Synthesis and decarboxylation of Δ^2-cephem-4,4-dicarboxylic acids

Saul Wolfe, Stephen Ro, Chan-Kyung Kim, and Zheng Shi

Abstract: Penicillin V was converted in 14 steps into Δ^2-cephems having hydrogen at C-3, hydrogen or methyl at C-2, and two methoxycarbonyl, two benzyloxycarbonyl, or one methoxycarbonyl and one benzyloxycarbonyl substituent at C-4. Deprotection of these Δ^2-cephem-4,4-dicarboxylic acid esters by alkaline hydrolysis (in the case of methyl esters) or hydrogenolysis (in the case of benzyl esters) led in all cases to rapid decarboxylation of the Δ^2-cephem-4,4-dicarboxylic acid or Δ^2-cephem-4,4-dicarboxylic acid monoester. With hydrogen at C-2, hydrolysis of the dimethyl ester with 1 equiv of base produced a Δ^2-cephem. With 2 equiv of base, and with all compounds having methyl at C-2, hydrolysis or hydrogenolysis afforded 4α-substituted-Δ^2-cephems.

In contrast, simpler benzyl or methyl acetamidomalonates could be deprotected without difficulty to afford stable malonic acids. Reasons for the differences in ease of decarboxylation were examined using semiempirical (AM1) and ab initio (3-21G) molecular orbital calculations. The decarboxylation barriers of unionized cephem or acetamido malonic acids were found to be high (35–40 kcal mol^{-1}). Although the monoanion of acetamidomalonic acid retained a high barrier, the epimeric monoanions of a Δ^2-cephem malonic acid decarboxylated with barriers of only 2 kcal mol^{-1}.

Key words: mercaptoazetidinone, bromomalonate esters, MO calculations, sulfoxides, hydrogenolysis.

Résumé : On a transformé la pénicilline V en quatorze étapes en Δ^2-céphèms portant un hydrogène en C-3, un hydrogène ou un méthyle en C-2 et deux méthoxycarbonyles, deux benzoyloxycarbonyles ou un méthoxycarbonyle et un benzoyloxycarbonyle comme substituants en C-4. Le déprotection de ces esters de Δ^2-céphem-4,4-dicarboxylique par hydrolyse alcaline (dans le cas des esters méthyliques) ou par hydrogénolyse (dans les cas des esters benzyliques) conduit dans tous les cas à une décarboxylation rapide de l'acide Δ^2-céphem-4,4-dicarboxylique ou de son monoester. L'hydrolyse de l'ester diméthylique du produit portant un hydrogène en C-2 à l'aide d'un équivalent de base conduit à un Δ^2-céphem. Avec deux équivalents de base ainsi qu'avec tous les composés portant un groupe méthyle en C-2, l'hydrolyse ou l'hydrogénolyse conduit à des Δ^2-céphems portant un substituant en position 4α.

Par ailleurs, il est possible de déprotéger sans difficulté les acétamidomalonates de benzyle ou de méthyle plus simples pour obtenir des acides maloniques stables. Faisant appel à des calculs d'orbitales moléculaires semi-empiriques (AM1) et ab initio, on a étudié les différences dans la facilité de ces décarboxylations. On a trouvé que les barrières à la décarboxylation des acides céphems dicarboxyliques et des acétamidomaloniques non ionisés sont relativement élevées (35-40 kcal/mol). Même si la barrière est encore élevée pour le monoanion de l'acide acétamidomalonique, les monoanions épimères d'un acide Δ^2-céphem malonique se décarboxylent avec une barrière qui n'est que d'environ 2 kcal mol^{-1}.

Mots clés : mercaptoazétidinone, esters de l'acide bromomalonique, calculs OM, sulxoydes, hydrogénolyse.

[Traduit par la Rédaction]

Introduction

The antibacterial activity of the Δ^2-cephem-4α-carboxylic acid **1** is 100 times less than that of the Δ^3-cephem **2** (1). Since cephalosporins undergo $\Delta^3 \rightleftarrows \Delta^2$ equilibration in solution to give mixtures in which the 4α-carboxy-Δ^2-isomers (**3a**) usually predominate (2), there is a resultant loss of activity, and the origin of this loss of activity has received considerable attention (3).

The cephalosporin receptor is a serine peptidase whose active site hydroxyl group is acylated by the β-lactam ring (4). Most workers accept that this chemical reaction proceeds by deprotonation of the serine OH, coupled to nucleophilic addition of the resulting anion to the β-lactam carbonyl group (5). In terms of this mechanism, the decrease in antibacterial activity that accompanies the isomerization to **3a** would be a consequence of the decreased susceptibility of the β-lactam carbonyl group of a Δ^2-cephem towards nucleophilic attack. Indeed **1** is most readily obtained by *alkaline hydrolysis* of the methyl ester of **2** (6).

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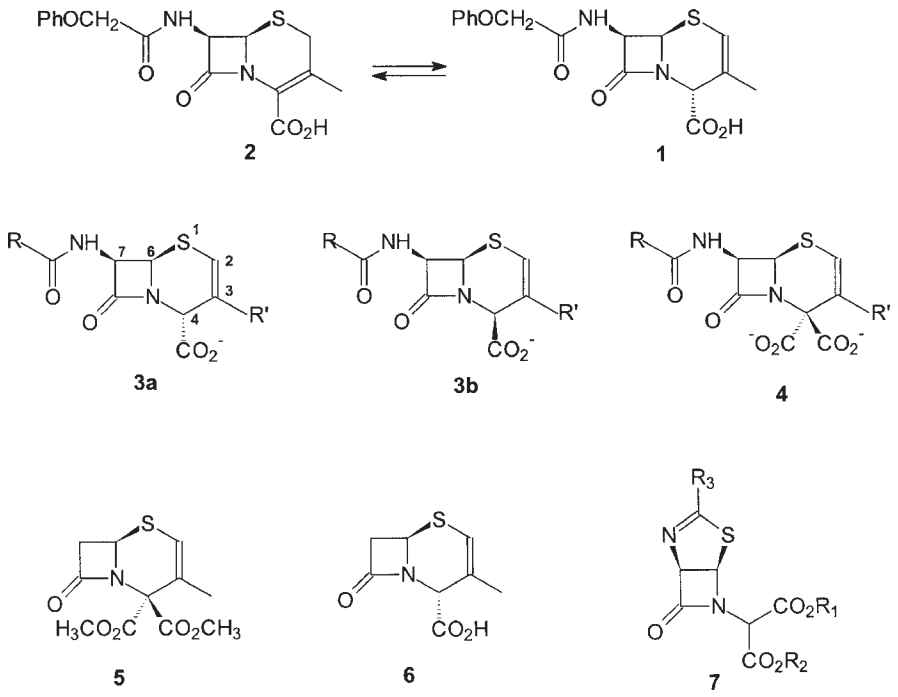
However, in the case of an exocellular peptidase from *Streptomyces* R61, which has been studied in some detail (7), including a crystal structure (8), the catalytic efficiencies towards 6-aminopenicillanic acid, cephaloglycine and penicillin G are 0.2, 22, and 13 000, respectively, but the corresponding second-order rate constants for alkaline hydrolysis of the β-lactam rings of these compounds are 0.15, 0.90, and 0.50 M^{-1} s^{-1} (7). The absence of any correlation between the trends in the enzymatic and nonenzymatic rate constants is not consistent with the claim that the acyl-enzyme is formed by nucleophilic addition to the β-lactam carbonyl group.

In a different approach to the problem, following an examination of the crystal structures of active and inactive β-lactam compounds, Cohen (9) proposed that **3a** are inactive as a consequence of a misfit with the receptor, and suggested that their 4β-carboxy epimers (**3b**) would exhibit a better fit, with restored activity. However, the activity of a Δ^2-cephem-4β-carboxylic acid proved to be less than that of its 4α-epimer (10).

Independently, structure-activity studies and calculations by Wolfe and Hoz (11) led to the proposal that **3a** react more rapidly than Δ^3-cephems with the hydroxyl group of the peptidase receptor, but are less effectively complexed; in addition, in agreement with Cohen, it was suggested that epimerization to **3b** would lead to improved complexation with the receptor, at the expense of an inherent decrease in reactivity with the serine hydroxyl group.

These findings led to the idea that the presence of the 4β-carboxyl group in a Δ^2-cephem-4,4-dicarboxylic acid such as **4** might allow effective complexation to the peptidase, and the concurrent presence of the 4α-carboxyl group might enhance the rate of the acylation step, the two effects together leading to enhanced antibacterial activity in a Δ^2-cephem. The work reported here was undertaken to test this idea. Although it was known that the malonate **5** had yielded only the decarboxylated product **6** following alkaline hydrolysis and acidification (12), that reaction mixture was maintained at pH 2 for 1 h prior to the isolation of the product. It was hoped that decarboxylation could be avoided in the present work by the elimination of an extended acidic treatment following the deprotection of a Δ^2-cephem-4,4-dicarboxylic acid diester.

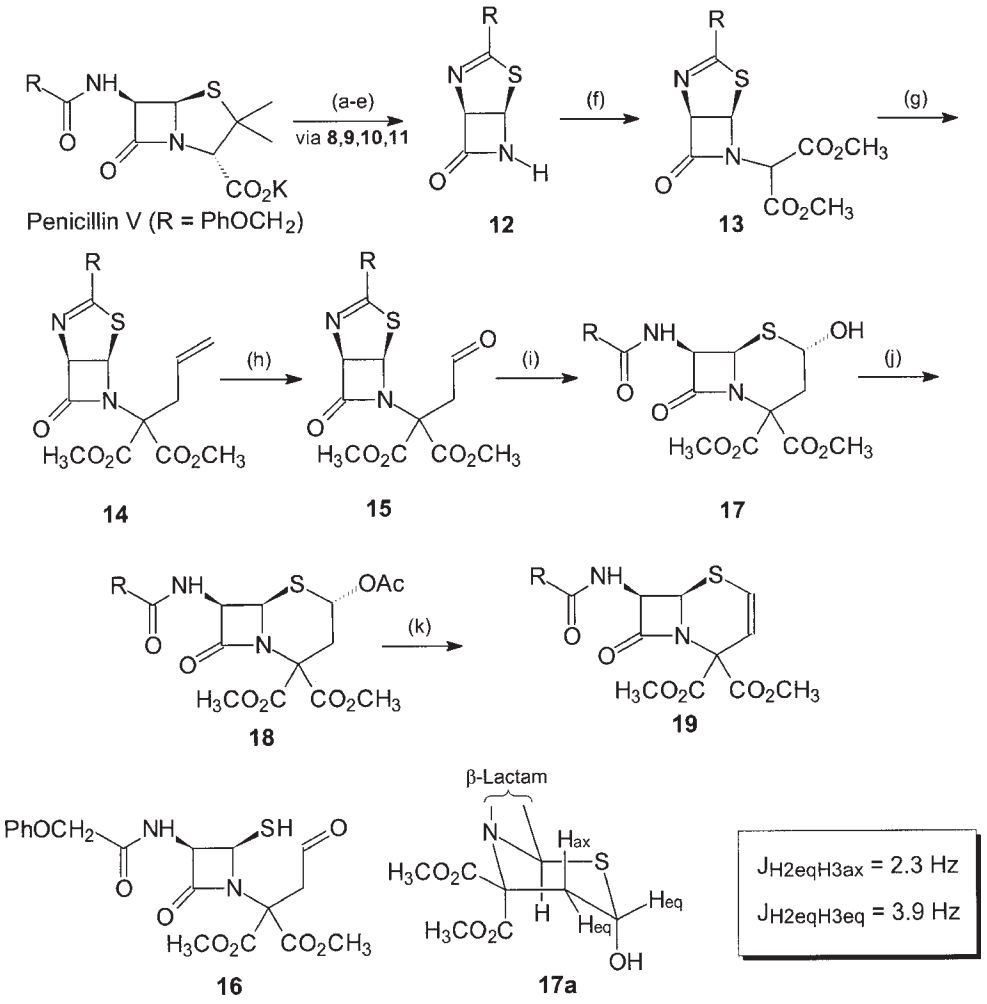


Syntheses of substrates

Malonyl-substituted thiazoline-azetidinones of type **7** have often been reported in the literature (13), usually as intermediates in syntheses requiring the attachment of an acetate chain to the β-lactam nitrogen. By virtue of its acidic α-proton, **7** also serves as a potential branch point for the construction of a new ring. The conversion of penicillin V into the Δ^2-cephem **19** is summarized in Scheme 1. Scheme 2 summarizes a different sequence leading to the 2-methyl-Δ^2-cephems **24**.

In Scheme 1, dimethyl bromomalonate, prepared by irradiating a solution of bromine and dimethyl malonate, was reacted with the thiazoline azetidinone **12** (14) in the presence of benzyl trimethylammonium hydroxide (Triton B) to give **13** in 50% yield. Coupling with allyl bromide in the presence of Triton B or sodium hydride produced **14** which, upon ozonolysis and treatment with dimethyl sulfide afforded an aldehyde (**15**) in quantitative yield. Exposure of this aldehyde to 3% perchloric acid in a 1:1 solution of dichloromethane–acetone (15), led to hydrolysis to the mercaptoazetidinone **16**, followed by cyclization to the hydroxycepham **17** in 94% from **14**.

Scheme 1. Reagents and conditions: (*a*) CH_3I, DMF; (*b*) AcOH, H_2O_2, CH_2Cl_2; (*c*) $P(OMe)_3$, $MgSO_4$, toluene; (*d*) Et_3N; (*e*) $KMnO_4$, $MgSO_4$, EtOH; (*f*) Triton B, $BrCH(CO_2CH_3)$, DMF, –50 to 20°C; (*g*) Triton B or NaH, allyl bromide; (*h*) O_3, CH_2Cl_2-CH_3OH, –78°C, then Me_2S; (*i*) $HClO_4$, CH_2Cl_2–acetone; (*j*) Ac_2O, H_2SO_4, AcOH; (*k*) pTsOH, toluene, Δ.



The configuration at C-2 and the conformation of the six-membered ring of **17** (see **17a**) were evident from the ^1H NMR spectrum, which showed J_{H2H3} and $J_{H2H3'}$ = 2.3 and 3.9 Hz, respectively. The axial orientation of the hydroxyl group is evidence of an S-C-O Edward–Lemieux effect (16).

The dehydration of **17** was unexpectedly difficult and was best achieved in 52% yield by acetylation to **18**, followed by heating with *p*-toluenesulfonic acid in refluxing toluene.

In Scheme 2, the dimethyl malonate **14** and its dibenzyl ester and mixed methyl benzyl ester analogs, prepared by the reaction of **12** with the appropriate bromomalonate followed by allylation, were treated with iodine in a mixture of methylene chloride and water to give the 2β-substituted iodomethylcephams **20** (13). In each case, the configuration at C-2 and the conformation shown in **20a** could be assigned on the basis of a positive NOE between H_2 and H_6, and from H_2H_3 coupling constants of 1.9 and 12.2 Hz.

At this point, the synthetic plan called for dehydrohalogenation of **20** to **23**, and isomerization to **24**. However, exposure of **20** to sodium hydride or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or Triton B produced complex mixtures. To circumvent the possibility that this was the result of participation by sulfur in the elimination of iodide, the iodomethylcephams were first oxidized to the sulfoxides **21** using sodium periodate in aqueous methanol. Dehydrohalogenation with DBU now proceeded smoothly to give the exomethylene sulfoxides **22**, which afforded the exomethylene cephams **23** following reduction with phosphorus tribromide. Isomerization to **24** was achieved using trifluoroacetic acid.

In the case of the epimeric methyl benzyl esters (R_1 = Me, R_2 = CH_2Ph), which were formed in a 1:1 ratio in the coupling with **12**, separation was achieved at the stage of the exomethylene sulfoxide **22**. Since 2D-NOESY experiments were inconclusive in allowing configurations to be assigned to the epimers of **22**–**24**, the technique of aromatic solvent-induced shifts (ASIS) (17) was applied to **24**. Changing the solvent from deuterated chloroform to benzene leads to an upfield chemical shift of atoms or groups on the convex (α) face of the molecule, because the V-shaped bicyclic ring system blocks access of the solvent to the concave (β) face.

As seen in Table 1, except for H_3, the change from chloroform to benzene leads to an upfield shift of the protons. The data suggest that epimer A has the benzyl ester on the α face and that epimer B has the methyl ester on the α face.

To corroborate these conclusions, ASIS measurements were performed on a compound of known stereochemistry, the methyl ester of penicillin V. In deuterated chloroform,

Scheme 2. Reagents and conditions: (*a*) Triton B, DMF, –50 to 20°C; (*b*) Triton B or NaH, allyl bromide; (*c*) I_2, CH_2Cl_2–H_2O; (*d*) $NaIO_4$, MeOH–H_2O; (*e*) DBU, CH_2Cl_2; (*f*) PBr_3, DMF, 0°C; (*g*) TFA, CH_2Cl_2, 0°C.

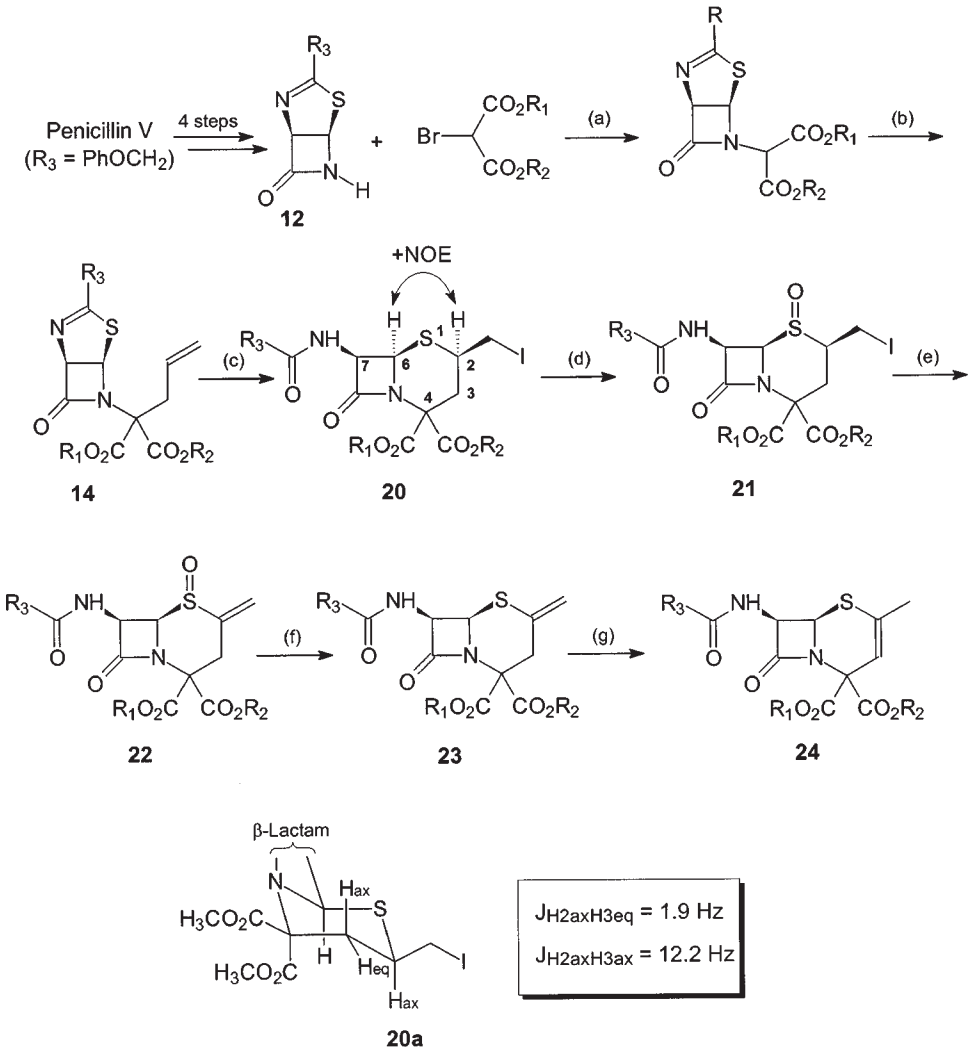
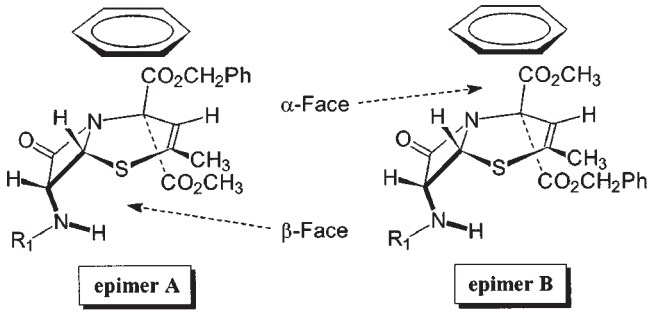


Table 1. Chemical shifts (δ) of epimer A and epimer B of **24**.



