Synthesis of Benzocarbacephem and Benzocarbapenem Derivatives by Copper-promoted Intramolecular Aromatic Substitution

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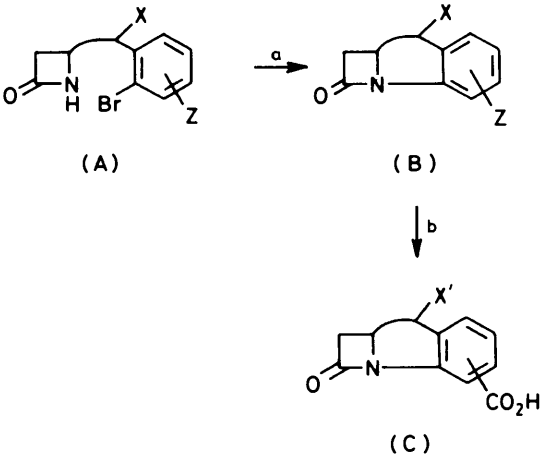
Copper-mediated cyclisation of 4-[2-(*o*-bromophenyl)ethyl]azetidinones and 4-[*o*-bromophenyl)-methyl]azetidinones proved to be a route to benzocarbacephem and benzocarbapenem derivatives respectively. The effect of functionalities present in the alkyl part of the ring to be formed was considered with regard to cyclisation efficiency and further chemical modifications. Conversion, into halide, of the diastereoisomeric mixture (4*R*,6*S*; 4*S*,6*R*; 4*R*,6*R*; and 4*S*,6*S*) of t-butyl 2-hydroxybenzocarbacephem-4'-carboxylate (**14f**) afforded either the chloride (**17a**) as racemic diastereoisomers or the fluoride (**17c**) as a single racemic diastereoisomer. The corresponding free carboxylic acids (**18a, c**) were designed as inactivators of beta-lactamases.

Pathogenic resistant bacteria are a serious concern in the fight against infectious deseases by beta-lactam antibiotics. It has long been known that bacterial resistance usually arises by the bacterium acquiring the ability to produce a beta-lactamase capable of quickly hydrolysing the beta-lactam ring of drugs thus preventing their access to target proteins.[1]

A growing attractive strategy consists of the co-administration of an antimicrobial agent and a suicide inhibitor[2] of the liable enzyme. The association may result in restoration of the activity of sensitive antibiotics by selectively inactivating beta-lactamases. Although several very active naturally occurring or semi-synthetic beta-lactamase suicide inactivators have been reported and studied extensively *in vitro*, very few, such as clavulanic acid,[3] possess features suitable for a clinical combination. Besides its potential pharmacological interest, any new suicide inhibitor would be welcome for the further study of beta-lactamase active sites.

Previously we described some *N*-arylazetidinones as good competitive inhibitors of beta-lactamases *in vitro*. Probably due



Scheme.

Table 1. Preparation and condensation of malonate anions (**1**) and Grignard reagent (**3**) with 4-acetoxyazetidinone or 4-phenylsulphonylazetidinone

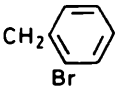
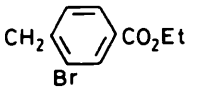
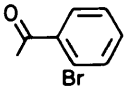
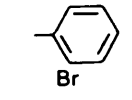
		Malonate (**1**) or Grignard reagent (**3**)		Azetidinone (**2**) or (**4**)	
R^1	R^2	Compound	Yield (%)	Compound	Yield (%)
Et		(**1a**)	72	(**2a**)	36
Et		(**1b**)	74	(**2b**)	48
CH_2Ph		(**1c**)	53	(**2c**)	45
CH_2Ph		(**1d**)	13	(**2d**)	33
		(**3**)		(**4**)	33

Table 2. Preparation and condensation of silyl enol ethers or silyl ketene acetal with 4-acetoxyazetidinone

	Enoxysilane or silyl ketene acetal		Azetidinone product	
Z	Compd.	Yield (%)	Compd.	Yield (%)
H	**(5a)**	**94**	**(6a)**	93
CO_2Me	**(5b)**	**95**	**(6b)**	27
CO_2Bu^t	**(5c)**	**85**	**(6c)**	79
CO_2CH_2Ph	**(5d)**	**83**	**(6d)**	80
	(7)	**85**	**(8)**	70

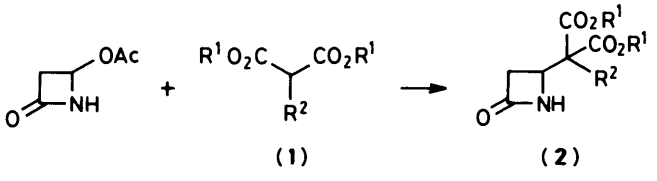
to an excessive stability of the azetidinone towards enzymatic ring opening, they were not substrates of the enzymes.[4a]

As part of our current interest in the design of synthetic suicide inhibitors based on the 1,4(or 1,6)-elimination mechanism,[4b] bromomethylated analogue of these *N*-arylazetidinones were also synthesized but failed to inactivate the enzymes.[4a] We deduced that suitable ring strain would induce the necessary chemical reactivity.

In this paper, we present the copper-induced * intramolecular aromatic substitution of monocyclic azetidinones (**A**) as the key step to benzocarbapenem and benzocarbacephem derivatives (**B**) (step a, Scheme)[5] and the further reactions of (**B**) to give the targetted tricyclic azetidinones (**C**) (step b). First, the preparation of the starting monocyclic azetidinones bearing a 4-(bromoaryl)alkyl substituent will be reported.

Preparation of the Monocyclic Azetidinones.—Generally, substitution of an azetidinone bearing a good leaving group at C-4 occurs by an elimination–addition mechanism *via* a dihydroazetone intermediate.[6] Some precursors (**2**) were obtained by substitution of 4-acetoxyazetidinone[7] with malonate anions.[8] The substituted malonates (**1b**), (**1c**), and (**1d**) were prepared by alkylation,[9] acylation,[10] and copper-catalysed arylation[11] of the corresponding unsubstituted dialkyl malonate.

When condensed with 4-phenylsulphonylazetidinone,[7] the benzylic Grignard reagent (**3**)[12] afforded the corresponding azetidinone (**4**) with some 4-(bromomethylphenyl)azetidinone as inevitable side-product (Table 1).



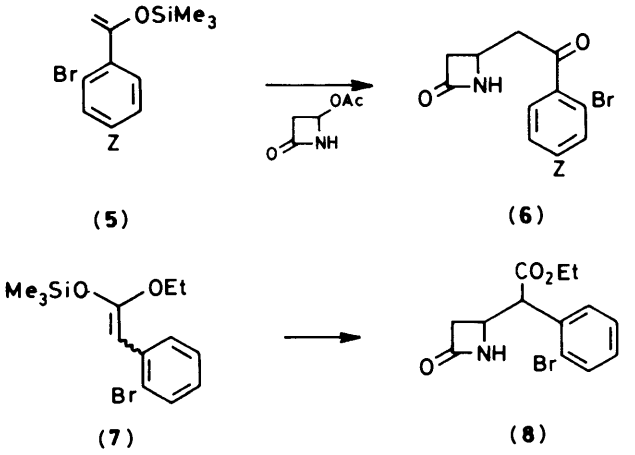
These different substitutions suffer from rather modest yields and we probably would meet some limitations concerning the further functional modifications of these azetidinones after the cyclisation step (Scheme, step b). This prompted us to develop the synthesis of more suitable precursors (**A**) (Scheme). Enoxysilanes underwent straightforward Lewis acid-induced alkylation with 4-acetoxyazetidinone.[13] Indeed monocyclic

* Preliminary communication: ref. 5.

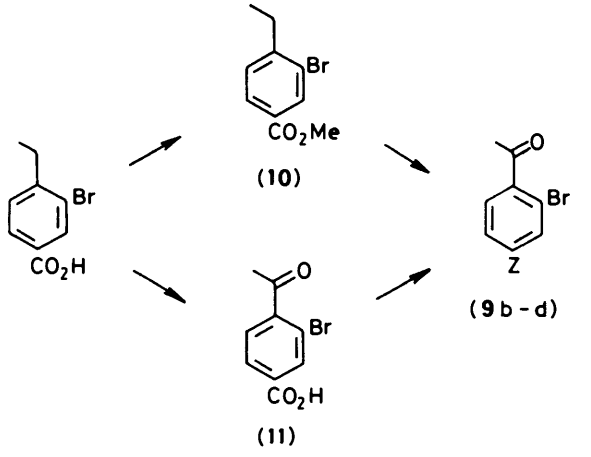
Table 3. Selective reduction of azetidinone (**6**)

		Alcohol product	
Z	Azetidinone	Compound	Yield (%)
H	**(6a)**	**(12a)**	85
CO_2Me	**(6b)**	**(12b)**	84
CO_2Bu^t	**(6c)**	**(12c)**	81
CO_2CH_2Ph	**(6d)**	**(12d)**	83

azetidinones (**6a**—**d**) or (**8**) were obtained in good yield by the slightly modified ZnI_2-catalysed substitution of 4-acetoxyazetidinone by enoxysilanes (**5**) or silyl ketene acetal (**7**) (Table 2).



