Nuclear analogs of β-lactam antibiotics. II. Synthesis of *O*-2-isocephems[1]

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The preparation by total synthesis of a new class of β-lactam antibiotics is reported. Conversion of alcohol **1***b* to its mesylate **9***b* followed by hydrolysis of the acetal to the enol **1***b* and base-catalyzed ring closure gave benzyl 7-β-azido-Δ^3-*O*-2-isocephem-4-carboxylate **8***b*. Similarly prepared were the 3-methyl, 3-benzyl, and 3-phenethyl analogs (**32***b–d*). Reduction of the azides followed by coupling of the resultant amines with phenoxyacetic acid and removal of the benzyl groups by hydrogenolysis gave the acids **35***a–e* which exhibited high antibacterial activity. The structural assignments to the *O*-2-isocephems which were made on the basis of their spectral characteristics (ir, uv, and nmr) are discussed.

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On rapporte la préparation, par synthèse totale, d'une nouvelle classe d'antibiotiques contenant une β-lactame. La conversion de l'alcool **1***b* en mésylate **9***b* suivie par une hydrolyse de l'acétal en énol **1***b* et par la fermeture de cycle catalysée par les bases, conduit à la β-azido-7 Δ^3-*O*-isocéphème-2 carboxylate-4 de benzyle **8***b*. On a préparé par la même procédure les analogues méthyl-3, benzyl-3 et phénéthyl-3 (**32***b–d*). La réduction des azotures, suivie par un couplage des amines qui en résultent avec l'acide phénoxyacétique et l'élimination des groupes benzyles par hydrogénolyse fournit les acides **35***a–e* qui montrent une grande activité antibactérielle. On discute des attributions de structures pour les *O*-isocéphèmes-2 qui ont été faites en se basant sur leurs caractéristiques spectrales (ir, uv et nmr).

[Traduit par le journal]

In the preceding paper the synthesis of **1***a*, its conversion to **2***a*, and the subsequent conversion of **2***a* to **2***e* was described. The low order of antibacterial activity exhibited by **2***e* was as had been anticipated.[5] It remained for us to effect the elimination of a mole of ethanol from **2***e* in order to complete our synthesis of the *O*-2-isocephem nuclear analog of cephalosporin.[6] In this paper we wish to report our efforts in this area and the synthesis of a number of *O*-2-isocephems which exhibit high antibacterial activity.

All efforts to effect direct elimination of ethanol from **2** (Scheme 1) failed as did attempted hydrolysis of **2** to its 3-hydroxy analogs. Treatment of **2***a* with zinc chloride in acetic anhydride gave **3***a* in 85% yield rather than the hoped for 3-acetoxy derivative. This result might have been anticipated from the stereochemistry of **2***a* (Fig. 1). In **2***a* the C_3—O_2 bond and the C_4—H_β bond are *trans* to one another thus facilitating cleavage of the C_3—O_2 bond with formation of the double bond in **3***a* which is formed as a single geometrical isomer. Alternatively, **3***a* could be

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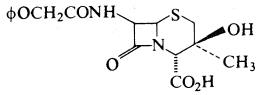
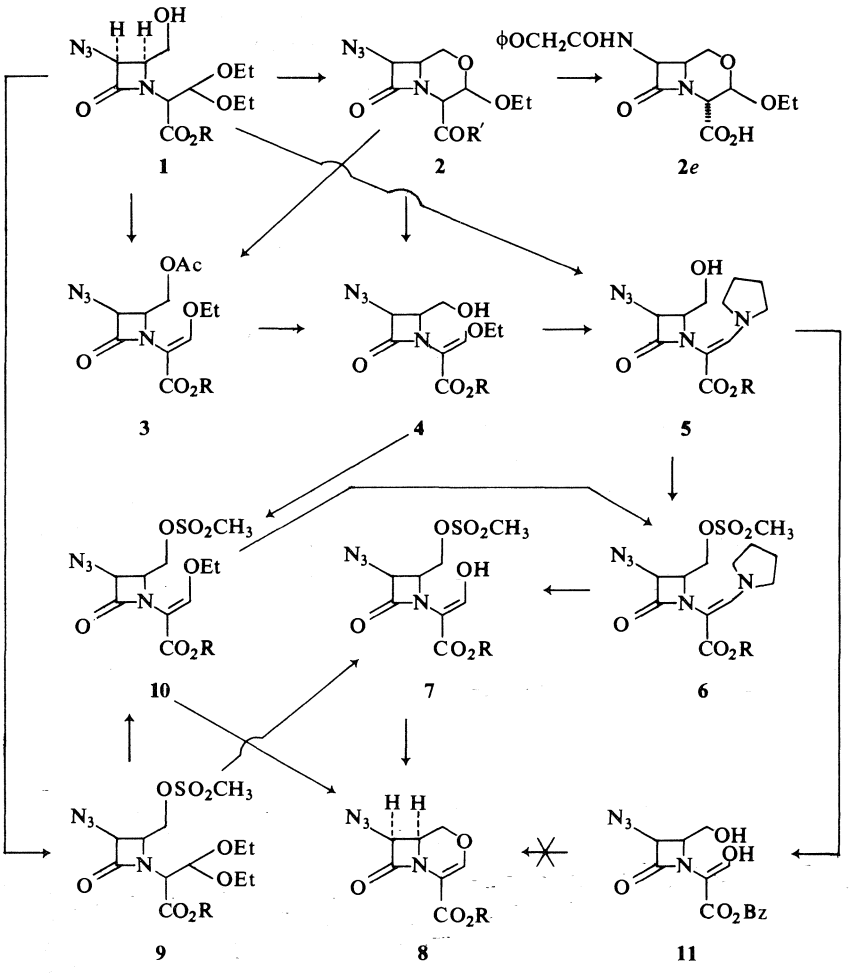
[5]Gutowski *et al.* have reported that compound **i** exhibits low antibacterial activity in comparison with its unsaturated counterpart (2).



i

[6]See ref. 1 for a review of the literature concerning nuclear analogs of the penicillins and cephalosporins and an explanation of the trivial nomenclature used in this and the accompanying papers.



SCHEME 1

obtained directly from **1***a* in 75% yield. In this case, **3***a* was obtained as a mixture of isomers in which the isomer obtained in major amount (>90%) was identical with that from **2***a*.

Hydrolysis of **3***a* gave **4***a* in 94.5% yield. Compound **4***a* could also be obtained in low yield (26%) by treatment of **2***a* with titanium tetrachloride in methylene chloride.

The nmr and ir spectra (Tables 2 and 4 respectively) of these compounds were in accord with the assigned structures. In the nmr compounds **3***a* and **4***a* showed signals at 7.34 and 7.73 δ respectively for the olefinic proton. In the

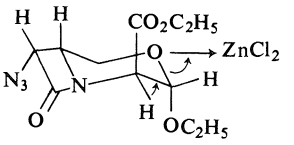


FIGURE 1

ir they exhibited $\diagdown C{=}C \diagup$ stretching frequencies at 1640 and 1645 cm^{-1} for enol ethers in addition to the expected carbonyl bands.

Treatment of compound **4***a* with pyrrolidine – acetic acid in refluxing benzene gave the vin-

ologous urethane **5***a* in 75% yield as a single isomer. The nmr spectrum of **5***a* showed considerable line broadening for all protons with the exception of the signals for the ethyl ester. We attribute this broadening-hindered rotation about the $N\rightarrow C(CO_2R)=CHNC_4H_8$ bond. Compound **5***a* was also prepared directly from **1***a* in 50% yield. Treatment of **5***a* with triethylamine and methane sulfonyl chloride in methylene chloride gave **6***a* in 73.5% yield. Alternatively **6***a* could be prepared by treatment of **4***a* with triethylamine – methane sulfonyl chloride to give **10***a* in 65% yield followed by treatment of **10***a* with pyrrolidine – acetic acid to give **6***a* in 63% yield. Hydrolysis of **6***a* with hydrochloric acid in aqueous acetone gave the enol mesylate **7***a* in 89% yield. The nmr spectrum of **7***a* suggested that it exists as a mixture of geometrical isomers of the enol as well as, to a small extent, the aldehydo form. The enolic hydroxyl appears as a singlet at 12 δ integrating for ~0.85 protons. The signals for the methyl group of the ester appears as a pair of triplets of approximately equal intensities. Compound **7***a* gave a strong ferric chloride test for an enol (deep purple). In the ir spectrum of **7***a* there are bands at 1680 and 1630 cm^{-1} which we assign to the aldehydo and enolic forms respectively.

Treatment of **7***a* with sodium hydride in dimethyl sulfoxide gave ethyl 7-β-azido-Δ^3-*O*-2-isocephem-4-carboxylate **8***a* in 91% yield. Alternatively **7***a* could be converted to **8***a* by refluxing **7***a* with 1 equiv. of triethylamine in chloroform in 47.5% yield. A third route to **8***a* consists of treating **10***a* with aqueous dilute sodium hydroxide in tetrahydrofuran, lyophilizing the resulting solution and taking up the residue in DMSO. The yield of **8***a* from **10***a* by this procedure was 33%. Compound **10***a* was also prepared by mesylation of **1***a* to give **9***a* in 86% yield. Treatment of **9***a* with zinc chloride – acetic anhydride or with triethyloxonium fluoroborate in methylene chloride gave **10***a* in 45% yield. Hydrolysis of the acetal function in **9***a* with trifluoroacetic acid at 50 °C effected the conversion of **9***a* to **7***a* in 58% yield. The overall yield of **8***a* from **1***a* proceeding via the best sequence **1***a* → **9***a* → **7***a* → **8***a* was 45%.

As we required an *O*-2-isocephem carrying an easily deblocked ester function the synthesis of benzyl 7-β-azido-Δ^3-*O*-2-isocephem-4-carboxylate **8***b* was attempted next.

Saponification of **2***a* with dilute sodium hydroxide solution gave **2***b* in 66% yield. The carboxylic acid was converted to its acid chloride **2***c* and subsequently to the benzyl ester **2***d* in 83.5% yield. Treatment of **2***d* with zinc chloride – acetic anhydride gave **3***b* in 94% yield. Alternatively **3***b* could be prepared directly from **1***b* in 41% yield.

The synthesis of **1***b* was accomplished by the following sequences (Scheme 2). Treatment of benzyl nitroacetate (3) **12** with triethylorthoformate in acetic anhydride at 80–90 °C gave a mixture of **13** and **14** in quantitative yield (4). The nmr spectrum of the mixture indicated that the ratio of **13** to **14** was 3:2 and that **13** was present as a mixture of geometric isomers one of which predominates. On distillation, the mixture decomposed extensively and yielded only the starting material **12**. Treatment of the mixture of **13** and **14** with ethanol in the presence of a catalytic amount of sodium ethoxide gave exclusively **14**. The yield of **14** from **12** was quantitative. Reduction of **14** to **15** with aluminum amalgam proceeded in 42.5% yield (not optimized) (5). The ir and nmr spectra of **15** were compatible with the assigned structure.[7] Compound **15** was converted to its cinnamylidene Schiff base **16** in quantitative yield as previously described (1) following which **16** was converted to the β-lactam **17** in 89% yield by treatment with triethylamine–azidoacetylchloride as before (1). The mixture of diastereoisomeric β-lactams could be separated chromatographically, although this was not done generally as the crude product was pure enough for use in the subsequent reactions. The nmr spectra of the isomers of **17** are recorded in Table 2. Compound **17** could also be prepared from the ethyl ester **19** (1). Saponification of **19** with sodium hydroxide gave the corresponding carboxylic acid **20** in 60% yield. Treatment of **20** with triethylamine and benzyl chloroformate gave the mixed anhydride which spontaneously decomposed to the ester **17** in 55% yield. Ozonolysis of **17** at −78 °C gave the aldehyde **18** in 95% yield. The nmr spectrum of crude **18** indicated at least 77% free aldehyde.[8] Reduction of **18** with sodium borohydride in ethanol gave **1***b* in 85% yield.

Hydrolysis of **3***b* gave **4***b* in 87% yield. Com-

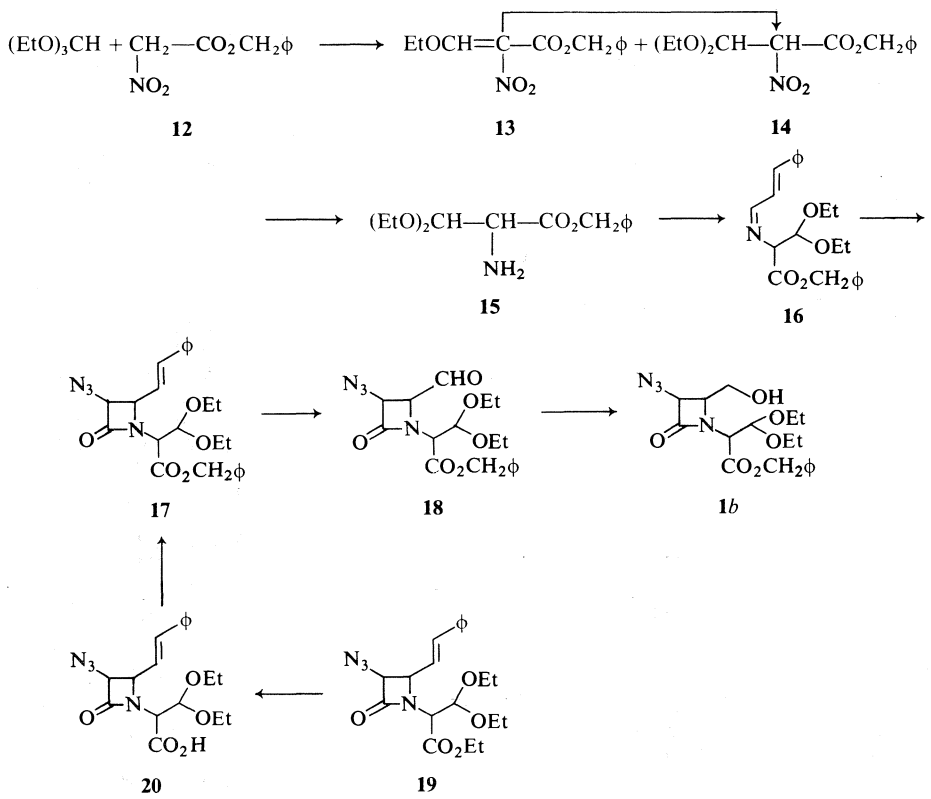
[7]In some runs the reduction step stopped at the hydroxylamine stage in which case the hydroxylamine was recycled over fresh aluminum amalgam.

[8]A number of the aldehydes prepared in this manner were found to form hydrates which on reduction gave the desired 4-hydroxymethyl 2-azetidinones.