	Epimer A		Epimer B		Δ ($CDCl_3$–C_6D_6, ppm)	
Proton	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6	Epimer A	Epimer B
H_3	5.85	6.02	5.86	6.05	–0.17	–0.18
H_6	5.31	5.18	5.33	5.13	0.13	0.20
H_7	5.77	5.61	5.80	5.58	0.17	0.22
$PhOCH_2$	4.56	3.99	4.56	4.03	0.57	0.53
4-CO2CH_3	3.77	3.52	3.74	3.23	0.26	0.50
4-CO_2CH_2PH	5.24	4.99	5.27	5.27	0.25	–0.03

the ester methyl group, which occupies the convex face of the molecule, is found at 3.76 ppm. In deuterated benzene the chemical shift is 3.20 ppm, a difference of 0.56 ppm. The corresponding difference in epimer B is 0.50 ppm.

Deprotection of the Δ^2-cephem-4,4-dicarboxylic acid esters

Alkaline hydrolysis of 19

In an initial set of experiments, **19** was treated at –8°C with 2 equiv of potassium hydroxide in aqueous pyridine, and the solvent was then removed under reduced pressure below 30°C. This afforded a product that exhibited significant antibacterial activity against a penicillin-sensitive strain of *Staphylococcus aureus*. However, the product was not the malonate salt **25**. As seen in **26** and **27**, the ^{1}HMR spectrum (in D_2O) was that of a mixture of *decarboxylated* Δ^2- and Δ^3-cephems. Cephems of type **27**, having hydrogen at C-3, are known to be active, and one of these, ceftizoxime, is a widely used antibiotic (18).

Following these initial experiments, subsequent hydrolyses were performed with a minimum of manipulation: reaction mixtures were acidified, and the products quickly extracted into an appropriate organic solvent and esterified with diazomethane. Using this protocol, the reaction of **19** with *2* equiv of potassium hydroxide produced a 7:1 mixture of decarboxylated Δ^2- and Δ^3-cephem esters (**28** and **29**, respectively). However, *1* equiv of potassium hydroxide reversed the **28**:**29** ratio to 1:4 (see Fig. 1).

These results suggest that a carboxylate anion **30**, formed in the first hydrolysis step, undergoes rapid decarboxylation concerted with a shift of the double bond, as depicted in **30** → **31**. Subsequently, C-2 deprotonation of **31**, leading, via **32**, to the more stable Δ^2-isomer **28**, competes with the hydrolysis of the second ester.

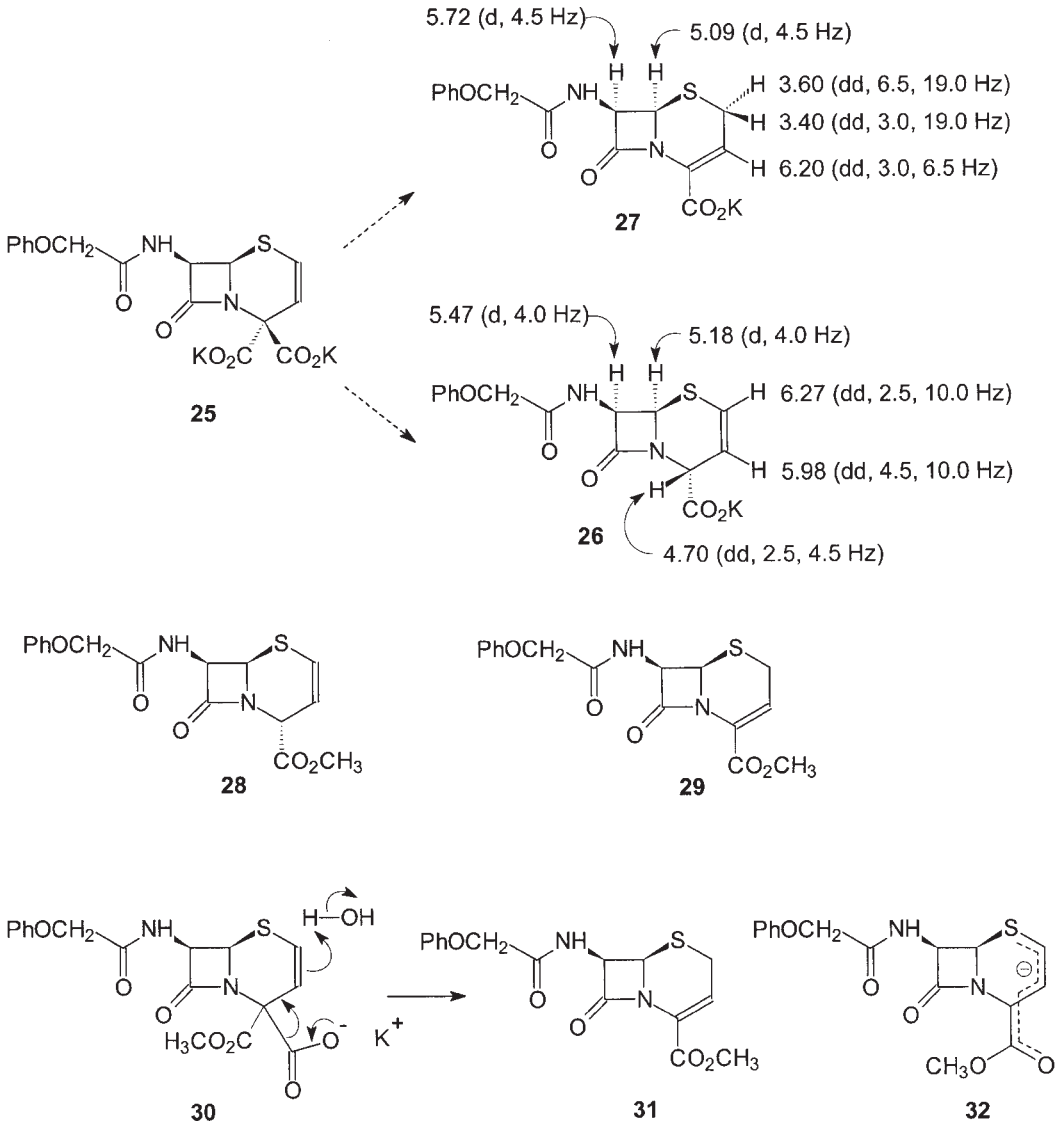
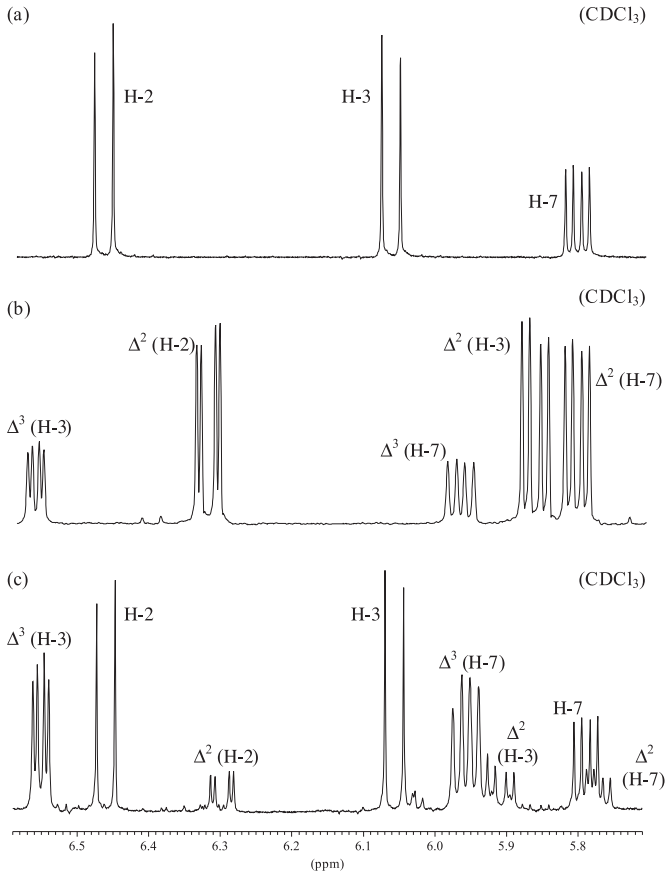


Fig. 1. (*a*) The 5.5–6.6 ppm region in the ^{1}H NMR spectrum of **1**; (*b*) spectrum of a mixture of **28** and **29**; (*c*) after exposure of **19** to 1 equiv of KOH in aqueous pyridine.



Alkaline hydrolysis of 24 ($R_1 = R_2 = Me$)

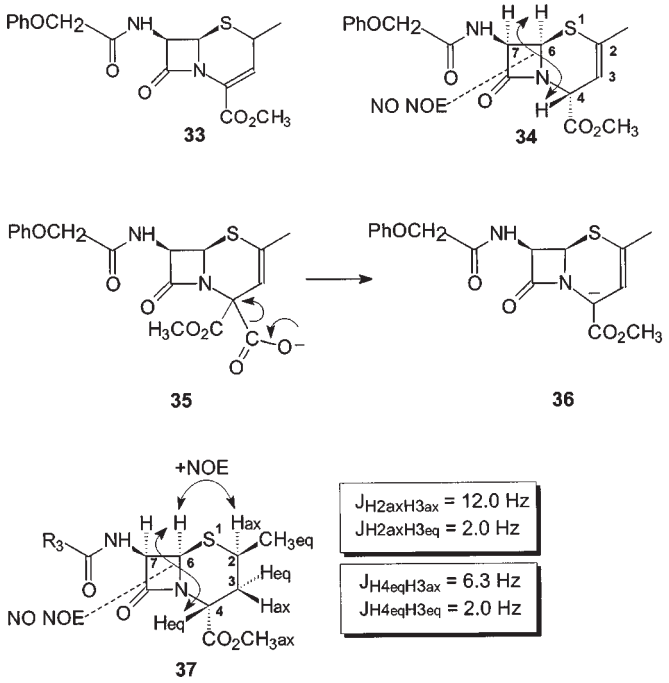
The foregoing analysis suggested that the introduction of an electron-releasing C-2-methyl group, as in **24**, might affect the results of alkaline hydrolysis in two ways: preferably, the concerted decarboxylation pathway that is presumed to cause the lability of the Δ^2-cephem-4,4-dicarboxylic acid would become disfavoured; alternatively, if this is not the case and the initial product is again a Δ^3-ester (**33**), this ester should resist isomerization of the double bond, because C-2 deprotonation leading to the more stable Δ^2-ester **34** would be disfavoured.

In the event, the hydrolysis of the dimethyl ester (**24**, $R_1 = R_2 = Me$) with either 1 or 2 equiv of potassium hydroxide in aqueous pyridine, followed by the usual work-up, afforded the *same* product in each case, the Δ^2-cephem **34**.

The simplest explanation of these results is that the carboxylate anion **35** decarboxylates rapidly to **36**. Although the concerted decarboxylation pathway leading initially to the Δ^3-isomer is disfavoured, the presence of the C-2-methyl group leads to direct decarboxylation to the Δ^2-isomer as the predominant pathway. An alternative explanation is that, despite our expectations regarding the kinetic acidity of **33**, under alkaline conditions the introduction of the C-2-methyl group somehow *enhances* the $\Delta^3 \rightarrow \Delta^2$ rearrangement. This point was addressed using the dibenzyl ester **24** ($R_1 = R_2 = CH_2Ph$).

Hydrogenolysis of 24 ($R_1 = R_2 = CH_2Ph$)

Experiments were performed using 10% palladium on carbon, in aqueous ethanol containing 2 equiv of sodium bicarbonate (Method A), and in aqueous acetic acid (pH 4 to 5) (Method B). Products were isolated by filtration through Celite, followed by evaporation or lyophilization and conversion to the methyl ester. This led, in ethanol, to the Δ^2-ester **34** as the sole product (>90%). In acetic acid, the products were **34** and the *cepham* **37**, whose stereochemistry was elucidated from the H_2H_3 coupling constants, a positive NOE between H_2 and H_6 and the absence of an NOE between H_4 and H_6.



Thus, in contrast to the C-2-unsubstituted diester **19**, which, following the exposure of one carboxyl group, decarboxylates with rearrangement of the double bond, in the case of the C-2-methylated esters there is rapid decarboxylation *without rearrangement of the double bond*.

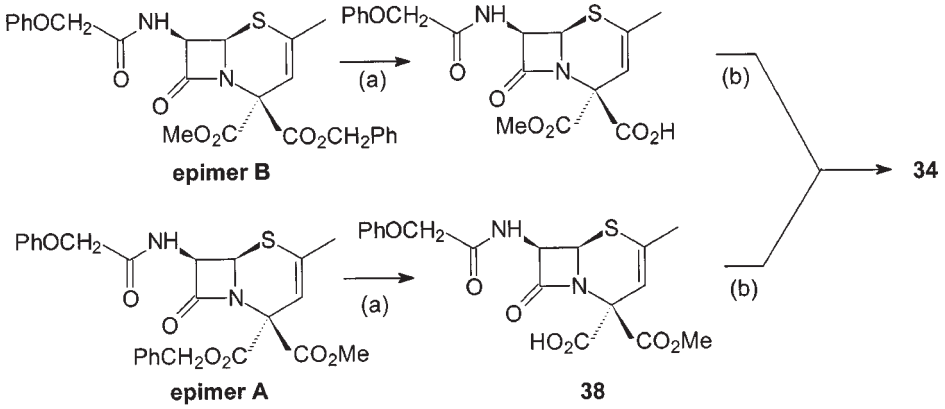
Hydrogenolysis of the epimeric methyl benzyl esters 24 (R_1, R_2 = Me, CH_2Ph)

As summarized in Scheme 3, hydrogenolysis using Method B resulted in decarboxylation with the formation of **34** in both cases. Carbanion **36** is implicated as an intermediate in these reactions since the decarboxylation of **38** proceeds with inversion of configuration at C-4. The pK_1 of malonic acid is 2.85 at 298 K (19), so that in aqueous acetic acid the Δ^2-cephem-4,4-dicarboxylic acid **38** would be fully ionized.

Preparation and deprotection of acetamidomalonate esters

There are numerous examples of stable β-lactam-containing malonic acids (20). The Meldrum acid derivative **39** hydrolyzes under basic conditions to give the malonic acid **40**, whose decarboxylation to **41** requires refluxing ethyl acetate in the presence of formic acid. The malonic

Scheme 3. Reagents and conditions: (*a*) H_2, Pd/C, HOAc–H_2O; (*b*) CH_2N_2, CH_2Cl_2–EtOH, 0°C.



acid **42** can be isolated and converted to the penam **43**. Based on these precedents, the rapid decarboxylation observed in all cases following deprotection of **19** and **24** was unexpected. In an effort to understand this result, the dibenzyl acetamidomalonates **44** and **45** were synthesized (see *Experimental*) and subjected to hydrogenolysis followed by esterification with diazomethane. The products, isolated in 81% and 82% yields, respectively, were the dimethyl malonates **46** and **47**. Subsequent experiments established that the malonic acid precursors of **46** and **47** could be maintained at room temperature for at least 24 h without noticeable decomposition.