The enoxysilanes (**5**) were easily obtained from the corresponding acetophenones (**9**) by means of the procedure described by P. Cazeau *et al.*[14] Starting from 3-bromo-4-ethylbenzoic acid,[15] the esterified acetophenones (**9b**) (Z = CO_2Me) and (**9c, d**) (Z = CO_2Bu^t, CO_2CH_2Ph) were prepared by oxidation[16] of methyl 3-bromo-4-ethylbenzoate (**10**), and by esterification of the corresponding carboxyacetophenone (**11**) respectively. The latter was obtained in excellent yield by application of a benzylic oxidation procedure[17] to 3-bromo-4-ethylbenzoic acid.

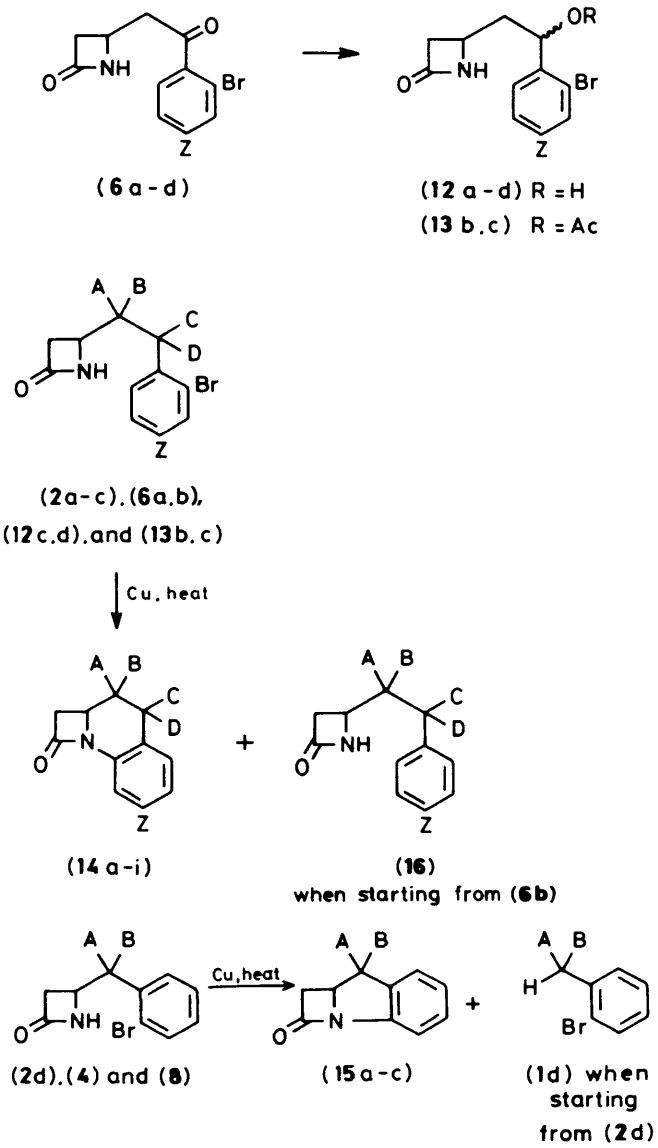


Subsequently, ketones (**6a**—**d**) were selectively reduced with $NaBH_4$ and the obtained diastereoisomeric mixtures of the alcohols (**12b, c**) were derivatised as acetates (**13**) (Table 3).

Table 4. Copper-promoted cyclisation of monocyclic azetidinones

A,B	C,D	Z	Starting azetidinone (compound)	Tricyclic azetidinone product	
				Compound	Yield (%)
$(CO_2Et)_2$	H,H	H	(**2a**)	(**14a**)	60
$(CO_2Et)_2$	H,H	CO_2Et	(**2b**)	(**14b**)	45
$(CO_2CH_2Ph)_2$	O	H	(**2c**)	(**14c**)	5
H,H	O	H	(**6a**)	(**14d**)	13
H,H	O	CO_2Me	(**6b**)	(**14e**)	10
H,H	OH,H	CO_2Bu^t	(**12c**)	(**14f**)	41
H,H	OH,H	CO_2CH_2Ph	(**12b**)	(**14g**)	68
H,H	OAc,H	CO_2Me	(**13b**)	(**14h**)	65
H,H	OAc,H	CO_2Bu^t	(**13c**)	(**14i**)	50
$(CO_2CH_2Ph)_2$			(**2d**)	(**15a**)	23
H,CO_2Et			(**8**)	(**15b**)	19
H,H			(**4**)	(**15c**)	8

Cyclisation of the Monocyclic Azetidinones.—After some unsuccessful attempts to cyclise 4-[*o*-bromophenyl)alkyl]-azetidinones under basic conditions,[18] we found that copper metal[19] could promote the aromatic substitution[5] with low-to-reasonable yields depending on ring size and functionalities. We noticed that structures leading to a six-membered ring are more prone to cyclisation than those giving a five-membered ring [(**2d**), (**4**), (**8**); (Table 4)]. A *gem* bis(alkoxycarbonyl) group probably induces strain in the ground state of the starting monocyclic azetidinone, which is relieved in both the tricyclic product and the transition state leading to it [a kind of Thorpe–Ingold effect;[20] compare for instance (**15c**) with (**15a**) in Table 4]. On the other hand, if an sp^2 carbon was present in the alkyl part of the ring to be formed, the internal angle of the chain increased and the yield fell seriously [(**2c**), (**6a, b**)]. The alcohols (**14f, g**) were obtained as a mixture of diastereoisomers but the potential diastereoselectivity of the cyclisation step was not determined as we were unable, from the n.m.r. spectra, to assess the diastereoisomeric ratio of the hydroxy monocyclic azetidinones. The hydroxy group did not seem to affect the copper-mediated ring formation; only a slightly improved yield was observed with the corresponding acetates (**13b, c**).



If some attention had been devoted to carbacephems fused with benzene rings along their 1,2-, 2,3-, or 3,4-bond,[21] much less was known about 2,3-benzo-fused carbapenems.[22] Our method proved to be a route to these highly strained benzo-carbapenem derivatives. The ring strain leads to a relatively high i.r. carbonyl absorption (1 770—1 790 cm^{-1}). However, the chemical instability of the tricyclic azetidinones (**15a—c**), which probably explains the low yields of the cyclisation step, was a major obstacle toward any further functional modification.

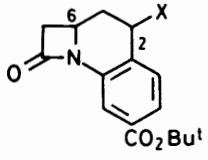
From a general point of view, we observed at least two side-reactions which competed with the cyclisation process. First, copper treatment of malonate (**2d**) gave rise to a noticeable amount of the dibenzyl malonate (**1d**) as a consequence of the easy thermal elimination of the relatively acidic arylmalonate. On the other hand, when processed with copper, the ketone (**6b**) underwent some reductive dehalogenation, since we isolated the corresponding monocyclic azetidinone (**16**; A = B = H, CD = O, Z = CO_2Me) (6% yield). It was furthermore ascertained that neither oxygen nor radical scavengers affected the outcome of the reaction in the case of stable tricyclic azetidinones. The above observations are in accord with some previous comments on copper-assisted nucleophilic substitutions.[23]

Functional Modification of the Fused Tricyclic Beta-lactams.—At that stage, we needed to introduce an appropriate leaving group at the benzylic position of the tricyclic structure (**14**) (Table 5). In this respect, the conversion of the diastereoisomeric mixture of the alcohol (**14f**) into the corresponding chloride was achieved by dimethylformamide (DMF)–thionyl chloride treatment;[24] predictably, the halide (**17a**) was obtained as a mixture of diastereoisomers.