TABLE 1. Nuclear magnetic resonance spectra of non-β-lactams[a]

Compound	Aromatic and vinyl	$CH_2\phi$	CH_3	O—CH_2—CH_2—O	Other
13	7.33 (s, 5H)	5.20 (s)	1.24 (t)[b]	—	4.20 (q, J=7.0)[b,h]
	8.27 (s)[c]		1.34 (t)[c]		4.26 (q, J=7.0)[c,h]
	7.58 (s)[b]				
14	7.16 (s, 5H)	5.12 (s)	1.06 (t)	—	3.53 (q, J=7.0)[h]
			1.14 (t)		3.60 (q, J=7.0)[h,d]
			J=7.0		
15	7.30 (s, 5H)	5.16 (s)	1.15 (t)	—	1.60 (s, 2H)[e]
			1.13 (t)		4.58 (d, 1H, J=5.0)[f]
			J=7.0		3.64 (d, 1H, J=5.0)[g]
16	7.30 (m, 10H)	5.16 (s)	1.10 (t)	—	7.99 (t, 1H, J=4.0)[i]
	6.92 (d, 2H)[o]		1.12 (t)		3.55 (m, 4H)[h]
	J=4.0		J=7.0		4.92 (d, 1H, J=7.5)[f]
					4.05 (d, 1H, J=7.5)[g]
22*a*	—	—	2.48 (s)	—	6–8 (bs, 1H)[j]
			1.39 (t)		4.46 (q, 2H, J=7.0)[k]
			J=7.0		
22*b*	7.50 (s, 5H)	5.43 (s)	2.43 (s)		9.84 (s, 1H)[j]
22*c*	7.26 (s, 5H)	5.25 (s)	—		10.14 (s, 1H)[j]
	7.16 (s, 5H)	4.0 (s)[m]			
22*d*	7.27 (s, 5H)	5.25 (s)			10.3 (s, 1H)[j]
	7.12 (s, 5H)				2.90 (m, 4H)[l]
23*a*	7.43 (s, 5H)	5.37 (s)	1.65 (s)	3.97 (s)	9.12 (s, 1H)[j]
23*b*	7.30 (s, 5H)	5.26 (s)	—	3.62 (m)	9.0 (s, 1H)[j]
	7.17 (s, 5H)	3.20 (s)[m]			
23*c*	7.28 (m, 5H)	5.25 (s)	—	3.87 (s)	2.20 (m, 2H)[l]
	7.12 (s, 5H)	2.70 (m)[l]			
24[m]	—	—	2.40 (s)	—	4.70 (s, 1H)[g]
			1.32 (t)		4.25 (q, 2H, J=7.0)[k]
			J=7.0		
25*a*	—	—	1.41 (s)	3.73 (s)	4.07 (s, 1H)[g]
			1.31 (t)		3.26 (s, 2H)[e]
			J=7.0		4.30 (q, 2H, J=7.0)[k]
25*b*	7.36 (s, 5H)	5.18 (s)	1.36 (s)	3.91 (s)	3.60 (s, 1H)[g]
					1.83 (s, 2H)[e]
25*c*	7.20 (m, 5H)	5.10 (s)	—	3.40 (m)	3.58 (s, 1H)[g]
	7.15 (s, 5H)	3.99 (s)[m]			2.38 (s, 2H)[e]
25*d*	7.34 (m, 5H)	5.18 (s)	—	3.90 (bs)	3.72 (s, 1H)[g]
	7.19 (s, 5H)	2.70 (s)[l]			1.91 (s, 2H)[e]
					2.20 (m, 2H)[l]
26*a*	7.45 (m, 5H)	—	1.58 (s)	4.05 (m, 5H)	4.28 (q, 2H, J=7.0)[k]
	7.05 (d, 2H)[o]		1.32 (t)		8.10 (t, J=4.7)[i]
	J=4.7		J=7.0		
26*b*	7.30 (10H, s)	5.22 (s)	1.53 (s)	3.97 (s)	4.05 (s, 1H)[g]
	6.94 (d, 2H)[o]				7.95 (dd, 1H, J=4.0, J=5.0)[i]
	J=4.0				
26*c*	7.30 (m, 5H)	5.20 (s)	—	3.54 (m)	4.12 (s, 1H)[g]
	7.17 (s, 10H)	3.06 (d)[m]			7.88 (dd, 1H, J_1=5.5, J_2=3.0)[i]
	6.97 (d)[o]	J=14.0			
	J=3.0	3.32 (d)[m]			
	6.89 (s, 1H)[o]	J=14.0			
26*d*	7.33 (m, 5H)	5.21 (s)	—	4.00 (s)	4.17 (s, 1H)[g]
	7.17 (m, 10H)	2.65 (m, 2H)[l]			2.40 (m, 2H)[l]
	7.01 (d, J=3.0)				7.95 (dd, J_1=5.5, J_2=3.0)[i]
	6.93 (s)[o]				

[a]All spectra were recorded at 60 MHz as $CDCl_3$ solutions using tetramethylsilane as internal reference unless otherwise noted. The chemical shifts are reported in δ units and the coupling constants in Hz. [b]Major isomer. [c]Minor isomer. [d]The proton signals for C*H*(OR)$_2$ and C*H*—NO_2 are obscured under the CH(OC*H*$_2$—CH_3) signals. [e]Assigned to N*H*$_2$. [f]Assigned to C*H*(OR)$_2$. [g]Assigned to C*H*—CO_2R. [h]Assigned to CH-(OC*H*$_2$—CH_3)$_2$. [i]Assigned to —N=C*H*—. [j]Assigned to =N—O*H*. [k]Assigned to CO_2CH_2—CH_3. [l]Assigned to CH_2—CH_2—φ. [m]Taken in D_2O. [n]Assigned to φCH_2—C≡. [o]Assigned to φC*H*=C*H*.



SCHEME 2

pound **4***b* was converted to **5***b* in 71% yield following which it was converted to its mesylate **6***b* in 90% yield. Hydrolysis of **6***b* gave **7***b* (81%) which was converted to **8***b* by treatment with sodium hydride in DMSO in 42% yield. On refluxing **7***b* with 1 equiv. of triethylamine in methylene chloride **8***b* was obtained in 71.5% yield. As in the case of the ethyl ester series compound **4***b* was converted to **10***b* (70%) and thence to **8***b* (40%). The conversion of **1***b* to **9***b* (83.5%) and the hydrolysis of **9***b* to **7***b* (91%) followed by ring closure also gave **8***b* in 54.5% overall yield from **1***b*.

Compound **9***b* could also be obtained from **9***a* via saponification to **9***c* in 55% yield (in addition to **9***c* there was also produced **10***a* in this reaction). Treatment of **9***c* with triethylamine – benzyl chloroformate as before gave **9***b* in 84% yield. Hydrolysis of **5***b* to **11** was carried out in 75% yield. All attempts to prepare **8***b* via the elimination of 1 mol of water from **11** failed.

The structural assignments to **8***a* and **8***b* rest on their mode of synthesis, correct elemental analyses, and their ir, uv, and nmr spectral characteristics. The ir spectra of **8***a* and **8***b* show absorptions at 2110 cm^{-1} for the azide, 1790 cm^{-1} for the β-lactam carbonyl, 1715 cm^{-1} for the α,β-unsaturated ester carbonyl, and an absorption at ~1625 cm^{-1} for the double bond. In the uv spectra of **8***a* and **8***b* there are bands at 268 nm with extinction coefficients of 6800 and 6700 respectively. These values are in accord with those observed in the cephalosporins (6). The pronounced bathochromic shift observed in going from the non-cyclized chromophore in **3**, **4**, and **10** to the chromophores in **8***a* and **8***b* may be explained as being due to participation of the amide lone pair in the chromophore of the latter compounds (the uv spectra are recorded in Table 4). This is further borne out by comparison of the uv spectra of **3**, **4**, and **10** with that of genepin (7) and the simpler dihydropyran system (8) (see Fig. 2) both of which contain the $-O-\overset{R}{C}=\overset{R'}{C}-CO_2CH_2CH_3$ chromophore. The λ_{max} and extinction coefficients for **3**, **4**, and **10** are very similar to those for genepin and the dihydropyran system indicating little contribution of the β-lactam chromophore to the β-alk-

TABLE 2. Nuclear magnetic resonance spectra of monocyclic β-lactams[a]

Compound	Aromatic and olefinic	N_3—CH—	ϕCH_2	CH_3	Other
1*b*[b]	7.27 (s, 5H)	—	5.12 (s)	1.10 (m, 6H)	3.1–4.3 (m, 8H)[c] 4.6–4.7 (m, 2H)[d]
3*a*	7.34 (s, 1H)	4.80 (dd) J_1=3.25 J_2=1.75	—	1.98 (s, 3H)[e] 1.25 (t, 3H)[g] 1.32 (t, 3H)[g] J=7.0	4.30 (m, 3H)[f] 4.11 (q, 2H, J=7.0)[g] 4.09 (q, 2H, J=7.0)[g]
3*b*[h]	7.40 (s, 1H) 7.26 (s, 5H)	4.75 (dd) J_1=3.5 J_2=1.5	5.13 (s)	1.33 (t, 3H)[i] J=7.0 1.95 (s, 3H)[e]	4.25 (m, 3H)[f] 4.10 (q, 2H)[i]
4*a*	7.73 (s, 1H)	4.88 (d) J=5.0	—	1.33 (t, 3H) 1.42 (t, 3H) J=7.0	4.00 (m, 3H)[f] 4.30 (q, 2H)[g] 4.33 (q, 2H)[g]
4*b*	7.45 (s, 1H) 7.28 (s, 5H)	4.66 (d) J=5.0	5.13 (s)	1.31 (t, 3H) J=7.0	4.11 (q, 2H)[i] 4.00 (m, 3H)[f]
5*a*[j]	7.60 (s, 1H)	4.5 (m)[j]	—	1.25 (t, 3H)[k] J=7.0	4.12 (q, 2H)[k] 5.1 (s, O*H*) 3.8 (m, 3H)[f] 3.41 (m, 4H) 1.90 (m, 4H)[l]
5*b*[j]	7.66 (s, 1H) 7.30 (s, 5H)	4.57 (m)[j]	5.13 (s)	—	3.90 (m, 3H)[f] 3.48 (m, 4H) 1.95 (m, 4H)[l]
6*a*[j]	7.51 (s, 1H)	4.83 (dd) J=4.5 J=1.5	—	1.25 (t, 3H) J=7.0 3.00 (s, 3H)[m]	4.40 (m, 3H)[f] 4.10 (q, 2H, J=7.0)[k] 3.42 (m, 4H), 1.90 (m, 4H)[l]
6*b*[j]	7.70 (s, 1H) 7.40 (s, 5H)	4.90 (d) J=5.0	5.17 (s)	3.00 (s, 3H)[m]	4.45 (m, 3H)[f] 3.5 (m, 4H), 1.95 (m, 4H)[l]
7*a*[n]	7.52 (bs, ~1H)	5.01 (d) J=5.0	—	3.04 (s, 3H)[m] 1.30 (t) 1.35 (t) J=7.0	4.18 (q, 2H, J=7.0)[k] 4.5 (m, 3H)[f]
7*b*[n]	7.36 (s, 5H) 7.39 (s, 5H) 7.55 (s, 1H)	4.86 (d, 1H) 4.94 (d, 1H) J=4.5	5.18 (s, 2H) 5.27	2.95 (s, 3H)[m]	4.50 (m, 3H)[f]
9*a*[b]	—	—	—	3.04 (s, 3H)[m] 1.20 (m, 9H)	3.2–3.9 (m, 4H)[o] 4.7–4.9 (m, 2H)[d] 4.16 (q, 2H)[k] 4.2–4.6 (m, 4H)[p]
9*b*[b]	7.38 (s, 5H)	—	5.20 (s)	3.00 (s, 3H)[m] 1.20 (m, 6H)	3.55 (m, 4H)[o] 4.7–4.9 (m, 2H)[d] 4.2–4.6 (m, 4H)[p]
9*c*	—	—	—	3.10 (s, 3H)[m]	3.70 (m, 4H)[o] 5.1–4.9 (m, 2H)[d] 4.2–4.8 (m, 3H)[p] 9.86 (s, 1H, CO_2H)
10*a*	7.46 (s, 1H)	4.95 (dd) J_1=4.0 J_2=1.5	—	3.04 (s, 3H)[m] 1.23 (t, 3H) 1.36 (t, 3H) J=7.0	4.19 (q, 4H, J=7.0)[j] 4.40 (m, 3H)[f]
10*b*	7.68 (s, 1H) 7.51 (s, 5H)	4.94 (dd) J_1=4.2 J_2=1.25	5.25 (s)	2.95 (s, 3H)[m] 1.35 (t, 3H)[i] J=7.0	4.20 (q, 2H, J=7.0)[i] 4.50 (m, 3H)[f]
17[q]	7.28 (s, 5H) 7.25 (m, 5H) 6.60 (d)[u] J=16.0 6.13 (ddt)[v] J_1=16.0 J_2=6.2 J_3=1.5	4.85 (d) J=6.0	5.14 (s, 2H)	1.06 (t, 3H) 1.08 (t, 3H) J=7.0	3.52 (m, 4H)[o] 4.73 (m, 1H)[s] 4.61 (dd, 1H, J_1=8.0, J_2=6.0)[t]

TABLE 2 (*Continued*)

Compound	Aromatic and olefinic	N_3—CH—	ϕCH_2	CH_3	Other
17[r]	7.20 (s, 5H) 7.25 (m, 5H) 6 61 (d)[u] J=16.0 6.17 (ddt)[v] J_1=16.0 J_2=6.2 J_3=1.5	—	5.06 (s, 2H)	1.10 (t, 3H) 1.12 (t, 3H) J=7 0	3.52 (m, 4H)[o] 4.6–4.9 (m, 3H)[w]
18*b*	7.32 (s, 5H) 9.74 (d, J=4.5)[x] 9.63 (d, J=4.5)	4.96 (d, 1H) 4.79 (d, 1H) J=5.5	5.14 (s, 2H) 5.19	0.94 0.97 (t, 6H) 1.14 1.19 J=7.0	3.0–3.9 (m, 5H)[y] 4.78–4.80 (m, 2H)[z] 4.42 (m, 1H)[z]
27*a*[h]	7.38 (m, 5H) 6.77 (d, 1H)[u] J=16.0 6.16 (dd, 1H)[v] J_1=16.0 J_2=8.0	—	—	1.48 (s, 3H) 1.30 (t, 3H)[k] J=7.0	4.23 (q, 2H, J=7.0)[k] 4.27 (s, 1H)[aa] 4.0 (m, 4H)[bb] 4.80 (m, 2H)[cc]
27*b*[h]	7.40 (m, 5H) 6.74 (d, 1H)[u] J=16.0 6.20 (ddd, 1H)[v] J_1=16.0 J_2=8.0 J_3=2.5 7.38 (s, 5H)	—	5.22 (s)	1.48 (s, 3H)	4.35 (s, 1H)[aa] 3.85 (s, 4H)[bb] 4.95 (m, 2H)[cc]
27*e*[h]	7.39 (m, 5H) 6.73 (d, 1H)[u] J=16.0 6.21 (ddd, 1H)[v] J_1=16.0 J_2=8.0 J_3=2.5	—	—	1.47 (s, 3H)	4.36 (s, 1H)[aa] 3.95 (s, 4H)[bb] 4.90 (m, 2H)[cc]
27*d*[b]	7.20 (m, 15H) 6.67 (d, 1H)[u] J=16.0 6.18 (m, 1H)[v]	—	5.20 (2H)	—	3.85 (m, 4H)[bb] 2.10 (m, 2H) 2.68 (m, 2H)[dd] 4.7–5.1 (m, 3H)[cc]
27*c*[b]	7.3 (m, 15H) 6.62 (d, 1H)[u] J=16.0 6.15 (m, 1H)[v]	—	4.98 (s, 2H) 5.13 (s, 2H)	—	4.36 (s), 4.54 (s)[aa] 4.75 (m, 2H)[cc] 2.9–3.9 (m, 6H)[ff]
28*a*[h]	7.35 (s, 5H)	4.95 (d) J=6.0	5.28 (d)[gg] 5.07 (d) J=12.0	1.46 (s, 3H)	3.80 (m, 4H)[bb] 4.73 (s, 1H)[aa] 4.60 (dd, 1H, J_1=6.0, J_2=4.5)[hh] 9.55 (d, 1H)[x]
28*b*[b]	7.16 (s, 5H) 7.28 (s, 5H)	4.84 (d) J=5.5 4.88 (d) J=5.0	5.10 (s) 5.23 (d)[gg] J=9.5 5.01 (d)[gg] J=9.5	—	2.8–3.9 (m, 6H)[ff] 4.42 (dd, J_1=4.0, J_2=5.0)[hh] 4.64 (dd, J_1=4.0, J_2=5.5)[hh] 4.77 (s, 1H)[aa] 9.67 (d, J=4.0) 9.77 (d, J=4.0)[x]
28*c*[b]	7.17 (m, 5H) 7.34 (s, 5H)	4.90 (d) J=4.0 4.89 (d) J=4.0	5.17 (m)	—	3.82 (m, 4H)[bb] 2.64 (m, 2H) 2.0 (m, 2H)[dd] 4.83 (s) 4.87 (s)[aa] 4.3–4.8 (m, 1H)[hh] 9.53 (d, J=3.0) 9.63 (d, J=3.0)[x]

