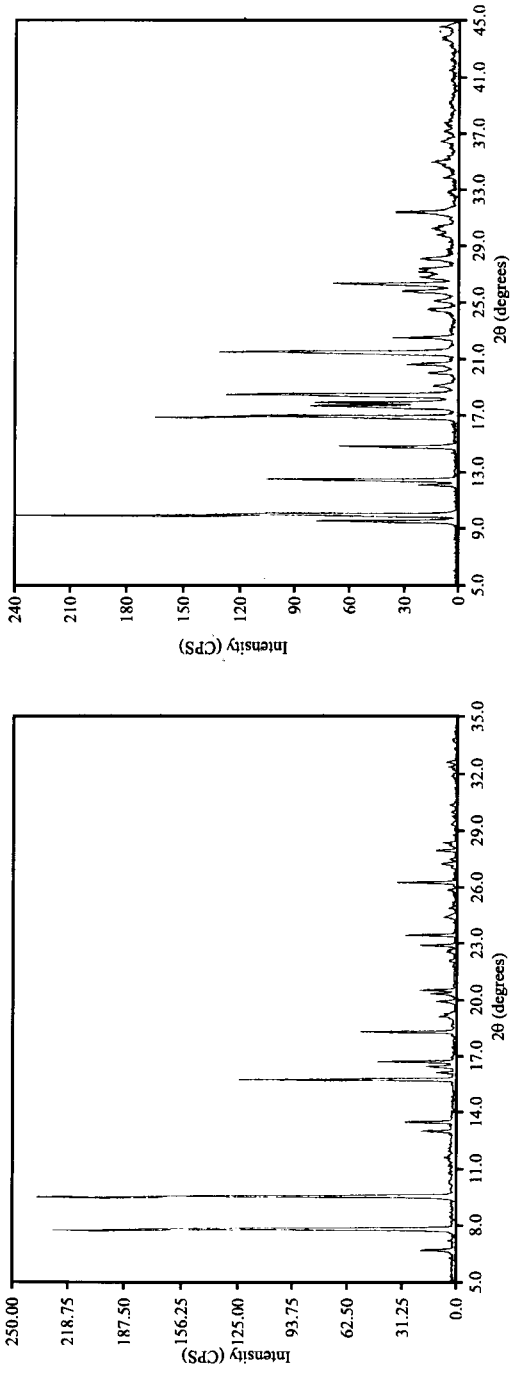

Intensity (CPS)
0.0
31.25
62.50
93.75
125.00
156.25
187.50
218.75
250.00
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
2θ (degrees)
Intensity (CPS)
0
30
60
90
120
150
180
210
240
5.0
9.0
13.0
17.0
21.0
25.0
29.0
33.0
37.0
41.0
45.0
2θ (degrees)

Figure 5.

solvents, unless otherwise noted. Yields refer to apparently chromatographically and spectroscopically (^{1}H NMR) homogenous materials, unless otherwise indicated. Reagents were used as obtained from commercial sources or purified according to published procedures.[37] The X-ray single crystal analyses were performed by the staff of Chemical Crystallography, University of Oxford. The X-ray powder diffraction analyses were performed by Dr Martin Vickers, Department of Crystallography, Birkbeck College, London. Diazomethane was generated according to the method described in *Aldrich Technical Bulletin* No. AL-113.

(+)-(2*S*,5*R*,6*R*)-3,3-Dimethyl-7-oxo-6-phthalimido-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (10). To a vigorously stirred solution of 6-aminopenicillanic acid **9** (6-APA, 49.3 g, 228 mmol) and Na_2CO_3 (24.2 g, 228 mmol) in water (350 ml) was added finely ground *N*-carboethoxyphthalimide (50.0 g, 228 mmol). The mixture was stirred at room temperature for 2 h and then washed with CH_2Cl_2 (3×100 ml). The aqueous layer was mixed with a fresh portion of CH_2Cl_2 (300 ml) and acidified during vigorous stirring with 1 M HCl (456 ml, 456 mmol). Phases were separated and the extraction was completed with two additional portions of CH_2Cl_2 (2×100 ml). The combined organic extracts were washed with water (2×250 ml) and satd. brine (100 ml). The organic layer was dried over $MgSO_4$, decolourised with activated carbon (15 g), and evaporated in vacuo to afford the title compound **10** (38.8 g, 49%) as an off-white solid which was used in the next step without further purification. An analytical sample, as a white crystalline solid, was obtained by triple crystallisation from acetone: mp 168–170°C (from acetone) {lit.[16] mp 167–170°C (dec.) (from acetone)}; (Found: C, 55.31; H, 3.95; N, 7.95. Calcd for $C_{16}H_{14}N_2O_5S$: C, 55.48; H, 4.08; N, 8.09%); $[\alpha]_D^{25}=+276$ (*c* 0.50 in $CHCl_3$) {lit.[16] $[\alpha]_D^{28}=+278$ (*c* 1.0 in *n*-butyl acetate)}; FT IR (KBr disc) ν_{max}/cm^{-1} 3480s (carboxylic acid), 1790s and 1779s (β-lactam, phthalimide), and 1723s (phthalimide, carboxylic acid); ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.62 and 1.85 (2×3H, 2×s, 2×C*H*$_3$), 2.96 (1H, br s, CO_2H), 4.71 (1H, s, 2-*H*), 5.60 and 5.70 (2×1H, 2×d, *J*=4 Hz, 5-*H* and 6-*H*), and 7.76–7.92 (4H$_{arom}$, m, Pht); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 27.97 and 30.38 (2×*C*H$_3$), 58.33, 66.64, and 70.88 (2-*C*, 5-*C*, and 6-*C*), 65.65 (3-*C*), 123.9 (Pht 3, 6-*C*H's), 131.5 (Pht *ipso C*), 134.6 (Pht 4, 5-*C*H's), 166.5, 168.8, and 171.3 (3×*C*=O); and LRMS [DCI (NH_3)] *m*/*z* 347 (MH^+, 20%), 187 ($PhtCHCO^+$, 20), 160 ($MH^+-PhtCHCO$, 100), 142 ($M^+-PhtCHCO-H_2O$, 55), and 100 ($Me_2C{=}CH-CO_2H^+$, 20).

Benzyl (+)-(2*S*,5*R*,6*R*)-3,3-dimethyl-7-oxo-6-phthalimido-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (11). To a stirred solution of acid **10** (26.1 g, 75.4 mmol) in DMF (135 ml) was added triethylamine (10.5 ml, 75.4 mmol) followed by benzyl bromide (11.5 ml, 96.7 mmol). The mixture was stirred at room temperature for 6 h and then poured into vigorously stirred ice water (700 ml). The resulting suspension was extracted with $CHCl_3$ (3×250 ml) and the combined organic layers were washed with satd. $NaHCO_3$ (3×150 ml), water (3×150 ml), and satd. brine (150 ml). The organic phase was dried over $MgSO_4$ and evaporated in vacuo to give a light yellow oil which was crystallised from Et_2O to afford ester **10** (23.5 g, 71%). The two polymorphic forms of penam **11** were also distinguished by X-ray powder diffraction analysis [Fig. 5, Form I (left) and Form II (right)].

White crystalline solid; mp 136–138°C (Form I) and 153–154°C (Form II) (both from Me_2CO) {lit.[14] mp 138–140°C (from Me_2CO-Et_2O)}; (Found: C, 63.38; H, 4.49; N, 6.42. Calcd for $C_{23}H_{20}N_2O_5S$: C, 63.28; H, 4.63; N, 6.42%); R_f 0.60 (petrol 40/60: EtOAc, 6:4); $[\alpha]_D^{25}=+269$ (*c* 1.1 in $CHCl_3$) {lit.[14] $[\alpha]_D^{25}=+253$ (*c* 1.0 in $CHCl_3$)}; FT IR ($CHCl_3$) ν_{max}/cm^{-1} 1799s and 1789s (β-lactam, phthalimide), 1729s (phthalimide, ester), and 1387*S*; FT IR (KBr disc, Form I) ν_{max}/cm^{-1} 1777s (split in three; β-lactam, phthalimide), 1741m (phthalimide), 1725s (ester), 1468w, 1394s, 1371m, 1313s, 1218w, 1198s, 1179m, 1155m, 1096m, 1086m, 959m, 937w, 925m, 893w, 764w, 747m, 729w, 713m, and 703m; FT IR (KBr disc, Form II) ν_{max}/cm^{-1} 1803s (phthalimide), 1776m (β-lactam), 1746s (phthalimide), 1723s (ester), 1467w (split in two), 1386s sh, 1303m, 1241w, 1202s, 1186m, 1160m, 1131w, 1109m, 1079m, 959w, 934w, 893w, 750w, 726m, and 699w; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.44 and 1.80 (2×3H, 2×s, 2×C*H*$_3$), 4.70 (1H, s, 2-*H*), 5.22 (2H, s, C*H*$_2$Ph), 5.60 and 5.67 (2×1H, 2×d, *J*=4 Hz, 5-*H* and 6-*H*), 7.39 (5H$_{arom}$, s, Ph), and 7.74–7.90 (4H$_{arom}$, m, Pht); ^{1}H NMR n.O.e. (500 MHz, $CDCl_3$) δ_H 1.44 α-C*H*$_3$→β-C*H*$_3$ (4.5%), →2-*H* (3.0%), →5-*H* (6.0%); 1.80 β-C*H*$_3$→α-C*H*$_3$ (4.5%), →2-*H* (16%); 4.70 2-*H*→β-C*H*$_3$ (3.0%); 5.60 5-*H*→α-C*H*$_3$ (1.5%), →6-*H* (11%); and 5.67 6-*H*→5-*H* (8.0%); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C 27.78 and 30.95 (q, 2×*C*H$_3$), 58.46, 66.94, and 70.87 (d, 2-*C*, 5-*C*, and 6-*C*), 66.07 (s, 3-*C*), 67.47 (t, *C*H$_2$Ph), 124.0 (d, Pht 3, 6-*C*H's), 128.9, 128.9, and 129.2 (d, Ph *C*H's), 131.6 (s, Pht *ipso C*), 134.8 (d, Pht 4, 5-*C*H's), 1345.0 (s, Ph *ipso C*), 166.9, 168.1, and 168.6 (s, 3×*C*=O); and LRMS [DCI (NH_3)] *m*/*z* 454 (MNH_4^+, 5%), 437 (MH^+, 50), 250 ($MH^+-PhtCHCO$, 100), 187 ($PhtCHCO^+$, 10), and 91 ($C_7H_7^+$, 35).

Benzyl (+)-(2*S*,5*R*,6*S*)-3,3-dimethyl-7-oxo-6-phthalimido-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (12). The title compound was synthesised according to the either one of the two following methods.

The first method—using DBU. To a solution of ester **11** (35.1 g, 80.5 mmol) in CH_2Cl_2 (300 ml) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.8 ml, 5.4 mmol) and the mixture was stirred at room temperature for 90 min. The solution was washed with 1 M NH_4Cl (2×150 ml), water (3×200 ml), and satd. brine (100 ml). The organic phase was dried over $MgSO_4$ and evaporated in vacuo to afford a white foam (34.8 g). Purification by flash chromatography (silica gel, benzene/EtOAc, 9:1) gave ester **12** (34.3 g, 98%) identical [^{1}H NMR (200 MHz), TLC, and FT IR] with the product of the second method.

The second method—using sodium hydride. Sodium hydride (~60% w/w suspension in mineral oil, 95 mg, ~2.4 mmol) was pre-washed with THF (2×5 ml) and added, as a suspension in THF (5 ml), to a solution of ester **11** (1.04 g, 2.38 mmol) in THF (40 ml). The mixture was stirred at room temperature for 17 h and then the

solvent evaporated in vacuo. The residual oil was dissolved in EtOAc (50 ml) and quenched with water (5 ml). The organic phase was washed with water (3×20 ml) and satd. brine (10 ml), dried over $MgSO_4$, and evaporated in vacuo to afford a yellow foam (980 mg). Purification as described in the first method gave the title compound **12** (884 mg, 85%): white crystalline solid; mp 115–116°C (from EtOAc/petrol 40/60); (Found: C, 63.16; H, 4.31; N, 6.30. Calcd for $C_{23}H_{20}N_2O_5S$: C, 63.28; H, 4.63; N, 6.42%); R_f 0.50 (C_6H_6/EtOAc, 9:1); $[\alpha]_D^{25}=+195$ (*c* 1.8 in $CHCl_3$); FT IR ($CHCl_3$) ν_{max}/cm^{-1} 1778s br (β-lactam, phthalimide), 1728s (phthalimide, ester), and 1390s; ^1H NMR (200 MHz, $CDCl_3$) δ_H 1.43 and 1.64 (2×3H, 2×s, 2×CH_3), 4.67 (1H, s, 2-*H*), 5.23 (2H, s, CH_2Ph), 5.40 and 5.58 (2×1H, 2×d, *J*=2 Hz, 5-*H* and 6-*H*), 7.36–7.39 (5H_{arom}, m, Ph), and 7.76–7.93 (4H_{arom}, m, Pht); ^1H NMR n.O.e. (500 MHz, $CDCl_3$) δ_H 1.43 α-CH_3→β-CH_3 (7.5%), →2-*H* (9.0%), →5-*H* (4.5%); 1.64 β-CH_3→α-CH_3 (6.5%), →2-*H* (20%), →6-*H* (12%), →5-*H* (1.5%); 4.67 2-*H*→α-CH_3 (1.5%), →β-CH_3 (4.0%), →6-*H* (1.0%), →5-*H* (1.5%); 5.40 6-*H*→β-CH_3 (2.0%), →5-*H* (3.5%); and 5.58 5-*H*→2-*H* (1.0%), →6-*H* (3.0%); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C 25.19 and 34.47 (q, 2×*C*H_3), 64.35 and 69.09 (d, 2-*C*, 5-*C*, and 6-*C*; two signals overlapped), 67.15 (s, 3-*C*), 67.31 (t, *C*H_2Ph), 124.1 (d, Pht 3, 6-*C*H's), 128.5, 128.7, and 128.9 (d, Ph *C*H's), 131.1 (s, Pht *ipso C*), 134.9 (d, Pht 4, 5-*C*H's), 135.1 (s, Ph *ipso C*), 166.7, 167.3, and 167.6 (s, 3×*C*=O); and LRMS [DCI (NH_3)] *m*/*z* 454 (MNH_4^+, 15%), 437 (MH^+, 25), 250 (MH^+−PhtCHCO, 100), 187 (PhtCHCO$^+$, 5), and 91 ($C_7H_7^+$, 40).