Table 5. Functional modifications of fused tricyclic beta-lactams

Starting azetidinone			Resulting beta-lactam		
	Z	Reagent		X	Yield (%)
(14f)	CO_2Bu^t	$SOCl_2$–DMF	**(17a)**	Cl	48
(14g)	CO_2CH_2Ph	$SOCl_2$–DMF	**(17b)**	Cl	47
(14f)	CO_2Bu^t	DAST	**(17c)**	F	51
(14i)	CO_2Bu^t	TFA	**(18d)**	OAc	84
(17a)	CO_2Bu^t	TFA	**(18a)**	Cl	82
(17b)	CO_2CH_2Ph	Pd/C	**(18b)**	H	91
(17c)	CO_2Bu^t	TFA	**(18c)**	F	79

Table 6. Coupling constants (Hz) for some benzocarbacephems



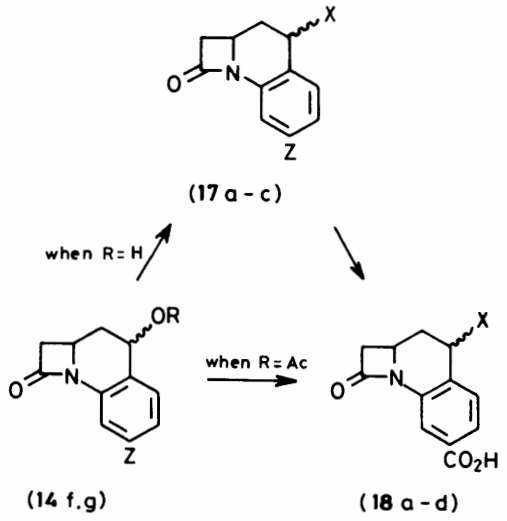
(17 a,c)

Compound	X	Stereochemistry	1-H–2-H	1-H–6-H	2-H–F	1-H–F
(14f)	OH	(ax)	2.8, 3.2	3.2, 12		
		(eq)	4.8, 11.2	3.5, 11.2		
(17a)	Cl	(ax)	2.6, 3.1	3.06, 12.04		
		(eq)	5.21, 12.15	3.34, 12.15		
(17c)	F		2.5, 2.9	2.9, 12.5	48.7	11.5, 39

Introduction of a fluorine atom seemed to be very appealing as well. When treated by diethylaminosulphur trifluoride (DAST), the diastereoisomeric mixture of alcohol (**14f**) (1:3, eq:ax) afforded the fluoride (**17c**) as a single diastereoisomer which could be assigned as an axial halide (Table 6). The low and close coupling constants for 1-H—2-H and the opposite range coupling constants for 1-H–F strongly support this assignment.[25] Conversion of alcoholics into fluorides using DAST is known to proceed through a S_N2 mechanism while reaction through free carbonium ions is said to lead mainly to elimination and/or rearrangement.[26] However, in our case it seems we escaped this usual behaviour since both the axial and the equatorial diastereoisomer of the alcohol (**14f**) provided exclusively axial fluoride (**17c**) with a yield close to 50%. We did not observe any elimination product which might be formed, but this would most likely be too unstable to be isolated. Finally, these observations suggest the existence of carbonium ion-like intermediate during the conversion of alcohol into fluoride.

Subsequent ester cleavage provided the target molecules (**C**) (Scheme). Selective alkaline hydrolysis[4a,27] of the methyl ester group of the tricyclic beta-lactam (**14h**) failed. It turned out that the t-butyl group in (**14i**) and (**17a, c**) was easily cleaved by trifluoroacetic acid treatment. The tricyclic beta-lactam acid (**18b**), with an unsubstituted benzylic position C-2, was directly obtained through extensive catalytic hydrogenolysis of the corresponding chloride (**17b**).

The sodium salts of the differently substituted acids (**18a—c**) have been examined for TEM-1 beta-lactamase inhibition.* Compounds (**18a, c, d**) failed to behave as mechanism-based enzyme inactivators; nevertheless, the benzocarbacephems



(**18a—d**) exhibited good competitive inhibition of the enzyme (K_i 20—55 μM).

In summary, copper-promoted intramolecular aromatic substitution proved to be a valuable route to benzocarbacephem and benzocarbapenem derivatives. Application of this methodology to the synthesis of carbapenems and carbacephems themselves is in progress.

Experimental

M.p.s were measured using a Büchi apparatus and are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 1420 spectrophotometer. When not otherwise specified, the ^1H n.m.r. data were determined on a 90 MHz Brucker WH90DS apparatus. The 250 MHz spectra were recorded on a Brucker

* We thank Dr. R. Labia and his colleagues, Museum d'Histoire Naturelle, Paris, for carrying out these assays. Details on the enzyme determinations will be presented elsewhere.

WM250 instrument, and mass spectra were determined using a Ribermag R1010 spectrometer by electron-impact unless otherwise stated. Reactions were performed in dry solvents under argon. Purification was carried out either by flash chromatography on Merck silica gel 60 (230—400 mesh) or by thick layer chromatography on Merck silica gel 60PF254. The unstable condensed azetidinones were characterised mainly by mass spectrometry.

Diethyl (o-*Bromo*-p-*ethoxycarbonylbenzyl*)*malonate* (**1b**).—To sodium (230 mg, 10 mmol) in EtOH (4 ml) was added diethyl malonate (32 g, 20 mmol) at room temperature. After 15 min, a solution of ethyl 3-bromo-4-bromomethylbenzoate (3.08 g, 10 mmol) in EtOH (6 ml) was added and the mixture was heated at reflux for 2 h. The solvent was partially evaporated off and the residue was diluted with water before extraction (ether) and drying (Na_2SO_4). The title compound was obtained as an oil (2.86 g), b.p. 210 °C/1mmHg (Found: C, 51.2; H, 5.2. $C_{17}H_{21}BrO_6$ requires C, 50.88; H, 5.27%); $\nu_{max.}$(film) 1 750, 1 730, and 1 720 cm^{-1}; $\delta_H(CDCl_3)$ 1.22 (6 H, t, *J* 7 Hz), 1.39 (3 H, t, *J* 7 Hz), 3.35 (2 H, d, *J* 7 Hz), 2.83 (1 H, m), 4.13 (4 H, q, *J* 7 Hz), 4.23 (2 H, q, *J* 7 Hz), and 7.19—8.1 (3 H, ArH).

Dibenzyl (o-*Bromobenzoyl*)*malonate* (**1c**).—To the magnesium salt obtained from magnesium turnings (0.54 g, 22 mmol) in EtOH (2 ml) and CCl_4 (0.1 ml) was added a solution of dibenzyl malonate (6.25 g), 22 mmol) in tetrahydrofuran (THF) (1 ml). The mixture was refluxed for 0.5 h, then *o*-bromobenzoyl chloride (4.38 g, 20 mmol) was added dropwise. After a further period of reflux (0.5 h), the reaction mixture was cooled and shaken with dil. sulphuric acid and the product was extracted with ether. Finally, the acylmalonate was purified by column chromatography (ether–pentane; 1:7) to afford the *title compound* (4.9 g), m.p. 53—54 °C (Found: C, 61.7; H, 4.3. $C_{24}H_{19}BrO_5$ requires C, 61.68; H, 4.10%); $\nu_{max.}(CH_2Cl_2)$ 1 720 cm^{-1}; $\delta_H(CDCl_3)$ 4.94 (2 H, s), 5.39 (2 H, s), 7—7.55 (14 H, ArH), and 13.64 (1 H, s).

Dibenzyl (o-*Bromophenyl*)*malonate* (**1d**).—To a suspension of sodium hydride (576 mg, 12 mmol) in dioxane was added dibenzyl malonate (3.4 g, 12 mmol). Then CuBr (1.72 g) and 1,2-dibromobenzene (2.36 g, 10 mmol) were added successively. The reaction mixture was refluxed for 4 h, diluted with ethyl acetate, and filtered, and the residue was washed with saturated aqueous NH_4Cl. Work-up, followed by purification by column chromatography, afforded the *title compound* as an oil (574 mg) (Found: C, 63.0; H, 4.4. $C_{23}H_{19}BrO_4$ requires C, 62.88; H, 4.36%); $\nu_{max.}(CH_2Cl_2)$ 1 755 and 1 735 cm^{-1}; $\delta_H(CDCl_3)$ 5.19 (4 H, s), 5.37 (1 H, s), and 7.12—7.67 (14 H, ArH).

Diethyl (o-*Bromobenzyl*)-(4-*oxoazetidin*-2-*yl*)*malonate* (**2a**).—To a stirred suspension of 50% sodium hydride (100 mg, 2 mmol) in THF (3 ml) at 0 °C was added diethyl (*o*-bromobenzyl)malonate (**1a**) (724 mg, 2.2 mmol). When hydrogen evolution had ceased, 4-acetoxyazetidin-2-one (258 mg, 2 mmol) was added and the reaction mixture was warmed to room temperature. After 2 h, the mixture was diluted with ethyl acetate, washed with brine, and dried. Removal of the solvent under reduced pressure, followed by silica gel flash chromatography (EtOAc–pentane; 1:1), afforded homogeneous *title compound* (**2a**) (284 mg) as an oil; $\nu_{max.}(CH_2Cl_2)$ 3 400, 1 775, and 1 730 cm^{-1}; $\delta_H(CDCl_3)$ 1.17 and 1.20 (6 H, t, *J* 7.2 Hz), 3.03 (2 H, dd, *J* 1.5 and 3.5 Hz), 3.53 (2 H, s), 3.96 (1 H, dd, *J* 4 and 4 Hz), 4.2 and 4.25 (4 H, q, *J* 7.2 Hz), 6.33 (1 H, br s), and 7.38 (4 H, m,); (Found: M^+, 397.0525. $C_{17}H_{20}BrNO_5$ requires *M*, 397.0525); *m/z* 398 and 400 [$(M + H)^+$, bromine isotopes], 318, 276, 249, 203, 128, 116, 70, and 43.