TABLE 2 (*Concluded*)

Compound	Aromatic and olefinic	N_3—CH—	ϕCH_2	CH_3	Other
29*a*[b]	7.32 (s, 5H)	4.66 (d) $J=5.0$ 4.67 (d) $J=5.0$	5.19 (s) 5.35 (d)[gg] $J=12.0$ 5.08 (d)[gg] $J=12.0$	1.35 (s) 1.42 (s)	3.80 (m, 8H)[ii] 4.68 (s)[aa] 4.65 (s)[aa]
29*b*[b]	7.14 (s, 5H) 7.25 (s, 5H)	4.43 (d) $J=5.0$ 4.58 (d) $J=5.0$	2.87 (s) 3.04 (m) 5.08 (m)	—	4.69 (s) 4.72 (s)[aa] 4.0 (m, 3H)[f] 3.35 (m, 4H)[bb]
29*c*[b]	7.17 (m, 5H) 7.33 (s, 5H)	4.89 (d) $J=5.0$ 4.84 (d) $J=5.0$	5.18 (m)	—	4.62 (bs) 4.55 (bs)[aa] 3.84 (m, 5H)[ii] 2.70 (m, 2H) 2.0 (m, 2H)[dd]
30*a*[h]	7.34 (s, 5H)	4.85 (d) $J=5.0$	5.24 (d)[gg] $J=12.0$ 5.04 (d)[gg] $J=12.0$	2.99 (s, 3H)[m] 1.37 (s, 3H)	3.76 (m, 4H)[bb] 4.50 (s, 1H)[aa] 4.3–4.8 (m, 3H)[f]
30*b*[b]	7.15 (s, 5H) 7.26 (s, 5H)	—	5.10 (m) 2.90 (m)	2.91 (s, 3H) 2.94 (s, 3H)	3.50 (m, 4H)[bb] 4.1–4.9 (m, 5H)[jj]
30*c*	7.33 (s, 5H) 7.15 (m, 5H)	—	5.17 (m)	2.92 (s, 3H)	4.2–4.9 (m, 5H)[jj] 3.85 (m, 4H)[bb] 2.67 (m, 2H) 2.0 (m, 2H)[dd]
31*a*	7.30 (s, 5H)	4.84 (d) $J=5.0$	5.24 (s) 5.21 (s)	2.09 (s, 3H) 2.25 (d, $J=3$) 2.92 (s, 3H)[m]	4.25 (m, 3H)[f] 12.0 (s, 1H, enol)
31*b*	7.27 (s, 5H) 7.18 (m, 5H)	4.80 (d) $J=5.0$ 4.65 (d) $J=\sim 5.0$	5.13 (s) 5.24 (s) 3.63 (m)	2.72 (s, 3H)[m] 2.83 (s, 3H)[m]	3.8–4.5 (m, 3H)[f]
31*c*	7.33 (s, 5H) 7.20 (m, 5H)	4.84 (d) $J=5.0$ 4.70 (d) $J=5.0$	5.20 (m)	2.75 (s, 3H)[m] 2.87 (s, 3H)[m]	2.80 (m, 4H)[dd] 3.8–4.6 (m, 3H)[f]

[a]Recorded in $CDCl_3$ at 60 MHz unless otherwise noted. The chemical shifts are recorded in δ units and coupling constants in Hz. [b]A mixture of diastereoisomers. [c]Assigned to $CH(OCH_2—CH_3)_2$, CH_2OH, and the C_4 proton. [d]Assigned to N_3CH and $CH(OR)_2$. [e]Assigned to methyl group of acetate. [f]Assigned to —CH—CH_2—OR. [g]Assigned to $CO_2CH_2—CH_3$ and =CH—O—$CH_2—CH_3$. [h]For single isomer. [i]Assigned to =CH—$OCH_2—CH_3$. [j]Quadrupole broadening of all proton signals was observed. [k]Assigned to $CO_2CH_2—CH_3$. [l]Assigned to pyrrolidine protons. [m]Assigned to mesylate methyl protons. [n]Two geometrical isomers observed in the nmr. [o]Assigned to $CH(OCH_2CH_3)_2$. [p]Assigned to $CH—CO_2R$ and $CH—CH_2—OSO_2CH_3$. [q]Isomer *A*. [r]Isomer *B*. [s]Assigned to $CH(OR)_2$. [t]Assigned to CH—CH=CH—ϕ. [u]Assigned to ϕCH=CH—. [v]Assigned to ϕCH=CH—. [w]Assigned to CH—CH=$CH\phi$, N_3CH, and $CH(OR)_2$. [x]Assigned to —CHO. [y]Assigned to $CH(OCH_2CH_3)_2$ and $CH—CO_2R$. [z]Assigned to CHCHO and $CH(OR)_2$. [aa]Assigned to $CHCO_2R$. [bb]Assigned to $O—CH_2—CH_2—O$. [cc]Assigned to N_3CH and CH—CH=CH—ϕ. [dd]Assigned to $CH_2CH_2\phi$. [ee]Assigned to N_3CH, CH—C=, and $CH—CO_2R$. [ff]Assigned to $O—CH_2CH_2—O$ and $CH_2\phi$. [gg]Assigned to arms of AB quartet for CH_2—ϕ. [hh]Assigned to CH—CHO. [ii]Assigned to —O—$(CH_2)_2$—O, CH—CH_2—OH. [jj]Assigned to N_3CH, CH—CH_2—OR, $CHCO_2R$.

oxyacrylate chromophore in these systems. In contrast to these observations is the marked bathochromic shift (+23 mm) observed in **8***a* and **8***b* in comparison with **3**, **4**, and **10**.

While the nmr spectra of **8***a* and **8***b* in deuteriochloroform were not first order they provided confirmation of the structures. In **8***a* the C_7—H appears as a doublet J = 5.0 Hz confirming the *cis* stereochemistry of the protons on C_6 and C_7. In **8***b* the C_7—H was partially obscured by the signal of the benzylic protons. The $C_{1\alpha}$ protons in **8***a* and **8***b* appear at 4.63 and 4.58 δ respectively as complex multiplets (six lines). The protons at $C_{1\beta}$ and C_6 appear as sets of overlapping multiplets at ~3.9 and 3.8 δ respectively. In view of the complexity of the nmr spectrum of **8***a* in $CDCl_3$ the spectrum was recorded in $CDCl_3$–C_6D_6 (1:1) at 100 MHz which resulted in aromatic solvent induced shifts (ASIS) and enabled the assignment of each proton in the spectrum as well as an assignment of conformation to **8***a*.[9] The proton signals in the shifted spectrum were assigned on the basis of their coupling constants, spin decoupling experi-

[9]The use of ASIS for the configurational assignments to the isomeric penicillin and cephalosporin sulfoxides has been demonstrated (9).

TABLE 3. Nuclear magnetic resonance spectra of bicyclic β-lactams[a]

Compound	Aromatic	C_7—H	C_3—H	ϕ—CH_2	ϕOCH_2	CH_3	Other
2*b*	—	4.97 (dd) J=4.0 J=1.5	5.21 (s)	—	—	1.30 (t)[c] J=7.0	4.54 (s, 1H, C*H*—CO_2H) 9.70 (s, 1H, CO_2H) 3.4–4.3 (m, 5H)[b]
2*c*	—	4.86 (dd) J=4.0 J=7.0	5.17 (s)	—	—	1.25 (t)[c] J=7.0	4.60 (s, 1H, C*H*COCl) 3.3–4.1 (m, 5H)[b]
2*d*	7.25 (s, 5H)	4.72 (dd) J=4.0 J=1.0	4.99 (s)	5.17 (s)	—	1.23 (t)[c] J=7.0	4.38 (s, 1H, C*H*—CO_2Bz) 3.3–4.1 (m, 5H)[b]
8*a*	—	5.34 (d) J=5.0	7.37 (s)	—	—	1.30 (t) J=7.0	4.29 (q, 2H, OCH_2—CH_3, J=7.0) 4.63 (dt, 1H, J=7.5)[d] 3.94 (m, 1H), 3.82 (m, 1H)[e]
8*b*	7.37 (s, 5H)	5.25 (d) J=5.0	7.37[f]	5.28 (s)	—	—	4.58 (dd, 1H, J_1=9, J_2=3)[d] 3.92 (m, 1H),[e] 3.78 (m, 1H)[e]
32*a*	7.3 (s, 5H)	5.05 (d) J=5.0	—	5.19 (s)	—	2.35 (s)	4.45 (dd, 1H, J_1=9.0, J_2=3.0)[d] 3.25–4.0 (m, 2H)[e]
32*b*	7.21 (m, 5H) 7.10 (s, 5H)	4.95 (d) J=5.0	—	5.18 (s) 4.09 (d)[g] J=14.0 3.75 (d)[g] J=14.0	—	—	4.38 (dd, 1H, J_1=9.0, J_2=3.0)[d] 3.35–3.95 (m, 2H)[e]
32*c*	7.05 (s, 5H) 7.15 (m, 5H)	4.88 (d) J=4.5	—	5.12 (s)	—	—	3.17–3.89 (m, 2H)[e] 4.30 (dd, 1H, J_1=9.5, J_2=3.5)[d] 2.75 (m, 4H, ϕCH_2—CH_2—)
33*a*	—	4.78 (d) J=5.0	7.22 (s)	—	—	1.29 (t) J=7.0	4.57 (dd, 1H, J_1=10, J_2=3.0)[d] 4.22 (q, 2H, OCH_2CH_3, J=7.0) 3.50 (s, 2H, NH_2) 3.65–4.4 (m, 2H)[e]
33*b*	7.40 (m, 5H)	4.83 (d) J=5.0	~7.40	5.30 (s)	—	—	2.45 (s, 2H, NH_2) 4.60 (dd, 1H, J_1=11.0, J_2=3.0)[d] 3.6–4.4 (m, 2H)[e]
33*c*	7.40 (m, 5H)	4.68 (d) J=5.0	—	5.22 (s)	—	2.25 (s)	4.50 (dd, 1H, J_1=7.0, J_2=3.0)[d] 3.5–4.1 (m, 2H)[e] 1.50 (s, 2H, NH_2)
33*e*	7.35 (m, 5H) 7.17 (s, 5H)	4.58 (d) J=5.0	—	5.21 (s)	—	—	1.58 (bs, 2H, NH_2) 2.85 (m, 4H, CH_2CH_2ϕ) 3.3–4.1 (m, 2H)[e] 4.50 (dd, 1H, J=7.0, J=3.0)[d]

TABLE 3 (*Concluded*)

Compound	Aromatic	C_7—H	C_3—H	ϕ—CH_2	ϕOCH_2	CH_3	Other
34*a*	6.7–7.4 (m, 5H)	5.58 (dd) *J*=7.0 *J*=4.5	7.23 (s)	—	4.47 (s)	1.28 (t) *J*=7.0	7.77 (d, 1H, N*H*, *J*=7.0) 4.23 (q, 2H, OCH_2CH_3, *J*=7.0) 3.6–4.5 (m, 3H)[d,e]
34*b*	7.39 (s, 5H) 6.8–7.5 (m, 5H)	5.61 (dd) *J*=7.0 *J*=4.2	7.32 (s)	5.27 (s)	4.51 (s)	—	7.69 (d, 1H, N*H*, *J*=7.0) 3.6–4.5 (m, 3H)[d,e]
34*c*	7.30 (s, 5H) 6.7–7.6 (m, 5H)	5.44 (dd) *J*=6.5 *J*=4.5	—	5.18 (s)	4.45 (s)	2.25 (s)	3.6–4.3 (m, 3H)[d,e]
34*d*	7.18 (s, 5H) 7.26 (m, 5H) 6.7–7.5 (m, 6H)[h]	5.40 (dd) *J*=7.0 *J*=4.0	—	5.23 (s)	4.38 (s)	—	3.6–4.6 (m, 5H)
35*a*	6.7–7.5 (m, 6H)[j]	5.60 (m)	—	—	4.52 (s)	—	7.64 (d, 1H, N*H*, *J*=~7) 3.7–4.5 (m, 3*H*)[d,e]
35*c*[k]	6.9–7.5 (m, 5H)	5.60 (dd) *J*=9.0 *J*=5.0	—	—	4.25 (s)	2.16 (s)	8.85 (d, 1H, N*H*, *J*=9.0) 3.6–4.25 (m, 3H)[d,e]
35*d*[l]	7.25 (s, 5H) 6.7–7.5 (m, 6H)	5.46 (m)	—	—	4.50 (s)	—	9.0 (1H, CO_2H) 3.6–4.5 (m, 5H)[i]
35*e*	7.28 (s, 5H) 6.8–7.5 (m, 5H)	5.72 (dd) *J*=9.0 *J*=5.0	—	—	4.61 (s)	—	8.45 (d, 1H, N*H*, *J*=9.0) 3.6–4.6 (m, 3H)[d,e] 2.90 (m, 4H, CH_2CH_2ϕ)

[a]Recorded at 60 MHz in $CDCl_3$ with tetramethylsilane as internal reference. The chemical shifts are recorded in δ values and coupling constants in Hz. [b]Assigned to —CO_2-CH_2CH_3, and the protons at C_6 and C_1. [c]Assigned to $CO_2CH_2CH_3$. [d]Assigned to C_1-Hα proton, see text for discussion. [e]Assigned to C_1-Hβ proton and C_6-H, see text for discussion. [f]Obscured by aromatic signal. [g]Arms of AB quartet. [h]CON*H* appears obscured by aromatic resonance. [i]The benzylic protons, the protons at C_1 and the proton at C_6 appear as a complex multiplet. [j]The C_3-proton is obscured by the aromatic signals. [k]Recorded in DMSO-d_6. [l]Recorded in $CDCl_3$, $(CD_3)_2C{=}O$.