Benzyl (−)-(2*S*,5*S*,6*S*)-3,3-dimethyl-7-oxo-6-phthalimido-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (26). *The general procedure for the Kukolja protocol*. A solution of ester **12** (1.55 g, 3.56 mmol) in CH_2Cl_2 (40 ml) and CCl_4 (20 ml) was treated with the equimolar amount of chlorine (3.56 mmol, solution in CCl_4) and stirred at room temperature for 30 min. The solvents were evaporated in vacuo to give a mixture of two compounds, **24** and **25**, in a ratio of ca. 4:1 as a yellow foam. Major product: benzyl (2*S*)-2-[(3*S*,4*R*)-4-chloro-3-phthalimido)-2-oxazetidin-1-yl]-2-(1-chlorothio-1-methylethyl)-acetate 24; ^1H NMR (200 MHz, $CDCl_3$) δ_H 1.76 (6H, s, 2×CH_3), 4.41 (1H, s, 2-*H*), 5.24 and 5.32 (2×1H, ABq, *J*=12 Hz, CH_2Ph), 5.49 and 6.12 (2×1H, 2×d, *J*=1.5 Hz, 3-*H* and 4-*H*), 7.42 (5H_{arom}, s, Ph), and 7.79–7.94 (4H_{arom}, m, Pht). Minor product: benzyl (2*S*)-2-[(3*S*,4*S*)-4-chloro-3-phthalimido)-2-oxazetidin-1-yl]-2-(1-chlorothio-1-methylethyl)-acetate **25**; ^1H NMR (200 MHz, $CDCl_3$) δ_H 1.70 and 1.75 (2×3H, 2×s, 2×CH_3), 4.49 (1H, s, 2-*H*), 5.21 and 5.34 (2×1H, ABq, *J*=12 Hz, CH_2Ph), 5.53 and 5.94 (2×1H, 2×d, *J*=4 Hz, 3-*H* and 4-*H*), 7.42 (5H_{arom}, s, Ph), and 7.79–7.94 (4H_{arom}, m, Pht).

The foam was dissolved in THF (50 ml) and treated with anhydrous $SnCl_2$ (715 mg, 3.77 mmol). The mixture was stirred at room temperature for 2 h and then the solvent was evaporated in vacuo. The residual oil was dissolved in EtOAc (50 ml) and washed with water (3×50 ml) and satd. brine (50 ml). The organic phase was dried over $MgSO_4$ and evaporated in vacuo to give a white foam (1.47 g). Flash chromatography (silica gel, benzene/EtOAc, 10:1) afforded the starting material **12** (837 mg, 54%) and the title compound **26** (470 mg, 30 or 66% if based on recovered ester **12**). Penam **26**: white crystalline solid, mp 127–128°C (from petrol 40/60–EtOAc); (Found: C, 63.49; H, 4.39; N, 6.38. Calcd for $C_{23}H_{20}N_2O_5S$: C, 63.28; H, 4.63; N, 6.42%); R_f 0.30 (C_6H_6/EtOAc, 10:1); $[\alpha]_D^{25}=-282$ (*c* 1.1 in $CHCl_3$); FT IR ($CHCl_3$) ν_{max}/cm^{-1} 1796s, 1780m (β-lactam, phthalimide), 1730s (phthalimide, ester), and 1389s; ^1H NMR (200 MHz, $CDCl_3$) δ_H 1.69 and 1.70 (2×3H, 2×s, 2×CH_3), 4.03 (1H, s, 2-*H*), 5.27 and 5.62 (2×1H, 2×d, *J*=4 Hz, 5-*H* and 6-*H*), 5.30 and 5.36 (2×1H, ABq, *J*=12 Hz, CH_2Ph), 7.34–7.49 (5H_{arom}, s, Ph), and 7.74–7.92 (4H_{arom}, m, Pht); ^1H NMR n.O.e. (500 MHz, $CDCl_3$, frequency cycling) δ_H 1.69 β-CH_3→2-*H* (17%), →5-*H* (3.0%); 1.70 α-CH_3→2-*H* (3.0%); 4.03 2-*H*→α-CH_3 and β-CH_3 (5.5%), →5-*H* (5.5%); 5.27 5-*H*→α-CH_3 and β-CH_3 (7.5%), →2-*H* (6.0%), →6-*H* (15%); and 5.62 6-*H*→α-CH_3 and β-CH_3 (2.0%), →5-*H* (13%); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C 27.25 and 30.03 (q, 2×*C*H_3), 59.01, 63.20, and 72.95 (d, 2-*C*, 5-*C*, and 6-*C*), 64.94 (s, 3-*C*), 67.77 (t, *C*H_2Ph), 124.0 (d, Pht 3, 6-*C*H's), 128.8 and 129.0 (d, Ph *C*H's), 131.7 (s, Pht *ipso C*), 134.7 (d, Pht 4, 5-*C*H's), 135.1 (s, Ph *ipso C*), 165.1, 165.4, and 166.9 (s, 3×*C*=O); and LRMS [DCI (NH_3)] *m*/*z* 454 (MNH_4^+, 15%), 437 (MH^+, 50), 250 (MH^+−PhtCHCO, 100), 187 (PhtCHCO$^+$, 20), and 91 ($C_7H_7^+$, 95).

According to the general procedure, the following syntheses were also carried out.

Benzyl (−)-(2*S*,5*S*,6*R*)-3,3-dimethyl-7-oxo-6-phthalimido-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (15). Chlorinolysis of ester **11** (2.40 g, 5.50 mmol) gave a mixture of two β-lactams, **13** and **14**, in a ratio of ca. 4:1 as a light yellow foam (2.81 g). Major product: benzyl (2*S*)-2-[(3*R*,4*S*)-4-chloro-3-phthalimido)-2-oxazetidin-1-yl]-2-(1-chlorothio-1-methylethyl)-acetate **13**; ^1H NMR (200 MHz, $CDCl_3$) δ_H 1.72 and 1.74 (2×3H, 2×s, 2×CH_3), 4.65 (1H, s, 2-*H*), 5.27 and 5.37 (2×1H, ABq, *J*=12 Hz, CH_2Ph), 5.55 and 6.04 (2×1H, 2×d, *J*=1.5 Hz, 3-*H* and 4-*H*), 7.36–7.46 (5H_{arom}, m, Ph), and 7.79–7.95 (4H_{arom}, m, Pht). Minor product: benzyl (2*S*)-2-[(3*R*,4*R*)-4-chloro-3-phthalimido)-2-oxazetidin-1-yl]-2-(1-chlorothio-1-methylethyl)-acetate **14**; ^1H NMR (200 MHz, $CDCl_3$) δ_H 1.61 and 1.74 (2×3H, 2×s, 2×CH_3), 4.79 (1H, s, 2-*H*), 5.26 and 5.38 (2×1H, ABq, *J*=12 Hz, CH_2Ph), 5.62 and 6.23 (2×1H, 2×d, *J*=4 Hz, 3-*H* and 4-*H*), 7.36–7.46 (5H_{arom}, m, Ph), and 7.79–7.95 (4H_{arom}, m, Pht). Cyclisation in the presence of anhydrous $SnCl_2$ (1.10 g, 5.81 mmol) gave an off-white foam (2.42 g) containing two compounds, **15** and **11**, in a ratio of ca. 16:1. Purification by flash chromatography (silica gel, petrol 40/60–EtOAc, 6:4) afforded penam **15** (2.22 g, 92.5%): white foam; HRMS Calcd for $C_{23}H_{21}O_5N_2S$ (MH^+) 437.1188, found 437.1171; R_f 0.50 (petrol 40/60–EtOAc, 6:4); $[\alpha]_D^{25}=-123$ (*c* 1.0 in $CHCl_3$) {lit.[14] $[\alpha]_D^{25}=-104$ (*c* 1.0 in $CHCl_3$)}; FT IR ($CHCl_3$) ν_{max}/cm^{-1} 1790s and 1780m (β-lactam, phthalimide), 1728s (phthalimide, ester), and 1391s; ^1H NMR (200 MHz, $CDCl_3$) δ_H 1.39 and 1.66 (2×3H, 2×s, 2×CH_3), 3.92 (1H, s, 2-*H*), 5.23 and 5.30 (2×1H, ABq, *J*=12 Hz, CH_2Ph), 5.44 and 5.56 (2×1H, 2×d, *J*=2 Hz, 5-*H* and 6-*H*), 7.36–7.41 (5H_{arom}, m, Ph), and 7.75–7.94 (4H_{arom}, m, Pht); ^1H NMR n.O.e. (500 MHz, $CDCl_3$) δ_H 1.39 α-CH_3→β-CH_3 (4.5%), →2-*H* (6.0%), →6-*H* (4.5%); 1.66 β-CH_3→α-CH_3 (8.0%), →2-*H* (18%), →5-*H* (17%); 3.92 2-*H*→β-CH_3 (4.5%), →5-*H*

(2.0%); 5.44 5-*H*→β-C*H*$_3$ (3.5%), →2-*H* (2.0%), →6-*H* (3.5%); and 5.56 6-*H*→5-*H* (1.5%); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C 24.52 and 31.24 (q, 2×*C*H$_3$), 59.70, 66.40, and 70.15 (d, 2-*C*, 5-*C*, and 6-*C*), 66.14 (s, 3-*C*), 67.88 (t, *C*H$_2$Ph), 124.0 (d, Pht 3, 6-*C*H's), 128.9 and 129.1 (d, Ph *C*H's), 131.7 (s, Pht *ipso C*), 134.9 (d, Pht 4, 5-*C*H's), 134.9 (s, Ph *ipso C*), 166.0, 166.8, and 166.9 (s, 3×*C*=O); and LRMS [DCI (NH_3)] *m/z* 454 (MNH_4^+, 5%), 437 (MH^+, 5), 250 (MH^+−PhtCHCO, 100), 187 (PhtCHCO$^+$, 5), and 91 ($C_7H_7^+$, 40).

Methyl (−)-(2*S*,5*S*,6*S*)-3,3-dimethyl-7-oxo-6-phthalimido-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (30). Chlorinolysis of ester **27**[§§] (501 mg, 1.39 mmol) gave a mixture of two monocyclic β-lactams, **28** and **29**, in a ratio of ca. 5:1 as a light yellow foam (585 mg) Major product: methyl (2*S*)-2-[(3*R*,4*S*)-4-chloro-3-phthalimido)-2-oxazetidin-1-yl]-2-(1-chlorothio-1-methylethyl)-acetate **28**; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.68 and 1.72 (2×3H, 2×s, 2×C*H*$_3$), 3.83 (3H, s, CO_2CH_3), 4.34 (1H, s, 2-*H*), 5.52 and 6.12 (2×1H, 2×d, *J*=1.5 Hz, 3-*H* and 4-*H*), and 7.75–7.91 (4H$_{arom}$, m, Pht). Minor product: methyl (2*S*)-2-[(3*R*,4*R*)-4-chloro-3-phthalimido)-2-oxazetidin-1-yl]-2-(1-chlorothio-1-methylethyl)-acetate **29**; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.68 and 1.72 (2×3H, 2×s, 2×C*H*$_3$), 3.83 (3H, s, CO_2CH_3), 4.49 (1H, s, 2-*H*), 5.65 and 6.01 (2×1H, 2×d, *J*=4 Hz, 3-*H* and 4-*H*), and 7.75–7.91 (4H$_{arom}$, m, Pht). Cyclisation in the presence of anhydrous $SnCl_2$ (279 mg, 1.47 mmol) gave a pale yellow foam (495 mg) containing two compounds, **27** and **30**, in a ratio of ca. 1.5:1. Separation and purification by flash chromatography (silica gel, CH_2Cl_2/EtOAc, 35:1) gave penam **27** (275 mg, 55%) and the title compound **30** (163 mg, 33% or 72% if base on recovered ester **27**). Penam **30**: white crystalline solid; mp 164–166°C (from EtOAc/petrol 30/40); (Found: C, 56.88; H, 4.28; N, 7.65. Calcd for $C_{17}H_{16}N_2O_5S$: C, 56.66; H, 4.47; N, 7.77%); R_f 0.40 (CH_2Cl_2/EtOAc, 35:1); $[\alpha]_D^{25}$=−334 (*c* 1.2 in $CHCl_3$); FT IR (KBr disc) ν_{max}/cm^{-1} 1809m, 1797s (phthalimide), 1780s (β-lactam), 1752s (phthalimide), 1731s (ester), 1388s, 1252m, 1222m, 901m, and 715s; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.71 and 1.73 (2×3H, 2×s, 2×C*H*$_3$), 3.91 (3H, s, CO_2CH_3), 4.01 (1H, s, 2-*H*), 5.29 and 5.63 (2×1H, 2×d, *J*=4 Hz, 5-*H* and 6-*H*), and 7.73–7.92 (4H$_{arom}$, m, Pht); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 27.23 and 30.25 (2×*C*H$_3$), 52.55 (CO_2CH_3), 59.02, 63.46, 64.93, and 72.96 (2-*C*, 3-*C*, 5-*C*, and 6-*C*), 123.8 (Pht 3, 6-*C*H's), 131.6 (Pht *ipso C*), 134.4 (Pht 4, 5-*C*H's), 165.0, 165.5 and 166.5 (3×*C*=O); and LRMS [DCI (NH_3)] *m/z* 378 (MNH_4^+, 15%), 361 (MH^+, 30), 204 (10), 187 (PhtCHCO$^+$, 10), 174 (MH^+−PhtCHCO, 100), and 132 (10).