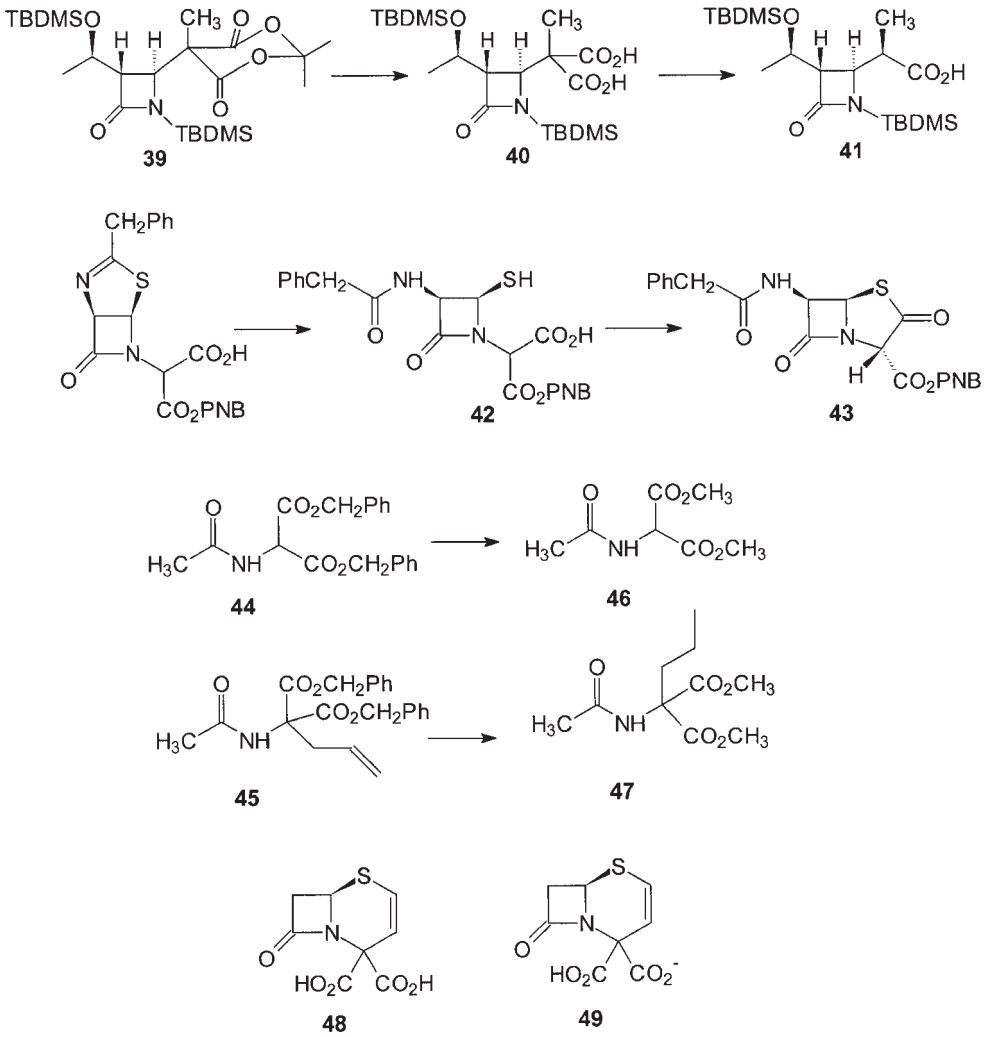
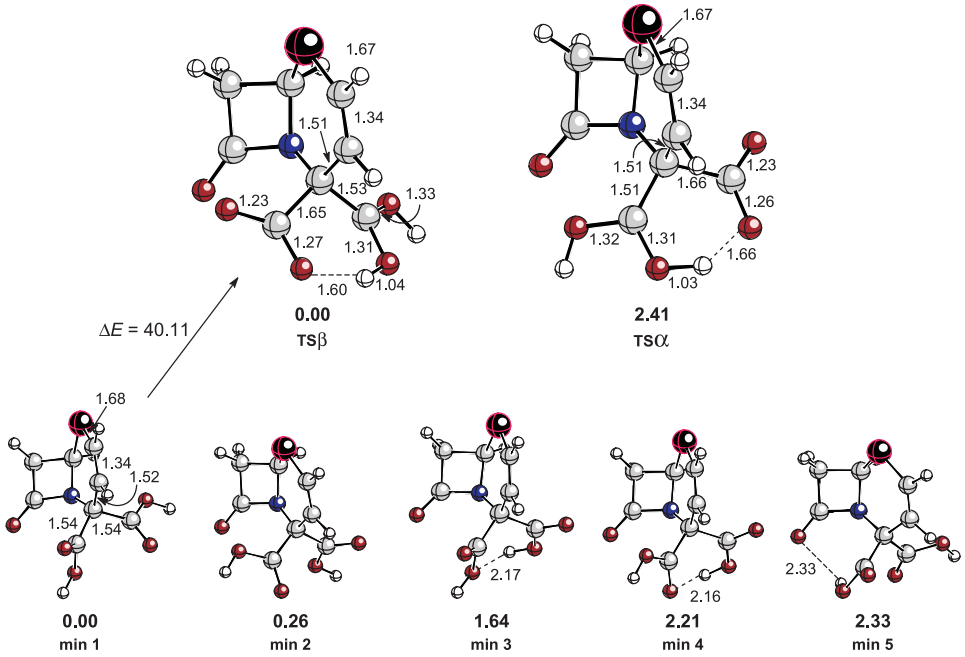


Fig. 2. Neutral decarboxylation of **48** (AM1 calculations). **Min 1**–**min 5** are the five lowest energy structures of the diacid; TSα and TSβ are the transition structures for α- and β-decarboxylation. Energies are in kcal mol^{-1}, relative to **min 1** and TSβ.



Theoretical considerations

The reasons for the differences in ease of decarboxylation were examined using semiempirical and ab initio molecular orbital calculations. With AM1 (21), calculations on 4,4-dicarboxy-Δ^2-cephem (**48**) yielded 5 minima corresponding to torsion within the carboxyl groups. The most stable structure (**min 1**) and the least stable structure (**min 5**) differ in energy by 2.3 kcal mol^{-1} (Fig. 2). The two most stable structures (**min 1** and **min 2**) have the *Z*-conformation (22). The next two (**min 3** and **min 4**) have one carboxyl group in the *Z*-conformation and other in the *E*-conformation. The least stable structure (**min 5**) has both carboxyl groups in the *E*-conformation.

The transition structures **TS**α and **TS**β, calculated for the decarboxylation of the α- and β-carboxyl groups of **48** are included in Fig. 2. The β-decarboxylation barrier, corresponding to decarboxylation from the concave face of the molecule, is lower by 2.4 kcal mol^{-1}.

The transition structures are late, as proton transfer is almost complete. The barrier, calculated from **min 1** is 40.1 kcal mol^{-1}. In Bach's high level ab initio calculations (23), malonic acid was found to have a decarboxylation barrier of 33.2 kcal mol^{-1}. The experimental barrier is 30.8 kcal mol^{-1} (23). Since the calculated neutral barriers are high, the facile decarboxylations observed experimentally cannot be attributed to the decarboxylation of a 4,4-dicarboxy-Δ^2-cephem or its monoester.

On the other hand, the α- and β-decarboxylation barriers of the monoanions **49** (Fig. 3) are vanishingly small (2.04 and 2.08 kcal mol^{-1}, respectively).

Figures 4 and 5 show the results of ab initio (3-21G) calculations of the decarboxylation barriers of acetamidomalonic acid (35.2 kcal mol^{-1}) and its monoanion (26.3 kcal mol^{-1}). The barrier decreases in the anion, but does not become vanishingly small. It is noteworthy that the monoanion of phenylmalonic acid decarboxylates 3 to 4 times faster than the undissociated acid (24).

The calculations are consistent with experiment: the undissociated cephem and acetamidomalonic acids have comparable (high) decarboxylation barriers, which disappear in the case of the cephem monoanions. Since these anions would be fully formed at pH > 3 in water solvent, it does not appear possible to test the prediction that 4,4-dicarboxy-Δ^2-cephems will have significant antibacterial activity.

Experimental

General

All reactions were performed under dry nitrogen using oven-dried (140°C, 24 h) glassware. The glassware was allowed to cool in a desiccator under vacuum and assembled cold, capped with rubber septa, and evacuated with dry nitrogen gas. Solvents were distilled prior to use and dried, as necessary, by literature procedures (25). Diazomethane was prepared by treatment of a cold solution of *N*-methyl-*N*-nitrosotoluene-4-sulfonamide (DIAZALD) in 95% ethanol with 1.0 mL portions of 12.5 M sodium hydroxide. Both ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Model AMX 400 Spectrometer operating at 400.1 MHz and 100.6 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS) in an appropriate deuterated solvent. Infrared (IR) spectra were obtained on a Bomen–Hartmann–Braun spectrometer (1% KBr or 1% solution). High-resolution mass spectra refer to either direct inlet electron impact (EI) measurements or chemical ionization (CI) measurements, using isobutane, and were provided by Dr. G. Eigendorf at the University of British Columbia. Low-

Fig. 3. Decarboxylation of the monoanions of **48** (AM1 calculations). Energies are in kcal mol^{-1}; bond lengths are in Å. Net atomic charges are shown in parentheses.

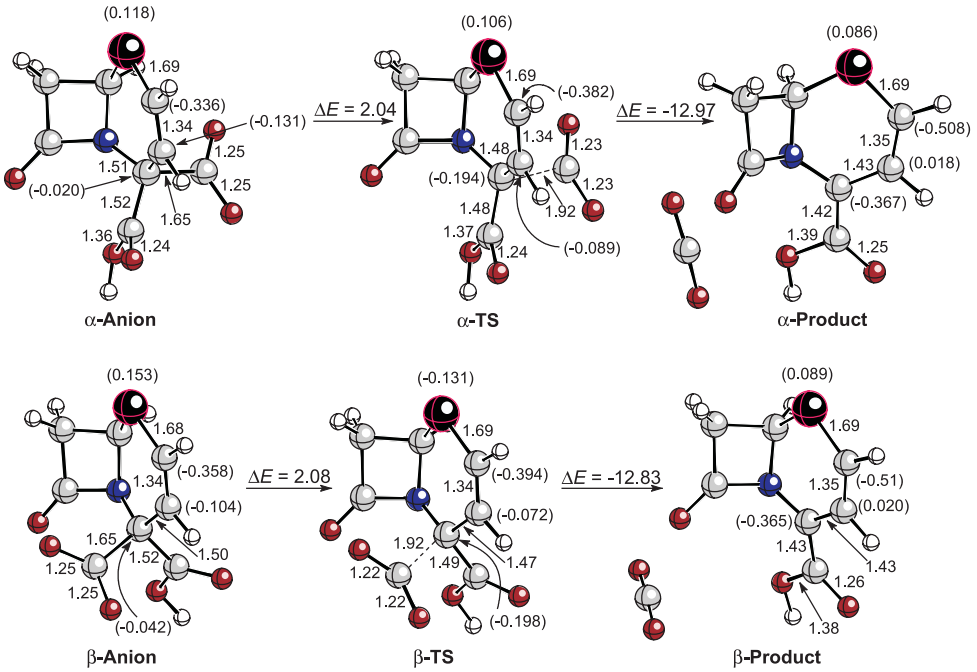


Fig. 4. Decarboxylation of acetamidomalonic acid (3-21G calculations). Energies are in kcal mol^{-1}; bond lengths are in Å.

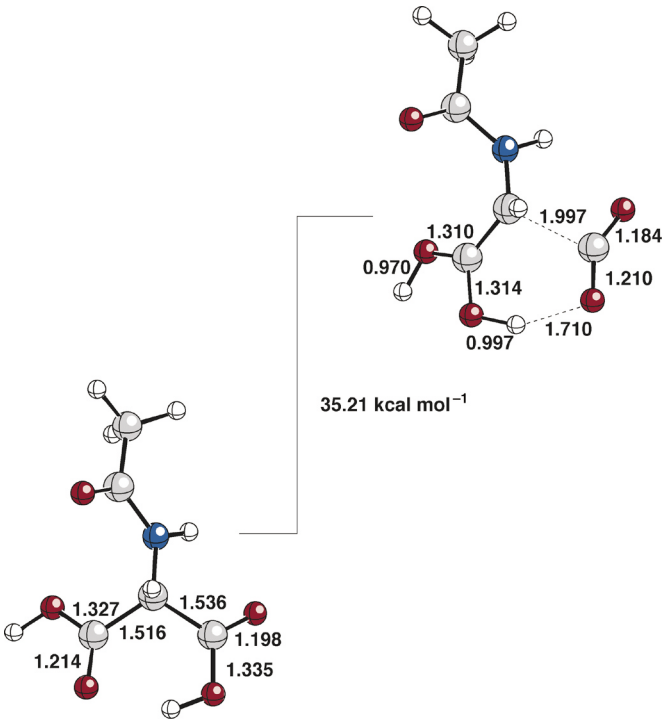
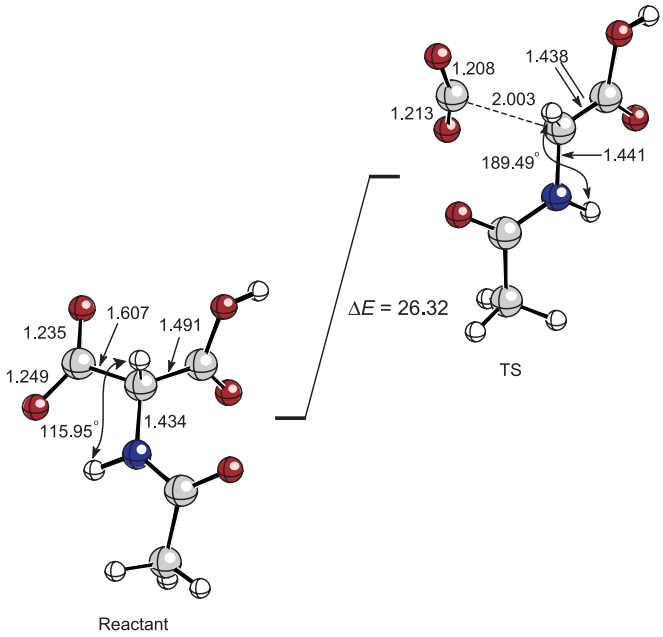


Fig. 5. Decarboxylation of the monoanion of acetamidomalonic acid (3-21G calculations). Bond lengths are in Å; bond angles are in deg.



resolution mass spectra refer to direct inlet EI measurements or CI measurements, using isobutane, or fast-atom bombardment (FAB), employing xenon gas, on a Kratos MS50 Spectrometer operated at 70 eV by G. Owens at Simon Fraser University. Melting points (mp) were determined on a Fisher–Johns apparatus, and are uncorrected. Optical rotations were obtained using a Rudolph automatic polarimeter. Analytical thin-layer chromatography was carried out on precoated Merck Silica gel 60 F-254 plates with aluminium backing. Spots were observed under short-wavelength ultraviolet light, or were visualized with iodine vapour, ninhydrin, or ceric sulfate. Flash column chromatography was carried out on Merck Silica gel 60 (230–400 Mesh), according to the method of Still et al. (26), unless stated otherwise, using only distilled solvents under dry nitrogen gas. Elemental analyses were performed by M.K. Yang on a

Carlo Erba model 1106 elemental analyzer at Simon Fraser University.

Penicillin V methyl ester (8)

Methyl iodide (14.0 mL, 31.9 g, 225 mmol) was added dropwise, with stirring, to a suspension of penicillin V (77.0 g, 198 mmol) in dimethylformamide (400 mL). Stirring was continued at room temperature for 17 h. The solvent was then removed under reduced pressure, and the residual oil was diluted with dichloromethane (300 mL), washed successively with water (4 × 150 mL), and saturated sodium chloride (300 mL), dried over magnesium sulfate and evaporated to give the product as an orange oil (72.3 g, 94%), which crystallized upon trituration with ether; mp 60 to 61°C. $[\alpha]_D^{20}$ +124.1° (c 0.137, $CHCl_3$). Mass spectrum (CI, *m*/*z*): 365 (M+1). IR (KBr) (cm^{-1}): 3366, 1786, 1744, 1701. ^1H NMR ($CDCl_3$): 7.35 (4H, t, Ar + NH), 7.05 (1H, t, Ar), 6.94 (1H, d, Ar), 5.75 (1H, dd, 4.3, 9.3 Hz, H-6), 5.59 (1H, d, 4.3 Hz, H-5), 4.57 (1H, d, 15.1 Hz, CHH), 4.55 (1H, d, 15.1 Hz, CHH), 4.47 (1H, s, H-3), 3.78 (3H, s, ester CH_3), 1.60 (3H, s, CH_3), 1.49 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$): 172.96 (acetamido C=O), 168.04 (β-lactam C=O), 167.87 (ester C=O), 157.11, 129.86, 122.47, 114.20 (aromatic), 70.57 (C-3), 67.85 (C-5), 67.38 ($PhOCH_2$), 64.79 (C-2), 58.23 (C-6), 52.35 (CO_2CH_3), 31.91 (CH_3), 26.91 (CH_3). Anal. calcd. for $C_{17}H_{20}N_2O_5S$: C 56.03, H 5.53, N 7.69; found: C 55.75, H 5.55, N 7.59.

Penicillin V methyl ester sulfoxide (9)

Hydrogen peroxide (34.0 mL of 50%, 17.0 g, 500 mmol) was added, with stirring during 1 h, to a solution of penicillin V methyl ester (72.3 g, 198 mmol) in dichloromethane (800 mL) and glacial acetic acid (92 mL). Stirring was continued for 17 h, and the yellow solution was then washed successively with saturated sodium bicarbonate (2 × 200 mL), water (2 × 200 mL), and saturated sodium chloride (400 mL), dried over magnesium sulfate and evaporated. The resulting yellow foam crystallized upon treatment with hot methanol (150 mL). The product was collected and washed with cold methanol (40 mL) to give 76.4 g (78%) of the methyl ester of penicillin V sulfoxide; mp 118–120°C (lit. (27) mp 121.5 to 122.5°C). $[\alpha]_D^{20}$ +202.7° (c 0.148, $CHCl_3$). Mass spectrum (CI, *m*/*z*): 381 (M+1). IR (KBr) (cm^{-1}): 3380, 1802, 1757, 1694, 1065. ^1H NMR ($CDCl_3$): 8.26 (1H, d, 10.4 Hz, NH), 7.29 (2H, m, Ar), 7.01 (1H, t, Ar), 6.94 (2H, d, Ar), 6.09 (1H, dd, 4.6, 10.5 Hz, H-6), 5.04 (1H, d, 4.6 Hz, H-5), 4.68 (1H, s, H-3), 4.53 (2H, s, $PhOCH_2$), 3.82 (3H, s, ester CH_3), 1.73 (3H, s, 2-CH_3), 1.22 (3H, s, shows nOe with H-5 at 5.04 ppm, 2-CH_3). ^{13}C NMR ($CDCl_3$): 173.08 (acetamido C=O), 168.30 (β-lactam, ester C=O), 157.20, 129.72, 122.26, 115.02 (aromatic), 76.57 (C5), 75.32 (C2), 67.29 ($PhOCH_2$), 66.55 (C-3), 55.67 (C-6), 52.91 (ester CH_3), 19.44 (CH_3), 18.73 (CH_3). Anal. calcd. for $C_{17}H_{20}N_2O_6S$: C 53.67, H 5.30, N 7.36; found: C 53.30, H 5.30, N 7.36.

Rearrangement of penicillin V sulfoxide

Trimethylphosphite (70.0 mL, 73.6 g, 593 mmol) was added to a mixture of penicillin V methyl ester sulfoxide (53.0 g, 139 mmol) and anhydrous magnesium sulfate (33.0 g, 274 mmol) in benzene (1100 mL). The reaction mixture was refluxed overnight, with stirring, and then cooled and filtered through Celite. The filtrate was concentrated under reduced pressure, using a Javex trap, to afford a yellow oil having a crude weight of 68 g (140%). Purification by column chromatography, using ethyl acetate – hexanes (1:1), afforded **10** as a white solid (43.9 g, 87%), mp 56–58°C. $[\alpha]_D^{20}$ –165.6° (c 0.157, $CHCl_3$). Mass spectrum (CI, *m*/*z*): 347 (M+1). IR (KBr) (cm^{-1}): 1765, 1738. ^1H NMR ($CDCl_3$): 7.28 (2H, t, Ar), 7.00 (1H, t, Ar), 6.93 (2H, d, Ar), 6.01 (1H, dt, 1.2, 4.1 Hz, H-3), 5.93 (1H, d, 4.2 Hz, H-4), 5.10 (1H, q, 1.4 Hz, allylic H), 4.97 (1H, dd, 1.4, 14.6 Hz, C*H*H), 4.92 (1H, br s, =CH*H*), 4.91 (1H, dd, 1.4, 14.6 Hz, C*H*H), 4.84 (1H, br s, =CH*H*), 3.76 (3H, s, ester CH_3), 1.75 (3H, br s, CH_3). ^{13}C NMR ($CDCl_3$): 173.23 (thiazoline N=C), 169.30 (ester C=O), 165.02 (β-lactam C=O), 157.73, 129.64, 121.97, 114.84 (aromatic), 134.67 (*C*H_2=CH), 117.46 (CH_2=*C*CH_3), 92.25 (C-3), 67.78 ($PhOCH_2$), 67.21 (C-4), 58.86 (*C*HCO_2CH_3), 52.52 (CO_2CH_3), 21.52 (CH_2=C*C*H_3). Anal. calcd. for $C_{17}H_{18}N_2O_4S$: C 58.94, H 5.24, N, 8.09; found: C 59.27, H 5.26, N 7.78.