TABLE 4. Infrared spectra, uv spectra, and elemental analyses

Compound	Infrared spectrum[a]	Ultraviolet spectrum[b]		Analysis (%)					
				Calculated			Found		
		λ_{max}	ε	C	H	N	C	H	N
1*b*	3460. 2110, 1770, 1745			55.09	6.17	14.28	55.39	6.01	14.43
2*b*	3420, 2120, 1775, 1745			42.19	4.72	21.87	42.18	4.83	22.01
2*c*	2110, 1780, 1750, 1630(w)								
2*d*	2110, 1780, 1755			55.49	5.24	16.18	55.81	5.36	16.40
3*a*	2080, 1775, 1765, 1745, 1710, 1640	245	10730	47.85	5.56	17.17	47.67	5.55	17.23
3*b*	2110, 1780, 1745, 1715, 1645			55.68	5.19	14.43	55.85	5.25	14.16
4*a*	3300, 2080, 1770, 1710, 1645	245	10270	46.48	5.67	19.71	46.23	5.76	19.77
4*b*	3500, 2110, 1770 1710, 1640	245	12200	55.49	5.24	16.18	55.21	5.15	15.96
5*a*	3310, 2120, 1765, 1660, 1620	286	25200	50.48	6.19	22.64	50.64	6.43	22.91
5*b*	3580, 3360, 2110, 1770, 1665, 1620	284	26400	58.21	5.70	18.86	58.23	5.72	19.10
6*a*	2110, 1770, 1685, 1630, 1615	285	29600	43.40	5.46	18.07	43.32	5.39	18.13
6*b*	2120, 1780, 1700, 1640, 1620	282	33000	50.77	5.16	15.58	50.66	5.20	15.65
7*a*	2110, 1775, 1710, 1680, 1630	235	8400	35.92	4.22	16.75	36.05	4.17	16.60
7*b*	2110, 1780, 1710, 1680, 1625	237	9500	43.95	4.30	13.67	43.71	4.24	13.47[c]
8*a*	2110, 1790, 1715, 1625	268	6800	45.38	4.23	23.62	45.13	4.18	23.73
8*b*	2100, 1790, 1715, 1622	268	6700	55.99	4.03	18.66	55.70	4.01	18.72
9*a*	2100, 1780, 1745								
9*b*	2110, 1775, 1745								
10*a*	2100, 1780, 1715, 1645	243	10500	39.77	5.00	15.46	39.72	4.90	15.63
10*b*	2105, 1780, 1715, 1645	244	12300						
11	2120, 1780, 1715, 1630	232	7700	51.38	4.62	17.12	51.16	4.46	17.22[e]
17	2100, 1770, 1745			64.64	6.08	12.06	64.42	6.09	11.96
18	2120, 1780, 1750								
20	2110, 1770, 1730								
22*c*	3550, 3200, 1745, 1695								
22*d*	3550, 3200, 1740, 1715, 1600								
23*b*	3550, 3260, 1740			58.86	5.70	5.28	58.97	5.68	5.12
23*c*	3560, 3240, 1745								
23*d*	3550, 3230, 1740								
25*a*				42.58	7.15	6.21	42.40	7.24	6.37
25*b*				54.26	6.31	4.87	53.96	6.19	4.60
25*c*				62.72	6.08	3.85	62.83	6.14	3.84
27*a*	2100, 1770, 1740[d]			59.06	5.94	14.50	59.08	5.73	14.58
27*b*	2100, 1760, 1735[g]			64.27	5.39	12.49	64.13	5.36	12.48
27*c*	2120, 1770, 1745								
27*d*	2120, 1765, 1745								
27*e*	2108, 1767, 1750[f]			56.98	5.06	15.64	57.06	5.13	15.78

TABLE 4 (*Concluded*)

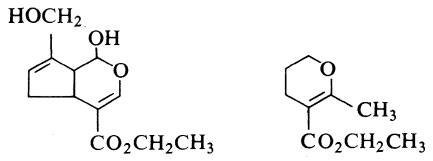
Compound	Infrared spectrum[a]	Ultraviolet spectrum[b]		Analysis (%)					
				Calculated			Found		
		λ_{max}	ε	C	H	N	C	H	N
28*a*	2120, 1775, 1730, (1740 sh)			54.54	4.84	14.96	54.75	4.87	14.89
28*b*	2110, 1780, 1770, 1745, 1735, 1695								
28*c*	2120, 1780, 1740, 1690								
29*a,c*	3500, 2120, 1765, 1770, 1740								
30*a*	2110, 1775, 1740			47.81	4.88	12.34	47.56	4.93	12.43
32*a*	2110, 1780, 1715, 1610[g]	273	10350	57.62	4.49	17.83	57.31	4.58	17.67
32*b*	2110, 1780, 1715, 1615								
32*c*				65.34	4.98	13.85	65.36	4.96	13.97
33*c*	3400, 1785, 1695, 1670, 1615[g]			62.49	5.59	9.72	62.54	5.51	9.65
34*a*	3410, 1785, 1710, 1695, 1625, 1520	268	11300	58.95	5.24	8.09	58.85	5.25	8.13
34*b*	3410, 3340, 1780, 1710, 1695, 1625, 1525	268	10500	64.70	4.94	6.86	64.62	4.83	6.94
34*c*	3270, 1782, 1710, 1660, 1610, 1530[g]	270, 275	11900, 11600	65.39	5.25	6.63	65.22	5.31	6.86
34*d*	3400, 1780, 1710, 1695, 1615, 1520								
34*e*	3410, 1780, 1710, 1695, 1600, 1520								
35*a*	3420, 3330, 1780, 1695, 1620, 1600, 1530	268	9550	55.06	4.62	8.56	55.19	4.70	9.00
35*b*	1770, 1685, 1630, 1590, 1530[g]	263	6200	49.31	3.82	7.67	49.35	3.94	8.01[e]
35*c*	3340, 1760, 1700, 1655, 1600, 1540[g]	269	10500	57.83	4.85	8.43	57.67	4.97	8.34
		274	9500						
35*d*	3400, 1780, 1695, 1610, 1600, 1520			64.70	4.94	6.86	64.78	4.87	6.80
35*e*	3400, 1778, 1695, 1600, 1520			65.39	5.25	6.63	65.28	5.36	6.56

[a]Recorded as a $CHCl_3$ solution unless otherwise noted. [b]Recorded in ethanol. [c]3/4 hydrate. [d]Liquid film. [e]1/2 hydrate. [f]Single isomer. [g]Nujol mull.

TABLE 5. Nuclear magnetic resonance data and ASIS ($\Delta = \delta(CDCl_3) - \delta(CDCl_3{-}C_6D_6(1:1))$)[a]

Compound	Solvent	H_7	H_6	$H_{1\alpha}$	$H_{1\beta}$	H_3	Other	
8*a*	$CDCl_3$[b]	5.34	3.82	4.63	3.94	7.37	4.29[c]	1.30[d]
	$CDCl_3{-}C_6D_6(1:1)$[b]	4.58[e]	3.08[f]	4.07[g]	3.51[h]	7.17[i]	4.18	1.17
	Δ	+0.76	+0.74	+0.56	+0.43	+0.20	+0.11	+0.13
8*b*	$CDCl_3$[j]	5.25	3.78	4.58	3.92	~7.37	5.28[k]	
	$CDCl_3{-}C_6D_6$[j]	4.45[e]	3.00[f]	3.92[g]	3.37[h]	—	4.96	
	Δ	+0.80	+0.78	+0.66	+0.55	—	+0.32	

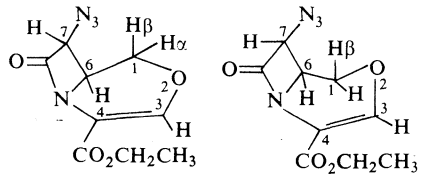
[a]Chemical shifts are reported in δ relative to internal TMS. [b]Recorded at 100 MHz. [c]CH_2—CH_3. [d]CH_2—CH_3. [e]Appears as doublet $J = 5.0$ Hz. [f]Appears as doublet of doublets $J_1 = 9.5$, $J_2 = 5.0$, $J_3 = 3.75$ Hz. [g]Appears as doublet of doublets $J_1 = 11.0$, $J_2 = 3.75$ Hz. [h]Appears as doublet of doublets of doublets $J_1 = 11.0$, $J_2 = 9.5$, $J_3 = 0.5$ Hz. [i]Appears as singlet. [j]Recorded at 60 MHz. [k]Assigned to CH_2—ϕ.



λ = 240
ε = 13 200

λ = 248
ε = 12 500

FIGURE 2



A *B*

FIGURE 3

ments, and the relative magnitudes of the ASIS (Fig. 3 and Table 5). From the data in Table 3, it is seen that $J_{H6H1\alpha} = 3.75$ Hz and $J_{H6H1\beta} = 9.5$ Hz. Of the two possible conformations for **8** *A* and *B* (Fig. 3) only conformer *A* would be expected to exhibit this splitting pattern for H_6. One would predict for conformer *B* that $J_{6H1\alpha} \simeq 3.20$ Hz and $J_{H6H1\beta} \simeq 0$ Hz.

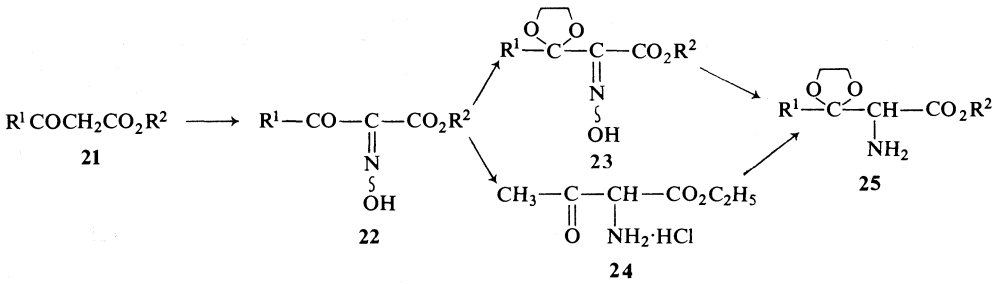
The assignment of the signals at ~4.6 to $H_{1\alpha}$ and ~3.9 to $H_{1\beta}$ is also in accord with the expectation that the axial proton $H_{1\beta}$ should appear at higher field than the equatorial proton $H_{1\alpha}$. These assignments are also supported by the relative magnitudes of the ASIS for $H_{1\alpha}$ and $H_{1\beta}$. One would expect that complexation of the solute with the C_6D_6 molecules would occur preferentially from the less hindered α face of the molecules and that the ASIS for protons on the α face would be greater than the ASIS for protons on the β-face. Our observations are fully in accord with this prediction, protons H_6 and H_7 show the greatest ASIS. The ASIS for $H_{1\alpha}$ is greater than the ASIS for $H_{1\beta}$ thus adding further evidence for the assignments.

With the experience gained in the synthesis of **8***a* and **8***b* the syntheses of the 3-methyl, 3-benzyl, and 3-phenethyl systems were attempted next.

The syntheses of the starting amines **25***a–d* for these systems were carried out as follows. Oximation of the β-keto esters **21***a–d* (Scheme 3) was achieved using the method of Adkins and Reeve (10) to yield the oximes **22***a–d* in good yields. Reduction of **23***a* with 10% Pd/C in ethanol in the presence of hydrochloric acid gave the amine hydrochloride **24** in 55% yield in accord with the results of Laver *et al.* (11). The amine hydrochloride **24** was readily converted to its ethylene ketal **25***a* in 70% yield. The presence of benzylic ester functions in **22***b–d* precluded the reduction of the oximes via Laver's method. Consequently, compounds **22***b–d* were converted to their ethylene ketals **23***a–c* in 94, 57, and 91% yields respectively. Reduction of **23***a–c* with aluminum amalgam in moist ether (12) gave compounds **25***b–d* in 71, 93, and 68% yields respectively.

Conversion of amines **25***a–d* to their Schiff bases **26***a–d* (Scheme 4) proceeded as before in quantitative yields. Treatment of the Schiff bases **26***a–d* with triethylamine and azidoacetyl chloride as before gave the *cis*-3-azido-4-styryl-*N*-substituted-2-azetidinones **27***a–d* in 98, 94, 100, and 100% crude yields[10] respectively. Saponification of **27***a* with sodium hydroxide in tetrahydrofuran gave the corresponding carboxylic acid **27***e* in 86% yield as a solid. Re-

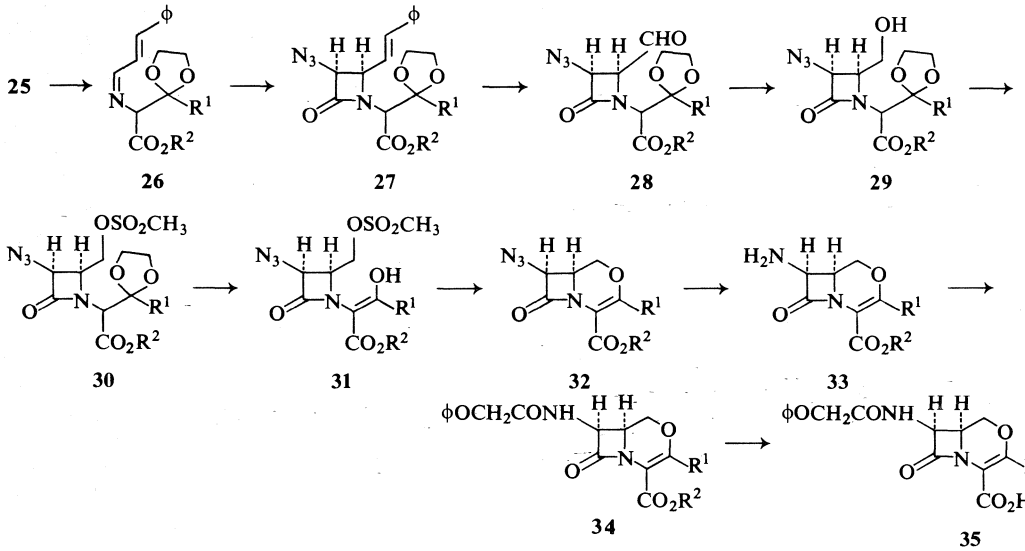
[10]The crude materials were generally of sufficient purity (as determined by nmr spectroscopy) to be used as such without further purification.



Compounds **21**, **22**, **25**
a $R^1 = Me$ $R^2 = Et$
b $R^1 = Me$ $R^2 = CH_2\phi$
c $R^1 = R^2 = CH_2\phi$
d $R^1 = (CH_2)_2\phi$ $R^2 = CH_2\phi$

Compound **23**
a $R^1 = CH_3$ $R^2 = CH_2\phi$
b $R^1 = CH_2\phi = R^2$
c $R^1 = CH_2CH_2\phi$ $R^2 = CH_2\phi$

SCHEME 3



Compounds **33–34**		Compounds **26–27**		Compound **35**	Compounds **28–32**	
R^1	R^2	R^1	R^2		R^1	R^2
a H	C_2H_5	*a* CH_3	CH_2CH_3	*a* $R^1 = H$	*a* CH_3	$CH_2\phi$
b H	$CH_2\phi$	*b* CH_3	$CH_2\phi$	*b* $R^1 = H$	*b* $CH_2\phi$	$CH_2\phi$
c CH_3	$CH_2\phi$	*c* $CH_2\phi$	$CH_2\phi$	*c* $R^1 = CH_3$	*c* $CH_2CH_2\phi$	$CH_2\phi$
d $CH_2\phi$	$CH_2\phi$	*d* $CH_2CH_2\phi$	$CH_2\phi$	*d* $R^1 = CH_2\phi$		
e $(CH_2)_2\phi$	$CH_2\phi$	*e* CH_3	H	*e* $R^1 = CH_2CH_2\phi$		

SCHEME 4

crystallization of **27***e* gave one of the diastereoisomeric acids.[11] Conversion of **27***e* to **27***b* (in 99% yield) was carried out using the triethylamine–benzylchloroformate method used earlier. Ozonolysis of **27***b* (single isomer) in methylene chloride at −78 °C followed by decomposition of the ozonide with dimethyl sulfide gave **28***a* as a crystalline solid in 69% yield. The yield of **28***a* (as a mixture of diastereomers) from **27***b* (isomer mixture) was 71%. Similarly, ozonolysis

[11]Compounds **27***a–d* were produced as mixtures of diastereoisomers epimeric about the carbon directly attached to the nitrogen of the β-lactam and the ester function.