Diphenylmethyl (−)-(2*S*,5*S*,6*S*)-3,3-dimethyl-7-oxo-6-phthalimido-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (34). Chlorinolysis of ester **31**[§§] (405 mg, 0.79 mmol) gave two compounds, **32** and **33**, in a ratio of ca. 9:1, as a light yellow foam (470 mg). Major product: diphenylmethyl (2*S*)-2-[(3*R*,4*S*)-4-chloro-3-phthalimido)-2-oxazetidin-1-yl]-2-(1-chlorothio-1-methylethyl)-acetate **32**; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.66 and 1.71 (2×3H, 2×s, 2×C*H*$_3$), 4.45 (1H, s, 2-*H*), 5.42 and 6.08 (2×1H, 2×d, *J*=1.5 Hz, 3-*H* and 4-*H*), 6.99 (1H, s, C*H*Ph$_2$), 7.31–7.51 (10H$_{arom}$, m, 2×Ph), and 7.77–7.95 (4H$_{arom}$, m, Pht). Minor product: diphenylmethyl (2*S*)-2-[(3*R*,4*R*)-4-chloro-3-phthalimido)-2-oxazetidin-1-yl]-2-(1-chlorothio-1-methylethyl)-acetate **33**; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.65 and 1.77 (2×3H, 2×s, 2×C*H*$_3$), 4.51 (1H, s, 2-*H*), 5.47 and 5.79 (2×1H, 2×d, *J*=4 Hz, 3-*H* and 4-*H*), 6.99 (1H, s, C*H*Ph$_2$), 7.31–7.51 (10H$_{arom}$, m, 2×Ph), and 7.77–7.95 (4H$_{arom}$, m, Pht). Cyclisation in the presence of anhydrous $SnCl_2$ (158 mg, 0.84 mmol) gave a pale yellow foam (357 mg). Purification by flash chromatography (silica gel, petrol 40/60/EtOAc, 7:3) afforded the starting material **31** (158 mg, 39%) and the title compound **34** (60 mg, 14.5 or 24% if based on recovered **31**). Penam **34**: white crystalline solid; mp 175–176°C (from EtOAc/petrol 40/60); (Found: C, 68.15; H, 4.70; N, 5.50. Calcd for $C_{29}H_{24}N_2O_5S$: C, 67.95; H, 4.72; N, 5.47%); R_f 0.35 (petrol 40/60/EtOAc, 7:3); $[\alpha]_D^{25}$=−216 (*c* 0.65 in acetone); FT IR (KBr disc) ν_{max}/cm^{-1} 1805m (phthalimide), 1779s (β-lactam), 1754s (phthalimide), 1727s (ester), 1399s, and 1175s; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.63 and 1.73 (2×3H, 2×s, 2×C*H*$_3$), 4.10 (1H, s, 2-*H*), 5.27 and 5.66 (2×1H, 2×d, *J*=4 Hz, 5-*H* and 6-*H*), 7.07 (1H, s, C*H*Ph$_2$), 7.28–7.54 (10H$_{arom}$, m, 2×Ph), and 7.71–7.92 (4H$_{arom}$, m, Pht); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 27.41 and 29.96 (2×*C*H$_3$), 59.06, 63.07, 65.13, 73.37, and 79.36 (2-*C*, 3-*C*, 5-*C*, 6-*C*, and *C*HPh$_2$), 123.8 (Pht 3, 6-*C*H's), 126.9, 127.7, 128.0, 128.3, 128.5, and 128.7 (Ph's *C*H's), 131.5 (Pht *ipso C*), 134.5 (Pht 4, 5-*C*H's), 139.3 (Ph *ipso C*), 164.2, 165.0, and 166.6 (3×*C*=O); LRMS [DCI (NH_3)] *m/z* 530 (MNH_4^+, <1%), 512 (M^+, <1), 326 (MH^+−PhtCHCO, <1), and 167 (Ph_2CH^+, 100); and LRMS (FAB, +) *m/z* 535 (MNa^+, 20) and 167 (Ph_2CH^+, 100).

Diphenylmethyl (2*S*,5*S*)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (46). Chlorinolysis of ester **43**[‖‖] [38,39] (455 mg, 1.24 mmol) gave two compounds, diphenylmethyl (2*S*)-2-[(4*S* and 4*R*)-4-chloro-2-oxazetidin-1-yl]-2-(1-chlorothio-1-methylethyl)-acetates, **44** and **45**, in a ratio of ca. 2.5:1 as a thick yellow oil (517 mg). Major product **44**: ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.55 and 1.59 (2×3H, 2×s, 2×C*H*$_3$), 3.18 (1H, dd, *J*=15.5 Hz, *J*=1.5 Hz, 3-*H trans* to 4-*H*), 3.57 (1H, dd, *J*=15.5 Hz, *J*=4 Hz, 3-*H cis* to 4-*H*), 4.36 (1H, s, 2-*H*), 5.80 (1H, dd, *J*=4 Hz, *J*=1.5 Hz, 4-*H*), 6.94 (1H, s, C*H*Ph$_2$), and 7.28–7.52 (10H$_{arom}$, m, 2×Ph). Minor product **45**: ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.58 and 1.61 (2×3H, 2×s, 2×C*H*$_3$), 3.18 (1H, dd, *J*=15.5 Hz, *J*=1.5 Hz, 3-*H*

[§§] Penam **27** was obtained from acid **10** by esterification with CH_2N_2 (CH_2Cl_2, rt, 5 min, 93%) followed by treatment of the resulting ester **16** with a catalytic amount of DBU (CH_2Cl_2, rt, 90 min, 98%). Penam **31** was prepared in a one-pot process from acid **10** by esterification with Ph_2CN_2 (CH_2Cl_2, 5 min, rt) followed by a catalytic amount of DBU (CH_2Cl_2, rt, 90 min, 69% overall).

[‖‖] Penam **35** was obtained from (6*S*)-bromopenicillanic acid[38,39] by esterification with BnBr (Et_3N, DMF, rt, 15 h, 67%) followed by dehalogenation with *n*-Bu_3SnH (PhH, reflux, 15 h, 97%) or from 6,6-dibromopenicillanic acid[40] by benzylation with BnBr (Et_3N, DMF, 10 h, 63%) followed by reductive dehalogenation with n-Bu_3SnH (PhH, reflux, 24 h, 81%). Similarly, penam **43** was prepared from (6*S*)-bromopenicillanic acid by esterification with Ph_2CN_2 (CH_2Cl_2, 5 min, 86%) followed by reduction with n-Bu_3SnH (AIBN, PhH, rt, 15 h, 59%). Penam **39** was prepared from (6*S*)-bromopenicillanic acid by esterification with CH_2N_2 (Et_2O, 5 min, 83%) followed by catalytic hydrogenation (H_2, Pd/$CaCO_3$, 1 atm, 3 h, 62%).

trans to 4-*H*), 3.52 (1H, dd, *J*=15.5 Hz, *J*=4 Hz, 3-*H cis* to 4-*H*), 4.49 (1H, s, 2-*H*), 5.55 (1H, dd, *J*=4 Hz, *J*=1.5 Hz, 4-*H*), 6.94 (1H, s, C*H*Ph_2), and 7.28–7.52 (10H_{arom}, m, 2×Ph). Cyclisation in the presence of anhydrous $SnCl_2$ (249 mg, 1.31 mmol) gave a thick yellow oil containing two compounds; the starting material **43** and its 5-epimer **46** in a ratio of ca. 8:1. Separation and purification by flash chromatography (silica gel, petrol 40/60/EtOAc, 6:1) afforded the starting material **43** (174 mg, 38%) and penam **46** (18 mg, 4 or 6.5% if based on recovered substrate **43**). Penam **46**: white solid; HRMS Calcd for $C_{21}H_{25}O_3N_2S$ (MNH_4^+) 385.1603, found 385.1586; R_f 0.25 (petrol 40/60/EtOAc, 6:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.29 and 1.62 (2×3H, 2×s, 2×CH_3), 3.18 (1H, dd, *J*=16 Hz, *J*=2 Hz, 6-α-*H*), 3.43 (1H, dd, *J*=16 Hz, *J*=4 Hz, 6-β-*H*), 3.85 (1H, s, 2-*H*), 5.08 (1H, dd, *J*=4 Hz, *J*=2 Hz, 5-*H*), 6.99 (1H, s, C*H*Ph_2), and 7.27–7.40 (10H_{arom}, m, 2×Ph); ^{1}H NMR n.O.e. (500 MHz, $CDCl_3$) δ_H 1.29 α-CH_3→β-CH_3 (14%), →6-α-*H* (7.5%), →2-*H* (13%); 1.62 β-CH_3→α-CH_3 (7.0%), →2-*H* (22%), →5-*H* (11%); 3.18 6-α-*H*→6-β-*H* (26%); 3.43 6-β-*H*→6-α-*H* (25%), →5-*H* (5.5%); 3.85 2-*H*→β-CH_3 (10%), →5-*H* (3.0%); and 5.08 5-*H*→α→β-CH_3 (4.0%), →6-β-*H* (5.5%), →2-*H* (2.0%); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 25.52, 30.30, 45.21, 58.15, 65.38, 71.50, 78.88, 127.0, 127.9, 128.0, 128.3, 128.4, 128.5, 139.2, 139.3, 165.6, and 169.9; and LRMS [CI (NH_3)] *m/z* 385 (MNH_4^+, <1%), 167 (Ph_2CH^+, 100), and 114 ($MH^+-CH_2CO-CO_2CHPh_2$, 5).

Benzyl (−)-(2*S*,5*S*)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (38). Chlorinolysis of ester **35**[III] [40] (440 mg, 1.51 mmol) gave two compounds, benzyl (2*S*)-2-[(4*S* and 4*R*)-4-chloro-2-oxazetidin-1-yl]-2-(1-chlorothio-1-methylethyl)-acetates, **36** and **37**, in a ratio of ca. 2:1, as a yellow oil (507 mg). Major product **36**: ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.56 and 1.65 (2×3H, 2×s, 2×CH_3), 3.21 (1H, dd, *J*=15.5 Hz, *J*=1 Hz, 3-*H trans* to 4-*H*), 3.61 (1H, dd, *J*=15.5 Hz, *J*=4 Hz, 3-*H cis* to 4-*H*), 4.29 (1H, s, 2-*H*), 5.20 and 5.29 (2×1H, ABq, *J*=12 Hz, CH_2Ph), 5.86 (1H, dd, *J*=4 Hz, *J*=1 Hz, 4-*H*), and 7.39 (5H_{arom}, s, Ph). Minor product **37**: ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.62 (6H, s, 2×CH_3), 3.21 (1H, dd, *J*=15.5 Hz, *J*=1.5 Hz, 3-*H trans* to 4-*H*), 3.59 (1H, dd, *J*=15.5 Hz, *J*=4 Hz, 3-*H cis* to 4-*H*), 4.48 (1H, s, 2-*H*), 5.19 and 5.27 (2×1H, ABq, *J*=12 Hz, CH_2Ph), 5.70 (1H, dd, *J*=4 Hz, *J*=1.5 Hz, 4-*H*), and 7.39 (5H_{arom}, s, Ph). FT IR ($CHCl_3$) ν_{max}/cm^{-1} 1784s (β-lactam) and 1742s (ester). Cyclisation with anhydrous $SnCl_2$ (304 mg, 1.60 mmol) afforded a mixture of the starting material **35** and its 5-epimer **38**, in a ratio of ca. 3:1. Separation and purification by flash chromatography (silica gel, CH_2Cl_2/EtOAc, 30:1) gave the starting material **35** (216 mg, 49%) and penam **38** (87 mg, 20 or 39% if based on recovered substrate **35**). Penam **38**: colourless oil; HRMS Calcd for $C_{15}H_{18}NO_3S$ (MH^+) 292.1024, found 292.1007; R_f 0.70 (CH_2Cl_2/EtOAc, 30:1); $[\alpha]_D^{25}$=−191 (*c* 1.0 in $CHCl_3$); FT IR ($CHCl_3$) ν_{max}/cm^{-1} 1779s (β-lactam) and 1745m (ester); ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.44 and 1.63 (2×3H, 2×s, 2×CH_3), 3.20 (1H, dd, *J*=15.5 Hz, *J*=2 Hz, 6-α-*H*), 3.42 (1H, dd, *J*=15.5 Hz, *J*=4 Hz, 6-β-*H*), 3.79 (1H, s, 2-*H*), 5.09 (1H, dd, *J*=4 Hz, *J*=2 Hz, 5-*H*), 5.24 (2H, s, CH_2Ph), and 7.35–7.43 (5H_{arom}, m, Ph); ^{1}H NMR n.O.e. (500 MHz, $CDCl_3$) δ_H 1.44 α-CH_3→β-CH_3 (3.0%), →2-*H* (5.0%); 1.63 β-CH_3→α-CH_3 (7.0%), →2-*H* (19%), →5-*H* (13%); 3.20 6-α-*H*→6-β-*H* (26%); 3.42 6-β-*H*→6-α-*H* (27%), →5-*H* (6.0%); 3.79 2-*H*→β-CH_3 (7.5%), →5-*H* (3.5%); and 5.09 5→β-CH_3 (2.5%), →6-β-*H* (5.0%), →2-*H* (2.5%); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C 25.27 and 30.42 (q, 2×CH_3), 44.85 (t, 6-CH_2), 58.35 and 71.72 (d, 2-*C* and 5-*C*), 65.38 (s, 3-*C*), 67.60 (t, CH_2Ph), 128.8 and 129.0 (d, Ph C*H*'s), 135.2 (s, Ph *ipso C*), 166.7 and 170.4 (s, 2×*C*=O); and LRMS [CI (NH_3)] *m/z* 309 (MNH_4^+, 5%), 292 (MH^+, 100), 250 (MH^+-CH_2CO, 35), and 114 ($MH^+-CH_2CO-CO_2CH_2Ph$, 20), and 91 ($C_7H_7^+$, 45).

Methyl (−)-(2*S*,5*S*)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (42). Chlorinolysis of ester **39**[III] (147 mg, 0.68 mmol) gave a brown oil (174 mg) containing two compounds, methyl (2*S*)-2-[(4*S* and 4*R*)-4-chloro-2-oxazetidin-1-yl]-2-(1-chlorothio-1-methylethyl)-acetates, **40** and **41**, in a ratio of ca. 2:1. Major product **40**: ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.54 and 1.66 (2×3H, 2×s, 2×CH_3), 3.23 (1H, dd, *J*=17 Hz, *J*=1.5 Hz, 3-*H trans* to 4-*H*), 3.61 (1H, dd, *J*=17 Hz, *J*=4 Hz, 3-*H cis* to 4-*H*), 3.79 (3H, s, CO_2CH_3), 4.22 (1H, s, 2-*H*), and 5.88 (1H, dd, *J*=4 Hz, *J*=1.5 Hz, 4-*H*). Minor product **41**: ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.60 and 1.61 (2×3H, 2×s, 2×CH_3), 3.22 (1H, dd, *J*=17 Hz, *J*=1.5 Hz, 3-*H trans* to 4-*H*), 3.64 (1H, dd, *J*=17 Hz, *J*=4 Hz, 3-*H cis* to 4-*H*), 3.78 (3H, s, CO_2CH_3), 4.46 (1H, s, 2-*H*), and 5.74 (1H, dd, *J*=4 Hz, *J*=1.5 Hz, 4-*H*). FT IR ($CHCl_3$) ν_{max}/cm^{-1} 1784s (β-lactam) and 1745s (ester). Cyclisation with anhydrous $SnCl_2$ (137 mg, 0.73 mmol) gave a light yellow oil (135 mg) containing the starting material **39** and its 5-epimer **42** in a ratio of ca. 5:1. Separation and purification by flash chromatography (silica gel, petrol 40/60/EtOAc, 7:3) gave the starting material **39** (104 mg, 71%) and penam **42** (31 mg, 21 or 72% if based on recovered substrate **39**). Penam **42**: light yellow solid; HRMS Calcd for $C_9H_{14}NO_3S$ (MH^+) 216.0711, found 216.0694; R_f 0.36 (petrol 40/60/EtOAc, 7:3); $[\alpha]_D^{25}$=−174 (*c* 0.45 in $CHCl_3$); FT IR ($CHCl_3$) ν_{max}/cm^{-1} 1779s (β-lactam) and 1748m (ester); ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.51 and 1.64 (2×3H, 2×s, 2×CH_3), 3.20 (1H, dd, *J*=16 Hz, *J*=2.5 Hz, 6-α-*H*), 3.42 (1H, ddd, *J*=16 Hz, *J*=4 Hz, *J*=1.5 Hz, 6-β-*H*), 3.76 (1H, d, *J*=1.5 Hz, 2-*H*), 3.82 (3H, s, CO_2CH_3), and 5.08 (1H, dd, *J*=4 Hz, *J*=2.5 Hz, 5-*H*); ^{1}H NMR n.O.e. (500 MHz, $CDCl_3$) δ_H 1.51 α-CH_3→β-CH_3 (5.0%), →6-α-*H* (4.0%), →2-*H* (4.0%); 1.64 β-CH_3→α-CH_3 (9.0%), →2-*H* (12%), →5-*H* (7.0%); 3.20 6-α-*H*→6-β-*H* (18%); 3.42 6-β-*H*→6-α-*H* (21%), →5-*H* (6.5%); 3.76 2-*H*→β-CH_3 (5.0%), →5-*H* (3.0%); and 5.08 5-*H*→β-CH_3 (4.0%), →6-β-*H* (5.0%); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 25.45, 30.45, 44.97, 52.35, 58.33, 65.13, 71.31, 166.9, and 170.1; and LRMS [CI (NH_3)] *m/z* 233 (MNH_4^+, 10%), 216 (MH^+, 100), 174 (MH^+-CH_2CO, 35), and 114 (10).