Isomerization of 10

Triethylamine (8.5 mL, 61 mmol) was added dropwise, with stirring, to a solution of **10** (48.3 g, 140 mmol) in dichloromethane (270 mL). The solution was stirred for 3 h, and the solvent was then evaporated under reduced pressure. The residue crystallized from warm methanol to give 30.1 g (62%) of **11**, mp 64–66°C. $[\alpha]_D^{20}$ +24.4° (c 0.205, $CHCl_3$). Mass spectrum (CI, *m*/*z*): 347 (M+1). IR (KBr) (cm^{-1}): 1759, 1723, 1643, 1597. ^1H NMR ($CDCl_3$): 7.26 (2H, m, Ar), 6.99 (1H, t, Ar), 6.94 (2H, d, Ar), 6.06 (1H, dt, 1.2, 4.0 Hz, H-3), 5.87 (1H, d, 4.0 Hz, H-4), 4.99 (1H, dd, 1.2, 14.3 Hz, C*H*H), 4.93 (1H, dd, 1.2, 14.3 Hz, CH*H*), 3.75 (3H, s, ester CH_3), 2.22 (3H, s, =CCH_3), 1.76 (3H, s, =CCH_3). ^{13}C NMR ($CDCl_3$): 172.09 (thiazoline N=C), 163.76 (β-lactam C=O), 163.37 (ester C=O), 157.74, 129.67, 122.03, 114.86 (aromatic), 155.79 (NC=C$(CH_3)_2$), 118.72 (N*C*=C$(CH_3)_2$), 92.70 (C-3), 69.51 (C-4), 67.74 ($PhOCH_2$), 51.90 (CO_2CH_3), 23.77, 21.88 (C=C(*C*$H_3)_2$). Anal. calcd. for $C_{17}H_{18}N_2O_4S$: C 58.94, H 5.24, N 8.09; found: C 59.25, H 5.20, N 8.10.

Thiazoline azetidinone (12)

A solution of potassium permanganate (12.2 g, 77 mmol) and magnesium sulfate (8.41 g, 70 mmol) in water (480 mL) was added during 80 min to a solution of **11** (30.1 g, 87 mmol) in 95% ethanol (600 mL). Additional potassium permanganate (5 × 3.6 g, 114 mmol) was subsequently added every 10 min. The solvent was then removed under reduced pressure, and the brown residue was shaken with ethyl acetate (720 mL) and water (360 mL), and filtered. The organic layer was separated and the aqueous phase was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with saturated sodium chloride (1000 mL), dried over magnesium sulfate, and evaporated. The residue was treated with hot ethyl acetate to give **12** as yellowish-white crystals (15.9 g, 78%), mp 157 to 158°C (lit. (27) mp 157 to 158°C). $[\alpha]_D^{20}$ +121.4° (c 0.14, $CHCl_3$). Mass spectrum (CI, *m*/*z*): 235 (M+1). IR (KBr) (cm^{-1}): 3216, 1757, 1719. ^1H NMR ($CDCl_3$): 7.29 (2H, m, Ar), 7.02

(1H, t, Ar), 6.98 (2H, d, Ar), 6.34 (1H, br s, NH), 6.08 (1H, dd, 0.9, 3.9 Hz, H-3), 5.33 (1H, d, 3.9 Hz, H-4), 5.02 (1H, dd, 0.9, 14.3 Hz, C*H*H), 4.93 (1H, dd, 0.9, 14.3 Hz, CH*H*). ^{13}C NMR ($CDCl_3$): 172.12 (thiazoline N=C), 164.36 (β-lactam C=O), 157.79, 129.69, 122.08, 114.92 (aromatic), 94.83 (C-3), 68.00 ($PhOCH_2$), 62.86 (C-4). Anal. calcd. for $C_{11}H_{10}N_2O_2S$: C 56.39, H 4.30, N 11.96; found: C 56.01, H 4.31, N 11.57.

Dimethyl bromomalonate (28)

Bromine (1.8 mL, 5.58 g, 35 mmol) was added dropwise with stirring, during 60 min, to a solution of dimethyl malonate (3.46 mL, 4.0 g, 35 mmol) in carbon tetrachloride (15 mL), with irradiation by a 150 W bulb mounted beneath the reaction vessel. When the evolution of gas had ceased, water (50 mL) was added and the phases were separated. The aqueous layer was extracted with chloroform (2 × 40 mL) and the combined organic extracts were washed successively with saturated sodium bicarbonate (2 × 75 mL) and saturated sodium chloride (100 mL), dried over magnesium sulfate, and evaporated. The residue was distilled, and the fraction boiling at 105–108°C and 11 torr (1 torr = 133.322 Pa) was collected as a colourless oil (5.02 g, 62%). ^{1}H NMR ($CDCl_3$): 4.85 (1H, s, CH), 3.83 (6H, s, CH_3).

Dibenzyl malonate

Concentrated sulfuric acid (0.2 mL of 96%, 0.2 g, 1.96 mmol) was slowly added to a suspension of malonic acid (20.1 g, 193 mmol) and benzyl alcohol (47.0 mL, 49.1 g, 454 mmol) in toluene (70 mL). Employing a Dean–Stark trap, the mixture was heated to reflux for 2 h, and approximately 7 mL of water were removed. The solution was cooled, diluted with ethyl acetate (100 mL), and washed successively with saturated sodium bicarbonate (2 × 100 mL), water (2 × 100 mL) and saturated sodium chloride (100 mL), dried over magnesium sulfate, and evaporated. The residue was distilled, and the fraction boiling at 188°C and 0.2 torr (1 torr = 133.322 Pa) was collected as a colourless oil (50.0 g, 91%). Mass spectrum (EI, *m*/*z*): 285 (M). IR (neat) (cm^{-1}): 1745. ^{1}H NMR ($CDCl_3$): 7.35–7.32 (10H, m, Ar), 5.18 (4H, s, benzyl CH_2), 3.48 (2H, s, malonyl CH_2).^{13}C NMR ($CDCl_3$): 166.18 (ester C=O), 135.34, 128.59, 128.41, 128.27 (aromatic), 67.26 ($PhCH_2O$), 41.61 ($COCH_2CO$).

Dibenzyl bromomalonate (20*a*, 29)

With irradiation by a 250 W bulb mounted beside the reaction vessel, bromine (6.5 mL, 20.2 g, 126 mmol) was added dropwise during 2 h, with stirring, to a solution of dibenzyl malonate (19.6 g, 69.0 mmol) in carbon tetrachloride (51 mL). Water (50 mL) was then added and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 40 mL) and the combined organic extracts were washed successively with saturated sodium bicarbonate (2 × 75 mL) and saturated sodium chloride (100 mL), dried over magnesium sulfate, and evaporated. The oily residue (22.0 g) was purified by column chromatography using ethyl acetate – hexanes (1:8) to yield 6.91 g (28%) of the product as a colourless oil, which solidified in the freezer as white crystals, mp 26 to 27°C. IR (neat) (cm^{-1}): 1744. ^{1}H NMR ($CDCl_3$): 7.36–7.30 (10H, m, Ar), 5.22 (4H, s, benzyl CH_2), 4.92 (1H, s, CH). ^{13}C NMR ($CDCl_3$): 164.28 (ester C=O), 134.58–128.29 (aromatic), 68.72 ($PhCH_2O$), 42.20 ($COCHBrCO$). Anal. calcd. for $C_{17}H_{15}O_4Br$: C 56.22, H 4.16; found: C 55.84, H 4.09.

Benzyl methyl bromomalonate

Dimethyl malonate (10 mL, 11.56 g, 87.5 mmol), in methanol (70 mL), was treated with a solution of potassium hydroxide (4.89 g, 87.2 mmol) in methanol (70 mL). The solution was stirred for 24 h, then refrigerated overnight. The white crystals were filtered, rinsed with cold methanol, and dried to give 9.72 g (65%) of potassium methyl malonate, mp 160–162°C (dec). Mass spectrum (CI, *m*/*z*): 103 (M+1-(K+CH_3)). IR (KBr) (cm^{-1}): 1738, 1728. ^{1}H NMR (D_2O): 3.56 (3H, s, CH_3), 3.15 (2H, s, CH_2). ^{13}C NMR (D_2O): 176.78 (carboxyl C=O), 174.80 (ester C=O), 55.36 (CO_2CH_3). Anal. calcd. for $C_4H_5O_4K$: C 30.76, H 3.23; found: C 30.69, H 3.19.

Benzyl bromide (3.8 mL, 5.46 g, 31.9 mmol) was added to a suspension of potassium methyl malonate (5.63 g, 32.7 mmol) in dimethylformamide (80 mL). The mixture was stirred for 22 h, diluted with ethyl acetate (150 mL), washed with water (3 × 150 mL), dried over magnesium sulfate, and evaporated to give benzyl methyl malonate as a colourless oil (6.47 g, 97%). IR (neat) (cm^{-1}): 1755, 1732. Mass spectrum (CI, *m*/*z*): 209 (M+1). ^{1}H NMR ($CDCl_3$): 7.36 (5H, m, Ar), 5.19 (2H, s, $PhCH_2$), 3.74 (3H, s, CH_3), 3.44 (2H, s, malonyl CH_2). ^{13}C NMR ($CDCl_3$): 166.83 (ester C=O), 166.31 (ester C=O), 135.42, 128.60, 128.42, 128.25 (aromatic), 67.18 (CO_2CH_2Ph), 52.41 (CO_2CH_3), 41.30 (malonyl CH_2). Anal. calcd. for $C_{11}H_{12}O_4$: C 46.01, H 3.86; found: C 46.03, H 3.88.

With irradiation by a 150 W Westinghouse reflector spotlight mounted underneath the reaction vessel, bromine (2.7 mL, 8.38 g, 52.4 mmol) was added dropwise during 60 min, with stirring, to a solution of benzyl methyl malonate (11.0 g, 52.8 mmol) in carbon tetrachloride (40 mL). Once the evolution of gas had ceased, water (40 mL) was added and the phases were separated. The aqueous layer was extracted with chloroform (2 × 40 mL) and the combined organic extracts were washed with saturated sodium bicarbonate (2 × 120 mL) and saturated sodium chloride (120 mL), dried over magnesium sulfate, and evaporated. The residue was purified by column chromatography using ethyl acetate – hexanes (30:70) to give the product as a colourless oil (10.3 g, 68%). Mass spectrum (CI, *m*/*z*): 287, 289 (M+1). IR (neat) (cm^{-1}): 1767, 1746. ^{1}H NMR ($CDCl_3$): 7.36 (5H, m, Ar), 5.25 (2H, s, $PhCH_2$), 4.89 (1H, s, malonyl CH), 3.80 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$): 164.97 (ester C=O), 164.38 (ester C=O), 134.68, 128.89, 128.74, 128.33 (aromatic), (CO_2CH_2Ph), 53.92 (CO_2CH_3), 42.02 (malonyl CH).

Coupling of 12 with dimethyl bromomalonate

A solution of **12** (4.45 g, 19 mmol) in dimethylformamide (40 mL) was cooled to –55°C and Triton B (15.0 mL of a 40% methanolic solution, 6.36 g, 38 mmol) was added dropwise. Stirring was continued for 30 min, and a solution of dimethylbromomalonate (4.85 g, 23 mmol) in dimethylformamide (20 mL) was then added dropwise. Stirring was continued overnight, and the mixture was

warmed to room temperature. Ethyl acetate (450 mL), saturated sodium chloride (110 mL), and 1.0 M hydrochloric acid (50 mL) were added, and the organic phase was separated, washed with water (2 × 120 mL) and saturated sodium chloride (150 mL), dried over magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography using ethyl acetate – hexanes (2:3) to give **13** (3.33 g, 50%). $[\alpha]_D^{20}$ –88.2° (c 0.17, $CHCl_3$). IR (neat) (cm^{-1}): 1782, 1755, 1748, 1682. Mass spectrum (EI, *m*/*z*): 364 (M). ^{1}H NMR ($CDCl_3$): 7.29 (2H, t, Ar), 7.00 (1H, t, Ar), 6.92 (2H, d, Ar), 6.09 (1H, dt, 1.2, 4.2 Hz, H-3), 6.00 (1H, d, 4.2 Hz, H-4), 5.12 (1H, s, CH), 4.98 (1H, dd, 1.2, 14.3 Hz, PhOC*H*H), 4.89 (1H, dd, 1.2, 14.3 Hz, PhOCH*H*), 3.82 (3H, s, CH_3), 3.72 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$): 172.99 (thiazoline N=C), 165.12 (β-lactam C=O), 164.29 (ester C=O), 157.78, 129.64, 122.02, 114.86 (aromatic), 93.17 (C-3), 68.10 (C-4), 67.90 ($PhOCH_2$), 60.29 (malonyl CH), 55.96 (CO_2CH_3), 53.40 (CO_2CH_3). Anal. calcd. for $C_{16}H_{16}N_2O_6S$: C 52.74, H 4.43, N 7.69; found: C 52.39, H 4.36, N 7.85.

Coupling of 12 with dibenzyl bromomalonate

Triton B (15.4 mL of a 40% methanolic solution, 6.52 g, 39 mmol) was slowly added at –55°C to a solution of the azetidinone (4.4 g, 19 mmol) in dimethylformamide (40 mL). The red solution was stirred for 30 min at –55°C and then treated dropwise with a solution of the bromomalonate (7.1 g, 20 mmol) in dimethylformamide (20 mL). When the addition was complete the reaction mixture was warmed to 0°C and stirring was continued for 2.5 h. Ethyl acetate (450 mL), saturated sodium chloride (110 mL), and 1.0 M hydrochloric acid (50 mL) were added and the organic phase was separated, washed with water (2 × 120 mL) and saturated sodium chloride (150 mL), dried over magnesium sulfate, and evaporated under reduced pressure. The residue crystallized from hot ethyl acetate – hexanes (1:2) to yield 4.8g (49%) of the product as yellow crystals, mp 90–92°C. $[\alpha]_D^{20}$ –71.8° (c 0.209, $CHCl_3$). Mass spectrum (FAB, *m*/*z*): 516 (M). IR (KBr) (cm^{-1}): 1768, 1744. ^{1}H NMR (acetone-d_6): 7.36 –7.29 (12H, m, Ar), 6.97 (3H, m, Ar), 6.14 (1H, dt, 1.2, 4.1 Hz, H-3), 6.03 (1H, d, 4.1 Hz, H-4), 5.32 (1H, s, CH), 5.24 (2H, s, benzyl CH_2), 5.19 (2H, s, benzyl CH_2), 4.96 (1H, dd, 1.2, 14.4 Hz, C*H*H), 4.76 (1H, dd, 1.2, 14.4 Hz, CH*H*). ^{13}C NMR ($CDCl_3$): 172.90 (thiazoline N=C), 164.50 (β-lactam C=O), 164.40 (ester C=O), 163.73 (ester C=O), 157.79, 134.43–114.86 (aromatic), 93.12 (C-3), 68.55 (CO_2CH_2Ph), 68.11 (C-4), 67.86 ($PhOCH_2$), 56.49 ($NCH(CO_2CH_2Ph)_2$). Anal. calcd. for $C_{28}H_{24}N_2O_6S$: C 65.10, H 4.68, N 5.42; found: C 64.81, H 4.62, N 5.48.

Coupling of 12 with the mixed bromomalonate

To a solution of the thiazoline azetidinone (4.01 g, 17.1 mmol), cooled to –55°C in dimethylformamide (40 mL), were added dropwise with stirring Triton B (13.5 mL of a 40% methanolic solution, 5.70 g, 34.1 mmol), followed by a solution of the bromomalonate (5.4 g, 16.9 mmol) in dimethylformamide (15 mL). When the addition was complete, the reaction mixture was warmed to –40°C and stirring was continued for 1 h. The cooling bath was then removed and stirring was continued for an additional 22 h. Ethyl acetate (200 mL) was added and the solution was washed successively with 0.1 M hydrochloric acid (200 mL), water (3 × 200 mL), and saturated sodium chloride (200 mL), dried over magnesium sulfate, and evaporated. Purification by column chromatography using ethyl acetate – hexanes (1:1) gave the product as a light yellow, viscous oil (5.45 g, 75%). Mass spectrum (CI, *m*/*z*): 365 ((M+1)-$PhCH_2$). IR (neat) (cm^{-1}): 1784, 1761, 1748. ^{1}H NMR ($CDCl_3$): isomer A: 7.32 (8H, m, Ar), 6.91 (2H, m, Ar), 6.08 (1H, dt, 1.2, 4.1 Hz, H-3), 5.98 (1H, d, 4.1 Hz, H-4), 5.25 (1H, d, 12.3 Hz, PhC*H*H), 5.22 (1H, d, 12.3 Hz, PhCH*H*), 5.15 (1H, s, malonyl CH), 4.97 (1H, dd, 1.2, 14.3 Hz, PhOC*H*H), 4.86 (1H, dd, 1.2, 14.3 Hz, PhOCH*H*), 3.69 (3H, s, CH_3); isomer B: 7.32 (8H, m, Ar), 7.01 (2H, m, Ar), 6.09 (1H, dt, 1.2, 4.1 Hz, H-3), 5.99 (1H, d, 4.1 Hz, H-4), 5.18 (2H, s, $PhCH_2$), 5.17 (1H, s, malonyl CH), 4.91 (1H, dd, 0.8, 14.3 Hz, PhOC*H*H), 4.68 (1H, 1.3, 14.3 Hz, PhOCH*H*), 3.80 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$): 173.02, 172.93 (thiazoline N=C, both isomers), 165.08, 164.55, 164.40, 164.32, 164.25, 163.79 (β-lactam C=O, ester C=O, both isomers), 157.74, 134.45–114.84 (aromatic, both isomers), 93.15, 93.10 (C-3, both isomers), 68.52, 68.47 (CO_2CH_2Ph, both isomers), 68.09, 68.03 (C-4, both isomers), 67.85, 67.80 ($PhOCH_2$, both isomers), 56.23, 56.13 (malonyl CH, both isomers). Anal. calcd. for $C_{22}H_{20}N_2O_6S \cdot 0.5H_2O$: C 58.79, H 4.71, N 6.23; found: C 58.95, H 4.55, N 6.41.