TABLE 6. Biological activities[a]

Compound	*D. pneumoniae*	*S. aureus* Smith	*S. aureus* + 50% serum	*Sal. enteritidis*	*Pr. mirabilis*
2*e*	125	250	> 500	1000	1000
34*a*	> 500	250	> 250	> 500	> 500
35*a*	0.6	0.6	1.0	8	63
35*c*	0.5	0.5	2.0	8	16
35*d*	0.25	0.25	1	32	> 125
35*e*	0.03	0.06	4	8	> 125
36	1	0.5	4	63	125

[a]Expressed as MIC's (μg/ml) and determined by a 2-fold serial dilution assay in Difco nutrient broth by the method of Pursiano *et al.* (20).

of **27***c* and **27***d* gave the aldehydes **28***b* (95% crude yield) and **28***c* (45% purified yield) respectively.

The aldehydes **28***a–c* were reduced to the corresponding alcohols **29***a–c* using sodium borohydride, following which **29***a–c* were converted to their mesylates **30***a–c*. The yields of **30***a–c* from the aldehydes **28***a–c* were 80, 84, and 42% respectively. In the reduction of **28***a* to **29***a* some epimerization of the product was observed in that a mixture of mesylates was obtained epimeric about the ester position in the side chain.

Hydrolysis of **30***a* with 95% trifluoroacetic acid at 25 °C gave the enol **31***a* in greater than 90% yield. Compound **31***a* was converted to benzyl 7-β-azido-3-methyl-Δ^3-*O*-2-isocephem-4-carboxylate **32***a* in 80% yield using triethylamine in refluxing methylene chloride. Similarly, compounds **30***b* and **30***c* were hydrolyzed to the enols **31***b* and **31***c*. In these cases it proved necessary to use higher temperatures (50–55 °C) to effect hydrolysis. The enols were converted to benzyl-7-β-azido-3-benzyl-Δ^3-*O*-2-isocephem-4-carboxylate **32***b* (33%) and benzyl 7-β-azido-3-phenethyl-Δ^3-*O*-2-isocephem-4-carboxylate **32***c* (33%) respectively. The structures of compounds **32***a–c* were confirmed by their elemental analyses, and ir, nmr, and uv spectral characteristics (Tables 3 and 4).

With the appropriately substituted *O*-2-isocephems **8***a–b*, **32***a–c* on hand the conversion of these to their 7-β-(phenoxyacetamido)-Δ^3-*O*-2-isocephem-4-carboxylic acids **35** was examined.

Reduction of **8***a* and **8***b* with hydrogen on 10% Pd/C gave the amines **33***a* and **33***b*. The amines were converted to the amides **34***a* and **34***b* using triethylamine – phenoxyacetyl chloride in 56 and 29% yields respectively. The ir, uv, and nmr spectra of **34***a* and **34***b* confirmed the structural assignments.

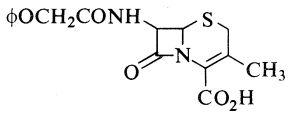
Reduction of **32***a* with hydrogen and PtO_2 in ethanol gave **33***c* which was coupled with phenoxyacetic acid using EEDQ (13) to give **34***c* in 65% yield. Compounds **32***b* and **32***c* were reduced to their amines **33***d* and **33***e* using triethylamine – hydrogen sulfide (1) and these were in turn converted to their amides **34***d* and **34***e* using phenoxyacetic acid – EEDQ.

Hydrogenolysis of the benzyl esters **34***b–e* (see Experimental) gave the desired acids **35***a*, **35***c–e* in 70, 84, 20, and 92% yields respectively. Compound **35***a* was also converted to its potassium salt **35***b* in 45% yield (14). The structures of **35***a–e* assigned on the basis of their elemental analyses, ir, uv, and nmr spectral characteristics.

Compounds **35***a*, **35***c*, **35***d*, and **35***e* all exhibited high antibacterial activity. The activities are listed in Table 6 along with those of **2***e*, **34***a*, and the phenoxyacetyl derivative of 7-aminodesacetyl cephalosporanic acid **36** (Fig. 4) for comparison purposes. The activities of these compounds are comparable with or better than those of the comparably substituted natural product (compare **35***c* and **36**).

It should also be noted that **35***a–e* are racemic materials whereas **36** is a single enantiomer. It has been shown (15) that all of the activity in the natural series resides in a single enantiomer, thus the MIC's reported for **35***a–e* are probably too high by a factor of two. A full discussion of structure–activity relationships in this series will be reserved to a later publication.

The obvious modifications of the syntheses reported herein to the syntheses of compounds of general formula **37** have been made and will be reported in subsequent papers of this series (Fig. 5).



36

FIGURE 4

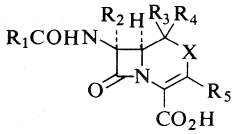


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FIGURE 5

Experimental

The infrared spectra were recorded on a Unicam SP-200G grating ir spectrophotometer. The uv spectra were recorded on a Unicam SP-800 uv spectrophotometer. The nmr spectra were determined on a Varian A60-A spectrometer using tetramethylsilane as an internal standard. The 100 MHz spectra and spin-decoupling experiments were performed by Dr. Perlin of McGill University whose assistance we gratefully acknowledge. Melting points are uncorrected except where noted and were determined on a Gallenkamp melting point apparatus. The analyses were performed by Micro-Tech Laboratories, Skokie, Illinois.

7-β-Azido-3-β-ethoxy-O-2-isocepham-4-α-carboxylic Acid 2b

To a solution of 12.2 g (43 mmol) of compound **2***a* in 180 ml ethanol was added 175 ml 1% sodium hydroxide over a period of 10 min at < 25 °C. The solution was stirred an additional 20 min. The ethanol was evaporated at reduced pressure and the alkaline solution was extracted with ether (2 × 100 ml). The organic layer was discarded and the aqueous solution acidified to p*H* 3–4 with 10% hydrochloric acid. The solution was extracted with chloroform (2 × 100 ml) and the organic layer washed with water (50 ml), brine (50 ml), and dried over $MgSO_4$. Evaporation gave 7.25 g (66%) of acid. Trituration with ether and filtration gave pure acid, mp 114–115 °C.

Benzyl 7-β-Azido-3-β-ethoxy-O-2-isocepham-4-α-carboxylate 2d

To a solution of 6.25 g (25.6 mmol) of compound **2***b* in 100 ml of ether was added 5.35 g (25.6 mmol) phosphorous pentachloride. The suspension was refluxed for 15 min after which the clear solution was decanted and evaporated to dryness. The residual oil was taken up in 50 ml benzene and evaporated to dryness at reduced pressure. This procedure was repeated three times to remove phosphorous oxychloride. The residual oil was then pumped in high vacuum (0.05 torr) at 30 °C for 1 h.

The acid chloride was taken up in 20 ml dry methylene chloride and was added to a mixture of 2.7 g (26 mmol) benzyl alcohol and 3.2 g triethylamine in 50 ml dry methylene chloride at 25 °C over a period of 10 min. The solution was stirred for 1 h, washed with water (2 × 20 ml) and brine, and filtered through 20 g of Florisil. The eluent was treated with Norite, dried over $MgSO_4$, filtered, and evaporated to give 7.4 g (83.5%) of crude benzyl ester **2***d*. Trituration with benzene – petroleum ether caused crystallization. The solid was recrystallized from benzene – petroleum ether to yield pure **2***d*, mp 79–79.5 °C.

cis-N-(α-Carboethoxy-β-ethoxyvinyl)-3-azido-4-acetoxymethyl-2-azetidinone 3a

From 1a

A mixture of 4.8 g (14.5 mmol) compound **1***a*, 2.1 g (15.1 mmol) zinc chloride, and 15 ml acetic anhydride was stirred at 25 °C for 18 h. The solvent was removed at reduced pressure and the residue taken up in $CHCl_3$ (100 ml) – H_2O (20 ml), dried over Na_2SO_4, filtered, and the filtrate passed through 50 g Al_2O_3 (activity III) column. Elution with $CHCl_3$ gave 2.5 g pure acetate. The other fractions were rechromatographed to give an additional 1.1 g (75% total yield).

From 2a

Treatment of 1.0 g (3.5 mmol) of **2***a* with 1.1 g zinc chloride in 12 ml of acetic anhydride as above gave **3***a* in 85% yield. The compound was identical in all respects with that obtained from **1***a*.

cis-N-(α-Carbobenzoxy-β-ethoxyvinyl)-3-azido-4-acetoxymethyl-2-azetidinone 3b

From 1b

A mixture of 3.2 g (8.17 mmol) compound **1***b*, 11 ml acetic anhydride, and 1.12 g (8.2 mmol) zinc chloride was stirred 18 h at 25 °C. The reaction mixture was evaporated at reduced pressure and the residue taken up in 40 ml methylene chloride – 20 ml water. The organic phase was separated, washed with water and brine, dried over $MgSO_4$, filtered, and the filtrate evaporated to yield 3.0 g of an oil. The oil was chromatographed on 50 g silica gel (deactivated, 5% water) by dry column technique using chloroform as an eluent. Evaporation of the eluent gave 1.3 g (41%) of pure **3***b* as an oil.

From 2d

Treatment of 104 mg (0.3 mmol) of **2***d* with 82 mg zinc chloride in 3 ml acetic anhydride as in the preparation of **3***a* from **2***a* gave 110 mg pure **3***b* (94%).

cis-N-(α-Carboethoxy-β-ethoxyvinyl)-3-azido-4-hydroxymethyl-2-azetidinone 4a

From 3a

A solution of 12.18 g (34.8 mmol) of compound **3***a* in 40 ml MeOH and 40 ml 10% HCl was boiled at reflux for 1 h. The methanol was distilled at reduced pressure and the aqueous residue extracted with $CHCl_3$ (3 × 50 ml). The extracts were washed with water and brine, dried over $MgSO_4$, filtered, and the filtrate was evaporated to yield 9.33 g (94.5%) pure alcohol.

From 2a

To a solution of 90 mg (0.316 mmol) of **2***a* in 5 ml of methylene chloride was added 3 drops (~ 20 mg) titanium tetrachloride at 25 °C. The solution was let stand for 24 h at 25 °C and filtered through 1.5 g of alumina (activity III). There was obtained 23.7 mg of pure **4***a* (26%) identical in all respects with that obtained from **3***a*.

cis-N-(α-Carbobenzoxy-β-ethoxyvinyl)-3-azido-4-hydroxymethyl-2-azetidinone ***4b***

Hydrolysis of 5.95 g (15.35 mmol) of **3***b* according to the procedure described above for the conversion of **3***a* to **4***a* gave 4.6 g (87%) of **4***b* as an oil.

cis-N-(α-Carboethoxy-β-N-pyrrolidinovinyl)-3-azido-4-hydroxymethyl-2-azetidinone ***5a***

From ***4a***

A solution of 224 mg (0.785 mmol) of **4***a*, 141 mg (2 mmol) pyrrolidine, and 200 mg acetic acid in 15 ml dry benzene was boiled at reflux for 22 h. The solution was washed with 5 ml of saturated sodium bicarbonate solution, washed with water (25 ml), and dried over sodium sulfate. The solution was filtered and evaporated to dryness to give an oil which crystallized on standing. The oil was triturated with ether and filtered to yield 175 mg (72%) pure **5***a*, mp 147–148 °C after recrystallization from benzene.

From ***1a***

Treatment of 2.78 g (8.45 mmol) of **1***a* with 2.5 g pyrrolidine and 2.5 g acetic acid in 50 ml benzene as described above gave 137 g (50%) of pure **5***a* identical in all respects to the sample prepared from **4***a*.

cis-N-(α-Carbobenzoxy-β-N-pyrrolidinovinyl)-3-azido-4-hydroxymethyl-2-azetidinone ***5b***

From ***4b***

In a manner analogous to the preparation of **5***a* from **4***a*, compound **5***b* was prepared from **4***b* in 71% yield; mp 111.5–112.5 °C.

cis-N-(α-Carboethoxy-β-N-pyrrolidinovinyl)-3-azido-4-mesyloxymethyl-2-azetidinone ***6a***

From ***5a***

To a solution of 618 mg (2 mmol) of **5***a* and 404 mg (4 mmol) triethylamine in 15 ml methylene chloride at 0 °C was added 456 mg (4 mmol) methane sulfonyl chloride in 5 ml methylene chloride over 15 min. The solution was allowed to come to 25 °C over 1 h and washed with water (10 ml) and brine (2 × 10 ml). The solution was dried over sodium sulfate and filtered through 4.0 g of alumina (activity III) to give 570 mg of pure **6***a*, mp 138–139 °C.

From ***10a***

Treatment of 181 mg (0.5 mmol) of **10***a* with pyrridineacetic acid according to the procedure given for the preparation of **5***a* gave 125 mg (63%) of **6***a* identical with the sample prepared from **5***a*.

cis-N-(α-Carbobenzoxy-β-N-pyrrolidinovinyl)-3-azido-4-mesyloxymethyl-2-azetidinone ***6b***

A solution of 2.44 g (6.6 mmol) compound **5***b*, 3.9 g (33 mmol) methane sulfonyl chloride, and 3.3 g (33 mmol) triethylamine in 50 ml methylene chloride was stirred at ambient (25 °C) temperature for 74 h. The reaction mixture was washed with water (2 × 10 ml) and brine and dried over Na_2SO_4. The drying agent was filtered and the filtrate evaporated to dryness. The oil was filtered through a silica gel column (deactivated, 15% water) (16 g) with chloroform to give 2.6 g (90%) of crystalline mesylate, mp 116–117 °C.

cis-N-(α-Carboethoxy-β-hydroxyvinyl)-3-azido-4-mesyloxymethyl-2-azetidinone ***7a***

From ***6a***

A solution of 1.27 g (33 mmol) of **6***a* in 20 ml acetone – 5 ml 10% hydrochloric acid was refluxed 20 min and diluted to 100 ml with water. The solution was extracted into methylene chloride (5 × 20 ml). The methylene chloride extracts were extracted with 10% sodium carbonate. The aqueous extracts were acidified with hydrochloric acid and the solution extracted into methylene chloride and dried over sodium sulfate, yielding 0.98 g of pure enol **7***a* as an oil on evaporation (89%).

From ***9a***

A solution of 207 mg (0.51 mmol) of **9***a* in 1 ml of 95% trifluoroacetic acid was warmed to 50 °C for 1 h. The trifluoroacetic acid was removed at reduced pressure and the residue partitioned between methylene chloride – water (50 ml:20 ml). The organic layer was extracted with sodium carbonate as above. Work-up yielded 95 mg (58%) of pure **7***a* identical with that obtained from **6***a*.

cis-N-(α-Carbobenzoxy-β-hydroxyvinyl)-3-azido-4-mesyloxymethyl-2-azetidinone ***7b***

From ***6b***

A solution of 2.28 g (5.26 mmol) compound **6***b* in 25 ml of acetone and 25 ml 10% hydrochloric acid was refluxed 15 min. The acetone was evaporated at reduced pressure and the residue extracted with chloroform (3 × 30 ml). The chloroform layer was washed with water and evaporated to dryness. The residual oil was dissolved in ether (20 ml) and the solution extracted with saturated sodium bicarbonate solution (4 × 8 ml). The bicarbonate was acidified to p*H* 4 with 10% HCl and reextracted with chloroform (3 × 50 ml). The chloroform was washed with water and brine and dried over $MgSO_4$. The drying agent was filtered and the filtrate evaporated to give 1.62 g (81%) of compound **7***b*.