Benzyl (−)-(2*S*,4*S*,5*S*,6*S*)-3,3-dimethyl-7-oxo-6-phthalimido-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 4-oxide (49). Following the method for the preparation of ester **26**, penicillin **12** (1.01 g, 2.31 mmol) was converted to a mixture of esters **12** and **26** in a ratio of ca. 1:2, respectively. The mixture was dissolved in acetone (50 ml), cooled in an ice bath, and treated with a stream of ozone until ester **26** had reacted (^{1}H NMR, 200 MHz). The solvent was evaporated in vacuo to give a white foam (999 mg).

Purification by flash chromatography (silica gel, CH_2Cl_2/EtOAc, 4:1) afforded the starting material **12** (610 mg, 60%) and sulfoxide **49** (265 mg, 25 or 64% if based on recovered penam **12**). Sulfoxide **49**: white crystalline solid; mp 125–126°C (from EtOAc); (Found: C, 61.29; H, 4.70; N, 6.14. Calcd for $C_{23}H_{20}N_2O_6S$: C, 61.04; H, 4.46; N, 6.19%); R_f 0.35 (CH_2Cl_2/EtOAc, 8:2); $[\alpha]_D^{25}=-74.9$ (*c* 1.1 in $CHCl_3$); FT IR ($CHCl_3$) ν_{max}/cm^{-1} 1809s (β-lactam), 1780m (phthalimide), 1732s (phthalimide, ester), 1309s, and 1054m br (sulfoxide); ^1H NMR (200 MHz, $CDCl_3$) δ_H 1.54 and 1.61 (2×3H, 2×s, 2×C*H*$_3$), 4.30 (1H, s, 2-*H*), 4.56 and 5.93 (2×1H, 2×d, *J*=4 Hz, 5-*H* and 6-*H*), 5.30 and 5.39 (2×1H, ABq, *J*=12 Hz, C*H*$_2$Ph), 7.36–7.49 (5H$_{arom}$, m, Ph), and 7.76–7.94 (4H$_{arom}$, m, Pht); ^1H NMR n.O.e. (500 MHz, $CDCl_3$) δ_H 1.54 β-C*H*$_3$→2-*H* (16%), →5-*H* (6.5%); 1.61 α-C*H*$_3$→2-*H* (2.5%); 4.30 2-*H*→β-C*H*$_3$ (4.0%), →5-*H* (4.5%); 4.56 5-*H*→β-C*H*$_3$ (1.5%), →2-*H* (5.0%), →6-*H* (16%); and 5.93 6-*H*→5-*H* (14%); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C 19.77 and 20.51 (q, 2×*C*H$_3$), 54.96, 63.34, and 84.32 (d, 2-*C*, 5-*C*, and 6-*C*), 68.10 (t, *C*H$_2$Ph), 73.85 (s, 3-*C*), 124.2 (d, Pht 3, 6-*C*H's), 128.9 and 129.2 (d, Ph *C*H's), 131.6 (s, Pht *ipso C*), 134.8 (s, Ph *ipso C*), 135.1 (d, Pht 4, 5-*C*H's), 163.5, 164.9, and 166.7 (s, 3×*C*=O); and LRMS [DCI (NH_3)] *m/z* 452 (M^+, 30%), 435 (MH^+-H_2O, 50), 248 ($MH^+-PhtCHCO-H_2O$, 100), 187 ($PhtCHCO^+$, 40), and 91 ($C_7H_7^+$, 100).

Competitive sulfoxidation of benzyl 6-phthalimidopenicillanates with ozone—general procedure

A solution of 'Penam 1' (200 mg, 0.46 mmol) and 'Penam 2' (200 mg, 0.46 mmol) in acetone (50 ml) was cooled in an ice bath and treated, during vigorous stirring, with a stream of ozone (O_3/O_2 mixture, ca. 0.14 mmol O_3/min). The reaction progress was monitored by ^1H NMR (200 MHz) and the reaction was stopped when ca. 50% of the more reactive penam was sulfoxidised. The solvent was evaporated in vacuo to give a white foam which was analysed by ^1H NMR (200 MHz). The results presented in Scheme 5 correspond to the final ratio of the appropriate sulfoxides, determined from ^1H NMR (200 MHz) spectra.

Benzyl (+)-(6*S*,7*S*)-3-methyl-8-oxo-7-phthalimido-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (50). A solution of sulfoxide **49** (500 mg, 1.11 mmol) and anhydrous *p*-toluenesulfonic acid (*p*TSA, 25 mg, 0.15 mmol) in DMF (20 ml) was stirred at 100°C until sulfoxide **49** had reacted (ca. 90 min). The reaction mixture was cooled in an ice bath and the solvent evaporated in vacuo. The residual yellow oil was dissolved in EtOAc (50 ml) and washed with satd. $NaHCO_3$ (50 ml), water (3×50 ml), and satd. brine (50 ml). The organic layer was dried over $MgSO_4$ and evaporated in vacuo to give a yellow foam (467 mg). Purification by flash chromatography (silica gel, CH_2Cl_2/EtOAc, 15:1) afforded cephalosporin **50** (238 mg, 50%): white crystalline solid; mp 147–149°C (from EtOAc); (Found: C, 63.88; H, 3.84; N, 6.42. Calcd for $C_{23}H_{18}N_2O_5S$: C, 63.58; H, 4.18; N, 6.42%); R_f 0.60 (CH_2Cl_2/EtOAc, 15:1); $[\alpha]_D^{25}=+11.1$ (*c* 1.1 in $CHCl_3$); FT IR ($CHCl_3$) ν_{max}/cm^{-1} 1785s br (β-lactam, phthalimide) 1726s (ester, phthalimide), and 1392s; ^1H NMR (200 MHz, $CDCl_3$) δ_H 2.33 (3H, s, C*H*$_3$), 3.01 and 3.63 (2×1H, ABq, *J*=18 Hz, SC*H*$_2$), 5.11 and 5.74 (2×1H, 2×d, *J*=4 Hz, 6-*H* and 7-*H*), 5.24 and 5.33 (2×1H, ABq, *J*=12 Hz, C*H*$_2$Ph), 7.36–7.42 (5H$_{arom}$, m, Ph), and 7.76–7.92 (4H$_{arom}$, m, Pht); ^{13}C NMR[¶] (50.3 MHz, $CDCl_3$) δ_C 20.25 (q, *C*H$_3$), 31.64 (t, S*C*H$_2$), 59.37 (d, 6-*C* and 7-*C*, overlapped), 67.27 (t, *C*H$_2$Ph), 124.1 (d, Pht 3, 6-*C*H's), 128.5 and 128.8 (d, Ph *C*H's), 131.7 (s, Pht *ipso C*), 134.9 (d, Pht 4, 5-*C*H's), 135.6 (s, Ph *ipso C*), 161.4, 162.2, and 167.2 (s, 3×*C*=O); and LRMS [DCI (NH_3)] *m/z* 452 (MNH_4^+, 10%), 435 (MH^+, 60), 248 ($MH^+-PhtCHCO$, 85), 187 ($PhtCHCO^+$, 10), and 91 ($C_7H_7^+$, 100).

Benzyl (−)-(6*S*,7*S*)-7-amino-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (51). The title compound was prepared according to the following methods.

The first method. To a cooled to −78°C solution of cephalosporin **50** (1.77 g, 4.08 mmol) in DMF (50 ml) was added 1 M $N_2H_4\cdot H_2O$ in DMF (5.9 ml, 5.9 mmol). The cold bath was removed and the reaction mixture stirred for 30 min. The phthalhydrazide complex was decomposed by addition of 1 M HCl (9.5 ml, 9.5 mmol) and the solvents were evaporated in vacuo. The residual oil was dissolved, with vigorous stirring, in water (80 ml) and the insoluble phthalhydrazide removed by filtration through a thin pad of Celite®. The aqueous filtrate was layered with EtOAc (100 ml) and basified with satd. $NaHCO_3$ to pH 8. Phases were separated and the extraction completed with two additional portions of EtOAc (2×50 ml). The combined organic extracts were washed with water (3×50 ml) and satd. brine (50 ml), dried over $MgSO_4$, and evaporated in vacuo to give a thick yellow oil (687 mg). Purification by flash chromatography (silica gel, CH_2Cl_2/EtOAc, 65:35) gave the title compound **51** (587 mg, 47%) as a colourless gum which solidified upon standing. An analytical sample, as a white crystalline solid, was obtained by double crystallisation from EtOAc: mp 129–130°C (from EtOAc); (Found: C, 59.37; H, 5.03; N, 9.08. Calcd for $C_{15}H_{16}N_2O_3S$: C, 59.18; H, 5.31; N, 9.21%); R_f 0.35 (CH_2Cl_2/EtOAc, 65:35); $[\alpha]_D^{25}=-67.9$ (*c* 1.0 in $CHCl_3$); FT IR ($CHCl_3$) ν_{max}/cm^{-1} 1776s (β-lactam) 1723s (ester), 1393s, and 1357m; ^1H NMR (200 MHz, $CDCl_3$) δ_H 1.76 (2H, br s, N*H*$_2$), 2.10 (3H, s, C*H*$_3$), 3.19 and 3.51 (2×1H, ABq, *J*=18 Hz, SC*H*$_2$), 4.70 and 4.91 (2×1H, 2×d, *J*=4.5 Hz, 6-*H* and 7-*H*), 5.27 (2H, s, C*H*$_2$Ph), and 7.34–7.40 (5H$_{arom}$, m, Ph); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C 19.98 (q, *C*H$_3$), 29.67 (t, S*C*H$_2$), 58.56 and 63.52 (d, 6-*C* and 7-*C*), 67.45 (t, *C*H$_2$Ph), 128.6, 128.7, and 128.8 (d, Ph *C*H's), 135.5 (s, Ph *ipso C*), 162.7 and 169.2 (s, 2×*C*=O); and LRMS [DCI (NH_3)] *m/z* 305 (MH^+, 10%), 277 (100), 248 (MH^+-NH_2CHCO, 20), 108 ($C_7H_7OH^+$, 15), and 91 ($C_7H_7^+$, 45).

The second method. A cooled in an ice bath solution of sulfenamide **72** (100 mg, 0.22 mmol) in CH_2Cl_2 (2 ml) was treated, during vigorous stirring, with a solution of KI (420 mg, 2.53 mmol) in methanol (5 ml) and glacial AcOH (0.8 ml, 14 mmol) followed by 1 M $Na_2S_2O_3$ (0.55 ml, 0.55 mmol). The mixture was stirred at 0°C until the starting material **72** disappeared (by TLC analysis, 2 h). After this time, the reaction mixture was diluted with EtOAc (20 ml)

[¶] Signals corresponding to vinylic quaternary carbon atoms of cephems were frequently not visible in ^{13}C NMR.

and washed successively with water (5×10 ml), satd. $NaHCO_3$ (10 ml), and satd. brine (10 ml). The organic layer was dried over $MgSO_4$ and evaporated in vacuo to afford a yellow solid (85 mg) which was purified by flash chromatography (silica gel, CH_2Cl_2/EtOAc, 65:35) to give amine **51** (66 mg, 99%), identical [^{1}H NMR (200 MHz), TLC, and FT IR] with the product obtained by the first method.

The third method. A cooled in an ice bath solution of sulfenamide **74** (92 mg, 0.22 mmol) in CH_2Cl_2 (2 ml) was treated, during vigorous stirring, with a solution of KI (420 mg, 2.53 mmol) in MeOH (5 ml) followed by glacial AcOH (0.8 ml) and 1 M $Na_2S_2O_3$ (0.55 ml, 0.55 mmol). The mixture was stirred at stirred at 0°C until the starting material **74** had reacted (by TLC analysis, 2 h). The reaction mixture was diluted with EtOAc (20 ml) and washed with water (5×20 ml), satd. $NaHCO_3$ (20 ml), and satd. brine (10 ml). The organic layer was dried over $MgSO_4$ and evaporated in vacuo to give an off-white solid (76 mg) which was purified by flash chromatography (silica gel, CH_2Cl_2/EtOAc, 65:35) to afford amine **51** (65 mg, ~100%), identical [^{1}H NMR (200 MHz), TLC, and FT IR] with the product obtained by the first method.

Benzyl (−)-(6*S*,7*S*)-3-methyl-8-oxo-7-phenylacetamido-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (52). To an ice bath cooled solution of amine **51** (129 mg, 0.42 mmol) and phenylacetic acid (187 mg, 0.64 mmol) in THF (5 ml) was added during vigorous stirring a cold solution of *N*,*N*′-dicyclohexylcarbodiimide (187 mg, 0.64 mmol) in THF (5 ml). The bath was removed and the mixture stirred at room temperature for 2 h. The solvent was evaporated in vacuo and the residual oil dissolved in EtOAc (20 ml). The *N*,*N*′-dicyclohexylurea formed was removed by filtration and the filtrate washed with satd. $NaHCO_3$ (20 ml), water (3×20 ml), and satd. brine (20 ml). The organic layer was dried over $MgSO_4$ and evaporated in vacuo to give a white foam (165 mg). Purification by flash chromatography (silica gel, CH_2Cl_2/EtOAc, 9:1) gave amide **52** (150 mg, 85%): white crystalline solid; mp 146–148°C (dec.) (from EtOAc/petrol 40/60); (Found: C, 65.41; H, 4.87; N, 6.63. Calcd for $C_{23}H_{22}N_2O_4S$: C, 65.38; H, 5.26; N, 6.63%); R_f 0.65 (CH_2Cl_2/EtOAc, 9:1); $[\alpha]_D^{25}=-118$ (*c* 0.3 in acetone); FT IR ($CHCl_3$) ν_{max}/cm^{-1} 1784s (β-lactam), 1723m (ester), 1686m br (amide), and 1517s (amide); ^{1}H NMR (200 MHz, CD_3CN) δ_H 2.15 (3H, s, C*H*$_3$), 3.28 and 3.55 (2×1H, ABq, *J*=18 Hz, SC*H*$_2$), 3.54 and 3.58 (2×1H, ABq, *J*=14.5 Hz, PhC*H*$_2$CO), 4.99 (1H, d, *J*=4.5 Hz, 6-*H*), 5.22 and 5.26 (2×1H, ABq, *J*=12 Hz, C*H*$_2$Ph), 5.67 (1H, dd, *J*=8.5 Hz, *J*=4.5 Hz, 7-*H*), 7.20 (1H, d, *J*=8.5 Hz, N*H*), and 7.28–7.43 (10H$_{arom}$, m, 2×Ph); ^{13}C NMR (126 MHz, CD_3CN) δ_C 19.42, 29.90, 42.49, 57.59, 59.65, 67.46, 127.3, 128.7, 128.8, 128.9, 129.6, 132.3, 135.9, 136.1, 162.8, 165.2, and 171.8; and LRMS [DCI (NH_3)] *m*/*z* 423 (MH^+, 2%), 248 ($MH^+-PhCH_2CONHCHCO$, 100), 176 ($PhCH_2CONHCHCOH^+$, 15), and 91 ($C_7H_7^+$, 20).