Diethyl (o-*Bromo*-p-*ethoxycarbonylbenzyl*)-(4-*oxoazetidin*-2-*yl*)*malonate* (**2b**).—4-Acetoxyazetidin-2-one (258 mg, 2 mmol) was treated with the sodium salt of diethyl (*o*-bromo-*p*-ethoxycarbonylbenzyl)malonate (**1b**) as above, to give the C-4-*substituted azetidinone* (**2b**) (450 mg, 48%) as an oil; $\nu_{max.}(CH_2Cl_2)$ 3 400, 1 770, and 1 720 cm^{-1}; $\delta_H(CDCl_3)$ 1.23, 1.25, and 1.4 (9 H, t, *J* 7 Hz), 3.06 (2 H, dd, *J* 1.5 and 3.5 Hz), 3.59 (2 H, s), 4.0 (1 H, dd, *J* 4 and 4 Hz), 4.22, 4.26, and 4.38 (6 H, q, *J* 7 Hz), 6.05 (1 H, br s), and 7.33—8.21 (3 H, ArH); (Found: M^+, 469.0738. $C_{20}H_{24}BrNO_7$ requires *M*, 469.0736); *m/z* 470, 472 [$(M + H)^+$, bromine isotopes], 390, 348, 321, 275, 129, 70, and 43.

Dibenzyl (o-*Bromobenzoyl*)-(4-*oxoazetidin*-2-*yl*)*malonate* (**2c**).—Dibenzyl (*o*-bromobenzoyl)malonate (**1c**) (513 mg, 1.1 mmol) was used to convert 4-acetoxyazetidin-2-one (129 mg, 1 mmol) into the azetidinone (**2c**) *via* the process described for the preparation of compound (**2a**). The title compound (**2c**) was obtained as white crystals (245 mg), m.p. 98 °C (from pentane–EtOAc); $\nu_{max.}(CH_2Cl_2)$ 3 400, 1 773, 1 750, 1 732, and 1 703 cm^{-1}; $\delta_H(CDCl_3)$ 3.05 (1 H, ddd, *J* 2.5, 5, and 15.5 Hz), 3.33 (1 H, ddd, *J* 1, 2.5, and 15.5 Hz), 4.55 (1 H, dd, *J* 2.8 and 5 Hz), 4.98 and 5.21 (4 H, s), 6.04 (1 H, br s), 7.2 and 7.27 (10 H, s), and 7.27 (4 H, m); *m/z* 535 and 537 (M^+, bromine isotopes), 183, 105, and 91.

Dibenzyl (o-*Bromophenyl*)-(4-*oxoazetidin*-2-*yl*)*malonate* (**2d**).—4-Acetoxyazetidin-2-one (258 mg, 2 mmol) was treated with the sodium salt of dibenzyl (*o*-bromophenyl)malonate (**1d**) according to the process described for the preparation of compound (**2a**). The *azetidinone* (**2d**) was obtained as a white solid (172 mg), m.p. 146 °C (from ether) (Found: C, 61.4; H, 4.4. $C_{26}H_{22}BrNO_5$ requires C, 61.42; H, 4.36%); $\nu_{max.}(CH_2Cl_2)$ 3 410, 1 775, and 1 745 cm^{-1}; $\delta_H(CDCl_3)$ 2.81 (1 H, ddd, *J* 2.5, 5, and 15 Hz), 3.1 (1 H, m), 5.0 (1 H, dd, *J* 2.5 and 5 Hz), 5.18 (4 H, m), 6.0 (1 H, br s), and 7.06—7.6 (14 H, ArH); *m/z* 507 and 509 (M^+, bromine isotopes), 181, 160, 133, 115, and 107.

4-(o-*Bromobenzyl*)*azetidin*-2-*one* (**4**).—A solution of the Grignard reagent prepared from Mg (480 mg, 20 mmol) and *o*-bromobenzyl bromide (4.9 g, 20 mmol) in ether (3 ml) at 20 °C[12] was cooled to −78 °C before being treated with a solution of 4-phenylsulphonylacetidin-2-one (1.055 mg, 5 mmol) in THF (4 ml). The temperature was maintained at −78 °C for 10 min, then at 0 °C for 1 h. The mixture was diluted with ethyl acetate, washed with saturated aqueous NH_4Cl, and dried. The solvent was removed, and the residue was purified by flash chromatography (CH_2Cl_2–ether; 14:1) to give the azetidinone (**4**) (400 mg) as white crystals, m.p. 75—76 °C (from pentane-EtOAc); $\nu_{max.}(CH_2Cl_2)$ 3 400 and 1 765 cm^{-1}; $\delta_H(CDCl_3)$ 2.74 (1 H, ddd, *J* 1, 2.5, and 15 Hz), 3.13 (3 H, m), 4.01 (1 H, m), 6.26 (1 H, br s), and 7.36 (4 H, ArH); *m/z* 240 and 242 [$(M + H)^+$, bromine isotopes], 118, 117, 115, and 91.

4-(o-*Bromobenzoylmethyl*)*azetidin*-2-*one* (**6a**).—To a stirred solution of the trimethylsilyl enol ether of *o*-bromoacetophenone, compound (**5a**) (2.9 g, 10 mmol) (prepared from *o*-bromoacetophenone, triethylamine, trimethylsilyl chloride, and sodium iodide),[14] in CH_2Cl_2 (4 ml) were added a solution of 4-acetoxyazetidin-2-one (606 mg, 4.7 mmol) in CH_2Cl_2 (3 ml) and freshly fused zinc iodide (1.5 g, 4.7 mmol). The mixture was stirred for 2 h at room temperature, diluted with AcOEt, washed successively with saturated aqueous $NaHCO_3$ and brine, and dried. Purification by flash chromatography (AcOEt) gave compound (**6a**) as an oil (1.17 g); $\nu_{max.}(CH_2Cl_2)$ 3 400, 1,765, and 1 705 cm^{-1}; $\delta_H(C_6D_6)$ 2.33 (1 H, ddd, *J* 1.2, 2.5, and 15 Hz), 2.63 (2 H, d, *J* 6.5 Hz), 2.84 (1 H, ddd, *J* 2.5, 2.5, and 15 Hz), 3.68 (1 H, m), and 6.97 (4 H, m); *m/z* 270 and 268 [$(M + H)^+$, bromine isotopes], 185, 183, 160, 146, and 76.

Methyl m-*Bromo*-p-[(4-*oxoazetidin*-2-*yl*)*acetyl*]*benzoate* (**6b**).—The silyl enol ether of *o*-bromo-*p*-methoxycarbonylacetophenone, compound (**5b**) (330 mg, 1 mmol), prepared according to the procedure indicated for (**5a**), was used to convert 4-acetoxyazetidin-2-one (60 mg, 0.5 mmol) into the title ester (**6b**) *via* the same experimental procedure. The azetidinone (**6b**) was obtained as a white solid (44 mg), m.p. 112 °C (from AcOEt); $\nu_{max.}(CH_2Cl_2)$ 3 400, 1 760, 1 730, and 1 710 cm^{-1}; $\delta_H(C_6D_6)$ 2.16 (1 H, ddd, *J* 1, 2.5, and 15 Hz), 2.32 (2 H, d, *J* 7 Hz), 2.7 (1 H, ddd, *J* 2.5, 5, and 15 Hz), 3.42 (3 H, s), 3.44 (1 H, m), 5.8 (1 H, br s), and 6.7—8.13 (3 H, ArH); *m/z* 327 and 325 (M^+, bromine isotopes), 243, 241, 218, 204, 84, 75, 59, and 44.

t-Butyl m-*Bromo*-p-[(4-*oxoazetidin*-2-*yl*)*acetyl*]*benzoate* (**6c**).—To a stirred solution of the crude trimethylsilyl enol ether of *o*-bromo-*p*-(t-butoxycarbonyl)acetophenone, compound (**5c**) (1.41 g, 3.8 mmol) (prepared according to the procedure described by P. Cazeau[14] except that the mixture was maintained at 40 °C overnight), in CH_2Cl_2 (8 ml) were added 4-acetoxyazetidin-2-one (245 mg, 1.9 mmol) and freshly fused zinc iodide (3.35 g, 10.5 mmol). The reaction mixture was stirred at room temperature for 15 min, then at 40 °C for 0.5 h. The product was isolated, according to the procedure used for compound (**6a**), as an oil (558 mg) (Found: C, 52.0; H, 4.9. $C_{16}H_{18}BrNO_4$ requires C, 52.19; H, 4.93%); $\nu_{max.}(CH_2Cl_2)$ 3 400, 1 765, and 1 715 cm^{-1}; $\delta_H(C_6H_6)$ 1.42 (9 H, s), 2.20 (1 H, dd, *J* 2 and 14.5 Hz), 2.46 (2 H, m), 2.75 (1 H, ddd, *J* 2.5, 5, and 14.5 Hz), 3.53 (1 H, m), 6.35 (1 H, br s), and 6.85—8.29 (3 H, ArH); *m/z* (ammonia chemical-ionisation) 387 and 389 [$(M + NH_4)^+$, bromine isotopes].