From ***9b***

A solution of 673 mg (1.43 mmol) of **9***b* in 4 ml 95% trifluoroacetic acid was warmed to 50 °C for 25 min. After the work-up (see **9***a* → **7***a*) there was obtained 513 mg (91%) of **7***b* identical with the sample prepared from **6***b*.

Ethyl 7-β-Azido-Δ³-O-2-isocephem-4-carboxylate ***8a***

Method A

To a suspension of 0.0665 g sodium hydride (1.5 mmol) (55% mineral oil dispersion washed three times with petroleum ether) in 2 ml dimethyl sulfoxide (DMSO) was added 500 mg (1.5 mmol) of **7***a* in 4 ml DMSO. The solution was stirred 1 h at 25 °C and then diluted to 30 ml with brine containing 2 ml 10% hydrochloric acid. The aqueous solution was extracted with methylene chloride (5 × 25 ml). The extracts were washed with water (3 × 25 ml) and brine (1 × 25 ml) and dried over sodium sulfate. Evaporation of the extracts gave 327 mg (91.5%) of **8***a*, mp 137–138 °C after recrystallization from benzene.

Method B

A solution of 268 mg (0.8 mmol) of **7***a* and 105 mg triethylamine in 10 ml of chloroform was refluxed for 50 min. The solution was cooled and washed with water,

10% hydrochloric acid, water, and brine. The solution was dried over sodium sulfate, filtered, and evaporated to yield 90 mg (47.5%) of pure **8***a* after crystallization.

From ***10a***

To a solution of 1.83 g (5.00 mmol) of compound **10***a* in 20 ml of tetrahydrofuran was added 20.0 ml of 0.25 *M* sodium hydroxide solution dropwise over 10 min. The resulting solution was concentrated to 20 ml on the rotary evaporator at 30 °C. The concentrate was washed with chloroform (3 × 10 ml). The aqueous layer was evaporated to dryness under high vacuum. The resulting residue was stirred with 7.5 ml of dimethyl sulfoxide for 1 h. Water (30 ml) and saturated sodium chloride (40 ml) followed by a few drops of 10% hydrochloric acid were added to the dimethyl sulfoxide solution. The resulting mixture was extracted with chloroform (3 × 40 ml) and the combined chloroform layers were washed with water and evaporated to give the crude product. Pure compound **8***a* was obtained by recrystallization from benzene–cyclohexane, then chloroform, as colorless crystals, 0.39 g (33% yield).

Benzyl 7-β-Azido-Δ³-O-2-isocephem-4-carboxylate ***8b***

Method A

To a suspension of 198 mg (4.70 mmol) sodium hydride (55% mineral oil dispersion, washed 3× with petroleum ether) in 5 ml dry DMSO was added a solution of 1.62 g (4.27 mmol) compound **7***b* in 5 ml DMSO over 5 min with stirring at 25 °C. After 1 h, the reaction mixture was poured into 50 ml 1% HCl – ice water and was extracted with chloroform (4 × 30 ml). The organic layer was washed with water (3 × 10 ml) and brine and dried over $MgSO_4$. Filtration and evaporation of the filtrate gave 1.2 g of an oil. Trituration with ether caused crystallization; 545 mg (42%) of **8***b*; mp 110 °C.

Method B

A solution of 370 mg (0.935 mmol) of **7***b* and 100 mg triethylamine in 10 ml methylene chloride was refluxed for 4 h. Work-up as in method *B* for **8***a* gave 200 mg (71.5%) of pure **8***b*.

From ***10b***

To a solution of 260 mg (0.64 mmol) of compound in 2.5 ml of tetrahydrofuran was added 2.55 ml of 0.25 *M* sodium hydroxide solution dropwise over 10 min. The solution was concentrated to 2 ml on the rotary evaporator. The concentrate was washed with chloroform (2 × 2 ml), then evaporated to dryness under high vacuum. The residue was stirred with 1 ml of dimethyl sulfoxide for 1 h. Water (1 ml), saturated sodium chloride (1 ml), and one drop of 10% hydrochloric acid were added. The mixture was extracted with chloroform (3 × 2 ml) and the combined chloroform layers were washed with water and evaporated to give crude compound as a yellow solid, 103 mg (54% yield). The nmr spectrum indicated the product to be only 75% pure (*i.e.* a true yield of 40%).

cis-N-(α-Carboethoxy-β,β-diethoxyethyl)-3-azido-4-mesyloxymethyl-2-azetidinone ***9a***

Treatment of 102.0 g (0.308 mol) of **1***a* with 34.3 g (0.34 mol) triethylamine and 39.4 g (0.34 mol) methane sulfonyl chloride according to procedure given for the preparation of **10***a* from **4***a* gave 108.4 g (86%) of **9***a* as an oil.

cis-N-(α-Carbobenzoxy-β,β-diethoxyethyl)-3-azido-4-mesyloxymethyl-2-azetidinone ***9b***

From ***1b***

Treatment of 12.2 g (31.2 mmol) of **1***b* with 3.42 g (34 mmol) triethylamine and 2.90 g (34 mmol) methanesulfonyl chloride as in the above experiment yielded 12.3 g (83.5%) of **9***b* as an oil.

From ***9a***

To a solution of 1.065 g (2.61 mmol) of **9***a* in 25 ml tetrahydrofuran was added 10 ml of 0.25 *N* sodium hydroxide over 5 min. The solution was stirred 30 min at 25 °C following which 3 ml 10% hydrochloric acid was added and the solution diluted to 100 ml with brine. The solution was extracted into ether (4 × 50 ml). The ethereal extracts were extracted with sodium carbonate solution (10%). The ethereal layer was dried over sodium sulfate and evaporated to yield an oil which crystallized on trituration with ether (5 ml). Filtration gave 283 mg (26.6%) pure **10***a*. The alkaline extracts were acidified with 10% hydrochloric acid and extracted into methylene chloride (5 × 20 ml). The extracts were dried over sodium sulfate and evaporated to yield 542 mg (55%) of the desired acid **9***c*. Compound **9***c* was characterized spectroscopically and used without further purification in the next step. The yields of **10***a* from this reaction ranged from10–30% while the yields of **9***c* ranged from 45–70%.

To a solution of 2.64 (7 mmol) of **9***c* and 2.0 g (20 mmol) triethylamine in 30 ml methylene chloride at 0–5 °C was added 2.0 g (11.7 mmol) of benzyl chloroformate. As the solution was stirred gas evolution was observed. After 15 min at 0–5 °C, the solution was refluxed for 30 min. The solution was washed with water (50 ml), 10% hydrochloric acid (10 ml), and brine (50 ml), dried over sodium sulfate, and evaporated to yield 3.07 g of an oil which yielded 2.76 g (84%) of **9***b* on chromatography over silica gel (deactivated with 15% water) using chloroform as eluent.

cis-N-(α-Carboethoxy-β-ethoxyvinyl)-3-azido-4-mesyloxymethyl-2-azetidinone ***10a***

From ***4a***

To a solution of 5.68 g (20 mmol) of **4***a* and 3.0 ml (21 mmol) triethylamine in 50 ml methylene chloride at 0–5 °C was added 2.28 g (20 mmol) methane sulfonyl chloride. The solution was stirred for 30 min at 25 °C after which it was washed with water (2 × 25 ml), 10% hydrochloric acid (2 × 10 ml), and brine (1 × 50 ml), dried over sodium sulfate, and concentrated to give an oil. The oil was triturated with 50 ml ether and the crystalline mesylate isolated by filtration, 4.37 g (60.2%). The mother liquors were chromatographed on a column of 50 g silica gel (deactivated with 15% water). An additional 380 mg (5%) of pure **10***a* was isolated from the latter fractions from ether elution; mp 101–102.5 °C (dec.).

From ***9a***

(A) A mixture of 4.9 g (12 mmol) of compound **9***a*, 10 ml of acetic anhydride, 10 ml of acetic acid, and 1.75 g (13 mmol) of zinc chloride was stirred at 25 °C for 17 h, then evaporated to a tar. A methylene chloride solution of the tar (50 ml) was washed with equal volumes of

water, 5% sodium bicarbonate, and dilute sodium chloride. The methylene chloride solution was filtered through 15 g of alumina (grade III) and evaporated to give an oil. Trituration of the oil with ether gave pure compound **10***a* as a colorless powder, 1.88 g (45% yield).

(B) Treatment of 1.90 g (4.65 mmol) of **9***a* with 2.0 g triethyloxonium fluoroborate in 20 ml methylene chloride for 18 h at 25 °C gave 0.75 g (46.5%) of **10***a*.

*cis-N-(α-Carbobenzoxy-β-ethoxyvinyl)-3-azido-4-mesyloxymethyl-2-azetidinone **10b***

Treatment of 15.2 g (43.8 mmol) of **4***b* with triethylamine and methanesulfonyl chloride as in the procedure for the preparation of **10***a* from **4***a* yielded upon work-up 13.0 g (70.4%) of pure **10***b*, as an oil.

*cis-N-(α-Carbobenzoxy-β-hydroxyvinyl)-3-azido-4-hydroxymethyl-2-azetidinone **11***

A solution of 3.71 g (10 mmol) compound **5***b* in 50 ml of acetone and 25 ml of 10% HCl was boiled at reflux for 30 min. The acetone was removed at reduced pressure and the oily aqueous residue extracted with ether (3 × 35 ml) and methylene chloride (3 × 25 ml). The organic layer was extracted with saturated aqueous $NaHCO_3$ (5 × 20 ml). The aqueous extracts were acidified with 10% HCl and saturated with NaCl. The aqueous layer was extracted thoroughly with ether (3 × 25 ml) then CH_2Cl_2 (3 × 25 ml). The extracts were dried over Na_2SO_4 and concentrated to yield 2.40 g of enol alcohol **11**, 75.5%, as an oil.

*Benzyl α-Amino-β,β-diethoxypropionate **15***

A solution of 62.0 g (0.325 mol) of benzyl nitroacetate **12**, 76.6 g (0.52 mol) triethylorthoformate and 65.0 g (0.64 mol) acetic anhydride was heated to 85–90 °C for 18 h. Following this the excess triethylorthoformate, acetic anhydride, and ethyl acetate were removed by evaporation of the solution at reduced pressure (50 °C/1 torr). There was obtained 85.2 g of an oil the nmr spectrum of which indicated that a mixture of the desired acetal **14** (40%) and the elimination product of **14** (**13**, 60% as *Z* and *E* isomers) had been obtained. To the oil was added 25 ml of ethanol followed by 1.0 g sodium ethoxide. A mildly exothermic reaction ensued. After 15 min the excess ethanol was removed by evaporation at reduced pressure (30 °C/1 torr). There was obtained 95.0 g (100%) of the desired acetal **14** which was used as such in the reduction step.

To 37.5 g aluminum amalgam (19) covered by 450 ml moist ether was added 95.0 g (0.325 mmol) of **14** in 250 ml ether. Initially 50% was added over 10 min. After 10–15 min a violent exothermic reaction ensued which was controlled by ice-bath cooling. When the reaction had subsided the remaining acetal was added over 30 min. After 1 h the reaction had subsided sufficiently that heating became necessary so as to maintain a gentle reflux. The solution was refluxed an additional 2 h then allowed to stand 24 h at 25 °C. The gelatinous aluminum hydroxide was removed by filtration. The filtrate was dried over sodium sulfate and evaporated to give 53.0 g of an oil. The oil was taken up in 1 litre of ether and extracted with 5% hydrochloric acid (5 × 150 ml). The extracts were neutralized with sodium carbonate and the resultant solution extracted with ether. The extracts were dried over sodium sulfate and evaporated to yield 35.0 g (42.5%) of benzyl α-amino-β,β-diethoxypropionate **15**. Compound **15** was characterized by nmr spectroscopy and used as such in the preparation of **17**.

*cis-N-(α-Carbobenzoxy-β,β-diethoxyethyl)-3-azido-4-styryl-2-azetidinone **17***

*From **15***

The cinnamylidene Schiff base **16** of **15** was prepared from 35.0 g (0.13 mol) of **15** and 17.3 g (0.13 mol) cinnamaldehyde by the previously described method (1) in quantitative yield. Treatment of 58.0 g (0.13 mol) of **17** with 13.3 g (0.13 mol) triethylamine followed by 15.7 g (0.13 mol) of azidoacetyl chloride (1) gave 54.14 g (89%) of the desired β-lactam **17** as an oil. A small sample (0.90 g) of the oil was chromatographed on 50 g of silica gel (deactivated with 15% water) using chloroform as eluent. The two isomers of **17** were isolated.

*From **19***

To a solution of 15.5 g (38.6 mmol) of **19** (1) in 300 ml ethanol was added 160 ml of 0.25 *N* sodium hydroxide over 20 min at 25 °C. The solution was stirred an additional 40 min. The solution was acidified to p*H* 3 with 10% hydrochloric acid and extracted into chloroform (3 × 50 ml). The extracts were evaporated to dryness and the resultant oil taken up into 50 ml ether. The ethereal solution was washed once with water and then extracted with saturated sodium bicarbonate (3 × 15 ml). The extracts were made acid with 10% hydrochloric acid and extracted with chloroform. The extracts were dried over sodium sulfate and concentrated to give 8.9 g (60%) of the acid **20**.

Treatment of 8.9 g (23.8 mmol) of **20** with 2.4 g (24 mmol) triethyl amine and 4.6 g (27 mmol) benzylchloroformate according to the procedure given for the conversion of **9***c* to **9***b* gave 6.16 g (55%) of the desired ester **17**.

*cis-N-(α-Carbobenzoxy-β,β-diethoxyethyl)-3-azido-4-hydroxymethyl-2-azetidinone **1b***

A solution of 4.8 g (10.04 mmol) compound **17** in 80 ml dry methylene chloride was prepared and cooled to −78 °C in an acetone – dry ice bath. To this was added ozone until a blue color persisted. The ozone addition was stopped and the excess ozone removed by bubbling dry nitrogen through the solution. To the solution was added 5 ml of dimethyl sulfide and the solution was allowed to come to room temperature over 1 h. The solution was then washed with water (20 ml), saturated $NaHCO_3$ (20 ml), water (10 ml), and brine and dried over $MgSO_4$. The solution was filtered and evaporated to give 5.0 g of an oil. The byproduct benzaldehyde was removed by distillation at 0.05 torr and a bath temperature of ~65 °C. The residual oil 4.0 g (95%) was analyzed by nmr which indicated 77% free aldehyde **18**.

To 3.5 g (9.0 mmol) of compound **18** in 30 ml 95% ethanol at 0–5 °C was added 255 mg (6.0 mmol) of sodium borohydride with stirring. After 30 min at 0–5 °C the solution was stirred an additional 30 min at 25 °C. The solution was acidified to p*H* ≃ 4 with 10% hydrochloric acid and diluted with 40 ml ice water. The aqueous layer was extracted with chloroform (3 × 30 ml). The combined extracts were washed with water (2 × 10 ml) and brine, dried over $MgSO_4$, filtered, and

evaporated to yield 3.4 g crude alcohol **1***b*. The oil was chromatographed on silica gel (5% water) with chloroform to yield 3.0 g pure alcohol **1***b* (85%).