Benzyl (−)-(6*S*,7*S*)-3-methyl-8-oxo-7-phenoxyacetamido-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (53). The title compound was prepared according to the following methods.

The first method. Following the method for the preparation of amide **52**, amine **51** (128 mg, 0.42 mmol) was reacted with phenoxyacetic acid (83 mg, 0.58 mmol) in the presence of DCC (94 mg, 0.47 mmol). Purification by flash chromatography (silica gel, CH_2Cl_2/EtOAc, 9:1) gave the title compound **53** (167 mg, 91%): white crystalline solid; mp 146–148°C (dec.) (from EtOAc/petrol 40/60); (Found: C, 62.87; H, 5.38; N, 6.42. Calcd for $C_{23}H_{22}N_2O_5S$: C, 62.99; H, 5.07; N, 6.39%); R_f 0.80 (CH_2Cl_2/EtOAc, 9:1); $[\alpha]_D^{25}=-58.6$ (*c* 0.3 in acetone); FT IR ($CHCl_3$) ν_{max}/cm^{-1} 3412s br (amide), 1785s (β-lactam), 1723m (ester), 1696s (amide), 1521s (amide), and 1424s; ^{1}H NMR (500 MHz, CD_3CN) δ_H 2.07 (3H, s, C*H*$_3$), 3.32 and 3.55 (2×1H, ABq, *J*=18 Hz, SC*H*$_2$), 4.59 (2H, s, PhOC*H*$_2$), 5.06 (1H, d, *J*=5 Hz, 6-*H*), 5.23 and 5.27 (2×1H, ABq, *J*=12.5 Hz, C*H*$_2$Ph), 5.75 (1H, dd, *J*=9 Hz, *J*=5 Hz, 7-*H*), 6.98–7.04 and 7.32–7.45 (10H$_{arom}$, m, 2×Ph), and 7.57 (1H, d, *J*=9 Hz, N*H*); ^{13}C NMR (126 MHz, CD_3CN) δ_C 19.41, 29.91, 57.41, 59.07, 67.18, 115.1, 122.2, 122.7, 128.7, 128.8, 128.9, 130.05, 132.6, 136.1, 158.0, 162.8, 164.6, and 169.3; and LRMS [DCI (NH_3)] *m*/*z* 439 (MH^+, 3%), 248 ($MH^+-PhOCH_2CONH-CHCO$, 100), 192 ($PhOCH_2CONHCHCOH^+$, 3), and 91 ($C_7H_7^+$, 10).

The second method. A solution of sulfenamide **72** (53 mg, 0.12 mmol) in CH_2Cl_2 (10 ml) was cooled in an ice bath, treated with phenoxyacetyl chloride (48 μl, 0.35 mmol), and the mixture was stirred at 0°C until the starting material **72** had reacted (by TLC analysis, 90 min). The solvent was evaporated in vacuo and the oily residue purified by flash chromatography (silica gel, CH_2Cl_2/EtOAc, 9:1) to afford cephem **53** (43 mg, 85%), identical [^{1}H NMR (200 MHz), TLC, and FT IR] with the product obtained by the first method.

The third method. A cooled in an ice bath solution of sulfenamide **74** (126 mg, 0.29 mmol) in CH_2Cl_2 (10 ml) was treated with phenoxyacetyl chloride (122 μl, 0.88 mmol) and the mixture was stirred at 0°C until the starting material **74** had reacted (by TLC analysis, 2 h). The solvent was evaporated in vacuo and the residue purified by flash chromatography (silica gel, CH_2Cl_2/EtOAc, 9:1) to give amide **53** (94 mg, 73%), identical [^{1}H NMR (200 MHz), TLC, and FT IR] with the product obtained by the first method.

The fourth method. As described for the preparation of cephem **77**, Schiff base **75** (250 mg, 0.57 mmol) in THF (10 ml) was treated with PhLi (1.8 M solution in cyclohexane/ether, 318 μl, 0.57 mmol) in the presence of DMF (8 ml). The standard AcOH/H_2O workup procedure as described above gave an off-white solid (253 mg) which was dissolved in CH_2Cl_2 (15 ml) and treated with phenoxyacetyl chloride (87 μl, 0.63 mmol). The mixture was stirred at room temperature for 20 h and the solvent evaporated in vacuo to give a light brown semi-solid (365 mg) which was purified by flash chromatography (silica gel, CH_2Cl_2/EtOAc, 9:1) to give amide **53** (128 mg, 51%) along with its 7-epimer **67** (50 mg, 20%), identical [^{1}H NMR (200 MHz), TLC, and FT IR] with the products obtained by other methods.

(−)-(6*S*,7*S*)-3-Methyl-8-oxo-7-phenylacetamido-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (54). To an

ice bath cooled solution of ester **52** (150 mg, 0.36 mmol) and anisole (232 μl, 2.13 mmol) in CH_2Cl_2 (10 ml) was added a cold solution of $AlCl_3$ (143 mg, 1.07 mmol) in $MeNO_2$ (10 ml). The bath was removed and stirring continued at room temperature for 6 h. The reaction mixture was diluted with EtOAc (30 ml) and washed with 1 M HCl (3×30 ml) and satd. brine (30 ml). The organic layer was extracted with 5% $NaHCO_3$ (3×35 ml). The combined aqueous extracts were washed with Et_2O (30 ml), acidified to pH 1 with 1 M HCl, and re-extracted with EtOAc (3×50 ml). The combined organic layers were washed with satd. brine (30 ml), dried over $MgSO_4$, and evaporated in vacuo to afford acid **54** (101 mg, 86%): white crystalline solid; mp 193–195°C (dec.) (from EtOAc/petrol 40/60); (Found: C, 57.70; H, 5.15; N, 8.44. Calcd for $C_{16}H_{16}N_2O_4S$: C, 57.81; H, 4.86; N, 8.44%); $[\alpha]_D^{25}=-127$ (*c* 0.3 in acetone); FT IR (KBr disc) ν_{max}/cm^{-1} 3200s br (carboxylic acid), 1765s (β-lactam), 1704s (carboxylic acid), 1658s (amide), 1551s (amide), 1367m, 1342m, 1261m, and 1236m; ^1H NMR (500 MHz, CD_3CN) δ_H 2.08 (3H, s, C*H*$_3$), 3.28 and 3.54 (2×1H, ABq, *J*=18 Hz, SC*H*$_2$), 3.55 and 3.58 (2×1H, ABq, *J*=14.5 Hz, PhC*H*$_2$), 4.99 (1H, d, *J*=4.5 Hz, 6-*H*), 5.67 (1H, dd, *J*=8 Hz, *J*=4.5 Hz, 7-*H*), 7.20 (1H, d, *J*=8 Hz, N*H*), and 7.26–7.36 (5H$_{arom}$, m, Ph); ^{13}C NMR (126 MHz, CD_3CN) δ_C 19.87, 30.35, 42.96, 57.97, 60.05, 123.8, 127.7, 129.4, 130.1, 133.0, 136.4, 163.7, 165.8, and 172.1; and LRMS (electrospray, −) *m/z* 331 (M−H$^+$, 100%), 287 (M−H$^+$−CO_2, 80), 265 (15), and 253 (85).

(−)-(6*S*,7*S*)-3-Methyl-8-oxo-7-phenoxyacetamido-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (55). Following the method for the preparation of acid **54**, ester **53** (167 mg, 0.38 mmol) was reacted with $AlCl_3$ (152 mg, 1.44 mmol) in the presence of anisole (248 μl, 2.29 mmol). The analogous workup procedure gave the title compound **55** (125 mg, 94%): white crystalline solid; mp 177–179°C (dec.) (from EtOAc/petrol 40/60); (Found: C, 55.43; H, 4.21; N, 7.76. Calcd for $C_{16}H_{16}N_2O_5S$: C, 55.15; H, 4.64; N, 8.04%); $[\alpha]_D^{25}=-78.0$ (*c* 0.4 in acetone); FT IR (KBr disc) ν_{max}/cm^{-1} 3200s br (carboxylic acid), 1759s (β-lactam), 1734s (carboxylic acid), 1651s (amide), 1527s (amide), 1228s, and 1196m; ^1H NMR (500 MHz, CD_3CN) δ_H 2.09 (3H, s, C*H*$_3$), 3.31 and 3.54 (2×1H, ABq, *J*=18 Hz, SC*H*$_2$), 4.59 (2H, s, PhOC*H*$_2$), 5.06 (1H, d, *J*=4.5 Hz, 6-*H*), 5.73 (1H, dd, *J*=8.5 Hz, *J*=4.5 Hz, 7-*H*), 6.99–7.04 and 7.32–7.36 (5H$_{arom}$, m, Ph), and 7.59 (1H, d, *J*=8.5 Hz, N*H*),^{13}C NMR (126 MHz, CD_3CN) δ_C 19.88, 30.39, 57.85, 59.48, 67.68, 115.6, 122.7, 123.3, 130.5, 133.3, 158.4, 165.2, and 169.7; and LRMS (electrospray, −) *m/z* 347 (M−H$^+$, 100%), 303 (M−H$^+$–CO_2, 60), 269 (45), and 250 (15).

Benzyl (−)-(2*S*,4*S*,5*S*,6*R*)-3,3-dimethyl-7-oxo-6-phthalimido-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 4-oxide (58). A vigorously stirred solution of penam **15** (20.0 g, 45.9 mmol, ~95% purity) in $CHCl_3$ (250 ml) was cooled in an ice bath and treated dropwise, over 30 min, with a solution of *m*-chloroperbenzoic acid (*m*CPBA, ~50% w/w, 14.4 g, ca. 45.9 mmol) in $CHCl_3$ (80 ml), which had been pre-dried (over $MgSO_4$). The mixture was stirred at 0°C for an additional hour and washed with water (2×250 ml), satd. $NaHCO_3$ (2×250 ml), and satd. brine (100 ml). The organic layer was dried over $MgSO_4$ and evaporated in vacuo to give a white foam (18.6 g). Purification by flash chromatography (silica gel, benzene/EtOAc, 7:3) afforded sulfoxide **58** (17.6 g, 85%): white crystalline solid; mp 143–144°C (from EtOAc/petrol 40/60); (Found: C, 60.83; H, 4.85; N, 6.02. Calcd for $C_{23}H_{20}N_2O_6S$: C, 61.04; H, 4.46; N, 6.19%); R_f 0.30 (C_6H_6/EtOAc, 7:3); $[\alpha]_D^{25}=-91.7$ (*c* 1.0 in $CHCl_3$); FT IR ($CHCl_3$) ν_{max}/cm^{-1} 1803s br (β-lactam, phthalimide), 1729s (phthalimide, ester), 1392s, and 1056m (sulfoxide); ^1H NMR (200 MHz, $CDCl_3$) δ_H 1.30 and 1.53 (2×3H, 2×s, 2×C*H*$_3$), 4.20 (1H, s, 2-*H*), 4.87 and 5.77 (2×1H, 2×d, *J*=2.5 Hz, 5-*H* and 6-*H*), 5.22 and 5.30 (2×1H, ABq, *J*=12 Hz, C*H*$_2$Ph), 7.39 (5H$_{arom}$, s, Ph), and 7.73–7.91 (4H$_{arom}$, m, Pht); ^1H NMR n.O.e. (500 MHz, $CDCl_3$) δ_H 1.30 α-C*H*$_3$→β-C*H*$_3$ (5.0%), →2-*H* (5.5%), →6-*H* (3.5%); 1.53 β-C*H*$_3$→α-C*H*$_3$ (3.5%), →2-*H* (15%), →5-*H* (16%); 4.20 2-*H*→β-C*H*$_3$ (4.0%), →5-*H* (2.0%); 4.87 5-*H*→β-C*H*$_3$ (4.0%), →2-*H* (1.5%), →6-*H* (4.5%); and 5.77 6-*H*→5-*H* (3.5%); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C 18.87 and 19.56 (q, 2×*C*H$_3$), 55.49, 66.52, and 79.23 (d, 2-*C*, 5-*C*, and 6-*C*), 68.59 (t, *C*H$_2$Ph), 71.16 (s, 3-*C*), 124.2 (d, Pht 3, 6-*C*H's), 129.0 and 129.2 (d, Ph *C*H's), 131.6 (s, Pht *ipso C*), 134.2 (s, Ph *ipso C*), 135.1 (d, Pht 4, 5-*C*H's), 165.2, 166.7, and 167.3 (s, 3×*C*═O); and LRMS [DCI (NH_3)] *m/z* 453 (MH$^+$, 10%), 435 (MH$^+$−H_2O, 80), 299 (25), 247 (10), 204 (15), 108 ($C_7H_7OH^+$, 30), and 91 ($C_7H_7^+$, 100).