Benzyl m-*Bromo*-p-[(4-*oxoazetidin*-2-*yl*)*acetyl*]*benzoate* (**6d**).—The silyl enol ether of *o*-bromo-*p*-benzyloxycarbonylacetophenone, compound (**5d**) (405 mg, 1 mmol), obtained as for the preparation of (**6c**), was used to convert 4-acetoxyazetidin-2-one (65 mg, 0.5 mmol) into the title compound (**6d**) *via* the process described above, compound (**6d**) (160 mg) was obtained as an oil; $\nu_{max.}(CH_2Cl_2)$ 3 450, 1 775, and 1 725 cm^{-1}; $\delta_H(C_6D_6)$ 2.15 (1 H, ddd, *J* 1.5, 2.5, and 15.5 Hz), 2.33 (2 H, m), 2.68 (1 H, ddd, *J* 2.5, 5.5, and 15.5 Hz), 3.43 (1 H, m), 5.12 (2 H, s), 5.78 (1 H, br s), and 6.7—8.25 (8 H, ArH).

Ethyl (o-*Bromophenyl*)-(4-*oxoazetidin*-2-*yl*)*acetate* (**8**).—Similarly the ketene trimethylsilyl acetal of ethyl (*o*-bromophenyl)acetate, compound (**7**) (817 mg, 2.6 mmol) [prepared from di-isopropylamine (285 mg, 2.83 mmol), n-BuLi (2.53 mmol; 1.6M-solution in hexane), the bromo ester (688 mg, 2.83 mmol), and trimethylsilyl chloride (765 mg, 7 mmol)], reacted with 4-acetoxyazetidin-2-one to give the title azetidinone as an oily mixture of diastereoisomers (263 mg); $\nu_{max.}(CH_2Cl_2)$ 3 400, 1 762, and 1 722 cm^{-1}; $\delta_H(CDCl_3)$ 1.17 and 1.19 (3 H, 2 × t, *J* 7 Hz, diastereoisomers), 2.66 (1 H, ddd, *J* 1, 2.5, and 15 Hz), 3.14 (1 H, ddd, *J* 2.2, 4, and 15 Hz), 4.12 and 4.23 (2 H, 2 × q, *J* 7 Hz, diastereoisomers), 4.23 (2 H, m), 5.97 (1 H, br s), and 7.0—7.6 (4 H, ArH); *m/z* 314 and 312 (M^+, bromine isotopes), 274, 272, and 70.

Methyl p-*Acetyl*-m-*bromobenzoate* (**9b**).—The ester (**10**) (2.44 g, 10 mmol) was dissolved in acetic acid (250 ml) and a solution of CrO_3 (1M; 26.7 ml) in acetic acid–water (95:5) was added dropwise (1 h). After being stirred at room temperature for 20 h, the reaction mixture was diluted with water (1 250 ml) and extracted with ether. The combined extracts were washed with aqueous sodium hydroxide and dried ($MgSO_4$). After evaporation, the residue was chromatographed on silica gel with CH_2Cl_2–ether as eluant to afford pure *oxidised ester* (**9b**) (1.25 g, 49%), as white crystals, m.p. 50 °C (from ether) (Found: C, 46.9; H, 3.75. $C_{10}H_9BrO_3$ requires C, 46.74; H, 3.53%); $\nu_{max.}(CH_2Cl_2)$ 1 730 and 1 710 cm^{-1}; $\delta_H(CDCl_3)$ 2.75 (3 H, s), 3.95 (3 H, s), and 7.69—8.21 (3 H, ArH); *m/z* 258 $(M + H)^+$, 243, 103, 75, and 43.

t-Butyl p-*Acetyl*-m-*bromobenzoate* (**9c**).—To a solution of the acid (**11**) (2.43 g, 10 mmol) in DMF (6 ml) under argon was added *N,N'*-carbonyldi-imidazole (2.47 g, 15 mmol) and the mixture was stirred for 1 h at 40 °C. t-Butyl alcohol (2.82 ml, 30 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (1.5 ml, 10 mmol) were added successively and the reaction mixture was stirred overnight at 40 °C. After dilution with ether (150 ml), the solution was washed with M-HCl (50 ml), water (25 ml), and saturated aqueous K_2CO_3 (25 ml), dried, and evaporated. After flash chromatography (ether–pentane; 1:9), the *ester* (**9c**) was obtained as an oil (1.64 g, 55%) (Found: C, 52.5; H, 5.2. $C_{13}H_{15}BrO_3$ requires C, 52.22; H, 5.05%); $\nu_{max.}(CH_2Cl_2)$ 1 710 cm^{-1}; $\delta_H(CDCl_3)$ 1.45 (9 H, s), 2.45 (3 H, s), and 7.26—8.11 (3 H, ArH).

Benzyl p-*Acetyl*-m-*bromobenzoate* (**9d**).—Benzyl bromide (1.71 g, 10 mmol) and DBU (760 mg, 5 mmol) were successively added to a solution of the acid (**11**) (1.215 g, 5 mmol) in acetonitrile (10 ml). After being stirred overnight, the mixture was diluted with ether and washed with aqueous $NaHCO_3$. After drying and removal of the solvent, flash chromatography of the residue afforded the *ester* (**9d**) as an oil (1.08 g, 65%) (Found: C, 58.1; H, 4.1. $C_{16}H_{13}BrO_3$ requires C, 57.67; H, 3.93%); $\nu_{max.}(CH_2Cl_2)$ 1 710 cm^{-1}; $\delta_H(CDCl_3)$ 2.55 (3 H, s), 5.05 (2 H, s), and 7.3—8.2 (8 H, ArH).

Methyl m-*Bromo*-p-*ethylbenzoate* (**10**).—3-Bromo-4-ethylbenzoic acid[15] (345 g, 15 mmol) in absolute methanol (75 ml) was treated with boron trifluoride–diethyl ether (5.6 ml) and the mixture was refluxed for 3 h. After having cooled, the reaction mixture was neutralised with aqueous sodium carbonate (pH 8—9) and the insoluble product was filtered off. The aqueous phase was extracted with ether. Drying and evaporation of the solvent gave the *ester* (**10**) as an oil (3.5 g, 96%) (Found: C, 49.4; H, 4.5. $C_{10}H_{11}BrO_2$ requires C, 49.40; H, 4.56%); $\nu_{max.}(CH_2Cl_2)$ 1 720 cm^{-1}; $\delta_H(CDCl_3)$ 1.2 (3 H, t, *J* 7.5 Hz), 2.8 (2 H, q, *J* 7.5 Hz), 3.9 (3 H, s), and 7.3—8.2 (3 H, ArH).

p-*Acetyl*-m-*bromobenzoic Acid* (**11**).—3-Bromo-4-ethylbenzoic acid[15] (9 g, 39 mmol) was dissolved in a minimum amount of acetic acid and the solution was added dropwise to a vigorously stirred solution of CrO_3 (21 g) in a mixture of acetic acid and acetic anhydride (2:1; 150 ml). The temperature was carefully maintained above 20 °C. The mixture was stirred for a further 1 h, then diluted with cold water and extracted with ether. The combined extracts were dried and evaporated to dryness. The *acid* (**11**) was obtained as a solid (9.2 g, 95%), m.p. 144 °C (Found: C, 44.7; H, 3.0. $C_9H_7BrO_3$ requires C, 44.47; H, 2.90%); $\nu_{max.}$(KBr) 1 700, 1 690, and 1 550 cm^{-1}; $\delta_H(CD_3OD)$ 2.45 (3 H, s) and 7.35—8.15 (3 H, ArH).