Benzyl γ-Phenylacetoacetate ***21c***

A mixture of 166 g (0.76 mol) of ethyl γ-phenylacetoacetate (16) and 100 g (0.92 mol) benzyl alcohol was heated to 170 °C at atmospheric pressure and the ethanol produced removed by distillation. When the still head temperature began to rise, the pot was cooled and the residue distilled at reduced pressure. Following removal of a forerun (bp 65–80 °C/100 torr) pure **21***c* was obtained 171 g (85%), bp 155–157 °C/0.002 torr.

Benzyl γ-Benzylacetoacetate ***21d***

From 204 g (1.1 mol) phenethyl bromide, 24.30 g (1 mol) magnesium and a trace of iodine in 250 ml of ether was prepared 2-phenylethyl magnesium bromide (17). The pot temperature was maintained at 25–30 °C and 45.2 g (0.40 mol) of ethyl cyanoacetate was added. The solution was stirred 24 h at 20–25 °C following which the excess Grignard reagent was decomposed by addition of saturated ammonium chloride and 10% hydrochloric acid. The phases were separated and the organic phase stirred vigorously with 10% hydrochloric acid for 3 h. The organic phase was washed with brine, dried over sodium sulfate, and concentrated to give 83.5 g of an oil which yielded 12.67 g (21%) of ethyl γ-benzylacetoacetate on distillation, bp 114–122 °C/0.1 torr.

From 12.67 g (50 mmol) of the ethyl ester and 8.1 g (75 mmol) benzyl alcohol was obtained 6.15 g pure **21***d*, bp 160–163 °C/0.1 torr in the same manner as the preparation of **21***c*.

Benzyl Oximinoacetoacetate ***22b***

Treatment of 173 g (0.9 mol) benzylacetoacetate (18) with sodium nitrite – acetic acid according to the method of Adkins and Reeve (10) gave 186.5 g (93.2%) of benzyl oximinoacetoacetate **22***b*; mp 81–82 °C, (lit. (11) mp 79–79.5 °C).

Benzyl γ-Phenyloximinoacetoacetate ***22c***

From 85.5 g (0.32 mol) of benzyl γ-phenylacetoacetate was prepared 92.50 g of oily oxime by the method of Adkins and Reeve (10). Trituration with carbon tetrachloride gave 52.8 g (56%) of pure **22***c*, mp 69–70 °C.

Benzyl γ-Benzyloximinoacetoacetate ***22d***

From 37.0 g (0.13 mmol) of **21***d* was prepared 40.1 g (98%) of **22***d* as a yellow oil by the method of Adkins and Reeve (10). The oil was characterized by its nmr and ir spectra and was used as such in subsequent experiments.

Benzyl Oximinoacetoacetate Ethylene Ketal ***23b***

In a 2 l flask fitted with a Dean Stark water separator and a condenser were placed 186.5 g (0.85 mol) of benzyl oximinoacetoacetate **22***b*, 62 g (1 mol) of ethylene glycol, 800 ml of benzene (reagent grade), and 2 g (10.5 mmol) of *p*-toluenesulfonic acid monohydrate. The reaction mixture was boiled at reflux until 15 ml of water was removed (3 h). The benzene solution was washed once with saturated sodium bicarbonate solution and once with brine. After drying over anhydrous sodium sulfate, the benzene solution was evaporated, leaving 212 g (94%) of benzyl oximinoacetoacetate ethylene ketal **23***b* as a mixture of *syn* and *anti* isomers. Generally, the product was used as such in subsequent reactions but one of the isomers could be crystallized from toluene – petroleum ether (bp 30–60 °C), mp 52 °C.

Benzyl γ-Phenyloximinoacetoacetate Ethylene Ketal ***23c***

From 5.94 g (20 mmol) of **22***c* and 1.36 g (22 mmol) ethylene glycol there was obtained 6.70 g of an oil which crystallized on standing in 20 ml carbon tetrachloride. On filtration 4.0 g (57%) of pure **23***c*, mp 90–92 °C was obtained.

Benzyl γ-Benzyloximinoacetoacetate Ethylene Ketal ***23d***

From 8.48 g (27 mmol) of **22***d* and 1.85 g (30 mmol) of ethylene glycol was obtained 9.40 g crude **23***d* which was used as such in the subsequent reaction.

Ethyl α-Aminoacetoacetate Hydrochloride ***24***

Ethyl α-oximinoacetoacetate **22***a* (10) (80 g; 0.5 mol) was dissolved in a mixture of 200 ml of ethanol and 70 ml of ethanolic HCl (9.28 *N* HCl–EtOH; 1.25 equiv). 10% palladium-on-carbon (8 g) was added carefully and the mixture was hydrogenated in a Parr hydrogenation apparatus starting at 70 psig (11). After absorption of the theoretical amount of hydrogen (1–2 h) the catalyst was filtered off and washed with ethanol. The ethanol was removed *in vacuo* at 40–50 °C leaving a thick red-brown oil. The oil was diluted with 8 volumes of acetone with vigorous stirring. Yellow crystals of the amine hydrochloride **24** separated out on cooling, 49 g (55%), mp 122–123 °C (corr.) (lit. (11) mp 114–116 °C (uncorr.)). This material was used without further purification.

Ethyl α-Aminoacetoacetate Ethylene Ketal ***25a***

To a mixture of 1.75 kg (28.2 mol) of ethylene glycol and 210 g (1.95 mol) *p*-toluenesulfonic acid monohydrate which had been warmed to 90 °C, 460 g (2.54 mol) of amine hydrochloride **24** was added with vigorous mechanical stirring. The mixture was stirred for 40 min at 90 °C, then poured into a mixture of water (2 l), concentrated ammonium hydroxide (650 ml), and ice (1 litre), and extracted four times with 500 ml of methylene chloride. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated to give 491 g of a dark red oil. The oil was diluted to 1.8 l with Et_2O, cooled in an ice bath, and ethanol saturated with hydrogen chloride was added until the p*H* reached 2–3. The resulting solid was filtered off and washed with ether to give 398 g (70%) of a light yellowish solid (70%), mp 153–156 °C (corr.). An analytical sample of **25***a* was recrystallized from 2-propanol–ether to give white crystals, mp 158–160 °C (corr.).

The free base of **25***a* is conveniently prepared from its hydrochloride by neutralization with concentrated ammonium hydroxide and extraction with CH_2Cl_2.

Benzyl α-Aminoacetoacetate Ethylene Ketal ***25b***

Freshly prepared aluminum amalgam (19) (from 27 g of aluminum foil) was covered with 500 ml of diethyl ether. The flask was fitted with a mechanical stirrer, a condenser, and a dropping funnel. A solution of benzyl oximinoacetoacetate ethylene ketal **23***b* (132.5 g; 0.5 mol) in 300 ml of wet diethyl ether was added dropwise at such a rate as to maintain boiling at reflux. After stirring for 4 h, the reaction mixture was filtered through a Buchner funnel. The filtrate was evaporated leaving

110 g of yellowish oil. The oil was dissolved in 800 ml of dry diethyl ether and dry hydrogen chloride gas was bubbled into the solution until no further precipitation occurred. The white precipitate was filtered off and washed once with diethyl ether and then dried *in vacuo*. This provided 108 g of benzyl aminoacetoacetate ethylene ketal hydrochloride, mp 157–158 °C.

To obtain the free base, the hydrochloride salt was suspended in 500 ml of diethyl ether and concentrated ammonium hydroxide was added with shaking until the solid went into solution. The diethyl ether layer was separated and washed twice with brine. After drying over anhydrous sodium sulfate, the solvent was evaporated leaving 90 g (71%) of colorless oil.

Benzyl α-Amino-γ-phenylacetoacetate Ethylene Ketal ***25c***

To freshly prepared aluminum amalgam (19) (from 6.9 g aluminum foil) in 100 ml ether was added solution of 29.5 g (85 mmol) of **23***c* in 600 ml of moist ether over 1 h. There was a mildly exothermic reaction and after the addition was complete, it was refluxed for 2 h. It was cooled, filtered through Celite, and extracted with 4 × 100 ml 10% hydrochloric acid. White crystals separated from the aqueous phase, were filtered, washed with cold water, and dried to give 29.0 g (93%) solid, mp 181–183 °C, recrystallized from ethanol–ether; mp 182–184 °C. The free base was obtained by suspending the hydrochloride in water and neutralizing with cold concentrated ammonium hydroxide.

Benzyl α-Amino-γ-benzyl Acetoacetate Ethylene Ketal ***25d***

To freshly prepared aluminum amalgam (19) (prepared from 27 g aluminum foil) covered with 300 ml moist ether was added with stirring a solution of 43 g (0.2 mol) of **23***d* in 300 ml ether. There was an exothermic reaction and after it subsided, the system was refluxed for 4 h. The inorganic material was filtered on Celite and the filtrate shaken well with 10% hydrochloric acid (100 ml). White crystals separated, were collected by filtration, washed with ether, and dried in a dessicator to give 54.0 g solid; mp 186–188 °C. The free base was obtained by suspending the solid in water, carefully neutralizing with cold concentrated ammonium hydroxide, and extracting with methylene chloride. After evaporation of the solvent, 27.91 g (69%) of a yellow oil was obtained.

Preparation of Schiff Bases ***26a–d***

The Schiff bases **26***a–d* were prepared from cinnamaldehyde and the appropriate amine **25***a–d* in quantitative yields according to our previously published method (1). The nmr spectra of **26***a–d* are listed in Table 1.

cis-N-(α-Carboethoxy-β,β-ethyleneketalpropyl)-3-azido-4-styryl-2-azetidinone ***27a***

From 197.2 g (0.65 mol) of **26***a*, 72 g (0.715 mol) triethylamine and 85.19 g (0.715 mol) azidoacetylchloride was prepared 245 g (98%) of crude **27***a* as a red oil according to our previously published method. A small sample crystallized from methanol to give a white solid, mp 81.5–82.5 °C.

cis-N-(α-Carbobenzoxy-β,β-ethyleneketalpropyl)-3-azido-4-styryl-2-azetidinone ***27b***

From ***27a***

To a solution of 64.31 g (0.168 mol) of **27***a* in 700 ml tetrahydrofuran was added 670 ml of 0.25 *N* sodium hydroxide solution (0.168 mol) at such a rate as to maintain the temperature at 25 °C. The addition took 1 h following which the solution was stirred an additional hour until thin layer chromatography indicated that no **27***a* remained in the mixture. The reaction mixture was carefully acidified to p*H* 3 with concentrated hydrochloric acid, saturated with salt, and extracted with methylene chloride (3 times). The methylene chloride extracts were washed with brine, dried over sodium sulfate, and evaporated at reduced pressure. The residue was dissolved in ether and extracted with 10% sodium bicarbonate solution until the extracts were colorless. The combined basic extracts were washed twice with ether, then carefully acidified to p*H* 3 with concentrated hydrochloric acid saturated with salt and extracted with methylene chloride. The extracts were washed with brine, dried over sodium sulfate, filtered, and evaporated to yield 51.86 g (86%) of the acid as a brown solid. Recrystallization from benzene gave pure **27***e*, mp 131–131.5 °C (dec.) (single isomer).

Treatment of **27***e* with triethylamine and benzyl chloroformate according to the procedure given for the conversion of **9***c* to **9***b* gave pure **27***b* in 99% yield, mp 65.5–66.5 °C after recrystallization from benzene – petroleum ether (30–60 °C) as a single isomer.

From ***25b***

Treatment of **26***b* with triethylamine and azidoacetyl chloride according to our previously published procedure (1) gave **27***b* in 94% yield as a mixture of diastereoisomers.

cis-N-(α-Carbobenzoxy-β,β-ethyleneketal-γ-phenylpropyl)-3-azido-4-styryl-2-azetidinone ***27c***

Treatment of **26***c* with triethyl amine and azidoacetyl chloride as in ref. 1 gave **27***c* as a mixture of diastereoisomers in quantitative yield. The crude oil was used as such in subsequent experiments.

cis-N-(α-Carbobenzoxy-β,β-ethyleneketal-γ-benzylpropyl)-3-azido-4-styryl-2-azetidinone ***27d***

Treatment of **26***d* with triethylamine and azidoacetyl chloride as in ref. 1 gave **27***d* as a red oil in quantitative yield and as a mixture of diastereoisomers. The crude oil was used as such in subsequent experiments.

cis-N-(α-Carbobenzoxy-β,β-ethyleneketalpropyl)-3-azido-4-formyl-2-azetidinone ***28a***

A solution of 117.5 g (0.262 mol) of **27***b* in 1 litre of methylene chloride was cooled to −50 to −60 °C in a dry ice – acetone bath, and ozonized until a faint blue-green color appeared. The solution was then flushed with nitrogen until the color faded. Methyl sulfide (100 ml) was added to the solution at −50 °C which was then allowed to slowly reach 25 °C as the cooling bath gradually melted. It was kept overnight at room temperature under nitrogen and then it was washed twice with 1% sodium bicarbonate solution and twice with brine, dried over anhydrous sodium sulfate, and evaporated to dryness. The resulting oil was triturated four times with 100 ml portions of petroleum ether (bp 30–60 °C) to remove benzaldehyde. The oil was then triturated carefully with diethyl ether whereupon it solidified. The solid was filtered off and dried to provide 75 g (71.5%) of aldehyde as a mixture of isomers diasteriomeric at the carbon α to the carbonyl of the benzyl ester.

In another experiment, 36.36 g (81.24 mmol) of a single isomer of **27***b* was ozonized at −78 °C in 300 ml

of methylene chloride. After work-up as above, there was obtained 32.92 g of an oil which crystallized on standing. This material was slurried with ether and filtered to provide 18.84 g (69%) off-white solid, mp 97–100 °C (corr). The analytical sample was recrystallized from ether; white crystals, mp 101–102 °C (corr.).

cis-N-(α-Carbobenzoxy-β,β-ethyleneketal-γ-phenylpropyl)-3-azido-4-formyl-2-azetidinone ***28b***

Ozonolysis of **27***c* according to the procedure described above for **28***a* gave **28***b* as an oil (95%). The nmr and ir spectra of **28***b* were compatible with the assigned structure and it was used as such in subsequent experiments.

cis-N-(α-Carbobenzoxy-β,β-ethyleneketal-γ-benzylpropyl)-3-azido-4-formyl-2-azetidinone ***28c***

Ozonolysis of **27***d* according to the procedure given for **28***a* to yield **28***c* as an oil. Chromatography of the oil (7.0 g) on silica gel (deactivated with 15% water) (250 g) using ether – petroleum ether (2:1) as eluent to remove the benzaldehyde followed by pure ether gave **28***c* in 45% yield. The oil was used as such in subsequent experiments.

cis-N-(α-Carbobenzoxy-β,β-ethyleneketalpropyl)-3-azido-4-mesyloxymethyl-2-azetidinone ***30a***

The aldehyde **28***a* (116.3 g; 0.31 mol) was dissolved in 600 ml of THF (reagent grade) and the solution was then cooled to −10 °C (ice–methanol bath). Sodium borohydride (5.88 g; 0.155 mol) was added and the reaction mixture was stirred 1 h. 10% aqueous hydrochloric acid was added until the mixture was slightly acidic, then 600 ml brine was added. The THF layer was separated and the aqueous phase was extracted twice with 250 ml portions of diethyl ether. The combined organic phases were washed twice with 400 ml portions of brine, dried over anhydrous sodium sulfate, and evaporated *in vacuo* to yield 117.3 g of crude alcohol **29***a* as an orange oil. This oil was used as such in the next reaction.