Benzyl (−)-(6*S*,7*R*)-3-methyl-8-oxo-7-phthalimido-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (59). A stirred solution of sulfoxide **58** (14.3 g, 31.6 mmol) and anhydrous *p*-toluenesulfonic acid (*p*TSA, 4.30 g, 24.9 mmol) in DMF (150 ml) was heated at 100±3°C for 17 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (200 ml) and washed with water (4×200 ml), satd. $NaHCO_3$ (3×100 ml), and satd. brine (100 ml). The organic layer was dried over $MgSO_4$ and evaporated in vacuo to yield a brown foam (10.7 g). Flash chromatography (silica gel, CH_2Cl_2/EtOAc, 20:1) followed by crystallisation from EtOAc/petrol 40/60 gave cephalosporin **59** (4.52 g, 33%): white crystalline solid; mp 171–173°C (from EtOAc/petrol 40/60); (Found: C, 63.84; H, 4.26; N, 6.47. Calcd for $C_{23}H_{18}N_2O_5S$: C, 63.58; H, 4.18; N, 6.42%); R_f 0.60 (CH_2Cl_2/EtOAc, 20:1); $[\alpha]_D^{25}=-17.8$ (*c* 1.0 in $CHCl_3$); FT IR ($CHCl_3$) ν_{max}/cm^{-1} 1786s br (β-lactam, phthalimide) 1728s (ester, phthalimide), and 1393m; ^1H NMR (200 MHz, $CDCl_3$) δ_H 2.14 (3H, s, C*H*$_3$), 3.24 and 3.48 (2×1H, ABq, *J*=18 Hz, SC*H*$_2$), 5.08 and 5.34 (2×1H, 2×d, *J*=2.5 Hz, 6-*H* and 7-*H*), 5.33 and 5.40 (2×1H, ABq, *J*=12.5 Hz, C*H*$_2$Ph), 7.32–7.54 (5H$_{arom}$, m, Ph), and 7.77–7.94 (4H$_{arom}$, m, Pht); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 19.45 (*C*H$_3$), 31.48 (S*C*H$_2$), 55.84 and 61.27 (6-*C* and 7-*C*), 67.49 (*C*H$_2$Ph), 123.9 (Pht 3, 6-*C*H's), 128.1, 128.3, and 128.4 (Ph *C*H's), 131.6 (Pht *ipso C*), 134.6 (Pht 4, 5-*C*H's), 135.3 (Ph *ipso C*), 159.1, 161.9, and 166.4 (3×*C*═O); and LRMS [DCI (NH_3)] *m/z* 452 (MNH$_4^+$, 85%), 434 (M$^+$, 100), 248 (MH$^+$−PhtCHCO, 80), 108 ($C_7H_7OH^+$, 45), and 91 ($C_7H_7^+$, 50).

Benzyl (+)-(2*S*,4*S*,5*R*)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 4-oxide (60). A stirred solution of penam **35**^{III} (107 mg, 0.37 mmol) in $CHCl_3$ (15 ml) was cooled in an ice bath and treated, dropwise over

45 min, with a solution of *m*CPBA (pre-dried with $MgSO_4$) (~50% w/w, 127 mg, ~0.37 mmol) in $CHCl_3$ (5 ml). The stirring was continued at 0°C until the starting material **35** had reacted (by TLC analysis, 40 min) and the reaction mixture was washed with 5% Na_2CO_3 (5 ml), water (3×10 ml), and satd. brine (10 ml). The organic layer was dried over $MgSO_4$ and evaporated in vacuo to afford a white foam (105 mg) which, on the basis of ^1H NMR (200 MHz) analysis, consisted of two compounds, sulfoxide **60** and its (4*R*)-epimer **82**, in a ratio of ca. 4:1. Purification by flash chromatography (silica gel, EtOAc/petrol 40/60, 7:3) gave the two products; sulfoxide **60** (77 mg, 68%) and its (4*R*)-epimer **82** (18 mg, 16%). The major product **60**: white crystalline solid; mp 117–119°C (from Me_2CO/petrol 40/60); (Found: C, 58.78; H, 5.32; N, 4.32. Calcd for $C_{15}H_{17}NO_4S$: C, 58.62; H, 5.57; N, 4.56%); R_f 0.33 (EtOAc/petrol 40/60, 7:3); $[\alpha]_D^{25}=+243$ (*c* 0.3 in $CHCl_3$); FT IR (KBr disc) ν_{max}/cm^{-1} 1771s (β-lactam), 1725s (ester), 1274s, 1210s, and 1051s (sulfoxide); ^1H NMR (200 MHz, $CDCl_3$) δ_H 1.11 and 1.67 (2×3H, 2×s, 2×C*H*$_3$), 3.35 (2H, d, *J*=3.5 Hz, 6-C*H*$_2$), 4.56 (1H, s, 2-*H*), 4.95 (1H, t, *J*=3.5 Hz, 5-*H*), 5.16 and 5.30 (2×1H, ABq, *J*=12 Hz, C*H*$_2$Ph), and 7.40 (5H$_{arom}$, s, Ph); ^1H NMR n.O.e. (500 MHz, $CDCl_3$) δ_H 1.11 α-C*H*$_3$→β-C*H*$_3$ (5.0%), →2-*H* (2.0%), →5-*H* (12%); 1.67 β-C*H*$_3$→α-C*H*$_3$ (1.0%), →2-*H* (16%); 3.35 6-C*H*$_2$→2-*H* (2.0%), →5-*H* (7.0%); 4.56 2-*H*→α-C*H*$_3$ (2.0%), →β-C*H*$_3$ (5.0%), →6-C*H*$_2$ (1.0%), and 4.95 5-*H*→α-C*H*$_3$ (6.5%), →β-C*H*$_3$ (2.0%), →6-C*H*$_2$ (6.0%); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 18.41, 20.13, 36.00, 65.54, 67.83, 70.89, 73.87, 128.7, 128.8, 128.8, 134.7, 168.2, and 170.6; and LRMS [CI (NH_3)] *m*/*z* 325 (MNH_4^+, 15%), 308 (MH^+, 100), 290 (MH^+-H_2O, 20), 108 ($C_7H_7OH^+$, 25), and 91 ($C_7H_7^+$, 75). The minor product **82**: white solid; R_f 0.22 (EtOAc/petrol 40/60, 7:3); $[\alpha]_D^{25}=+189$ (*c* 1.0 in $CHCl_3$); FT IR ($CHCl_3$) ν_{max}/cm^{-1} 1790s (β-lactam), 1753s (ester), and 1061s (sulfoxide); ^1H NMR (200 MHz, $CDCl_3$) δ_H 1.27 and 1.56 (2×3H, 2×s, 2×C*H*$_3$), 3.36 (1H, dd, *J*=16.5 Hz, *J*=2 Hz, 6-β-*H*), 3.61 (1H, dd, *J*=16.5 Hz, *J*=4.5 Hz, 6-α-*H*), 4.42 (1H, s, 2-*H*), 4.61 (1H, dd, *J*=4.5 Hz, *J*=2 Hz, 5-*H*), 5.18 and 5.28 (2×1H, ABq, *J*=12 Hz, C*H*$_2$Ph), and 7.39 (5H$_{arom}$, s, Ph); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 15.48, 24.29, 40.71, 64.03, 67.98, 70.77, 72.56, 128.8, 128.8, 128.9, 134.5, 167.1, and 169.0; and LRMS (AFCI) *m*/*z* 308 (MH^+, 100%), 290 (MH^+-H_2O, 15), 280 (15), and 206 (20).

Benzyl (−)-(6*S*,7*R*)-7-amino-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (66). Following the first method for the preparation of amine **51**, cephalosporin **59** (1.08 g, 2.49 mmol) in DMF (20 ml) was reacted with a 1 M solution of hydrazine hydrate in DMF (5.0 ml, 5.0 mmol) at −15°C for 30 min. Purification by flash chromatography (silica gel, EtOAc/CH_2Cl_2, 6:5) gave amine **66** (296 mg, 39%) as a yellow oil which solidified upon standing: R_f 0.35 (EtOAc/CH_2Cl_2, 5:4); HRMS Calcd for $C_{15}H_{17}N_2O_3S$ (MH^+) 305.0977, found 305.0960; $[\alpha]_D^{25}=-95.2$ (*c* 1.4 in $CHCl_3$); FT IR ($CHCl_3$) ν_{max}/cm^{-1} 1773s (β-lactam) 1726s (ester), 1392m, and 1362m; ^1H NMR (200 MHz, $CDCl_3$) δ_H 1.68 (2H, br s, N*H*$_2$), 2.06 (3H, s, C*H*$_3$), 3.15 and 3.47 (2×1H, ABq, *J*=18 Hz, SC*H*$_2$), 4.13 and 4.45 (2×1H, 2×d, *J*=2 Hz, 6-*H* and 7-*H*), 5.25 and 5.35 (2×1H, ABq, *J*=12 Hz, C*H*$_2$Ph), and 7.33–7.42 (5H$_{arom}$, m, Ph); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 19.57, 31.40, 59.21, 67.62, 68.83, 123.8, 128.2, 128.4, 128.5, 128.7, 135.3, 162.3, and 164.8; and LRMS [DCI (NH_3)] *m*/*z* 322 (MNH_4^+, 10%), 305 (MH^+, 50), 277 (100), 248 (MH^+-NH_2CHCO, 40), 108 ($C_7H_7OH^+$, 30), and 91 ($C_7H_7^+$, 35).

Benzyl (−)-(6*S*,7*R*)-3-methyl-8-oxo-7-phenoxyacetamido-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (67). According to the general coupling procedure described for the preparation of amide **52**, amine **66** (406 mg, 1.34 mmol) and phenoxyacetic acid (305 mg, 2.00 mmol) were reacted in the presence of DCC (362 mg, 1.74 mmol). The standard workup procedure, followed by flash chromatography (silica gel, CH_2Cl_2/EtOAc, 9:1), afforded amide **67** (519 mg, 89%): white crystalline solid; mp 182–184°C (dec.) (from EtOAc/petrol 40/60); (Found: C, 63.12; H, 4.92; N, 6.29. Calcd for $C_{23}H_{22}N_2O_5S$: C, 62.99; H, 5.07; N, 6.39%); R_f 0.80 (CH_2Cl_2/EtOAc, 9:1); $[\alpha]_D^{25}=-40.5$ (*c* 0.45 in acetone); FT IR ($CHCl_3$) ν_{max}/cm^{-1} 3416m br (amide), 1780s (β-lactam), 1724m (ester), 1698m (amide), 1521s (amide), 1441m, and 1424s; ^1H NMR (500 MHz, CD_3CN) δ_H 2.01 (3H, s, C*H*$_3$), 3.14 and 3.41 (2×1H, ABq, *J*=18 Hz, SC*H*$_2$), 4.48 (2H, s, PhOC*H*$_2$), 4.67 (1H, d, *J*=2 Hz, 6-*H*), 4.98 (1H, dd, *J*=8 Hz, *J*=2 Hz, 7-*H*), 5.16 and 5.29 (2×1H, ABq, *J*=12 Hz, C*H*$_2$Ph), 6.87–7.40 (10H$_{arom}$, m, 2×Ph), and 7.56 (1H, d, *J*=8 Hz, N*H*); ^{13}C NMR (126 MHz, CD_3CN) δ_C 19.33, 31.07, 56.88, 63.13, 66.85, 67.32, 114.5, 122.0, 123.5, 128.2, 128.3, 129.1, 129.6, 135.0, 156.8, 160.7, 161.9, and 168.4; and LRMS [DCI (NH_3)] *m*/*z* 456 (MNH_4^+, 10%), 439 (MH^+, 5), 248 ($MH^+-PhOCH_2CONHCHCO$, 100), 192 ($PhOCH_2CONHCHCOH^+$, 20), and 91 ($C_7H_7^+$, 20).

Diphenylmethyl (−)-(6*S*,7*R*)-3-methyl-8-oxo-7-phenoxyacetamido-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (68). Following the method for the preparation of acid **54**, a solution of ester **67** (445 mg, 1.02 mmol) and anisole (662 μl, 6.10 mmol) in CH_2Cl_2 (10 ml) was treated with a solution of $AlCl_3$ (405 mg, 3.05 mmol) in $MeNO_2$ (10 ml) and the reaction mixture was stirred at room temperature for 8 h. The standard workup procedure gave crude acid **69** (289 mg) contaminated, as judged from ^1H NMR (500 MHz) analysis, with its double bond isomer, (6*S*,7*R*)-3-methyl-8-oxo-7-phenoxyacetamido-5-thia-1-azabicyclo-[4.2.0]oct-3-ene-2-carboxylic acid; ^1H NMR (500 MHz, CD_3CN) δ_H 1.89 (3H, s, C*H*$_3$), 4.74 (1H, s, 4-*H*), 4.99 (1H, dd, *J*=8.5 Hz, *J*=1.5 Hz, 7-*H*), 4.55 (2H, s, PhOC*H*$_2$), 4.98 (1H, d, *J*=1.5 Hz, 6-*H*), 6.08 (1H, t, *J*=1.5 Hz, 2-*H*), 6.99–7.05 and 7.33–7.37 (5H$_{arom}$, m, Ph), and 7.90 (1H, d, *J*=8.5 Hz, N*H*).

The crude product was dissolved in CH_2Cl_2 (10 ml) and treated with diphenyldiazomethane over 5 min until light pink colour of the solution was persistent. Excess diphenyldiazomethane was decomposed by stirring with silica gel (3 g). After filtration (ether), the solvent was evaporated in vacuo to afford an off-white foam (410 mg). Purification by flash chromatography (silica gel, EtOAc/CH_2Cl_2, 10:1) gave ester **68** (273 mg, 52%): white solid; R_f 0.45 (CH_2Cl_2/EtOAc, 10:1); $[\alpha]_D^{25}=-26.2$ (*c* 0.50 in $CHCl_3$); FT IR ($CHCl_3$) ν_{max}/cm^{-1} 1780s (β-lactam), 1725m (ester), 1695s (amide), 1521m (amide), and 1496*S*; ^1H NMR (500 MHz, $CDCl_3$) δ_H 2.08 (3H, s, C*H*$_3$), 3.20 and 3.40

(2×1H, ABq, J=17.5 Hz, SCH_2), 4.57 (2H, s, PhOCH_2), 4.73 (1H, d, J=2 Hz, 6-*H*), 5.03 (1H, dd, J=8 Hz, J=2 Hz, 7-*H*), and 6.92–7.50 (17H, m, 3×Ph+N*H*+C*H*Ph$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 19.75, 31.47, 57.74, 63.73, 67.11, 79.15, 114.7, 122.4, 127.1, 127.6, 128.0, 128.1, 128.5, 128.5, 129.9, 131.9, 139.6, 156.9, 160.9, 161.4, and 168.5; and LRMS [DCI (NH_3)] m/z 532 (MNH_4^+, 5%), 192 ($PhOCH_2CONHCHCOH^+$, 30), and 167 (Ph_2CH^+, 65).

(−)-(6*S*,7*R*)-3-Methyl-8-oxo-7-phenoxyacetamido-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (69). To an ice bath cooled solution of ester **68** (126 mg, 0.25 mmol) and anisole (160 μl, 1.47 mmol) in CH_2Cl_2 (5 ml) was added a cold solution of $AlCl_3$ (99 mg, 0.735 mmol) in $MeNO_2$ (5 ml). The reaction mixture was stirred at 0°C until the starting material **68** disappeared (by TLC analysis, 30 min). The standard workup, as described for the preparation of acid **54**, gave the title compound **69** (82 mg, 96%): white crystalline solid; mp 183–185°C (dec.) (from EtOAc/petrol 40/60); (Found: C, 55.31; H, 4.42; N, 8.06. Calcd for $C_{16}H_{16}N_2O_5S$: C, 55.15; H, 4.64; N, 8.04%); $[\alpha]_D^{25}$=−98.8 (c 0.25 in acetone); FT IR (KBr disc) ν_{max}/cm^{-1} 3333s (amide), 3261s br (carboxylic acid), 1738s and 1734s (β-lactam and carboxylic acid), 1687s (amide), 1543s (amide), 1497m, and 1242s; ^{1}H NMR (500 MHz, CD_3CN) δ_H 2.10 (3H, s, CH_3), 2.26 (1H, br s, CO_2H), 3.26 and 3.55 (2×1H, ABq, J=18 Hz, SCH_2), 4.55 (2H, s, PhOCH_2), 4.81 (1H, d, J=2 Hz, 6-*H*), 4.85 (1H, dd, J=8 Hz, J=2 Hz, 7-*H*), 7.00–7.04 and 7.33–7.37 (5H$_{arom}$, m, Ph), and 7.91 (1H, d, J=8 Hz, N*H*); ^{13}C NMR (126 MHz, CD_3CN) δ_C 19.44, 31.51, 57.36, 64.28, 67.71, 115.6, 122.7, 124.3, 130.3, 130.6, 158.4, 162.6, 163.6, and 169.8; and LRMS [DCI (NH_3)] m/z 366 (MNH_4^+, <1%), 349 (MH^+, <1), 305 (MH^+-CO_2, 5), 210 (35), 192 ($PhOCH_2CONHCHCOH^+$, 35), 158 (MH^+-CO_2–$PhOCH_2CONHCHCO$, 40), and 94 (15).