Allylation of 13

The dimethyl ester (3.32 g, 9.53 mmol) was dissolved in dimethylformamide (33 mL), the solution was cooled to 0°C, and a 40% methanolic solution of Triton B (5.6 mL, 2.06 g, 12.3 mmol) was added dropwise during 20 min. Allyl bromide (2.5 mL, 3.5 g, 29 mmol) was then added in one portion. The reaction mixture was stirred at 0°C for 2 h and diluted with ethyl acetate (100 mL). The organic layer was washed successively with water (3 × 100 mL) and saturated sodium chloride (100 mL), dried over sodium sulfate, and evaporated to give an orange oil. Chromatography on silica gel using ethyl acetate – hexanes (3:7) gave **14** as a viscous pale yellow oil (3.47 g, 94%). $[\alpha]_D^{20}$ –21.1° (c 0.285, $CHCl_3$). Mass spectrum (EI, *m*/*z*): 404 (M). IR (neat) (cm^{-1}): 3401, 1778, 1755, 1748, 1678. ^{1}H NMR ($CDCl_3$): 7.30 (2H, t, Ar), 7.00 (1H, t, Ar), 6.94 (2h, d, Ar), 6.01 (1H, d, 4.2 Hz, H-4), 5.92 (1H, dt, 1.2, 4.2 Hz, H-3), 5.71 (1H, ddt, 7.2, 10.1, 17.4 Hz, C*H*=CH_2), 5.19–5.10 (2H, m, CH=CH_2), 4.99 (1H, dd, 1.2, 14.3 Hz, PhOC*H*H), 4.89 (1H, dd, 1.2, 14.3 Hz, PhOCH*H*), 3.80 (3H, s, CH_3), 3.76 (3H, s, CH_3), 3.10 (1H, ddt, 1.1, 7.2, 14.4 Hz, C*H*HCH=CH_2), 3.04 (1H, ddt, 1.1, 7.2, 14.4 Hz, CH*H*CH=CH_2). ^{13}C NMR ($CDCl_3$): 172.87 (thiazoline N=C), 166.67 (β-lactam C=O), 166.21 (ester C=O), 164.15 (ester C=O), 157.84, 129.63, 121.97, 114.87 (aromatic), 131.17 (CH=*C*H_2), 120.29 (*C*H=CH_2), 90.84 (C-3), 70.04 (C-4), 68.80 (malonyl CH), 67.95 ($PhOCH_2$), 53.46 (CO_2CH_3), 53.37 (CO_2CH_3), 38.18 (CH_2CH=CH_2). Anal. calcd. for $C_{19}H_{20}N_2O_6S$: C 56.43, H 4.98, N 6.93; found: C 56.39, H 4.92, N 6.91.

Allylation of the dibenzyl ester

Sodium hydride (0.658 g of a 60% suspension in mineral oil, 16.5 mmol) was added in portions at 0°C to a solution of the dibenzyl ester (4.05 g, 7.84 mmol) in

dimethylformamide (60 mL). The mixture was stirred for 20 min at 0°C, warmed to room temperature, recooled to 0° and treated, during 15 min, with allyl bromide (1.6 mL, 2.2 g, 18 mmol). The ice bath was removed after an additional 20 min, and the bright red reaction mixture was stirred for 16 h. Water (500 mL) was added and the mixture was extracted with dichloromethane (4 × 50 mL). The combined organic extracts were washed with water (3 × 100 mL) and saturated sodium chloride (200 mL), dried over magnesium sulfate, and evaporated to yield a yellow oil (2.4 g). Purification by column chromatography using ethyl acetate – hexanes (1:1) gave the product as a bright yellow viscous oil (1.5 g, 34%). $[\alpha]_D^{20}$ –26.9° (c 0.557, $CHCl_3$). Mass spectrum (CI, *m*/*z*): 557 (M+1). IR (CH_2Cl_2) (cm^{-1}): 1777, 1750. ^1H NMR ($CDCl_3$): 7.34–7.26 (12H, m, Ar), 7.00 (1H, t, Ar), 6.90 (2H, d, Ar), 5.92 (1H, d, 4.2 Hz, H-4), 5.84 (1H, dt, 1.2, 4.2 Hz, H-3), 5.66 (1H, ddt, 7.0, 8.5, 10.0 Hz, =CH), 5.16 (2H, s, benzyl CH_2), 5.11 (2H, s, benzyl CH_2), 5.07–5.04 (2H, m, $=CH_2$), 4.82 (1H, dd, 1.2, 14.2 Hz, PhOC*H*H), 4.52 (1H, dd, 1.2, 14.2 Hz, PhOCH*H*), 3.10 (1H, ddt, 1.0, 7.0, 14.0 Hz, allyl C*H*H), 3.07 (1H, ddt, 1.0, 7.0, 14.0 Hz, allyl CH*H*). ^{13}C NMR ($CDCl_3$): 172.83 (thiazoline N=C), 165.90 (β-lactam C=O), 165.53 (ester C=O), 164.17 (ester C=O), 134.60 (CH=*C*H_2), 157.82, 134.48–114.88 (aromatic), 120.46 (*C*H=CH_2), 90.76 (C-3), 70.14 (C-4), 68.83 (NCCH=CH_2), 68.43 (PhCH_2O), 67.83 (PhOCH_2), 38.16 (*C*H_2CH=CH_2). Anal. calcd. for $C_{31}H_{28}N_2O_6S$: C 66.89, H 5.07, N 5.03; found: C 67.20, H 5.37, N 5.19.

Allylation of the mixed ester

The azetidinone (4.35 g, 10.2 mmol) was dissolved in dimethylformamide (35 mL), the solution was cooled to 0°C, and 40% methanolic Triton B (6.0 mL, 2.21 g, 13.2 mmol) was added dropwise over 20 min, with stirring. Then allyl bromide (2.6 mL, 3.63 g, 30.0 mmol) was added and stirring was continued for 2 h at 0°C. Ethyl acetate (150 mL) was added and the solution was washed with water (3 × 150 mL) and saturated sodium chloride (150 mL), dried over sodium sulfate, and evaporated to give an orange oil. Chromatography on silica gel using ethyl acetate – hexanes (1:1) gave the product as a yellow oil (3.94 g, 83%). IR (neat) (cm^{-1}): 1778, 1755, 1746. ^1H NMR ($CDCl_3$): isomer A: 7.29 (8H, t, Ar), 6.91 (2H, t, Ar), 5.98 (1H, d, 4.1 Hz, H-4), 5.90 (1H, dt, 1.1, 4.2 Hz, H-3), 5.70 (1H, ddt, 6.5, 10.0, 17.0 Hz, CH_2C*H*=CH_2), 5.21 (2H, s, PhCH_2), 5.15–5.06 (2H, m, $CH_2CH=C$*H*$_2$), 4.93 (1H, dd, 1.1, 14.3 Hz, PhOC*H*H), 4.79 (1H, dd, 1.2, 14.3 Hz, PhOCH*H*), 3.73 (3H, s, CH_3), 3.14–3.01 (2H, m, C*H*$_2$CH=CH_2). Isomer B: 7.33 (8H, t, Ar), 7.00 (2H, t, Ar), 5.95 (1H, d, 4.2 Hz, H-4), 5.86 (1H, dt, 1.1, 4.2 Hz, H-3), 5.68 (1H, ddt, 6.5, 10.0, 17.0 Hz, CH_2C*H*=CH_2), 5.17 (2H, s, PhCH_2), 5.15–5.06 (2H, m, $CH_2CH=C$*H*$_2$), 4.86 (1H, dd, 1.0, 14.3 Hz, PhOC*H*H), 4.61 (1H, dd, 1.3, 14.2 Hz, PhOCH*H*), 3.69 (3H, s, CH_3), 3.14–3.01 (2H, C*H*$_2$CH=CH_2). ^{13}C NMR ($CDCl_3$): 172.93, 172.87 (thiazoline N=C, both isomers), 166.50, 166.124, 165.99, 165.58, 164.23, 164.12 (β-lactam C=O, ester C=O, both isomers), 157.78, 131.04–128.34, 127.60–121.94, 114.84 (aromatic, both isomers), 134.67, 134.53 (CH=*C*H_2, both isomers), 120.45, 120.41 (*C*H=CH_2, both isomers), 90.77 (C-3, both isomers), 70.11, 70.03 (CO_2CH_2Ph, both isomers), 68.86, 68.71 (malonyl C, both isomers), 68.39 (C-4, both isomers), 67.86, 67.80 (PhOCH_2, both isomers), 53.41, 53.31 (CO_2CH_3, both isomers), 38.23, 38.02 (*C*H_2CH=CH_2). Anal. calcd. for $C_{25}H_{24}N_2O_6S$: C 62.49, H 5.03, N 5.83;. Found: C 62.28, H 5.17, N 5.78.

Conversion of 14 into the hydroxycepham 17

A solution of **14** (8.14 g, 20.1 mmol) in dichloromethane (100mL) and methanol (50 mL) was cooled to –78°C, and treated with ozone at a rate of 1.5 L min^{-1} until a blue colour persisted. Excess ozone was purged using nitrogen gas, and the reaction was quenched with dimethyl sulfide (12.3 mL, 10.4 g, 167.5 mmol). The cooling bath was then removed and the solution was allowed to warm to room temperature. Evaporation of the solvent afforded a yellow syrup (9.0 g). This was dissolved in a mixture of dichloromethane (150 mL) and acetone (150 mL), and treated with 3% perchloric acid (25 mL, 0.75 g, 7.47 mmol). The mixture was stirred for 90 min and then diluted with ethyl acetate (300 mL), washed with saturated sodium chloride (6 × 100 mL), dried over magnesium sulfate, and evaporated to give a yellow oil. Purification by column chromatography using ethyl acetate – hexanes (1:1) yielded **17** (8.0 g, 94%). $[\alpha]_D^{20}$ +217.7° (c 0.40, $CHCl_3$). Mass spectrum (CI, *m*/*z*): 407 ((M+1)-H_2O). IR (KBr) (cm^{-1}): 3480, 3341, 1778, 1753, 1680. ^1H NMR ($CDCl_3$): 7.38 (1H, d, 9.3 Hz, NH), 7.31 (2H, t, Ar), 7.01 (1H, t, Ar), 6.92 (2H, d, Ar), 5.77 (1H, dd, 4.6, 9.3 Hz, H-7), 5.55 (1H, d, 4.6 Hz, H-6), 5.35 (1H, 2.3, 3.9, H2), 4.52 (2H, s, PhOCH_2), 3.85 (3H, s, CH_3), 3.81 (3H, s, CH_3), 2.78 (1H, dd, 3.9, 14.4 Hz, H-3), 2.53 (1H, dd, 2.3, 14.4 Hz, H-3). ^{13}C NMR ($CDCl_3$): 168.91 (acetamido C=O), 167.83 (β-lactam C=O), 165.04 (ester C=O), 163.76 (ester C=O), 156.94, 129.76, 122.36, 114.84 (aromatic), 70.71 (C-2), 67.11 (PhOCH_2), 61.70 (C-7), 59.01 (C-6), 54.63 (C-4), 53.94 (CO_2CH_3), 53.47 (CO_2CH_3), 35.62 (C-3). Anal. calcd. for $C_{18}H_{20}N_2O_8S$: C 50.94, H 4.75, N 6.60; found: C 50.58, H 4.89, N 6.16.

Dehydration of 17

A solution of **17** (200 mg, 0.47 mmol) in acetic anhydride (1.4 mL, 1.5 g, 14.8 mmol) was treated, with stirring, with a 1% w/v solution of sulfuric acid in acetic acid (0.3 mL, 3 mg, 0.03 mmol). After 2.5 h, sodium acetate hexahydrate (750 mg, 3.9 mmol) was added and stirring was continued overnight. Ethyl acetate (50 mL) was added and the organic layer was washed successively with water (2 × 50 mL) and saturated sodium bicarbonate (50 mL), dried over magnesium sulfate, and evaporated to give a pale yellow oil. A solution of this oil in toluene (150 mL) was treated with *p*-toluenesulfonic acid monohydrate (70 mg, 0.37 mmol), and the mixture, protected from moisture by a calcium chloride drying tube, was refluxed overnight. The solvent was then evaporated under reduced pressure. The residue was purified by column chromatography using ethyl acetate – hexanes (3:2) to give the 4,4-dimethoxycarbonyl-Δ^2-cephem **19** as a yellow foam (489 mg, 52%). $[\alpha]_D^{20}$ +400.0° (c 0.26, $CHCl_3$). Mass spectrum (CI, *m*/*z*): 407 (M+1). IR (KBr) (cm^{-1}): 3310, 1786, 1748, 1690. ^1H NMR ($CDCl_3$): 7.39 (1H, d, 9.0 Hz, NH), 7.33 (2H, t, Ar), 7.04 (1H, t, Ar), 6.94 (2H, d, Ar), 6.47 (1H, d, 10.4 Hz, H-2), 6.07 (1H, d, 10.4 Hz, H-3), 5.81 (1H, dd, 4.2, 9.0 Hz, H-7), 5.31 (1H, d, 4.2 Hz, H-6), 4.56 (2H, s, PhOCH_2), 3.87 (3H, s, CH_3), 3.84 (3H, s, CH_3).

^{13}C NMR ($CDCl_3$): 168.58 (acetamido C=O), 166.07 (β-lactam C=O), 164.28 (ester C=O), 163.23 (ester C=O), 157.10, 129.82, 122.48, 114.96 (aromatic), 122.20 (C-2), 115.18 (C-3), 67.37 ($PhOCH_2$), 63.67 (C-4), 59.67 (C-7), 55.08 (C-6), 54.00 (CO_2CH_3), 53.66 (CO_2CH_3). Anal. calcd. for $C_{18}H_{18}N_2O_7S$: C 53.20, H 4.46, N 6.89; found: C 53.38, H 4.66, N 6.55.

Conversion of the allylated dimethyl ester to 20 (R_1 = R_2 = Me)

A solution of the dimethyl ester (3.38 g, 8.70 mmol) in a mixture of dichloromethane (123 mL) and water (61 mL) was treated in two portions during 30 min with iodine (2.45 g, 9.65 mmol). The purple reaction mixture was stirred at room temperature for 5.5 h, and the reaction was then quenched with 1% sodium sulfite (50 mL). The organic layer was washed successively with water (2 × 150 mL) and saturated sodium chloride (150 mL), dried over magnesium sulfate, and evaporated to give a yellow foam. Purification by column chromatography using ethyl acetate – hexanes (1:1) afforded a white foam (3.24 g, 68%). $[\alpha]_D^{20}$ +177.8° (c 0.135, $CHCl_3$). Mass spectrum (CI, *m*/*z*): 423 ((M+1)-I). IR (KBr) (cm^{-1}): 3318, 1780, 1748, 1690. ^{1}H NMR ($CDCl_3$): 7.32 (3H, t, Ar + NH), 7.03 (1H, t, Ar), 6.93 (2H, d, Ar), 5.82 (1H, dd, 4.6, 9.5 Hz, H-7), 5.39 (1H, d, 4.6 Hz, H-6), 4.54 (2H, s, $PhOCH_2$), 3.86 (3H, s, CH_3), 3.85 (3H, s, CH_3), 3.28 (1H, dd, 5.4, 10.3 Hz, C*H*HI), 3.18 (1H, dd, 8.0, 10.3 Hz, CH*H*I), 2.95 (1H, m, H-2), 2.74 (1H, dd, 1.9, 14.1 Hz, H-3), 2.03 (1H, dd, 12.2, 14.1 Hz, H-3). Anal. calcd. for $C_{19}H_{21}IN_2O_7S$: C 41.62, H 3.86, N 5.11; found: C 41.81, H 3.86, N 5.02.

Conversion of the allylated dibenzyl ester to 20 (R_1 = R_2 = CH_2Ph)

Iodine (1.35 g, 5.3 mmol) was added in three portions over 30 min to a biphasic solution of the dibenzyl ester (2.8 g, 5.0 mmol) in dichloromethane (70 mL) and water (35 mL). The mixture was stirred for 3 h, additional dichloromethane (98 mL) was added, and the organic layer was then separated and washed successively with saturated sodium bicarbonate (200 mL), 0.01 M sodium sulfite (200 mL), water (200 mL), and saturated sodium chloride (200 mL), dried over magnesium sulfate, and evaporated. Chromatography using ethyl acetate – hexanes (1:1) gave 2.63 g (74%) of the iodomethylcepham as a yellow foam. $[\alpha]_D^{20}$ +162.5° (c 0.39, $CHCl_3$). Mass spectrum (CI, *m*/*z*): 439 ((M+1)-I-CO_2CH_2Ph). IR (KBr) (cm^{-1}): 3318, 1780, 1746, 1688. ^{1}H NMR ($CDCl_3$): 7.34–7.23 (13H, m, Ar + NH), 7.03 (1H, t, Ar), 6.94 (2H, d, Ar), 5.82 (1H, dd, 4.6, 9.6 Hz, H-7), 5.40 (1H, d, 4.6 Hz, H-6), 5.27 (1H, d, 12.0 Hz, benzyl C*H*H), 5.20 (1H, d, 11.9 Hz, benzyl CH*H*), 5.17 (1H, d, 12.0 Hz, benzyl C*H*H), 5.09 (1H, d, 11.9 Hz, benzyl CH*H*), 4.53 (2H, s, $PhOCH_2$), 3.20 (1H, dd, 5.3, 10.2 Hz, C*H*HI), 3.08 (1H, dd, 8.1, 10.2 Hz, CH*H*I), 2.84 (1H, m, shows nOe with H-6 at 5.40 ppm, H-2), 2.71 (1H, dd, 1.9, 14.1 Hz, H-3), 2.03 (1H, dd, 12.3, 14.1 Hz, H-3). ^{13}C NMR ($CDCl_3$): 168.42 (acetamido C=O), 166.33 (β-lactam C=O), 164.36 (ester C=O), 163.86 (ester C=O), 157.09, 134.46, 134.32, 129.82, 128.97, 128.80, 128.62, 128.56, 122.45, 114.99 (aromatic), 69.05, 68.58 (CO_2CH_2Ph), 67.33 ($PhOCH_2$), 66.16 (C-4), 58.88 (C-7), 58.28 (C-6), 38.72 ($CHCH_2I$), 37.31 (C-2), 5.95 (C-3). Anal. calcd. for $C_{31}H_{29}N_2IO_2S$: C 53.15, H 4.17, N 4.00; found: C 53.15, H 4.02, N 3.89.

Conversion of the allylated methyl benzyl ester to 20 (R_1 = Me, R_2 = CH_2Ph)

Iodine (1.64 g, 6.46 mmol) was added in two portions over 30 min to a solution of the mixed ester (both diastereomers) (2.75 g, 5.90 mmol) in a biphasic mixture of dichloromethane (83 mL) and water (41 mL). The purple solution was stirred at room temperature for 5 h, the reaction was quenched with 1% sodium sulfite (50 mL), and the organic layer was then washed successively with water (2 × 80 mL) and saturated sodium chloride (80 mL), dried over magnesium sulfate, and evaporated. Purification by column chromatography using ethyl acetate – hexanes (1:1) afforded the product as a white foam (3.34 g, 94%). Mass spectrum (CI, *m*/*z*): 363 ((M+1)-(I+CO_2CH_2Ph)).IR (KBr) (cm^{-1}): 3310, 1778, 1748, 1688. ^{1}H NMR ($CDCl_3$): isomer A: 7.41–7.29 (8H, m, Ar + NH), 7.03 (1H, t, Ar), 6.93 (2H, d, Ar), 5.80 (1H, dd, 4.6, 9.6 Hz, H-7), 5.38 (1H, d, 4.6 Hz, H-6), 5.25 (2H, s, $PhCH_2$), 4.53 (2H, s, $PhOCH_2$), 3.78 (3H, s, CH_3), 3.19 (1H, dd, 5.3, 10.3 C*H*HI), 3.09 (1H, dd, 8.0, 10.3 Hz, CH*H*I), 2.81 (1H, m, H-2), 2.70 (1H, dd, 1.9, 14.1 Hz, H-3), 2.00 (1H, dd, 12.2, 14.1 Hz, H-3). Isomer B: 7.41–7.30 (8H, m, Ar + NH), 7.04 (1H, t, Ar), 6.93 (2H, d, Ar), 5.84 (1H, dd, 4.6, 9.6 Hz, H-7), 5.39 (1H, d, 4.6 Hz, H-6), 5.28 (1H, d, 12.1 Hz, PhC*H*H), 5.17 (1H, d, 12.1 Hz, PhCH*H*), 4.54 (2H, s, $PhOCH_2$), 3.74 (3H, s, CH_3), 3.27 (1H, dd, 5.4, 10.3 Hz, C*H*HI), 3.18 (1H, dd, 7.8, 10.3 Hz, CH*H*I), 2.96 (1H, m, H-2), 2.73 (1H, dd, 1.8, 14.0 Hz, H-3), 2.04 (1H, dd, 12.4, 14.0 Hz, H-3). ^{13}C NMR ($CDCl_3$): 168.44 (acetamido C=O), 166.34 (β-lactam C=O), 164.40 (ester C=O), 164.29 (ester C=O), 157.09, 134.44, 129.81, 129.05, 128.83, 128.65, 122.45, 114.99 (aromatic), 68.60 (CO_2CH_2Ph), 67.33 ($PhOCH_2$), 65.96 (C-4), 58.88 (C-7), 58.23 (C-6), 53.74 (CO_2CH_3), 38.71 (CH_2I), 37.28 (C-2), 5.98 (C-3). Anal. calcd. for $C_{25}H_{25}N_2IO_7S$: C 48.09, H 4.04, N 4.49; found: C 48.41, H 4.02, N 4.29.