4-(2-o-*Bromo*-β-*hydroxyphenethyl*)*azetidin*-2-*one* (**12a**).—4-(*o*-Bromobenzoylmethyl)azetidin-2-one (**6a**) (190 mg, 0.7 mmol) was dissolved in MeOH (0.9 ml), and sodium borohydride (35 mg) was added to the solution at 0 °C. The mixture was stirred at between 0 and 20 °C for 1 h, then diluted with ethyl acetate and washed with brine. After drying and evaporation of the solvent, the alcohol (**12a**) was obtained as a white solid (164 mg), m.p. 121—122 °C (from AcOEt); $\nu_{max.}(CH_2Cl_2)$ 3 580, 3 400, and 1 760 cm^{-1}; $\delta_H(CDCl_3)$ 2.04 (2 H, m), 2.60 (1 H, m), 3.07 (1 H, m), 3.80 (1 H, m), 5.13 and 5.17 (1 H, tt, *J* 3.5 and 5 Hz, mixture of diastereoisomers), 5.03 (1 H, br s), and 7.0—7.59 (4 H, ArH); *m/z* 272 and 270 [$(M + H)^+$, bromine isotopes], 187, 185, 148, 130, 105, 77, 51, and 43.

Methyl m-*Bromo*-p-[1-*hydroxy*-2-(4-*oxoazetidin*-2-*yl*)*ethyl*]-*benzoate* (**12b**).—The ketone (**6b**) (119 mg, 0.36 mmol) was reduced following the procedure described for compound (**12a**). The title alcohol was obtained as a white solid (102 mg), m.p. 154—156 °C (from C_6H_6); $\nu_{max.}(CH_2Cl_2)$ 3 590, 3 400, 1 755, and 1 720 cm^{-1}; $\delta_H(CDCl_3$–$C_6H_6)$ 1.57 (2 H, m), 2.30 (1 H, m, diast. mixture), 2.72 (1 H, m, diast. mixture), 3.35 (1 H, m), 3.6 (3 H, s), 4.73 (1 H, m, diast. mixture), 5.74 (1 H, br s), and 7.34—8.32 (3 H, ArH); *m/z* 330 and 328 [$(M + H)^+$, bromine isotopes], 245, 243, 206, 188, 77, 59, 51, 43, 42, and 41.

t-Butyl m-*Bromo*-p-[1-*hydroxy*-2-(4-*oxoazetidin*-2-*yl*)*ethyl*]-*benzoate* (**12c**).—The title compound was obtained, following the process described for compound (**12a**), as a *white solid* (99 mg), m.p. 129.4 °C (from AcOEt) (Found: C, 51.9; H, 5.6. $C_{16}H_{20}BrNO_4$ requires C, 51.9; H, 5.45%); $\nu_{max.}(CH_2Cl_2)$ 3 590, 3 400, 1 760, and 1 715 cm^{-1}; $\delta_H(C_6D_6)$ 1.46 (9 H, s), 1.70 (2 H, m), 2.32 (1 H, m), 2.69 (1 H, m), 3.35 (1 H, m), 4.9 (1 H, m), 6.53 and 6.8 (1 H, br s), and 7.56—8.44 (3 H, ArH); *m/z* (ammonia chemical-ionization) 387 and 389 [$(M + NH_4)^+$, bromine isotopes], 331 and 333.

Benzyl m-*Bromo*-p-[1-*hydroxy*-2-(4-*oxoazetidin*-2-*yl*)*ethyl*]-*benzoate* (**12d**).—This alcohol was obtained in a similar manner to that described for the preparation of (**12a**), as white crystals (335 mg), m.p. 154 °C (from AcOEt) (Found: C, 56.5; H, 4.6. $C_{19}H_{18}BrNO_4$ requires C, 56.45; H, 4.49%); $\nu_{max.}(CH_2Cl_2)$ 3 600, 3 420, 1 768, and 1 728 cm^{-1}; $\delta_H(C_5D_5N)$ (diastereoisomeric mixture) 2.13 (2 H, m), 2.87 (1 H, m), 3.22 (1 H, m), 5.43 (2 H, s), 5.51 (1 H, m), 7.3—8.3 (8 H, ArH), and 8.73 and 9.16 (1 H, br s, diast. mixture); *m/z* 405 and 403 (M^+, bromine isotopes) and 91.

Methyl p-[1-*Acetoxy*-2-(4-*oxoazetidin*-2-*yl*)*ethyl*]-m-*bromo-benzoate* (**13b**).—The alcohol (**12c**) (264 mg, 0.8 mmol) was dissolved in dry pyridine (1.2 ml) and treated with acetic anhydride (80 μl) and dimethylaminopyridine (3 mg) at room temperature for 3 h. After removal of the solvent at 40 °C under reduced pressure, the residue was purified by flash chromatography (AcOEt) to give the title compound (277 mg, 93%), m.p. 219—220 °C (from ether–pentane); $\nu_{max.}(CH_2Cl_2)$ 3 400, 1 770, 1 750, and 1 730 cm^{-1}; $\delta_H(CDCl_3)$ 2.17 (3 H, s), 2.17 (2 H, m), 2.69 (1 H, m), 3.14 (1 H, m), 3.75 (1 H, m), 3.95 (3 H, s), 5.89 (1 H, m), 6.2 (1 H, m), and 7.44—8.29 (3 H, ArH); *m/z* 371 and 369 (M^+, bromine isotopes), 68 and 43.

t-Butyl p-[1-*Acetoxy*-2-(4-*oxoazetidin*-2-*yl*)*ethyl*]-m-*bromo-benzoate* (**13c**).—The title acetate was obtained from compound (**12c**) (170 mg, 0.46 mmol) *via* the process described for the acetylation of (**12b**), as a white solid (164 mg, 88%) m.p. 107 °C (from ether); $\nu_{max.}(CH_2Cl_2)$ 3 400, 1 762, 1 745, and 1 710 cm^{-1}; $\delta_H(CDCl_3)$ 1.57 (9 H, s), 2.16 (2 H, m), 2.12 and 2.13 (3 H, s for each of the diastereoisomers), 2.88 (2 H, m), 3.72 (1 H, m), 5.89 (1 H, br s), 6.15 (1 H, m), and 7.35—8.13 (3 H, ArH); *m/z* (ammonia chemical-ionization) 429 and 431 [$(M + NH_4)^+$, bromine isotopes] and 371 and 373.

Cyclisation of 4-*Substituted Azetidin*-2-*ones. General Procedure for the Preparation of Benzocarbacephems* (**14a**—**i**) *and Benzocarbapenems* (**15a**—**c**).—A suspension of the starting monocyclic azetidinone and activated Cu powder (5 mol equiv.) in DMF (2 ml g^{-1}) was stirred and heated. A temperature between 90 and 135 °C was chosen depending on the structure of the starting material. T.l.c. was used to determine the appropriate time of heating (18 min—3 h). Then the mixture was cooled, the solvent was removed under reduced pressure, and the product was purified by preparative layer chromatography (p.l.c.).

Diethyl benzocarbacephem-1,1-*dicarboxylate* (**14a**). 30 Min at 90 °C; yield 67 mg as *white crystals*, m.p. 62—63 °C (from ether); $\nu_{max.}(CH_2Cl_2)$ 1 760, 1 755, and 1 730 cm^{-1}; $\delta_H(CDCl_3)$ 1.04 and 1.32 (2 × 3 H, t, *J* 7.2 Hz), 3.31 (1 H, dd, *J* 5 and 15.5 Hz), 3.36 (2 H, s), 3.57 (1 H, dd, *J* 2.5 and 15.5 Hz), 4.02 (1 H, dd, *J* 2.5 and 5 Hz), 4.08 and 4.3 (2 × 2 H, q, *J* 7.2 Hz), and 6.88—7.5 (4 H, ArH) (Found: M^+, 317.1258. $C_{17}H_{19}NO_5$ requires *M*, 317.1263); *m/z* 317 (M^+), 216, 202, 174, 130, 83, and 77.

Triethyl benzocarbacephem-1,1,4′-*tricarboxylate* (**14b**). 45 Min at 90 °C; yield 85 mg as an *oil* (Found: C, 61.6; H, 5.9. $C_{20}H_{23}NO_7$ requires C, 61.75; H, 5.96%); $\nu_{max.}(CH_2Cl_2)$ 1 760, 1 720, and 1 710 cm^{-1}; $\delta_H(CDCl_3)$ 1.00, 1.28, and 1.34 (3 × 3 H, t, *J* 7.2 Hz), 3.29 (1 H, dd, *J* 5 and 15.5 Hz), 3.35 (2 H, s), 3.52 (1 H, dd, *J* 3 and 15.5 Hz), 4.02 (1 H, dd, *J* 3 and 5 Hz), 4.02, 4.25, and 4.31 (3 × 2 H, t, *J* 7.2 Hz), and 7.15—8.05 (3 H, ArH); *m/z* 389 (M^+), 344, 274, and 86.