Benzyl (−)-(6*S*,7*R*)-3-methyl-7-(4-nitrobenzenesulfenamido)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (70). The title compound was obtained according to the following methods.

The first method. To an ice bath cooled solution of amine **66** (427 mg, 1.40 mmol) in CH_2Cl_2 (15 ml) was added potassium carbonate (427 mg, 3.09 mmol) followed by a solution of *p*-nitrobenzenesulfenyl chloride (564 mg, 2.83 mmol) in CH_2Cl_2 (5 ml). The reaction mixture was stirred at 0°C for 1 h and washed with water (3×30 ml) and satd. brine (20 ml). The organic layer was dried over $MgSO_4$ and evaporated in vacuo to afford a yellow oil (730 mg) which was purified by flash chromatography (silica gel, CH_2Cl_2/EtOAc, 50:1) to give sulfenamide **70** (536 mg, 83%): bright yellow foam; HRMS Calcd for $C_{21}H_{23}N_4O_5S_2$ (MNH_4^+) 475.1144, found 475.1110; R_f 0.35 (CH_2Cl_2/EtOAc, 50:1); $[\alpha]_D^{25}$=−31.7 (c 0.65 in $CHCl_3$); FT IR ($CHCl_3$) ν_{max}/cm^{-1} 1776s (β-lactam) and 1726m (ester); ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 2.04 (3H, s, CH_3), 3.15 and 3.44 (2×1H, ABq, J=18 Hz, SCH_2), 3.97 (1H, d, J=6.5 Hz, N*H*), 4.43 (1H, dd, J=6.5 Hz, J=2 Hz, 7-*H*), 4.59 (1H, d, J=2 Hz, 6-*H*), 5.21 and 5.29 (2×1H, ABq, J=12 Hz, CH_2Ph), 7.29–7.43 (5H$_{arom}$, m, Ph), 7.40 and 8.14 (2×2H$_{arom}$, 2×d, J=9 Hz, $C_6H_4NO_2$); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C 19.44 (q, *C*H$_3$), 31.25 (t, S*C*H$_2$), 56.76 and 75.84 (d, 6-*C* and 7-*C*), 67.63 (t, *C*H$_2$Ph), 122.2 and 124.3 (d, $O_2NC_6H_4$ *C*H's), 123.7 and 129.6 (s, 2-*C* and 3-*C*), 128.7 (d, Ph *C*H's), 135.3 (s, Ph *ipso C*), 145.8 and 151.6 (s, 2×Ar *ipso C*), 161.8 and 162.3 (s, 2×*C*=O); and LRMS [DCI (NH_3)] m/z 475 (MNH_4^+, 10%), 458 (MH^+, 7), 305 (30), 277 (40), 248 ($MH^+-O_2NC_6H_4SNHCHCO$, 100), 108 ($C_7H_7OH^+$, 20), and 91 ($C_7H_7^+$, 20).

The second method. An ice bath cooled solution of amine **66** (373 mg, 1.23 mmol) and triethylamine (205 μl, 1.47 mmol) in THF (10 ml) was treated with a solution of *p*-nitrobenzenesulfenyl chloride (294 mg, 1.47 mmol) in THF (10 ml) and the mixture was stirred at 0°C and for 3 h at room temperature. The reaction mixture was diluted with EtOAc (50 ml) and washed with satd. $NaHCO_3$ (10 ml), water (3×10 ml), and satd. brine (10 ml). The organic layer was dried over $MgSO_4$ and evaporated in vacuo to give a yellow foam (430 mg) which was purified by flash chromatography (silica gel, CH_2Cl_2/EtOAc, 50:1) to afford sulfenamide **70** (356 mg, 63%), identical [^{1}H NMR (200 MHz), TLC, and FT IR] with the product obtained by the first method.

Benzyl (−)-(6*S*)-3-methyl-7-[[(4-nitrophenyl)thio]imino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (71). To a solution of sulfenamide **70** (165 mg, 0.36 mmol) in benzene (10 ml) was added active manganese dioxide (Merck, 6.0 g) and the mixture was vigorously stirred at room temperature until the starting material **70** had reacted (by TLC analysis, 1 h). The reaction mixture was filtered through a thin pad of Celite® and the filtrate was evaporated in vacuo to give a brown foam (158 mg). Purification by flash chromatography (silica gel, CH_2Cl_2/EtOAc, 50:1) afforded thiooxime **71** (79 mg, 48%): bright yellow crystalline solid; mp 148–149°C (from EtOAc/petrol 40/60); (Found: C, 55.60; H, 3.50; N, 9.33. Calcd for $C_{21}H_{17}N_3O_5S_2$: C, 55.37; H, 3.77; N, 9.23%); R_f 0.60 (CH_2Cl_2/EtOAc, 50:1); $[\alpha]_D^{25}$=−132 (c 0.75 in $CHCl_3$); FT IR ($CHCl_3$) ν_{max}/cm^{-1} 1780s (β-lactam) and 1726m (ester); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 2.22 (3H, s, CH_3), 3.27 (1H, d, J=18 Hz, SC*H*), 3.50 (1H, br s, SC*H*), 5.27 and 5.38 (3H, m, 6-*H*+CH_2Ph), 7.35–7.46 (5H$_{arom}$, m, Ph), 7.69 (2H$_{arom}$, br d, J=8.5 Hz, $C_6H_4NO_2$), and 8.27 (2H$_{arom}$, ddd, J=8.5 Hz, J=2.5 Hz, J=2 Hz, $C_6H_4NO_2$); and LRMS [DCI (NH_3)] m/z 473 (MNH_4^+, 15%), 456 (MH^+, 15), 305 (30), 277 (40), 248 ($MH^+-O_2NC_6H_4SNHCHCO$, 100), 108 ($C_7H_7OH^+$, 20), and 91 ($C_7H_7^+$, 20).

Benzyl (−)-(6*S*,7*S*)-3-methyl-7-(4-nitrobenzenesulfenamido)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (72). To an ice bath cooled solution of thiooxime **71** (92 mg, 0.20 mmol) in THF (4 ml) and DMSO (1 ml) was added during vigorous stirring a solution of sodium borohydride (34 mg, 0.85 mmol) in THF (2.5 ml) and DMSO (2.5 ml). After 10 min at 0°C the reaction mixture was quenched with glacial AcOH (1 ml), diluted with EtOAc (50 ml), and washed with water (3×20 ml), satd. $NaHCO_3$ (40 ml), and satd. brine (20 ml). The organic layer was dried over $MgSO_4$ and evaporated in vacuo to give a brown oil (90 mg) which was purified by flash chromatography (silica gel, CH_2Cl_2/EtOAc, 50:1) to afford sulfenamide **72** (49 mg, 53%): bright yellow foam; HRMS

Calcd for $C_{21}H_{23}N_4O_5S_2$ (MNH_4^+) 475.1144, found 475.1110; R_f 0.50 (CH_2Cl_2/EtOAc, 50:1); $[\alpha]_D^{25}=-140$ (*c* 0.65 in $CHCl_3$); FT IR ($CHCl_3$) ν_{max}/cm^{-1} 1781s (β-lactam), 1724s (ester), 1598m, 1581m, 1517*S*, and 1341s; ^1H NMR (200 MHz, $CDCl_3$) δ_H 2.12 (3H, s, C*H*$_3$), 3.24 and 3.51 (2×1H, ABq, *J*=18 Hz, SC*H*$_2$), 3.89 (1H, d, *J*=9 Hz, N*H*), 4.77 (1H, dd, *J*=9 Hz, *J*=4.5 Hz, 7-*H*), 4.94 (1H, d, *J*=4.5 Hz, 6-*H*), 5.19 and 5.29 (2×1H, ABq, *J*=12 Hz, C*H*$_2$Ph), 7.30–7.46 (5H$_{arom}$, m, Ph), 7.45 and 8.14 (2×2H$_{arom}$, 2×d, *J*=9 Hz, $C_6H_4NO_2$); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C 20.06 (q, *C*H$_3$), 30.08 (t, S*C*H$_2$), 58.49 and 72.98 (d, 6-*C* and 7-*C*), 67.63 (t, *C*H$_2$Ph), 121.9 and 124.3 (d, $O_2NC_6H_4$'s *C*H's), 122.6 and 132.4 (s, 2-*C* and 3-*C*), 128.7 and 128.9 (d, Ph *C*H's), 135.4 (s, Ph *ipso C*), 145.8 and 151.9 (s, 2×Ar *ipso C*), 162.4 and 165.1 (s, 2×*C*=O); and LRMS [DCI (NH_3)] *m/z* 475 (MNH_4^+, 2%), 458 (MH^+, 1), 303 (25), 277 (60), 248 ($MH^+-O_2NC_6H_4SNH$–CHCO, 30), 126 (100), 108 ($C_7H_7OH^+$, 20), and 91 ($C_7H_7^+$, 50).

Benzyl (−)-(6*S*)-3-methyl-7-[[(4-methylphenyl)thio]imino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (73). To a vigorously stirred and cooled in an ice bath solution of amine **66** (471 mg, 1.55 mmol) in CH_2Cl_2 (30 ml) was added propylene oxide (4 ml) followed by pulverised molecular 4 Å sieves (3.3 g) and the resulting mixture was treated with a solution of *p*-toluenesulfenyl chloride (786 mg, 4.96 mmol) in CH_2Cl_2 (5 ml). The reaction mixture was allowed to warm to room temperature over 3 h and then filtered through a thin pad of Celite®. The filtrate was evaporated in vacuo to give a brown oil (570 mg) which was purified by flash chromatography (silica gel, CH_2Cl_2) to afford thiooxime **73** (490 mg, 75%): white crystalline solid; mp 140–142°C (from EtOAc/petrol 40/60); (Found: C, 62.18; H, 4.49; N, 6.49. Calcd for $C_{22}H_{20}N_2O_3S_2$: C, 62.24; H, 4.75; N, 6.60%); R_f 0.50 (CH_2Cl_2); $[\alpha]_D^{25}=-134$ (*c* 1.3 in $CHCl_3$); FT IR (KBr disc) ν_{max}/cm^{-1} 1778s (β-lactam), 1717s (ester), and 1358s; ^1H NMR (500 MHz, $CDCl_3$) δ_H 2.19 (3H, br s, C*H*$_3$), 2.38 (3H, s, ArC*H*$_3$), 3.23 (1H, d, *J*=18 Hz, SC*H*), 3.46 (1H, br d, *J*=18 Hz, SC*H*), 5.28 and 5.30 (2×1H, ABq, *J*=12.5 Hz, C*H*$_2$Ph), 5.34 (1H, br s, 6-*H*), and 7.34–7.48 (9H$_{arom}$, m, aromatic C*H*'s); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 19.99, 21.17, 31.14, 60.92, 67.77, 123.8, 127.2, 128.5, 128.6, 128.8, 129.9, 135.1, 138.4, and 161.6; and LRMS [DCI (NH_3)] *m/z* 442 (MNH_4^+, 5%), 425 (MH^+, 25), 320 (30), 303 (30), 248 ($MH^+-H_3CC_6H_4SN$=CCO, 30), 124 (45), 108 ($C_7H_7OH^+$, 50), and 91 ($C_7H_7^+$, 100).

Benzyl (−)-(6*S*,7*S*)-3-methyl-8-oxo-5-thia-7-(4-toluenesulfenamido)-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (74). To an ice bath cooled solution of thiooxime **73** (312 mg, 0.74 mmol) in THF (30 ml) and DMSO (5 ml) was added, dropwise over 10 min, a solution of sodium borohydride (122 mg, 3.22 mmol) in THF (5 ml) and DMSO (5 ml). The resulting solution, deep violet in colour, was stirred at 0°C for 40 min and quenched with glacial AcOH (1.3 ml). The reaction mixture was washed with satd. $NaHCO_3$ (50 ml), water (3×30 ml), and satd. brine (30 ml). The organic layer was dried over $MgSO_4$ and evaporated in vacuo to afford a yellow foam (315 mg). Purification by flash chromatography (silica gel, CH_2Cl_2/EtOAc, 50:1) gave sulfenamide **74** (157 mg, 50%): light yellow oil; HRMS Calcd for $C_{22}H_{23}N_2O_3S_2$ (MH^+) 427.1184, found 427.1150; R_f 0.50 (CH_2Cl_2/EtOAc, 50:1); $[\alpha]_D^{25}=-151$ (*c* 1.3 in acetone); FT IR ($CHCl_3$) ν_{max}/cm^{-1} 1779s (β-lactam), 1723s (ester), 1493m, 1384m, 1360s, 1303m, 1152m, and 1105m; ^1H NMR (200 MHz, $CDCl_3$) δ_H 2.12 (3H, s, C*H*$_3$), 2.34 (3H, s, ArC*H*$_3$), 3.20 and 3.48 (2×1H, ABq, *J*=18 Hz, SC*H*$_2$), 3.59 (1H, d, *J*=8.5 Hz, N*H*), 4.80 (1H, dd, *J*=8.5 Hz, *J*=4.5 Hz, 7-*H*), 4.87 (1H, d, *J*=4.5 Hz, 6-*H*), 5.24 and 5.32 (2×1H, ABq, *J*=12.5 Hz, C*H*$_2$Ph), and 7.15–7.39 (9H$_{arom}$, m, aromatic C*H*'s); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C 20.04 and 21.01 (q, 2×*C*H$_3$), 30.14 (t, S*C*H$_2$), 58.68 and 73.16 (d, 6-*C* and 7-*C*), 67.54 (t, *C*H$_2$Ph), 112.7 and 132.1 (s, 2-*C* and 3-*C*), 125.5, 128.6, 128.9, and 130.0 (d, aromatic *C*H's), 135.5, 136.7, and 137.3 (s, 3×Ar *ipso C*), 162.6 and 165.7 (s, 2×*C*=O); and LRMS [DCI (NH_3)] *m/z* 444 (MNH_4^+, 4%), 427 (MH^+, 20), 399 (100), 303 (30), 277 (50), 248 ($MH^+-H_3CC_6H_4SNH$–CHCO, 65), 204 (20), 108 ($C_7H_7OH^+$, 10), and 91 ($C_7H_7^+$, 100).