Synthesis of 21 (R_1 = R_2 = Me)

A solution of the iodomethylcepham (3.24 g, 5.91 mmol) in methanol (250 mL) was treated dropwise with stirring, during 15 min, with a solution of sodium periodate (1.34 g, 6.27 mmol) in methanol (28 mL) and water (28 mL). When the addition was complete, the mixture was heated to 35°C, and stirring was continued for 2.0 h. A white precipitate was removed by filtration, and washed with ethyl acetate (200 mL). The combined filtrates were washed successively with water (200 mL) and saturated sodium chloride (200 mL), dried over magnesium sulfate, and evaporated to give a brown foam. Column chromatography using ethyl acetate – hexanes (2:3) gave the sulfoxide as a pale yellow foam (1.19 g, 36%). Mass spectrum (CI, *m*/*z*): 437 ((M+1)-I). ^{1}H NMR ($CDCl_3$): 8.05 (1H, d, 10.6 Hz, NH), 7.30 (2H, t, Ar), 7.01 (1H, t, Ar), 6.93 (2H, d, Ar), 6.12 (1H, dd, 4.8, 10.6 Hz, H-7), 4.85 (1H, d, 4.7 Hz, H-6), 4.55 (2H, s, $PhOCH_2$), 3.89 (3H, s, CH_3), 3.86 (3H, s, CH_3), 3.46 (1H, dd, 7.2, 10.7 Hz, C*H*HI), 3.26 (1H, dd, 8.0, 10.7 Hz, CH*H*I), 2.86 (1H, dd, 12.7, 14.7 Hz, H-3), 2.68 (1H, m, H-2), 2.30 (1H, dd, 2.0, 14.7 Hz, H-3).

Synthesis of 21 (R_1 = R_2 = CH_2Ph)

A solution of sodium periodate (44.0 mg, 0.21 mmol) in 50% methanol (0.7 mL) was added dropwise at 55°C to a solution of the iodomethylcepham (113.6 mg, 0.16 mmol) in methanol (7 mL). When the addition was complete, more 50% methanol (2 mL) was added, and the solution was stirred at 60°C for 2 h and then diluted with water (20 mL). Extraction with dichloromethane (4 × 10 mL), drying over magnesium sulfate and evaporation, followed by column chromatography using ethyl acetate – hexanes (1:1) yielded the β-sulfoxide (53.7 mg, 62%). Mass spectrum (CI, *m*/*z*): 455 ((M+1)-I-CO_2CH_2Ph). IR (KBr) (cm^{-1}): 3381, 1788, 1746, 1692, 1082. ^{1}H NMR ($CDCl_3$): 8.07 (1H, d, 10.5 Hz, NH), 7.34–7.23 (12H, m, Ar), 7.03 (1H, t, Ar), 6.92 (2H, d, Ar), 6.11 (1H, dd, 4.8, 10.5 Hz, H-7), 5.29 (1H, d, 12.0 Hz, benzyl C*H*H), 5.21 (1H, d, 11.8 Hz, benzyl CH*H*), 5.19 (1H, d, 12.0 Hz, benzyl C*H*H), 5.11 (1H, d, 11.8 Hz, benzyl CH*H*), 4.85 (1H, d, 4.8 Hz, H-6), 4.54 (2H, s, $PhOCH_2$), 3.38 (1H, dd, 7.6, 10.7 Hz, C*H*HI), 3.16 (1H, dd, 7.9, 10.7 Hz, CH*H*I), 2.84 (1H, dd, 12.7, 14.7 Hz, β-H-3), 2.52 (1H, m, H-2), 2.23 (1H, dd, 1.8, 14.7 Hz, α-H-3). ^{13}C NMR ($CDCl_3$): 168.65 (acetamido C=O), 166.30 (β-lactam C=O), 163.95 (ester C=O), 162.97 (ester C=O), 157.18, 134.38, 134.21, 129.91, 129.80, 129.72, 129.17, 128.90, 128.74, 128.66, 128.63, 128.58, 128.49, 128.36, 122.38, 122.28, 115.00, 114.92 (aromatic), 69.31 (CO_2CH_2Ph), 69.26 (C-6) 68.85 (CO_2CH_2Ph), 67.23 ($PhOCH_2$), 65.21 (C-4), 58.97 (C-7), 55.36 (C-2), 24.96 ($CHCH_2I$), 1.16 (C-3).

Synthesis of 21 (R_1 = Me, R_2 = CH_2Ph)

A solution of the mixed iodomethylcephams (2.83 g, 4.71 mmol) in methanol (200 mL) was treated, during 15 min, with a solution of sodium periodate (1.32 g, 6.17 mmol) in 50% methanol (46 mL). The reaction mixture was heated to 35°C and stirred for 2.5 h. A white precipitate was then removed by filtration and washed with ethyl acetate (200 mL). The filtrate was washed successively with water (200 mL) and saturated sodium chloride (200 mL), dried over magnesium sulfate, and evaporated to give a brown foam. Column chromatography using ethyl acetate – hexanes (1:1) yielded the mixed sulfoxides as a pale yellow foam (1.52 g, 52%). Mass spectrum (CI, *m*/*z*): 378 ((M+1)-(I+CO_2CH_2Ph)). IR ($CHCl_3$) (cm^{-1}): 3364, 1782, 1748, 1692. ^{1}H NMR ($CDCl_3$): isomer A: 8.04 (1H, d, 10.6 Hz, NH), 7.40–7.26 (7H, m, Ar), 7.00 (1H, t, Ar), 6.92 (2H, d, Ar), 6.10 (1H, dd, 4.8, 10.6 Hz, H-7), 5.26 (2H, s, $PhCH_2$), 4.81 (1H, d, 4.8 Hz, H-6), 4.54 (2H, s, $PhOCH_2$), 3.81 (3H, s, CH_3), 3.36 (1H, dd, 7.7, 10.7 Hz, C*H*HI), 3.11 (1H, dd, 7.8, 10.7 Hz, CH*H*I), 2.81 (1H, dd, 12.7, 14.8 Hz, H-3), 2.22 (1H, dd, 2.0, 14.8 Hz, H3), 2.48 (1H, m, H-2). Isomer B: 8.08 (1H, d, 10.6 Hz, NH), 7.40–7.26 (7H, m, Ar), 7.00 (1H, t, Ar), 6.92 (2H, d, Ar), 6.13 (1H, dd, 4.8, 10.6 Hz, H-7), 5.30 (1H, d, 11.9 Hz, PhC*H*H), 5.23 (1H, d, 11.9 Hz, PhCH*H*), 4.87 (1H, d, 4.8 Hz, H-6), 4.54 (2H, s, $PhOCH_2$), 3.76 (3H, s, CH_3), 3.46 (1H, dd, 7.4, 10.7 Hz, C*H*HI), 3.26 (1H, dd, 8.0, 10.7 Hz, CH*H*I), 2.87 (1H, dd, 12.7, 14.1 Hz, H-3), 2.28 (1H, dd, 1.8, 14.7 Hz, H-3), 2.69 (1H, m, H-2).

Dehydroiodination of 21 (R_1 = R_2 = Me)

1,8-Diazabicyclo[5.4.0]undec-7-ene (0.26 mL, 0.27 g, 1.74 mmol) was added to a solution of the sulfoxide (814 mg, 1.44 mmol) in dichloromethane (30 mL). The solution was stirred for 1.0 h, and then washed successively with 0.5 M hydrochloric acid (50 mL) and water (50 mL), dried over sodium sulfate, and evaporated. Purification by column chromatography using ethyl acetate – hexanes (3:2) gave the exomethylene compound as a white foam (226 mg, 36%). $[\alpha]_D^{20}$ +136.8° (c 0.095, $CHCl_3$). Mass spectrum (CI, *m*/*z*): 437 (M+1). IR (KBr) (cm^{-1}): 3370, 1786, 1750, 1694. ^{1}H NMR ($CDCl_3$): 8.21 (1H, d, 10.8 Hz, NH), 7.30 (2H, t, Ar), 7.01 (1H, t, Ar), 6.93 (2H, d, Ar), 6.05 (1H, dd, 4.7, 10.8 Hz, H-7), 5.93 (1H, s, CH=C*H*H), 5.65 (1H, s, CH=CH*H*), 4.80 (1H, d, 4.7 Hz, H-6), 4.55 (2H, s, $PhOCH_2$), 3.90 (3H, s, CH_3), 3.88 (1H, d, 14.3 Hz, H-3), 3.82 (3H, s, CH_3), 2.75 (1H, d, 14.3 Hz, H-3). ^{13}C NMR ($CDCl_3$): 168.56 (acetamido C=O), 166.29 (β-lactam C=O), 164.00 (ester C=O), 163.58 (ester C=O), 157.23, 129.69, 122.19, 114.93 (aromatic), 144.42 (C-2), 122.64 (C=*C*H_2), 71.40 (C-6), 67.21 ($PhOCH_2$), 66.60 (C-4), 59.34 (C-7), 54.06 (CO_2CH_3), 53.63 (CO_2CH_3), 27.59 (C-3). Anal. calcd. for $C_{19}H_{20}N_2O_8S\cdot H_2O$: C 50.22, H 4.88, N 6.16; found: C 49.91, H 4.86, N 5.87.

Dehydroiodination of 21 (R_1 = R_2 = CH_2Ph)

1,8-Diazabicyclo[5.4.0]undec-7-ene (0.40 mL, 0.41 g, 2.7 mmol) was added dropwise to a solution of the sulfoxide (0.44 g, 0.61 mmol) in dichloromethane (20 mL). The solution was stirred for 40 min and 0.5 M hydrochloric acid (20 mL) was then added. The organic layer was separated and washed successively with water (20 mL), saturated sodium bicarbonate (20 mL), and saturated sodium chloride (20 mL), dried over magnesium sulfate, and evaporated. Chromatography using ethyl acetate – hexanes (1:1) gave 0.19 g (52%) of the product as a white foam, mp 55–57°C. $[\alpha]_D^{20}$ +166.7° (c 0.072, $CHCl_3$). Mass spectrum (CI, *m*/*z*): 454 ((M+1)-CO_2CH_2Ph). IR (KBr) (cm^{-1}): 3362, 1788, 1748, 1694, 1044. ^{1}H NMR ($CDCl_3$): 8.23 (1H, d, 10.6 Hz, NH), 7.35–7.23 (12H, m, Ar), 7.00 (1H, t, Ar), 6.92 (2H, d, Ar), 6.03 (1H, dd, 4.7, 10.6 Hz, H-7), 5.71 (1H, s, =C*H*H), 5.31 (1H, d, 12.0 Hz, benzyl C*H*H), 5.24 (1H, s, benzyl CH*H*), 5.21 (1H, s, benzyl C*H*H), 5.12 (1H, s, =CH*H*), 5.03 (1H, d, 12.0 Hz, benzyl CH*H*), 4.81 (1H, d, 4.7 Hz, H-6), 3.84 (1H, d, 14.2 Hz, H-3), 2.66 (1H, d, 14.2 Hz, H-3). ^{13}C NMR ($CDCl_3$): 168.54 (acetamido C=O), 165.54 (β-lactam C=O), 164.18 (ester C=O), 163.00 (ester, C=O), 157.24, 134.43, 129.69, 129.12, 128.88, 128.80, 128.68, 128.65, 128.58, 122.18, 114.94 (aromatic), 143.87 (C-2), 122.77 (=CH_2), 71.33 (C-6), 69.24 (CO_2CH_2Ph), 68.52 (CO_2CH_2Ph), 67.21 ($PhOCH_2$), 66.52 (C-4), 59.28 (C-7), 27.49 (C-3). Anal. calcd. for $C_{31}H_{28}N_2O_8S$: C 62.91, H 4.98, N 5.10; found: C 63.25, H 4.79, N 4.76.

Dehydroiodination of 21 (R_1 = Me, R_2 = CH_2Ph)

1,8-Diazabicyclo[5.4.0]undec-7-ene (0.4 mL, 0.41 g, 2.67 mmol) was added to a solution of the mixed sulfoxides (1.27 mg, 2.07 mmol) in dichloromethane (42 mL). The solution was stirred for 1.5 h and then washed successively with 0.5 M hydrochloric acid (50 mL) and water (50 mL), dried over sodium sulfate, and evaporated. Purification by column chromatography using ethyl acetate – hexanes (1:1) afforded two compounds (514 mg, 49%): epimer B (R_f 0.25,

308 mg) and epimer A (R_f 0.14, 207 mg). Epimer A: $[\alpha]_D^{20}$ +123.8° (c 0.84, $CHCl_3$). IR (KBr) (cm^{-1}): 3363, 1789, 1749, 1695. ^1H NMR ($CDCl_3$): 8.21 (1H, d, 10.6 Hz, NH), 7.39–7.27 (7H, m, Ar), 7.00 (1H, t, Ar), 6.94 (2H, d, Ar), 6.02 (1H, dd, 4.7, 10.6 Hz, H-7), 5.70 (1H, s, C=C*H*H), 5.29 (1H, d, 11.7 Hz, PhC*H*H), 5.17 (1H, d, 11.7 Hz, PhCH*H*), 5.10 (1H, br s, C=CH*H*), 4.78 (1H, d, 4.7 Hz, H-6), 4.54 (2H, s, $PhOCH_2$), 3.85 (3H, s, CH_3), 3.83 (1H, br d, 14.2 Hz, H-3), 2.74 (1H, d, 14.2 Hz, H-3). ^{13}C NMR ($CDCl_3$): 168.57 (acetamido C=O), 166.20 (β-lactam C=O), 164.08 (ester C=O), 162.95 (C=O), 157.24, 134.48, 129.70, 129.02, 128.66, 128.57, 122.19, 114.94 (aromatic), 144.34 (C-2), 122.74 (C=*C*H_2), 71.40 (C6), 69.17 (CO_2CH_2Ph), 67.21 ($PhOCH_2$), 66.78 (C-4), 59.34 (C-7), 53.50 (CO_2CH_3), 27.57 (C-3). Anal. calcd. for $C_{25}H_{24}N_2O_8S$: C 58.59, H 4.72, N 5.47; found: C 58.44, H 4.77, N 5.17. Epimer B: $[\alpha]_D^{20}$ +122.7° (c 0.073, $CHCl_3$). IR (KBr) (cm^{-1}): 3364, 1786, 1750, 1694. ^1H NMR ($CDCl_3$): 8.24 (1H, d, 10.6 Hz, NH), 7.37–7.26 (7H, m, Ar), 7.01 (1H, t, Ar), 6.94 (2H, d, Ar), 6.06 (1H, dd, 4.6, 10.6 Hz, H-7), 5.92 (1H, s, C=C*H*H), 5.64 (1H, br s, C=CH*H*), 5.40 (1H, d, 12.0 Hz, PhC*H*H), 5.22 (1H, d, 12.0 Hz, PhCH*H*), 4.83 (1H, d, 4.6 Hz, H-6), 4.55 (2H, s, $PhOCH_2$), 3.89 (1H, br d, 14.3 Hz, H-3), 3.71 (3H, s, CH_3), 2.74 (1H, d, 14.3 Hz, H-3). ^{13}C NMR ($CDCl_3$): 168.55 (acetamido C=O), 165.58 (β-lactam C=O), 164.09 (ester C=O), 163.55 (C=O), 157.21, 134.52, 129.68, 129.19, 129.00, 128.82, 122.17, 114.91 (aromatic), 143.86 (C-2), 122.69 (C=*C*H_2), 71.29 (C-6), 68.55 (CO_2CH_2Ph), 67.18 ($PhOCH_2$), 66.32 (C-4), 59.27 (C-7), 53.93 (CO_2CH_3), 27.41 (C-3). Anal. calcd. for $C_{25}H_{24}N_2O_8S{\cdot}0.5H_2O$: C 57.57, H 4.86, N 5.37; found: C 57.62, H 4.76, N 5.27.

Reduction of 22 (R_1 = R_2 = Me)

A solution of the sulfoxide (175 mg, 0.40 mmol) in dimethylformamide (10 mL) was cooled to 0°C, and treated with phosphorus tribromide (75 μL, 114 mg, 0.42 mmol). The reaction mixture was stirred for 30 min at 0°C, poured onto ice (20 g), and extracted with ethyl acetate (2 × 20 mL). The organic layer was washed successively with water (2 × 40 mL) and saturated sodium chloride (40 mL), dried over anhydrous sodium sulfate, and evaporated. Chromatography using ethyl acetate – hexanes (1:1) afforded the exomethylene cepham as a white foam (171 mg, 95%). $[\alpha]_D^{20}$ +305.9° (c 0.085, $CHCl_3$). IR (KBr) (cm^{-1}): 3370, 1782, 1751, 1688. ^1H NMR ($CDCl_3$): 7.41 (1H, d, 9.3 Hz, NH), 7.33 (2H, t, Ar), 7.04 (1H, t, Ar), 6.94 (2H, d, Ar), 5.75 (1H, dd, 4.4, 9.3 Hz, H-7), 5.48 (1H, d, 0.9 Hz, C=C*H*H), 5.41 (1H, d, 4.4 Hz, H-6), 5.41 (1H, d, 0.9 Hz, C=CH*H*), 4.55 (2H, s, $PhOCH_2$), 3.87 (3H, s, CH_3), 3.82 (3H, s, CH_3), 3.03 (1H, d, 14.0 Hz, H-3), 2.99 (1H, dt, 0.9, 14.0 Hz, H-3). ^{13}C NMR ($CDCl_3$): 168.49 (acetamido C=O), 166.39 (β-lactam C=O), 164.74 (esters C=O), 157.12, 129.79, 122.37, 114.94 (aromatic), 132.58 (C2), 121.39 (C=*C*H_2), 67.31 ($PhOCH_2$), 66.54 (C-4), 58.92 (C-7), 57.91 (C-6), 53.86 (CO_2CH_3), 53.50 (CO_2CH_3), 39.46 (C-3). Anal. calcd. for $C_{19}H_{20}N_2O_7S{\cdot}0.25H_2O$: C 53.70, H 4.86, N 6.59; found: C 53.63, H 5.08, N 6.70.