Dibenzyl 2-*oxobenzocarbacephem*-1,1-*dicarboxylate* (**14c**). 45 Min at 90 °C; yield 14 mg as an oil; $\nu_{max.}(CH_2Cl_2)$ 1 770, 1 730, and 1 700 cm^{-1}; $\delta_H(CDCl_3)$ 3.37 (1 H, dd, *J* 5.5 and 16 Hz), 3.95 (1 H, dd, *J* 2.8 and 16 Hz), 4.77 (1 H, dd, *J* 2.8 and 5.5 Hz), 5.03 and 5.12 (2 × 2 H, s), and 6.82—7.88 (14 H, ArH); *m/z* 455 (M^+) and 91.

2-*Oxobenzocarbacephem* (**14d**). 50 Min at 120 °C; yield 10 mg as a *white solid*, m.p. 121 °C (from ether) (Found: C, 70.8; H, 5.0. $C_{11}H_9NO_2$ requires C, 70.69; H, 4.85%); $\lambda_{max.}$(EtOH) 237 nm (ε 22 600); $\nu_{max.}(CH_2Cl_2)$ 1 765 and 1 685 cm^{-1}; $\delta_H(CDCl_3)$ 2.73 (1 H, dd, *J* 13 and 15.5 Hz), 3.02 (1 H, dd, *J* 2.5 and 15.5 Hz), 3.05 (1 H, dd, *J* 4.5 and 15.5 Hz), 3.47 (1 H, dd, *J* 5 and 15.5 Hz), 4.26 (1 H, m), and 7.05—7.94 (4 H, ArH); *m/z* 187 (M^+), 145, 117, and 91.

Methyl 2-*Oxobenzocarbacephem*-4′-*carboxylate* (**14e**). 45 Min at 100 °C; yield 4 mg as white crystals, m.p. 164 °C (from EtOAc); $\lambda_{max.}$(EtOH) 242 nm (25 700); $\nu_{max.}(CH_2Cl_2)$ 1 771, 1 730, and 1 696 cm^{-1}; $\delta_H(CDCl_3)$ 2.78 (1 H, dd, *J* 13 and 15.6 Hz), 3.1 (1 H, dd, *J* 3 and 15.6 Hz), 3.14 (1 H, dd, *J* 4.6 and 15.6 Hz), 3.57 (1 H, dd, *J* 4.6 and 15.6 Hz), 3.97 (3 H, s), 4.33 (1 H, m), and 7.79—8.22 (3 H, ArH) (Found: M^+, 245.0683. $C_{13}H_{11}NO_4$ requires *M*, 245.0688); *m/z* 245 (M^+), 204, and 172.

t-Butyl 2-*hydroxybenzocarbacephem*-4′-*carboxylate* (**14f**). 18 Min at 136 °C; yield 14 mg as an *oil*; $\nu_{max.}(CH_2Cl_2)$ 3 580, 1 755, and 1 710 cm^{-1}. The diastereoisomeric mixture (axial hydroxy:equatorial hydroxy 3:1) could be separated by p.l.c. (AcOEt–ether); the less polar product had m.p. 130—131 °C (from ether); $\delta_H(CDCl_3)$ 1.56 (9 H, s), 1.59 (1 H, ddd, *J* 3.2, 12, and 13.5 Hz), 2.49 (1 H, ddd, *J* 2.8. 3.2, and 13.5 Hz), 2.86 (1 H, dd, *J* 2.5 and 15.5 Hz), 3.4 (1 H, dd, *J* 4.5 and 15.5 Hz), 4.15 (1 H, m), 4.9 (1 H, dd, *J* 2.8 and 3.2 Hz), and 7.27—8.01 (3 H, ArH) (Found: M^+, 289.1316. $C_{16}H_{19}NO_4$ requires *M*, 289.1314); *m/z* 289 (M^+), 233, 216, 191, 174, 163, 57, and 41; the more polar product had m.p. 110—102 °C; $\delta_H(CDCl_3)$ 1.56 (9 H, s), 1.64 (1 H, m), 2.62 (1 H, ddd, *J* 3.5, 4.8, and 11.2 Hz), 2.83 (1 H, dd, *J* 2.5 and 15.5 Hz), 3.30 (1 H, dd, *J* 4.5 and 15.5 Hz), 3.94 (1 H, m), 4.87 (1 H, dd, *J* 4.8 and 11.2 Hz), and 7.59—7.93 (3 H, ArH).

Benzyl 2-*hydroxybenzocarbacephem*-4′-*carboxylate* (**14g**). 35 Min at 136 °C; yield 17 mg as an *oil*; $\nu_{max.}(CH_2Cl_2)$ 3 600, 1 760, and 1 720 cm^{-1}; $\delta_H(CDCl_3)$ (diastereoisomeric mixture; only the major product is described) 1.61 (1 H, ddd, *J* 2.9, 12, and 13.5 Hz), 2.49 (1 H, ddd, *J* 2.6, 3.5, and 13.5 Hz), 2.87 (1 H, dd, *J* 3 and 15.5 Hz), 3.41 (1 H, dd, *J* 5 and 15.5 Hz), 4.16 (1 H, m), 4.92 (1 H, dd, *J* 2.6 and 2.9 Hz), 5.35 (1 H, s), 5.37 (1 H, s), and 7.28—8.12 (8 H, ArH) (Found: M^+, 323.1154. $C_{19}H_{17}NO_4$ requires *M*, 323.1157); *m/z* 323 (M^+), 174 and 91.

Methyl 2-*acetoxybenzocarbacephem*-4′-*carboxylate* (**14h**). 3.5 H at 138 °C; yield 142 mg as an *oil*; $\nu_{max.}$ 1 770, 1 750, 1 735, and 1 690 cm^{-1}; $\delta_H(CDCl_3)$ (mixture of diastereoisomers, 1 : 2.2 ratio; only axial acetate is described) 1.78 (1 H, ddd, *J* 2.75, 12.5, and 14 Hz), 2.1 (3 H, s), 2.58 (1 H, ddd, *J* 3, 3, and 14 Hz), 2.97 (1 H, dd, *J* 2.5 and 15.5 Hz), 3.5 (1 H, dd, *J* 5 and 15.5 Hz), 3.96 (3

H, s), 4.16 (1 H, m), 6.18 (1 H, dd, *J* 2.75), and 7.52—8.22 (3 H, ArH) (Found: M^+, 289.0947. $C_{15}H_{15}NO_5$ requires *M*, 289.0950); *m/z* 289 (M^+), 230, 201, 188, 156, and 43.

t-Butyl 2-acetoxybenzocarbacephem-4'-carboxylate (**14i**). 2.5 H at 135 °C; yield 20 mg as an *oil*; $\nu_{max.}(CH_2Cl_2)$ 1 760, 1 735, and 1 710 cm^{-1}; $\delta_H(CDCl_3)$ (diastereoisomeric mixture, ratio 1:1.78; only the major product is described) 1.58 (9 H, s), 1.74 (1 H, ddd, *J* 3.1, 12.5, and 14.5 Hz), 2.06 (3 H, s), 2.54 (1 H, ddd, *J* 2.8, 3.5, and 14.5 Hz), 2.92 (1 H, dd, *J* 2.5 and 15.5 Hz), 3.46 (1 H, dd, *J* 5 and 15.5 Hz), 4.12 (1 H, m), 6.15 (1 H, dd, *J* 2.8 and 3.1 Hz), 7.46—8.13 (3 H, ArH) (Found: M^+, 331.1418. $C_{18}H_{21}NO_5$ requires *M*, 331.1419); *m/z* 331 (M^+), 258, 187, 173, 174, 69, 57, and 43.

Dibenzyl benzocarbapenem-1,1-dicarboxylate (**15a**). 30 Min at 130 °C; yield 12 mg, m.p. 146 °C; $\nu_{max.}(CH_2Cl_2)$ 1 790 and 1 730 cm^{-1}; $\delta_H(CDCl_3)$ 2.65 (1 H, dd, *J* 3.5 and 17 Hz), 3.42 (1 H, dd, *J* 6 and 17 Hz), 5.18 (5 H, m), 7.2—7.62 (14 H, ArH); *m/z* 427 (M^+), 220 and 91.

Ethyl benzocarbapenem-1-carboxylate (**15b**). 30 Min at 130 °C; yield 8 mg as an oil; $\nu_{max.}(CH_2Cl_2)$ 1 780 and 1 730 cm^{-1}; $\delta_H(CDCl_3)$ 1.25 and 1.35 (3 H, 2 × t, *J* 7 Hz, diastereoisomers), 3.03 (1 H, dd, *J* 3.5 and 16 Hz), 3.33 and 3.38 (1 H, 2 × d, *J* 4.8 Hz, diastereoisomers), 3.61 (1 H, dd, *J* 5.5 and 16 Hz), 4.26 and 4.3 (2 H, 2 × q, *J* 7 Hz), 4.72 (1 H, m), and 7.0—7.48 (4 H, ArH); *m/z* 231 (M^+), 189, 185, 161, 144, 130, 117, 89, 77, 71, 57, and 43.