Benzyl (−)-(6*S*,7*R*)-3-methyl-7-(4-nitrobenzylideneamino)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (75). To a solution of amine **66** (266 mg, 0.88 mmol) in CH_2Cl_2 (20 ml) was added anhydrous $MgSO_4$ (2.5 g) followed by *p*-nitrobenzaldehyde (132 mg, 0.88 mmol) and the mixture was stirred at room temperature for 10 h. Filtration, followed by evaporation of the solvent in vacuo, gave an off-white solid (340 mg) which was purified by flash chromatography (silica gel, CH_2Cl_2/EtOAc, 25:1) to give imine **75** (317 mg, 83%): white crystalline solid; mp 150–151°C (from EtOAc/petrol 40/60); (Found: C, 60.05; H, 4.09; N, 9.49. Calcd for $C_{22}H_{19}N_3O_5S$: C, 60.39; H, 4.36; N, 9.61%); R_f 0.60 (CH_2Cl_2: EtOAc, 25:1); $[\alpha]_D^{25}=-228$ (*c* 0.15 in acetone); FT IR ($CHCl_3$) ν_{max}/cm^{-1} 1769s (β-lactam), 1719s (ester), 1519s, and 1346*S*; ^1H NMR (200 MHz, $CDCl_3$) δ_H 2.13 (3H, s, C*H*$_3$), 3.24 (1H, d, *J*=18 Hz, SC*H*), 3.56 (1H, dd, *J*=18 Hz, *J*=1 Hz, SC*H*), 4.84 and 4.92 (2×1H, 2×d, *J*=1.5 Hz, 6-*H* and 7-*H*), 5.26 and 5.38 (2×1H, ABq, *J*=12 Hz, C*H*$_2$Ph), 7.33–7.49 (5H$_{arom}$, m, Ph), 7.93 and 8.29 (2×2H$_{arom}$, 2×dd, *J*=9 Hz, *J*=2 Hz, $C_6H_4NO_2$), and 8.57 (1H, d, *J*=1 Hz, *H*C=N); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 19.71, 31.57, 57.10, 67.59, 80.88, 123.7, 123.8, 128.4, 128.5, 128.6, 129.3, 129.7, 135.3, 140.6, 160.7, 162.0, and 162.2; and LRMS [DCI (NH_3)] *m/z* 438 (MH^+, 10%), 248 ($MH^+-O_2NC_6H_4CHNCHCO$, 100), 112 (50), and 91 ($C_7H_7^+$, 60).

Preparation of *p*-toluenesulfonic salt of benzyl (−)-(6*S*,7*S*)-7-amino-3-methyl-8-oxo-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylate (77). To a cooled (−78°C) solution of Schiff base **75** (132 mg, 0.30 mmol) in THF (5 ml) was added, with vigorous stirring, phenyl lithium (1.8 M solution in cyclohexane/ether, 168 μl, 0.30 mmol) followed by DMF (4 ml) to give a deep blue solution. After 2 min at −78°C the mixture was quenched with a solution of glacial AcOH (19 μl, 0.33 mmol) and water (27 μl, 1.5 mmol) in THF (1 ml). The resulting yellow solution was diluted with EtOAc (50 ml) and washed successively with 1 M NaH_2PO_4 (2×20 ml), water (3×30 ml), 1 M Na_2HPO_4 (2×20 ml), and satd. brine (20 ml). The organic layer was dried over $MgSO_4$ and evaporated in vacuo to afford an off-white solid (135 mg). Purification by flash chromatography (silica gel, CH_2Cl_2/EtOAc, 25:1) gave a white solid (123 mg, 93%) which, on the basis of ^1H

NMR (200 MHz,) analysis, consisted of two epimeric imines, **76** and **75**, in a ratio of ca. 2.5:1. The solid was dissolved in EtOAc (2.5 ml) containing water (82 μl, 4.5 mmol) and treated with *p*-toluenesulfonic acid monohydrate (86 mg, 0.45 mmol). The mixture was stirred at room temperature for 30 min and a white solid which crystallised from the reaction mixture was filtered and washed on the filter with EtOAc (3×1 ml) and Et_2O (2×1 ml). Drying in vacuo afforded salt **77** (65 mg, 49% or 45% from imine **75**): white crystalline solid; mp 173–174°C (dec.) (from EtOAc); FT IR (KBr disc) ν_{max}/cm^{-1} 1784s (β-lactam) 1722s (ester), 1640m, 1597m, 1546*S*, 1499m, 1454m, 1387*S*, 1371s, 1295s, 1251s, 1224s, and 1185s; ^1H NMR (500 MHz, $CDCl_3$) δ_H 2.16 (3H, s, CH_3), 2.35 (3H, s, Ar CH_3), 3.47 and 3.54 (2×1H, ABq, J=17.5 Hz, SCH_2), 5.00 and 5.19 (2×1H, 2×d, J=4.5 Hz, 6-*H* and 7-*H*), 5.27 and 5.30 (2×1H, ABq, J=12 Hz, CH_2Ph), 7.32 and 7.65 (2×2H_{arom}, 2×d, J=8 Hz, $C_6H_4CH_3$), and 7.39–7.46 (5H_{arom}, m, Ph); and LRMS (electrospray, +) *m/z* 305 (MH^+, 40%) and 277 (MH^+-CO, 100).

Coordinates for crystal strcutures will be deposited with the Cambridge Crystallographic Database. Selected data are:

Penam 26. $C_{23}H_{20}N_2O_5S$, M_r=436.4814. Orthorhombic, a=5.907(5), b=16.138(2), c=21.958(3) Å, V=2093.4 Å^3 (by least-squares refinement for 25 reflections, λ=1.5412 Å), space group $P2_1P2_1P2_1$, Z=4 Hz, D_x=1.3850 Mg m^{-3}. Colourless needles.

Cephem 50. $C_{23}H_{18}N_2O_5S$, M_r=434.4656. Orthorhombic, a=5.491(1), b=13.441(3), c=27.756(5) Å, V=2048.5 Å^3 (25 reflections, λ=1.5412 Å), space group $P2_1P2_1P2_1$, Z=4 Hz, D_x=1.4087 Mg m^{-3}.

Amine 51. $C_{15}H_{16}N_2O_3S$, M_r=304.363. Orthorhombic, a=12.184(2), b=12.145(1), c=9.924(2) Å, V=1468.4 Å^3 (25 reflections, λ=1.5412 Å), space group $P2_1P2_1P2_1$, Z=4 Hz, D_x=1.37.68 Mg m^{-3}. Colourless cubes.

Sulfoxide 58. $(C_{23}H_{20}N_2O_6S)_2$, M_r=904.96. Monoclinic, a=13.280(3), b=14.947(3), c=11.086(1) Å, β=95.17(1)°, V=2191.6 Å^3 (25 reflections, λ=1.5412 Å), space group $P2_1$, Z=2 Hz, D_x=1.37 Mg m^{-3}. Colourless prisms.

Acknowledgements

We thank ICI for a scholarship (to T. F.) and F. Hoffmann-La Roche for a gift of 6-APA. We thank Dr R. T. Aplin for mass spectroscopic analyses, Dr M. Vickers for powder diffraction studies, Mrs E. McGuinness and Dr T. Claridge for their assistance with high-field NMR experiments.

References

1. Knight, W. B.; Chabin, R.; Green, B. *Arch. Biochem. Biophys.* **1992**, *296* (2), 704–708.
2. Queener, S. W.; Neuss, N. The Biosynthesis of β-Lactam Antibiotics; In *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic: London, 1982; Vol. 3, pp 1–81.
3. Waxman, D. J.; Strominger, J. L. β-Lactam Antibiotics: Biochemical Modes of Action; In *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic: London, 1982; Vol. 3, pp 209–295.
4. Baggaley, K. H.; Brown, A. G.; Schofield, C. *J. Nat. Prod. Rep.* **1997**, *14*, 309–333.
5. Pfaendler, H. R.; Neumann, T.; Bartsch, R. *Synthesis* **1992**, 1179–1184.
6. Woodward, R. B.; Heusler, K.; Gosteli, J.; Naegeli, P.; Oppolzer, W.; Ramage, R.; Ranganathan, S.; Vorbrüggen, H. *J. Am. Chem. Soc.* **1966**, *88*, 852–853.
7. Oberhauser, T.; Meduna, V. *Tetrahedron* **1996**, *52*, 7691–7702.
8. (a) US Patent 3,489,751, 1970. (b) US Patent 3,489,752, 1970. (c) US Patent 3,985,741, 1976. (d) US Patent 4,504,657, 1985.
9. Fekner, T. *Syntheses of Unnaturally Configured Penicillins and Cephalosporins*, University of Oxford, 1996.
10. Fekner, T.; Baldwin, J. E.; Adlington, R. M.; Schofield, C. J. *Chem. Commun.* **1996**, 1989–1990.
11. De Angelis, F.; Mozzetti, C.; Di Tullio, A.; Nicoletti, R. *Chem. Commun.* **1999**, 253–254.
12. Morin, R. B.; Jackson, B. G.; Mueller, R. A.; Lavagnino, E. R.; Scanlon, W. B.; Andrews, S. L. *J. Am. Chem. Soc.* **1963**, *85*, 1896–1897.
13. Morin, R. B.; Jackson, B. G.; Mueller, R. A.; Lavagnino, E. R.; Scanlon, W. B.; Andrews, S. L. *J. Am. Chem. Soc.* **1969**, *91*, 1401–1407.
14. Busson, R.; Vanderhaeghe, H. *J. Org. Chem.* **1976**, *41*, 2561–2565.
15. Nefkens, G. H. L.; Tesser, G. I.; Nivard, R. J. F. *Recl. Trav. Chim. Pays-Bas.* **1960**, *79*, 688–698.
16. Sheehan, J. C.; Henery-Logan, K. R. *J. Am. Chem. Soc.* **1962**, *84*, 2983–2990.
17. (a) Wolfe, S.; Lee, W. H. *J. Chem. Soc., Chem. Commun.* **1968**, 242–245. (b) Cooper, R. D. G.; Demarco, P. V.; Spry, D. O. *J. Am. Chem. Soc.* **1969**, *91*, 1528–1529. (c) Jackson, J. R.; Stoodley, R. J. *J. Chem. Soc., Chem. Commun.* **1971**, 647–648. (d) Jackson, J. R.; Stoodley, R. J. *J. Chem. Soc., Perkin Trans. 1* **1972**, 895–899.
18. Kukolja, S. *J. Am. Chem. Soc.* **1971**, *93*, 6267–6269.
19. Kukolja, S. *J. Am. Chem. Soc.* **1971**, *93*, 6269–6270.
20. Spry, D. O. *J. Am. Chem. Soc.* **1970**, *92*, 5006–5008.
21. Spry, D. O. *J. Org. Chem.* **1972**, *37*, 793–795.
22. Ing, H. R.; Manske, R. H. F. *J. Chem. Soc.* **1926**, 2348–2351.
23. Heymes, R.; Amiard, G.; Nominé, G. *Bull. Soc. Chim. Fr.* **1974**, *3-4*, 563–566.
24. Naito, T.; Hoshi, H.; Aburaki, S.; Abe, Y.; Okumura, J.; Tomatsu, K.; Kawaguchi, H. *J. Antibiot.* **1987**, *40*, 991–1006.
25. Tsuji, T.; Kataoka, T.; Yoshioka, M.; Sendo, Y.; Nishitani, Y.; Hirai, S.; Maeda, T.; Nagata, W. *Tetrahedron Lett.* **1979**, *30*, 2793–2796.
26. Cooper, R. D. G. *J. Am. Chem. Soc.* **1970**, *92*, 5010–5011.
27. Cooper, R. D. G.; Spry, D. O. Rearrangements of Cephalosporins and Penicillins; In *Cephalosporins and Penicillins. Chemistry and Biology*; Flynn, E. H., Ed.; Academic: New York, 1972, pp 183–254.
28. Fekner, T.; Baldwin, J. E.; Adlington, R. M.; Schofield, C. J. *Tetrahedron Lett.* **1998**, *39*, 6983–6986.
29. (a) Kobayashi, T.; Iino, K.; Hiraoka, T. *Chem. Pharm. Bull.* **1979**, *27*, 2718–2726. (b) Kobayashi, T.; Hiraoka, T. *Chem. Pharm. Bull.* **1979**, *27*, 2727–2734. (c) Kobayashi, T.; Hiraoka, T. *Bull. Chem. Soc. Jpn* **1979**, *52*, 3366–3370. (d) Aoki, T.; Haga, N.; Sendo, Y.; Konoike, T.; Yoshioka, M.; Nagata, W. *Tetrahedron Lett.* **1985**, *26*, 339–342.

30. Gordon, E. M.; Chang, H. W.; Cimarusti, C. M. *J. Am. Chem. Soc.* **1977**, *99*, 5504–5505.
31. Gordon, E. M.; Chang, H. W.; Cimarusti, C. M.; Toeplitz, B.; Gougoutas, J. Z. *J. Am. Chem. Soc.* **1980**, *102*, 1690–1702.
32. Kurzer, F.; Powell, R. *Org. Synth.* **1955**, *35*, 99–101.
33. Firestone, R. A.; Maciejewicz, N. S.; Ratcliffe, R. W.; Christensen, B. G. *J. Org. Chem.* **1974**, *39*, 437–440.
34. Bohme, E. H. W.; Applegate, H. E.; Ewing, J. B.; Funke, P. T.; Puar, M. S.; Dolfini, J. E. *J. Org. Chem.* **1973**, *38*, 230–236.
35. (a) Applegate, H. E.; Dolfini, J. E.; Puar, M. S.; Slusarchyk, W. A.; Toeplitz, B.; Gougoutas, J. Z. *J. Org. Chem.* **1974**, *39*, 2794–2796. (b) Heuser, L. J.; Anderson, C. F.; Applegate, H. E.; Böhme, E. H.; Dolfini, J. E.; Puar, M. S. *J. Org. Chem.* **1974**, *39*, 929–3932. (c) Dunlap, N. K.; Dezube, M.; Keith, D. K.; Weigele, M. *Tetrahedron Lett.* **1992**, *33*, 6103–6106.
36. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.
37. Perrin, D. P.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon: Oxford, 1988.
38. Cignarella, G.; Pifferi, G.; Testa, E. *J. Org. Chem.* **1962**, *27*, 2268–2269.
39. Hauser, D.; Sigg, H. P. *Helv. Chim. Acta* **1967**, *50*, 1327–1335.
40. Volkmann, R. A.; Carroll, R. D.; Drolet, R. B.; Elliott, M. L.; Moore, B. S. *J. Org. Chem.* **1982**, *47*, 3344–3345.