Reduction of 22 (R_1 = R_2 = CH_2Ph)

Phosphorus tribromide (0.046 mL, 0.13 g, 0.48 mmol) was added, with stirring, at 0°C to a solution of the exomethylene sulfoxide (0.14 g, 0.24 mmol) in dimethylformamide (5.4 mL). Stirring was continued for 1 h and the mixture was then poured onto ice (60 g) and extracted with ethyl acetate (3 × 40 mL). The organic extract was washed successively with water (4 × 40 mL) and saturated sodium chloride (100 mL), dried over anhydrous sodium sulfate, and evaporated to give the product as a yellow foam. Chromatography on Brockmann neutral alumina (40–200 mm mesh) and elution with ethyl acetate – hexanes (1:1) gave a white foam (0.13 g, 97%). $[\alpha]_D^{20}$ +206.1° (c 0.165, $CHCl_3$). IR (KBr) (cm^{-1}): 3414, 1783, 1747, 1690. ^1H NMR ($CDCl_3$): 7.40 (1H, d, 9.5 Hz, NH), 7.34–7.24 (12H, m, Ar), 7.03 (1H, t, Ar), 6.93 (2H, d, Ar), 5.74 (1H, dd, 4.4, 9.5 Hz, H-7), 5.41 (1H, d, 4.4 Hz, H-6), 5.37 (1H, s, =C*H*H), 5.27 (1H, d, 12.0 Hz, benzyl C*H*H), 5.20 (1H, 7.6 Hz, benzyl CH*H*), 5.18 (1H, d, 7.6 Hz, benzyl C*H*H), 5.09 (1H, d, 12.0 Hz, benzyl CH*H*), 5.15 (1H, s, =C*H*H), 4.54 (2H, s, $PhOCH_2$), 3.01 (1H, d, 14.0 Hz, H-3), 2.97 (1H, dt, 0.5, 14.0 Hz, H-3). ^{13}C NMR ($CDCl_3$): 168.40 (acetamido C=O), 165.68 (β-lactam C=O), 164.74 (ester C=O), 164.08 (ester C=O), 157.13, 134.52, 129.80, 128.82, 128.67, 128.60, 128.54, 122.44, 115.00 (aromatic), 132.25 (C-2), 121.46 (=CH_2), 68.93 (CO_2CH_2Ph), 68.31 (CO_2CH_2Ph), 67.40 ($PhOCH_2$), 66.68 (C-4), 58.91 (C-7), 57.89 (C-6), 39.40 (C-3). Anal. calcd. for $C_{31}H_{28}N_2O_7S{\cdot}H_2O$: C 63.04, H 5.12, N 4.74; found: C 62.89, H 4.96, N 4.99.

Reduction of 22 (R_1 = Me, R_2 = CH_2Ph) (epimer A)

A solution of the exomethylene sulfoxide (epimer A) (135 mg, 0.26 mmol) in dimethylformamide (6 mL) was cooled to 0°C and treated with phosphorus tribromide (53 μL, 151 mg, 0.56 mmol). The solution was stirred for 20 min at 0°C and then poured onto ice (10 g) and extracted with ethyl acetate (2 × 20 mL). The organic layer was washed successively with water (3 × 40 mL) and saturated sodium chloride (40 mL), dried over sodium sulfate, and evaporated. Purification by chromatography using ethyl acetate – hexanes (1:1) afforded a white foam (120 mg, 79%). IR (KBr) (cm^{-1}): 3302, 1786, 1748, 1692. ^1H NMR ($CDCl_3$): 7.41 (1H, d, 9.4 Hz, NH), 7.37–7.29 (7H, m, Ar), 7.03 (1H, t, Ar), 6.93 (2H, d, Ar), 5.74 (1H, dd, 4.4, 9.4 Hz, H-7), 5.43 (1H, s, C=C*H*H), 5.40 (1H, d, 4.4 Hz, H-6), 5.36 (1H, d, 12.1 Hz, PhC*H*H), 5.34 (1H, s, C=CH*H*), 5.18 (1H, d, 12.1 Hz, PhCH*H*), 4.54 (2H, s, $PhOCH_2$), 3.72 (3H, s, CH_3), 3.02 (1H, d, 14.1 Hz, H-3), 2.99 (1H, d, 14.1 Hz, H-3). ^{13}C NMR ($CDCl_3$): 168.45 (acetamido C=O), 166.31 (β-lactam C=O), 164.10 (ester C=O), 164.00 (ester C=O), 157.16, 134.62, 129.80, 128.54, 128.63, 128.36, 122.42, 115.02 (aromatic), 132.63 (C-2), 121.00 (C=*C*H_2), 68.84 (CO_2CH_2Ph), 67.41 ($PhOCH_2$), 66.77 (C-4), 58.95 (C-7), 57.87 (C-6), 53.31 (C-3), 39.40 (C-3). Anal. calcd. for $C_{25}H_{24}N_2O_7S$: C 60.47, H 4.87, N 5.64; found: C 60.50, H 4.84, N 5.50.

Reduction of 22 (R_1 = Me, R_2 = CH_2Ph) (epimer B)

A solution of the exomethylene sulfoxide (epimer B) (135 mg, 0.26 mmol) in dimethylformamide (6 mL) was cooled to 0°C and treated with phosphorus tribromide (53 μL, 151 mg, 0.56 mmol). The solution was stirred for 20 min at 0°C and then poured onto ice (10 g) and extracted

with ethyl acetate (2 × 20 mL). The organic layer was washed successively with water (3 × 40 mL) and saturated sodium chloride (40 mL), dried over anhydrous sodium sulfate, and evaporated. Purification by chromatography using ethyl acetate – hexanes (1:1) afforded a white foam (115 mg, 76%). Mass spectrum (CI, *m*/*z*): 362 ((M+1)-CO_2CH_2Ph). IR (KBr) (cm^{-1}): 3333, 1782, 1750, 1690. ^1H NMR ($CDCl_3$): 7.39 (1H, d, 9.4 Hz, NH), 7.38–7.29 (7H, m, Ar), 7.03 (1H, t, Ar), 6.93 (2H, d, Ar), 5.72 (1H, dd, 4.4, 9.4 Hz, H-7), 5.39 (1H, d, 4.4 Hz, H-6), 5.38 (1H, d, 0.8 Hz, C=C*H*H), 5.23 (1H, d, 12.0 Hz, PhC*H*H), 5.22 (1H, d, 12.0 Hz, PhCH*H*), 5.17 (1H, d, 0.8 Hz, C=CH*H*), 4.53 (2H, s, $PhOCH_2$), 3.79 (3H, s, CH_3), 2.99 (1H, d, 14.0 Hz, H-3), 2.95 (1H, dt, 0.8, 14.0 Hz, H-3). ^{13}C NMR ($CDCl_3$): 168.43 (acetamido C=O), 165.73 (β-lactam C=O), 164.75 (ester C=O), 164.65 (ester C=O), 157.15, 134.58, 129.80, 128.90, 128.70, 128.62, 122.41, 114.99 (aromatic), 132.23 (C-2), 121.71 (C=*C*H_2), 68.34 (CO_2CH_2Ph), 67.39 ($PhOCH_2$), 66.49 (C-4), 58.95 (C-7), 57.93 (C-6), 53.70 (CO_2CH_3), 39.36 (C-3). Anal. calcd. for $C_{25}H_{24}N_2O_7S$: C 60.47, H 4.87, N 5.64; found: C 60.47, H 4.87, N 5.39.

Isomerization of 23 (R_1 = R_2 = Me)

The exomethylenecepham (150 mg, 0.36 mmol) was dissolved in dichloromethane (5 mL), the solution was cooled to 0°C, and trifluoroacetic acid (4.0 mL, 2.70 g, 51.9 mmol) was added with stirring. Stirring was continued for 45 min at 0°C, and the solvent was then removed under reduced pressure. Column chromatography using ethyl acetate – hexanes (1:1) gave the 2-methyl-Δ^2-cephem as a white foam (122 mg, 81%). $[\alpha]_D^{20}$ +187.5° (c 0.08, $CHCl_3$). IR (KBr) (cm^{-1}): 3306, 1786, 1748, 1688. ^1H NMR ($CDCl_3$): 7.39 (1H, d, 9.0 Hz, NH), 7.32 (2H, t, Ar), 7.04 (1H, t, Ar), 6.94 (2H, d, Ar), 5.85 (1H, q, 1.4 Hz, H-3), 5.79 (1H, dd, 4.2, 9.0 Hz, H-7), 5.31 (1H, d, 4.2 Hz, H-6), 4.57 (2H, s, $PhOCH_2$), 3.86 (3H, s, CH_3), 3.83 (3H, s, CH_3), 2.01 (3H, d, 1.4 Hz, CH_3). ^{13}C NMR ($CDCl_3$): 168.70 (acetamido C=O), 166.39 (β-lactam C=O), 164.68 (ester C=O), 163.59 (ester C=O), 157.13, 129.82, 122.45, 114.98 (aromatic), 132.58 (C-2), 110.65 (C-3), 67.34 ($PhOCH_2$), 64.40 (C4), 59.49 (C-7), 56.13 (C-6), 53.90 (CO_2CH_3), 53.54 (CO_2CH_3), 24.34 (CH_3). Anal. calcd. for $C_{19}H_{20}N_2O_7S$: C 54.28, H 4.79, N 6.66; found: C 54.33, H 4.87, N 6.77.

Isomerization of 23 (R_1 = R_2 = CH_2Ph)

Trifluoroacetic acid (3 mL) was added dropwise, with stirring at 0°C, to a solution of the exomethylene cepham (0.13 g, 0.23 mmol) in dichloromethane (3 mL). The solution was stirred for 40 min and then evaporated to afford the 2-methyl-Δ^2-cephem (0.13 g, 100%) as a yellow foam. $[\alpha]_D^{20}$ +227.8° (c 0.18, $CHCl_3$). Mass spectrum (CI, *m*/*z*): 439 ((M+1)-(CO_2CH_2Ph)). IR ($CHCl_3$) (cm^{-1}): 3418, 1788, 1748, 1696. ^1H NMR ($CDCl_3$): 7.35–7.22 (13H, m, Ar + NH), 7.04 (1H, t, Ar), 6.93 (2H, d, Ar), 5.87 (1H, 1.3 Hz, H-3), 5.78 (1H, q, 4.2, 9.1 Hz, H-7), 5.33 (1H, d, 4.2 Hz, H-6), 5.24 (1H, d, 12.2 Hz, benzyl C*H*H), 5.21 (1H, d, 12.3 Hz, benzyl CH*H*), 5.18 (1H, d, 12.2 Hz, benzyl C*H*H), 5.11 (1H, d, 12.3 Hz, benzyl CH*H*), 1.99 (3H, d, 1.3 Hz, CH_3). ^{13}C NMR ($CDCl_3$): 168.50 (acetamido C=O), 165.63 (β-lactam C=O), 163.99 (ester C=O), 163.75 (ester C=O), 157.10, 134.56, 129.82, 128.65, 128.53, 128.10, 122.44, 114.96 (aromatic), 132.91 (C-2), 110.48 (C-3), 68.99 (CO_2CH_2Ph), 68.36 (CO_2CH_2Ph), 67.32 ($PhOCH_2$), 64.66 (C-4), 59.44 (C-7), 56.26 (C-6), 24.30 (CH_3). Anal. calcd. for $C_{31}H_{28}N_2O_7S$: C 64.71, H 5.01, N 5.35; found: C 65.02, H 4.93, N 4.89.

Isomerization of 23 (R_1 = Me, R_2 = CH_2Ph) (isomer A)

A solution of the exomethylenecepham (isomer A) (77 mg, 0.13 mmol) in dichloromethane (5 mL) was cooled to 0°C, treated with trifluoroacetic acid (1.7 mL, 2.52 g, 22.1 mmol), stirred for 45 min, and then evaporated to dryness. Column chromatography using ethyl acetate – hexanes (1:1) gave a white foam (63 mg, 88%). $[\alpha]_D^{20}$ +227.6° (c 0.145, $CHCl_3$). IR (KBr) (cm^{-1}): 3422, 1788, 1748, 1692, 1686. ^1H NMR ($CDCl_3$): 7.39–7.30 (8H, m, Ar + NH), 7.04 (1H, t, Ar), 6.94 (2H, d, Ar), 5.86 (1H, q, 1.3 Hz, H-3), 5.77 (1H, dd, 4.2, 9.1 Hz, H-7), 5.34 (1H, d, 16.4 Hz, PhC*H*H), 5.31 (1H, d, 4.2 Hz, H-6), 5.14 (1H, d, 16.4 Hz, PhCH*H*), 4.56 (2H, s, $PhOCH_2$), 3.74 (3H, s, CH_3), 1.99 (3H, d, 1.2 Hz, CH_3). ^{13}C NMR ($CDCl_3$): 168.64 (acetamido C=O), 165.66 (β-lactam C=O), 164.57 (ester C=O), 163.64 (ester C=O), 157.10, 134.68, 129.82, 128.68, 128.15, 122.45, 114.96 (aromatic), 68.33 (CO_2CH_2Ph), 67.31 ($PhOCH_2$), 64.51 (C-4), 59.48 (C-7), 56.15 (C-6), 53.75 (CO_2CH_3), 24.31 (CH_3). Anal. calcd. for $C_{25}H_{24}N_2O_7S$: C 60.47, H 4.87, N 5.64; found: C 60.21, H 4.73, N 5.78.

Isomerization of 23 (R_1 = Me, R_2 = CH_2Ph) (isomer B)

The exomethylenecepham (isomer B) (46 mg, 0.08 mmol) was dissolved in dichloromethane (5 mL), and the solution was cooled to 0°C and treated with trifluoroacetic acid (1.0 mL, 1.48 g, 13.0 mmol). The solution was stirred at 0°C for 45 min, and then evaporated. Purification by column chromatography using ethyl acetate – hexanes (1:1) gave a white foam (42 mg, 91%). $[\alpha]_D^{20}$ +253.9° (c 0.086, $CHCl_3$). IR (KBr) (cm^{-1}): 3412, 1788, 1748, 1692. ^1H NMR ($CDCl_3$): 7.38–7.30 (8H, m, Ar + NH), 7.04 (1H, t, Ar), 6.93 (2H, d, Ar), 5.87 (1H, q, 1.3 Hz, H-3), 5.79 (1H, dd, 4.1, 9.0 Hz, H-7), 5.35 (1H, d, 12.1 Hz, PhC*H*H), 5.33 (1H, d, 4.1 Hz, H-6), 5.20 (1H, d, 12.1 Hz, PhCH*H*), 4.56 (2H, s, $PhOCH_2$), 3.74 (3H, s, CH_3), 2.00 (3H, d, 1.2 Hz, CH_3). ^{13}C NMR ($CDCl_3$): 168.27 (acetamido C=O), 166.01 (β-lactam C=O), 163.73 (ester C=O), 163.45 (ester C=O), 156.86, 134.44, 129.55, 128.28, 128.10, 122.18, 114.72 (aromatic), 132.55 (C-2), 110.35 (C-3), 68.60 (CO_2CH_2Ph), 67.09 ($PhOCH_2$), 64.33 (C-4), 59.19 (C-7), 55.99 (C-6), 53.13 (CO_2CH_3), 24.06 (CH_3). Anal. calcd. for $C_{25}H_{24}N_2O_7S$: C 60.47, H 4.87, N 5.64; found: C 59.92, H 4.96, N 5.69.

Diazotization of dibenzyl malonate (30)

Anhydrous potassium carbonate (6.58 g, 47.6 mmol) was added to a solution of dibenzyl malonate (4.50 g, 15.8 mmol) in acetone (45 mL). The mixture was stirred for 15 min, cooled to 0°C, and a solution of benzenediazonium chloride, prepared by addition of a solution of sodium nitrite (1.10 g, 16 mmol) in water (13.2 mL) to a solution of aniline hydrochloride (2.07 g, 16.0 mmol) in 1.0 M hydrochloric acid (16.2 mL), was added dropwise. The ice bath was removed and stirring was continued at room temperature for 10 min. The reaction mixture was then poured onto crushed

ice and extracted with ethyl acetate (3 × 100 mL), dried over magnesium sulfate, and evaporated to afford a red oil which slowly solidified in the freezer. Trituration with anhydrous methanol produced yellow needles (5.21 g, 85%), mp 47–49°C. Mass spectrum (CI, *m/z*): 389 (M+1). IR (KBr) (cm^{-1}): 1726, 1530. ^1H NMR ($CDCl_3$): 7.42–7.13 (15H, m, Ar), 5.34 (2H, s, benzyl CH_2), 5.33 (2H, s, benzyl CH_2), 3.48 (1H, s, NH). ^{13}C NMR ($CDCl_3$): 163.17 (ester C=O), 163.04 (ester C=O), 141.80–115.73 (aromatic), 66.74 (CO_2CH_2Ph). Anal. calcd. for $C_{23}H_{20}N_2O_4$: C 71.12, H 5.19, N 7.21; found: C 71.17, H 4.97, N 7.10.

Dibenzyl acetamidomalonate

Zinc dust (7.23 g, 110.6 mg-atoms) was added to a solution of the diazo compound (6.50 g, 16.7 mmol) in acetic anhydride (29.0 mL, 31.4 g, 307.4 mmol) and glacial acetic acid (116 mL). The mixture was stirred at room temperature for 1 h, at 40°C for 20 min, and then filtered. The insoluble material was rinsed with glacial acetic acid (10 mL) and the combined filtrates were treated with water to the cloud point. The product was allowed to crystallize, collected, and recrystallized from absolute ethanol to give dibenzyl acetamidomalonate (1.97 g, 35%) as white needles, mp 107–109°C. Mass spectrum (CI, *m/z*): 342 (M+1). IR (KBr) (cm^{-1}): 3299, 1753, 1657. ^1H NMR ($CDCl_3$): 7.32 (6H, m, Ar), 7.25 (4H, m, Ar), 6.54 (1H, s, 7.0 Hz, NH), 5.29 (1H, d, 7.0 Hz, CH), 5.20, 5.16 (4H, ABq, 18.7 Hz, benzyl CH_2), 2.07 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$): 169.66 (acetyl C=O), 166.17 (ester C=O), 134.72–128.19 (aromatic), 68.18 (CO_2CH_2Ph), 56.55 ($CH_3CONHCH$), 22.71 (CH_3CO). Anal. calcd. for $C_{19}H_{19}NO_5$: C 66.85, H 5.61, N 4.10; found: C 66.65, H 5.59, N 4.25.