A solution of methanesulfonyl chloride (37.8 g; 0.34 mol) in 100 ml of methylene chloride was added dropwise at 0 °C (ice–water bath) to a stirring solution of alcohol **29***a* (105.6 g; 0.28 mol), triethylamine (56.6 g; 0.34 mol), and 1 litre of methylene chloride. Afterwards, the reaction was stirred for 30 h at 25 °C. It was then washed twice with brine (500 ml portions), dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The resulting oil was dissolved in methylene chloride, treated with Norite, and then filtered over *ca.* 200 g of activity I silica gel. The silica gel was then washed with *ca.* 2 l of methylene chloride. The filtrate was evaporated to dryness and the resulting oil (116 g) was covered with diethyl ether. It crystallized on standing giving 87.2 g (80% from aldehyde **28***a*) of mesylate **30***a* as an off-white solid, mp 97–99 °C (corr.) after recrystallization from benzene–ether.

cis-N-(α-Carbobenzoxy-β,β-ethyleneketal-γ-phenylpropyl)-3-azido-4-mesyloxymethyl-2-azetidinone ***30b***

Reduction of **28***b* with sodium borohydride as in **28***a* gave **29***b* in 89% yield. The alcohol was mesylated as in the above example to yield **30***b* as an oil in 95% yield. This oil was used as such in subsequent reactions.

cis-N-(α-Carbobenzoxy-β,β-ethyleneketal-γ-benzylpropyl)-3-azido-4-mesyloxymethyl-2-azetidinone ***30c***

Reduction of **28***c* with sodium borohydride as in **28***a* gave **29***c* in 92% yield. The alcohol was mesylated as in the conversion of **29***a* to **30***a* to give **30***c* in 46% yield after chromatography on silica gel (deactivated with 15% water) (4.0 g substrate to 250 g silica gel) using ether – petroleum ether (3:1) as eluent. The oil was used as such in subsequent reactions.

Benzyl 7-β-Azido-3-methyl-Δ³-O-2-isocephem-4-carboxylate ***32a***

A mixture of mesylate **30***a* (3.19 g; 6.43 mmol) and 30 ml of 95% trifluoroacetic acid was stirred at 25 °C for 2 h. The mixture was diluted with 300 ml of brine and extracted three times with methylene chloride (100 ml portions). The combined extracts were washed three times with water (50 ml portions, until neutral), dried (anhydrous sodium sulfate), and evaporated to dryness *in vacuo* leaving 3.17 g of a brown oil. The nmr spectrum of this oil indicates the presence of >90% enol **31***a*.

A solution of 12.02 g (29.4 mmol) of **31***a* and 2.95 g (29.5 mmol) triethylamine in 100 ml of methylene chloride was refluxed for 2 h. The solution was washed with 10% hydrochloric acid and brine, and dried over sodium sulfate. Evaporation gave 8.56 g of an oil which was filtered through 100 g silica gel in methylene chloride. Evaporation of the filtrate gave 6.58 g (80.5%) of **32***a*, mp 87–88 °C after recrystallization from ether.

Benzyl 7-Azido-3-benzyl-Δ³-O-2-isocephem-4-carboxylate ***32b***

The ketal mesylate **30***b* (1.36 g; 2.5 mmol) was dissolved in 95% trifluoroacetic acid (15 ml) and stirred at 50–55 °C for 2 h on an oil bath. It was poured into brine and extracted with CH_2Cl_2. After washing the organic extracts with water and drying over Na_2SO_4, the solvent was removed on the aspirator and left 1.20 g red oil, **31***b*. No further purification was attempted.

A mixture of crude enol mesylate **31***b* (5.4 g) and triethylamine (2 ml) in dry CH_2Cl_2 (100 ml) was refluxed for 5 h. It was cooled, washed with 10% HCl and water, dried over Na_2SO_4 and evaporated on the aspirator to give 4.24 g oil. This was purified by chromatography on 200 g of silica gel (deactivated with 15% water) eluting with ether – petroleum ether (2:1) to give 1.3 g (33%) of **32***b*, mp 117–118 °C, recrystallized from methanol.

Benzyl 7-Azido-3-phenethyl-Δ³-O-2-isocephem-4-carboxylate ***32c***

Ketal mesylate **30***c* (2.05 g; 3.7 mmol) was dissolved in 95% trifluoroacetic acid (200 ml) and stirred at 50–55 °C for 2 h on an oil bath. It was then poured into a mixture of crushed ice and brine and extracted with CH_2Cl_2. After washing the organic extracts with water, and drying over Na_2SO_4, the solvent was removed on the aspirator and left 1.73 g oil. No further purification was attempted.

A mixture of crude 'enol mesylate' **31***c* (1.71 g; 3.4 mmol) and triethylamine (0.48 ml; 3.4 mmol) in CH_2Cl_2 (50 ml) was refluxed for 5 h. It was cooled, washed with 10% HCl and water, dried over Na_2SO_4, and evaporated on the aspirator to give 1.35 g oil. This was purified by chromatography on 75 g silica gel (deactivated with 15% water) eluting with ether – petroleum ether (2:1) to yield 0.45 g (33%) pure **32***c*, mp 97–98 °C after recrystallization from methanol.

Ethyl 7-β-(Aminophenoxyacetoyl)-Δ³-O-2-isocephem-4-carboxylate ***34a***

A suspension of 242.5 mg (1.02 mmol) of **8***a* and

260 mg 10% Pd/C in 15 ml ethyl acetate was stirred under hydrogen at atmospheric pressure for 30 min. The suspension was filtered through diatomaceous earth and evaporated to yield 220 mg of an oil. The nmr and ir spectra of which were compatible with the amine **33***a*.

The oil was taken up in 15 ml methylene chloride and 101 mg (1 mmol) triethylamine was added. The solution was cooled to 0–5 °C and a solution of 170.5 mg (1 mmol) phenoxyacetyl chloride in 5 ml methylene chloride was added over 5 min. The solution was stirred 30 min at 25 °C and washed with water, 10% hydrochloric acid, and saturated sodium bicarbonate solution. The solution was dried over sodium sulfate and concentrated to yield 316 mg of an oil. The oil was chromatographed on 25 g silica gel with benzene–acetone as eluent (initially 100% benzene gradually changed to 1:1 5% every 50 ml). There was obtained 194 mg (56%) of **34***a*, mp 148–148.5 °C, recrystallized from benzene–ether.

Benzyl 7-β-(Aminophenoxyacetoyl)-Δ³-O-2-isocephem-4-carboxylate ***34b***

Compound **8***b*, 500 mg (1.66 mmol) was dissolved in 20 ml of dry ethyl acetate. To this was added 450 mg of 10% Pd/C and the solution was stirred under hydrogen at atmospheric pressure and room temperature for 30 min. The solution was filtered through Celite and the filter cake washed thoroughly with methylene chloride. Evaporation of the filtrate yielded 500 mg of crude amine. The nmr and ir spectra of the compound were compatible with the assigned structure.

Compound **33***b* (500 mg) was dissolved in 10 ml of dry methylene chloride and cooled to 0–5 °C in an ice bath. To this was added 280 mg (2.8 mmol) of triethylamine and 346 mg (2.0 mmol) of phenoxyacetyl chloride was added slowly. After stirring for 1 h at 0–5 °C, the solution was washed with water (2 × 10 ml) and dried over Na_2SO_4. After evaporation, the residual oil was taken up in 50 ml of ether and filtered. The filtrate was evaporated and triturated with ether – petroleum ether (1:1). The solid thus obtained was filtered to yield 570 mg crude amide. The amide was chromatographed on a silica gel column (not deactivated) (25 g) with benzene–acetone (initially in a ratio 50:1, gradually changed to 1:1, 2% more acetone every 25 ml). The desired amide was obtained pure, 195 mg (29%), as a gum.

Benzyl 7-β-(Aminophenoxyacetoyl)-3-methyl-Δ³-O-2-isocephem-4-carboxylate ***34c***

A suspension of 210 mg (0.64 mmol) of **32***a* and 100 mg PtO_2 in 35 ml absolute ethanol was hydrogenated at atmospheric pressure for 7 min. Filtration and evaporation of the filtrate gave 190 mg (100%) of **33***c*, mp 91–92 °C. The nmr and ir spectra of **33***c* were compatible with the assigned structure.

To a solution of 190 mg (0.64 mmol) of **33***c* in 20 ml methylene chloride was added 97.4 mg (0.64 mmol) of phenoxyacetic acid followed by 158 mg (0.64 mmol) EEDQ. The solution was let stand 1 h. It was washed with 1% sodium bicarbonate solution (2 × 10 ml), 10% hydrochloric acid (2 × 10 ml), and brine (50 ml), and dried over sodium sulfate. Evaporation of the solvent gave 180 mg (65%) of **34***c* which crystallized on trituration with ether, mp 133–135 °C (dec.).

Benzyl 7-β-(Aminophenoxyacetoyl)-3-benzyl-Δ³-O-2-isocephem-4-carboxylate ***34d***

A mixture of compound **32***b* (0.49 g; 1.25 mmol) and triethylamine (0.9 ml; 6.5 mmol) in CH_2Cl_2 (50 ml) was cooled in an ice bath and while being stirred, was saturated with H_2S. The cooling bath was removed and there was gas evolution which subsided in 10 min. At this point, tlc showed no starting material remained. Attempts to extract the amine from the solution as its hydrochloride failed as it is more soluble in CH_2Cl_2 than in water. The CH_2Cl_2 solution of the free base was dried over Na_2SO_4 and evaporated on the aspirator to leave 0.49 g (87%) of **33***d* as a semisolid. It was used as such with no further purification.

A solution of **33***d* (0.46 g; 1.25 mmol), phenoxyacetic acid (0.19 g; 1.25 mmol), and EEDQ (0.31 g; 1.25 mmol) in CH_2Cl_2 (100 ml) was stirred at room temperature for 16 h. It was washed with 1% $NaHCO_3$ solution, then with brine, dried over Na_2SO_4, and evaporated on the aspirator to leave 0.56 g (89%) of a slightly yellow gum. It was used as such with no further purification.

Benzyl 7-β-(Aminophenoxyacetoyl)-3-phenethyl-Δ³-O-2-isocephem-4-carboxylate ***34e***

A mixture of **32***c* (0.81 g; 2 mmol) and triethylamine (0.56 ml; 4 mmol) in methylene chloride (50 ml) was cooled in an ice bath and while being stirred, was saturated with H_2S. The cooling bath was removed and there was gas evolution. After stirring at room temperature for 1 h, the solution was evaporated at room temperature and partitioned between ether and 10% HCl. White crystals separated and were collected by filtration, washed with ether, and dried to give 1.12 g white solid, mp 120–123 °C. The free base was obtained by suspending the solid in water, alkalizing with cold concentrated ammonium hydroxide and extracting with methylene chloride. This was washed with brine, dried over sodium sulfate, and evaporated on the aspirator. There was obtained 0.68 g (90%) of **33***d* as an oil.

A solution of **33***e* (0.40 g; 1.05 mmol), phenoxyacetic acid (0.16 g; 1.05 mmol), and EEDQ (0.26 g; 1.05 mmol) in CH_2Cl_2 (50 ml) was stirred at room temperature for 2 h. It was washed with 1% $NaHCO_3$ solution, then with brine, dried over Na_2SO_4, and evaporated on the aspirator to leave 0.49 g (91%) white solid, mp 146–148 °C. This was used as such in the subsequent step.

7-β-(Aminophenoxyacetoyl)-Δ³-O-2-isocephem-4-carboxylic acid ***35a***

Compound **34***b* 210 mg (0.514 mmol) was dissolved in 40 ml ethyl acetate and 1 ml glacial acetic acid was added. Using 610 mg (~20%) palladium hydroxide on charcoal as catalyst, the solution was hydrogenated at 58 psi for 50 min.

The reaction mixture was filtered through Celite (twice) and the catalyst was washed thoroughly with chloroform (20 ml). The filtrate was evaporated to dryness. It was evaporated 3 times with benzene in order to strip off the acetic acid. A very viscous oil was obtained which was washed with 10 ml benzene. The residual oil was scratched with 10 ml ether. The solid material formed was filtered out. Yield: 115 mg (70.5%). Compound **35***a* did not show a sharp melting point but decomposed in the range of 215–250 °C. The ir and nmr spectra of **35***a* were compatible with the assigned structure.

Compound **35***a* was converted to its potassium salt **35***b*.

To a solution of 30 mg, compound **35***a* in 3 ml methylisobutylketone was added one or two drops of 50% solution of potassium 2-ethylhexanoate in butanol. A

white crystalline material separated almost immediately which was filtered out and washed with methyl isobutylketone and dried over P_2O_5 for 48 h under high vacuum. There was obtained 18 mg (53.5%) of **35***b*. This compound slowly decomposed on heating 230–260 °C.

7-β-(Aminophenoxyacetoyl)-3-methyl-Δ³-O-2-isocephem-4-carboxylic Acid 35c

Benzyl ester **34***c* (100 mg; 0.237 mmol) was dissolved in a mixture of absolute ethanol (10 ml) and tetrahydrofuran (7 ml). 10% Pd–C (100 mg) was carefully added and the mixture was hydrogenated at atmospheric pressure. Hydrogen uptake was complete after *ca.* 7 min. The catalyst was filtered off and washed once with EtOH. The EtOH was removed *in vacuo* leaving 90 mg of partly crystalline residue. The residue was crystallized from acetone–ether to give **35***c*, mp 171–172 °C (dec.), 65 mg (84%).

7-β-(Aminophenoxyacetoyl)-3-benzyl-Δ³-O-2-isocephem-4-carboxylic Acid 35d

Compound **34***d* (0.49; 1 mmol) was dissolved in ethyl acetate (100 ml) and glacial acetic acid (10 ml), 20% $Pd(OH)_2$-on-carbon (0.50 g) was added, and the mixture was agitated on a Paar apparatus at 60 psi of H_2 for 2 h. The solid was filtered off on Celite and the filtrate evaporated to dryness. The residue was extracted with saturated $NaHCO_3$, the aqueous phase was acidified with 10% HCl, and extracted with CH_2Cl_2. This was then washed with water, dried over Na_2SO_4 and evaporated to dryness. The resulting solid was recrystallized from benzene and gave white crystals, mp 123–125 °C. There was obtained 0.08 g (20%) of **35***d*.

7-β-(Aminophenoxyacetoyl)-3-phenethyl-Δ³-O-2-isocephem-4-carboxylic Acid 35e

A solution of compound **34***e* (0.49 g; 0.9 mmol) in ethyl acetate (75 ml) was added to a prehydrogenated sample of 20% $Pd(OH)_2$-on-carbon (0.50 g) in ethyl acetate (25 ml). It was then stirred under hydrogen at atmospheric pressure and after 15 min, gas consumption had ceased. It was filtered through a Celite pad, washed well with ethyl acetate, and the solvent was removed on the aspirator to leave 0.40 g of an amorphous solid. This was suspended in ether and extracted with 2% $NaHCO_3$. The aqueous extract was acidified with 10% HCl and the white solid collected by suction filtration, washed with water, and dried to give a white solid, mp 160–162 °C. Recrystallized from $CHCl_3$–ether, mp 162–163 °C. There was obtained 0.35 g (92%) of **35***e*.

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