Dibenzyl allyl acetamidomalonate

A solution of dibenzyl acetamidomalonate (38.1 mg, 0.112 mmol) in acetone (4.0 mL) was treated with anhydrous potassium carbonate (40.5 mg, 0.293 mmol) and sodium iodide (23.9 mg, 0.159 mmol). The mixture was stirred for 10 min, and allyl bromide (0.02 mL, 28.0 g, 0.231 mmol) was added. The mixture was then refluxed, with stirring, for 19 h, cooled, and ethyl acetate (10 mL) and water (2 mL) were added. The organic layer was separated, washed successively with 5% hydrochloric acid (10 mL), water (10 mL) and saturated sodium chloride (10 mL), dried over magnesium sulfate, and evaporated to give an oil which slowly solidified. Crystallization using hot ethyl acetate – hexanes afforded white needles (30.9 mg, 82%), mp 81 to 82°C. Mass spectrum (CI, *m/z*): 382 (M+1). IR (KBr) (cm^{-1}): 3231, 1744, 1642. ^1H NMR ($CDCl_3$): 7.30 (6H, m, Ar), 7.24 (4H, m, Ar), 6.75 (1H, s, NH), 5.48 (1H, ddt, 7.4, 10.2, 16.9 Hz, =CH), 5.16, 5.10 (4H, ABq, 12.2 Hz, benzyl CH_2), 5.02 (1H, ddt, 1.0, 1.0, 10.2 Hz, =C*H*H), 4.97 (1H, ddt, 1.0, 1.0, 16.9 Hz, =CH*H*), 3.10 (2H, ddd, 1.0, 1.0, 7.4 Hz, allyl CH_2), 2.01 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$): 169.00 (acetyl C=O), 167.44 (ester C=O), 134.94, 128.57, 128.52, 128.30 (aromatic), 131.08 ($CH_2CH=CH_2$), 119.96 ($CH_2CH=CH_2$), 68.14 (CO_2CH_2Ph), 66.51 (CH_3CONHC), 37.05 ($CH_2CH=CH_2$), 22.92 (CH_3CONH). Anal. calcd. for $C_{22}H_{23}NO_5$: C 69.28, H 6.08, N 3.67; found: C 69.23, H 6.08, N 4.40.

Hydrolysis of 19

A

A solution of **19** (79 mg, 0.19 mmol) in pyridine (12 mL) was cooled to –8°C and 0.99 M potassium hydroxide (0.4 mL, 22.2 mg, 0.40 mmol, 2.1 mol equiv) was added, with stirring. Stirring was continued for 2.5 h, and the solvent was then removed under reduced pressure. The residue was dissolved in water (20 mL) and the solution was extracted with ethyl acetate (2 × 20 mL). The organic layer was dried and evaporated to give unreacted diester (4 mg). The aqueous layer was acidified to pH 4 with 0.1 N hydrochloric acid and extracted with ethyl acetate (2 × 10 mL). The extract was dried over anhydrous sodium sulfate and evaporated to give a 7:1 mixture (by ^1H NMR) of 4-carboxy-Δ^2- and 4-carboxy-Δ^3-cephems.

Δ^2-Cephem: ^1H NMR (acetone-d_6): 8.17 (1H, d, 8.7 Hz, NH), 7.30 (2H,m, Ar), 7.00 (3H, m, Ar), 6.50 (1H, dd, 2.5, 10.4 Hz, H-2), 5.97 4.1 Hz, H-6), 4.94 (1H, d, 2.5, 4.4 Hz, H-4), 4.64 (2H, s, $PhOCH_2$).

Δ^3-Cephem: ^1H NMR (acetone-d_6): 8.00 (1H, d, 9.2 Hz, NH), 7.28 (2H, m, Ar), 6.94 (3H, m, Ar), 6.58 (1H, dd, 2.6, 6.4 Hz, H-3), 5.94 (1H, dd, 4.9, 9.2 Hz, H-7), 5.15 (1H, d, 4.9 Hz, H-6), 4.70 (2H, s, $PhOCH_2$), 3.65(1H, dd, 2.6, 19.1 Hz, SC*H*H), 3.51 (1H, dd, 6.4, 19.1 Hz, SCH*H*).

A solution of the mixed 4-carboxy-Δ^2- and 4-carboxy-Δ^3-cephems in dichloromethane (10 mL) was cooled to 0°C and diazomethane was added, followed after 5 min by one drop of acetic acid. The solvent was evaporated and the residue was purified by preparative layer chromatography, using ethyl acetate – hexanes (1:1), to give a 7:1 mixture of Δ^2- and Δ^3-esters (8 mg).

Δ^2-Ester: Mass spectrum (CI, *m/z*): 349 (M+1). IR (KBr) (cm^{-1}): 3408, 1784, 1751, 1697. ^1H NMR ($CDCl_3$): 7.40 (1H, d, 9.2 Hz, NH), 7.32 (2H, t, Ar), 7.04 (1H, t, Ar), 6.93 (2H, d, Ar), 6.32 (1H, dd, 2.5, 10.4 Hz, H-2), 5.87 (1H, dd, 4.3, 10.4 Hz, H-3), 5.81 (1H, dd, 4.2, 9.2 Hz, H-7), 5.23 (1H, d, 4.2 Hz, H-6), 4.95 (1H, dd, 2.5, 4.3 Hz, H-4), 4.5 (2H, s, $PhOCH_2$). ^{13}C NMR ($CDCl_3$): 168.50 (acetamido C=O), 167.55 (β-lactam C=O), 164.37 (ester C=O), 156.97, 129.79, 122.40, 114.82 (aromatic), 119.65 (C-2), 113.35 (C-3), 67.20 ($PhOCH_2$), 60.03 (C-7), 53.32 (C-6), 53.04 (CO_2CH_3), 49.33 (C-4). Anal. calcd. for $C_{16}H_{16}N_2O_5S\cdot0.25H_2O$: C 54.46, H 4.71, N 7.84; found: C 54.21, H 4.90, N 7.44.

Δ^3-Ester: Mass spectrum (CI, *m/z*): 349 (M+1). ^1H NMR ($CDCl_3$): 7.28 (1H, d, 9.4 Hz, NH), 7.31 (2H, t, Ar), 7.04 (1H, t, Ar), 6.93 (2H, d, Ar), 6.56 (1H, dd, 2.5, 6.3 Hz, H-3), 5.97 (1H, dd, 5.0, 9.4 Hz, H-7), 5.00 (1H, d, 5.0 Hz, H-6), 4.57 (2H, s, $PhOCH_2$), 3.60 (1H, dd, 2.5, 19.2 Hz, SC*H*H), 3.42 (1H, dd, 6.4, 19.2 Hz, SCH*H*).

B

A solution of **19** (80 mg, 0.23 mmol) in pyridine (1 mL) was cooled to –8°C, and 0.99 M potassium hydroxide (0.2 mL, 0.20 mmol, 0.9 mol equiv) was added, with stirring. Stirring was continued for 2.5 h, and the solvent was then removed under reduced pressure. The residue was dis-

solved in water (10 mL) and the solution was extracted with ethyl acetate (2 × 25 mL). The organic layer was dried and evaporated to give unreacted diester (3 mg). The aqueous layer was acidified to pH 4 with 0.1 N hydrochloric acid and extracted with ethyl acetate (2 × 10 mL). The extract was dried over sodium sulfat and evaporated to give a 5.4:1 Δ^3:Δ^2 mixture of 4-carboxycephems. A solution of this mixture in dichloromethane (10 mL) was cooled to 0°C and treated with diazomethane. After 5 min, one drop of acetic acid was added, and the solvent was evaporated. The residue was purified by preparatory layer chromatography, using ethyl acetate – hexanes (1:1), to give a 5.4:1 Δ^2:Δ^3 mixture of 4-methoxycarbonylcephems (7 mg).

C

A solution of **19** (24 mg, 0.06 mmol) in acetonitrile (4 mL) and water (2 mL) was cooled to –5°C, and treated, with stirring, with 0.99 M potassium hydroxide (1.2 mL, 6.7 mg, 0.12 mmol). Stirring was continued for 1.5 h, and the solvent was then evaporated under reduced pressure. The residue was dissolved in water (20 mL) and the solution was extracted with ethyl acetate (2 × 20 mL). The organic layer was dried and evaporated to give unreacted diester (4 mg). The aqueous layer was acidified to pH 4 with 0.1 N sulfuric acid and extracted with ethyl acetate (2 × 10 mL). The extract was dried over sodium sulfate and evaporated to give the 4-carboxy-Δ^2-cephem. A solution of this compound in dichloromethane (10 mL) was cooled to 0°C and treated with diazomethane. After 5 min, one drop of acetic acid was added and the solvent was then removed. The residue was purified by preparatory layer chromatography using ethyl acetate – hexanes (1:1) to give the Δ^2-ester (5 mg, 29%).

Deprotection of 24

A

A solution of the dimethyl ester (19 mg, 0.045 mmol) in pyridine (0.24 mL) was cooled to 0°C and treated with 1 M potassium hydroxide (0.048 mL, 1.9 mg, 0.045 mmol, 1 mol equiv). Stirring was continued for 2.5 h, and the solvent was then removed under reduced pressure. The residue was dissolved in water (20 mL) and this solution was extracted with ethyl acetate (2 × 20 mL). The organic layer was evaporated and dried to give unreacted diester (7 mg). The aqueous layer was acidified to pH 4 with 0.1 N hydrochloric acid and extracted with ethyl acetate (2 × 10 mL). The extract was dried over sodium sulfate and evaporated. The residue was dissolved in dichloromethane (7 mL), cooled to 0°C, and diazomethane was added. After 30 min, one drop of acetic acid was added, and the solvent was removed. Column chromatography of the residue, using ethyl acetate – hexanes (2:3), afforded the 4-methoxycarbonyl-Δ^2-ester. $[\alpha]_D^{20}$ +424.2° (c 0.165, $CHCl_3$). Mass spectrum (CI, *m*/*z*): 363 (M+1). HR-MS-CI calcd. for $C_{17}H_{18}N_2O_5S$: 363.1015 (M+1); found: 363.1018 (M+1). IR ($CHCl_3$) (cm^{-1}): 3412, 1778, 1751, 1694. ^1H NMR ($CDCl_3$): 7.36–7.30 (3H, m, Ar + NH), 7.04 (1H, t, Ar), 6.94 (2H, d, Ar), 5.81 (1H, dd, 4.1, 9.2 Hz, H-7), 5.62 (1H, dq, 1.3, 2.7 Hz, =CH), 5.23 (1H, dd, 0.4, 4.1 Hz, H-6), 4.96 (1H, ddq, 0.4, 2.0, 2.7 Hz, shows nOe with H-3 and CH_3 at 5.62 and 1.96 ppm, respectively, allyl CH), 1.96 (3H, dd, 1.3, 2.0 Hz, CH_3). ^{13}C NMR ($CDCl_3$): 168.52 (acetamido C=O), 168.37 (ester C=O), 164.74 (β-lactam C=O), 157.13, 129.82, 122.44, 114.96 (aromatic), 130.07 (C-2), 108.68 (C-3), 67.36 ($PhOCH_2$), 59.97 (C-7), 54.57 (C-6), 52.84 (ester CH_3), 50.07 (C-4), 24.28 (CH_3).

B

To a solution of the dibenzyl ester (26.5 mg, 0.046 mmol) in 95% ethanol (6.0 mL) and water (3.0 mL) were added sodium bicarbonate (8.9 mg, 0.106 mmol) and 10% palladium on carbon (82.3 mg). The apparatus was flushed thrice with nitrogen and thrice with hydrogen, and then stirred rapidly under hydrogen for 25 min. The mixture was filtered through Celite and the Celite was rinsed with water (3 × 5 mL). The filtrate was concentrated under reduced pressure to remove ethanol, and then lyophilized to give a white solid (16.9 mg). This material, in dimethylformamide (0.2 mL), was treated with methyl iodide (5.5 μL, 12.5 mg, 0.088 mmol). The mixture was stirred for 2.5 h and then diluted with dichloromethane (5 mL), washed successively with water (3 × 5 mL) and saturated sodium chloride (5 mL), dried over magnesium sulfate, and evaporated to give the methyl ester of 2-methyl-Δ^2-cephem V (3.5 mg, 91%).

C

To a solution of the dibenzyl ester (34.3 mg, 0.056 mmol) in glacial acetic acid (7.5 mL) and water (3.6 mL) was added 10% palladium on carbon (71.2 mg). The apparatus was purged in the usual manner and the mixture was stirred rapidly under hydrogen for 20 min and then centrifuged. The pellet was suspended in ice-cold 68% acetic acid (5.0 mL) and centrifuged again. The combined supernatants were lyophilized, and the white residue, in a mixture of absolute ethanol (2.0 mL) and dichloromethane (5.0 mL), was treated with diazomethane. The solution was stirred for 2 h and the solvent was then removed under reduced pressure. Chromatography of the residue using ethyl acetate – hexanes (1:1) gave two products, the 4-methoxycarbonyl-Δ^2-cephem (R_f 0.50, 4.3 mg, 21%) as a white solid, mp 125 to 126°C, and the 4-methoxycarbonyl-Δ^2-cepham (R_f 0.44, 1.5 mg, 2%) as a colourless film. $[\alpha]_D^{20}$ +160.0° (c 0.050, $CHCl_3$). Mass spectrum (CI, *m*/*z*): 365 (M+1). HR-MS-CI calcd. for $C_{17}H_{20}N_2O_5S$: 365.1171 (M+1); found: 365.1164. IR ($CHCl_3$) (cm^{-1}): 3414, 1778, 1751, 1694. ^1H NMR ($CDCl_3$): 7.31 (3H, m, Ar + NH), 7.05 (1H, t, Ar), 6.96 (2H, d, Ar), 5.76 (1H, dd, 4.5, 9.7 Hz, H-7), 5.27 (1H, d, 4.5 Hz, H-6), 4.80 (1H, dd, 2.0, 6.2 Hz, H-4), 4.55 (2H, s, $PhOCH_2$), 3.78 (3H, s, ester CH_3), 3.06 (1H, ddq, 2.0, 6.3, 6.8 Hz, $CHCH_3$), 2.25 (1H, ddd, 2.0, 2.0, 14.1 Hz, α-H-3), 1.69 (1H, ddd, 6.3, 12.0, 14.1 Hz, β-H-3), 1.25 (3H, d, 6.8 Hz, CH_3). ^{13}C NMR ($CDCl_3$): 169.75 (acetamido C=O), 168.36 (ester C=O), 165.39 (β-lactam C=O), 157.83, 129.78, 122.40, 115.03 (aromatic), 67.43 ($PhOCH_2$), 59.13 (C-7), 56.25 (C-6), 52.68 (ester CH_3), 50.26 (C-4), 34.86 (C-2), 31.81 (C-3), 21.34 (CH_3).

D

To a solution of isomer A (46 mg, 0.093 mmol) in glacial acetic acid (10 mL) and water (4.7 mL) was added 10% palladium on carbon (103 mg). The apparatus was purged in the

usual manner and the mixture was stirred rapidly under hydrogen for 20 min and then centrifuged. The pellet was suspended in ice-cold 67% acetic acid (5.0 mL) and centrifuged again. The combined supernatants were lyophilized, and the white residue, in a mixture of absolute ethanol (2.0 mL) and dichloromethane (5.0 mL), was treated with diazomethane. The solution was stirred for 2 h and the solvent was then removed under reduced pressure. Chromatography using ethyl acetate – hexanes (1:1) gave the 4-methoxycarbonyl-Δ^2-cephem (23.3 mg).

E

To a solution of isomer B (46 mg, 0.093 mmol) in glacial acetic acid (10 mL) and water (4.7 mL) was added 10% palladium on carbon (110 mg). The apparatus was purged in the usual manner and the mixture was stirred rapidly under hydrogen for 20 min and then centrifuged. The pellet was suspended in ice-cold 68% acetic acid (5.0 mL) and centrifuged again. The combined supernatants were lyophilized, and the residue, in a mixture of absolute ethanol (2.0 mL) and dichloromethane (5.0 mL), was treated with diazomethane. The solution was stirred for 2 h and the solvent was then removed under reduced pressure. Chromatography using ethyl acetate – hexanes (1:1) afforded the Δ^2-cephem (8.8 mg) and the cepham (7.0 mg).

Deprotection of model malonates

A

To a solution of dibenzyl acetamidomalonate (29.9 mg, 0.088 mmol) in glacial acetic acid (4.1 mL) and water (2.6 mL) was added 10% palladium on carbon (119.8 mg). The apparatus was flushed thrice with nitrogen, thrice with hydrogen and the mixture was then stirred rapidly under hydrogen for 55 min and centrifuged. While the supernatant was cooled in an ice bath, the pellet was suspended in ice-cold 61% acetic acid (4 mL) and centrifuged again. The combined supernatants were lyophilized to give acetamidomalonic acid as a fluffy white solid. An ice-cold solution of this material in a mixture of dichloromethane (1.8 mL) and 95% ethanol (0.3 mL) was treated, in 10 min intervals, with diazomethane, bubbled in from a DIAZALD reaction mixture using a stream of dry nitrogen. The solvent was removed under reduced pressure and the residue, in ethyl acetate, was filtered through a short layer of silica gel. Crystallization from hot methanol gave dimethyl acetamidomalonate as white needles (13.5 mg, 81%), mp 126–128°C. Mass spectrum (EI, *m*/*z*): 189 (M). IR (KBr) (cm^{-1}): 3304, 1750, 1740, 1651. ^{1}H NMR ($CDCl_3$): 6.47 (1H, d, 7.0 Hz, NH), 5.21 (1H, d, 7.0 Hz, CH), 3.82 (6H, s, ester CH_3), 2.08 (3H, s, acetamido CH_3). ^{13}C NMR ($CDCl_3$): 169.61 (acetamido C=O), 166.81 (ester C=O), 56.14 ($CH_3CONHCH$), 53.33 (CO_2CH_3), 22.68 (CH_3CONH). Anal. calcd. for $C_7H_{11}NO_5$: C 44.45, H 5.86, N 7.40; found: C 44.35, H 5.79, N 7.41.

B

To a solution of dibenzyl allylacetamidomalonate (32.5 mg, 0.0852 mmol) in glacial acetic acid (4.2 mL) and water (2.7 mL) was added 10% palladium catalyst (116.3 mg). The mixture was purged thrice with nitrogen and thrice with hydrogen and then stirred under hydrogen for 1 h and centrifuged. The pellet was suspended in 61% acetic acid (4.0 mL), centrifuged again, and the combined supernatants were lyophilized to give the malonic acid. This was dissolved in a mixture of dichloromethane (1.8 mL) and 95% ethanol (0.3 mL), the solution was cooled in an ice bath, and excess diazomethane was introduced in a stream of dry nitrogen. The solution was stirred for 2 h, evaporated, and the residue, in ethyl acetate (2 mL), was flushed through a short column of silica gel. Evaporation and crystallization from ethyl acetate – hexanes afforded dimethyl *n*-propyl acetamidomalonate as white needles (19.2 mg, 82%) mp 127 to 128°C. Mass spectrum (CI, *m*/*z*): 232 (M+1). IR (KBr) (cm^{-1}): 3273, 1748, 1642. ^{1}H NMR ($CDCl_3$): 6.77 (1H, br s, NH), 3.77 (6H, s, ester CH_3), 2.29 (2H, m, CH_2), 2.03 (3H, s, acetamido CH_3), 1.12 (2H, m, CH_2), 0.90 (3H, t, 7.3 Hz, CH_3). ^{13}C NMR ($CDCl_3$): 168.89 (acetamido C=O), 168.75 (ester C=O), 66.62 ($CH_3CONHC(CO_2CH_3)_2$), 53.30 (CO_2CH_3), 34.52 ($CH_3CONHCCH_2CH_2CH_3$), 22.96 (CH_3CONH), 17.08 ($CH_3CONHCCH_2CH_2CH_3$), 13.74 ($NHCCH_2CH_2CH_3$). Anal. calcd. for $C_{10}H_{17}NO_5$: C 51.94, H 7.41, N 6.06; found: C 52.13, H 7.44, N 5.88.

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