Benzocarbapenem (**15c**). 20 Min at 135 °C; yield 6 mg as an oil; $\nu_{max.}(CH_2Cl_2)$ 1 770 cm^{-1}; $\delta_H(CDCl_3$; 250 MHz) 2.98 (1 H, dd, *J* 3 and 16.4 Hz), 3.15 (1 H, dd, *J* 7.8 and 16.8 Hz), 3.37 (1 H, dd, *J* 8.8 and 16.7 Hz), 3.53 (1 H, dd, *J* 5.2 and 16.4 Hz), 4.38 (1 H, m), and 7.0—7.24 (4 H, ArH); *m/z* 159 (M^+), 117, 57, 55, 44, and 43.

t-Butyl 2-Chlorobenzocarbacephem-4'-carboxylate (**17a**).—Thionyl chloride (11.8 mg, 0.1 mmol) was added to dry DMF (0.2 ml) at 4 °C; the mixture was then stirred for 5 min, then added to a solution of the diastereoisomeric alcohols (**14f**) (24 mg, 0.08 mmol) in DMF (0.2 ml) under argon at room temperature. After being stirred for 10 min, the mixture was purified directly on preparative plates (ether–pentane). The product was obtained as an oily diastereoisomeric mixture (ratio 1:2.3, equatorial:axial with regard to the chlorine on C-2) (12 mg) which could be separated by further p.l.c.; the less polar product (axial chloride) had $\nu_{max.}(CH_2Cl_2)$ 1 758 and 1 704 cm^{-1}; $\delta_H(CDCl_3$; 250 MHz) 1.59 (9 H, s), 2.04 (1 H, ddd, *J* 3.1, 12.04, and 14.15 Hz), 2.69 (1 H, ddd, *J* 2.6, 3.06, and 14.15 Hz), 2.96 (1 H, dd, *J* 2.68 and 15.7 Hz), 3.47 (1 H, dd, *J* 5.17 and 15.7 Hz), 4.36 (1 H, m), 5.30 (1 H, dd, *J* 2.6 and 3.1 Hz), and 7.37—8.07 (3 H, ArH) (Found: M^+, 307.0973. $C_{16}H_{18}ClNO_3$ requires *M*, 307.0975); *m/z* 309 and 307 (M^+, chlorine isotopes), 174, 130, and 57. The more polar product (equatorial chloride) had $\delta_H(CDCl_3$; 250 MHz) 1.59 (9 H, s), 2.07 (1 H, m), 2.84 (1 H, ddd, *J* 3.34, 5.21, and 12.15 Hz), 2.96 (1 H, dd, *J* 2.65 and 15.7 Hz), 3.38 (1 H, dd, *J* 5.12 and 15.7 Hz), 3.94 (1 H, m), 5.19 (1 H, dd, *J* 5.21 and 12.15 Hz), and 7.74—8.03 (3 H, ArH).

Benzyl 2-Chlorobenzocarbacephem-4'-carboxylate (**17b**).—The *title chloride* was obtained from the alcohol (**14g**) *via* the process described for the preparation of (**17a**), as an oil (17 mg); $\nu_{max.}(CH_2Cl_2)$ 1 760 and 1 720 cm^{-1}; $\delta_H(CDCl_3)$ (diastereoisomeric mixture, ratio 1:6.7 equatorial:axial respectively in relation to chlorine on C-2; only the major diastereoisomer is described) 2.03 (1 H, ddd, *J* 3.2, 11.5, and 13.5 Hz), 2.7 (1 H, ddd, *J* 2.8, 2.8 and 13.5 Hz), 2.94 (1 H, dd, *J* 3 and 15.5 Hz), 3.46 (1 H, dd, *J* 5 and 15.5 Hz), 5.25 (1 H, dd, *J* 2.8 and 3.2 Hz), 5.34 (1 H, s), 5.36 (1 H, s), and 7.29—8.11 (8 H, ArH) (Found: M^+, 341.0822. $C_{19}H_{16}ClNO_3$ requires *M*, 341.0818); *m/z* 341 and 343 (M^+, chlorine isotopes), 264, 194, 192, 156, 129, 91, and 65.

t-Butyl 2-Fluorobenzocarbacephem-4'-carboxylate (**17c**).—To a solution of DAST (14 μl, 0.11 mmol) in CH_2Cl_2 (0.2 ml) at −80 °C under argon was added a solution of the diastereoisomeric alcohols (**14f**) (35 mg, 0.12 mmol) in CH_2Cl_2 (0.2 ml). The temperature was slowly raised to −20 °C (2 h), then the mixture was directly purified by p.l.c. (ether–EtOAc; 9:1). The product was obtained as an *oil* (18 mg, 51%), $\nu_{max.}(CH_2Cl_2)$ 1 760 and 1 710 cm^{-1}; $\delta_H(CDCl_3)$ (no trace of equatorial fluoride) 1.6 (9 H, s), 1.72 (1 H, dddd, *J* 2.5, 12.5, 14.5, and 39 Hz), 2.72 (1 H, dddd, *J* 2.9, 2.9, 11.5, and 14.5 Hz), 2.9 (1 H, dd, *J* 2.5 and 15.4 Hz), 3.44 (1 H, dd, *J* 4.95 and 15.4 Hz), 4.11 (1 H, m), 5.6 (1 H, ddd, *J* 2.5, 2.9, and 48.7 Hz), and 7.4—8.4 (3 H, ArH); $\delta_F(CDCl_3)$ −10.3 p.p.m. (ddd, *J* 11.7, 38.1, and 48.8 Hz) (Found: M^+, 291.1267. $C_{16}H_{18}FNO_3$ requires *M*, 291.1270); *m/z* 291 (M^+), 218, 192, and 57.

2-Chlorobenzocarbacephem-4'-carboxylic Acid (**18a**).—The ester (**17a**) (12 mg, 0.045 mmol) was treated with CF_3CO_2H (0.3 ml) at between −10 and 0 °C (45 min). The residue obtained by evaporation under reduced pressure was triturated in ether and provided the acid (**18a**) as a solid (8 mg); m.p. 168 °C (decomp.); $\nu_{max.}$(KBr) 1 758 and 1 688 cm^{-1}; $\delta_H(C_5D_5N$; 250 MHz) [only major product, axial chloride isomer (1:8.8 ratio) is described] 1.98 (1 H, ddd, *J* 3.3, 12.83, and 14.62 Hz), 2.49 (1 H, ddd, *J* 2.76, 3.3, and 14.62 Hz), 2.92 (1 H, dd, *J* 3.16 and 16 Hz), 3.31 (1 H, dd, *J* 5.25 and 16 Hz), 4.18 (1 H, m), 5.48 (1 H, dd, *J* 2.76 and 3.3 Hz), and 7.52—8.09 (3 H, ArH); *m/z* 251—253 (M^+, chlorine isotopes), 174, 173, 156, 130, 128, 69, 44, 43, 41, and 36.

Benzocarbacephem-4'-carboxylic Acid (**18b**).—The benzyl ester (**17b**) (14 mg, 0.041 mmol) was hydrogenolysed in 95% EtOH (2 ml) with 10% Pd–C (20 mg) and H_2 (1 atm). After being stirred for 30 min at room temperature, the mixture was filtered off and the filtrate was evaporated under reduced pressure. The residue was triturated in ether and the acid (**18b**) was obtained as a solid (8.1 mg), m.p. 187 °C (decomp.); $\nu_{max.}$(KBr) 3 450, 1 755, and 1 685 cm^{-1}; $\delta_H(D_2O)$ (as sodium salt) 1.61 (1 H, m), 2.37 (1 H, m), 2.91 (2 H, m), 2.92 (1 H, dd, *J* 2 and 15.5 Hz), 3.38 (1 H, dd, *J* 4.5 and 15.5 Hz), 3.87 (1 H, m), and 7.22—7.75 (3 H, m); *m/z* 217 (M^+), 175, 130, 73, 60, and 55.

2-Fluorobenzocarbacephem-4'-carboxylic Acid (**18c**).—This compound was obtained in a manner similar to the procedure for the preparation of acid (**18a**), as a solid (7.6 mg), m.p. 175 °C; $\nu_{max.}$(KBr) 1 755 and 1 688 cm^{-1}; $\delta_H(D_2O)$ (as sodium salt) 1.76 (1 H, dddd, *J* 2.5, 12.5, 15, and 41.5 Hz), 2.70 (1 H, dddd, *J* 2.8, 2.8, 12.5, and 15 Hz), 2.95 (1 H, dd, *J* 2.5 and 15.5 Hz), 3.42 (1 H, dd, *J* 4.5 and 15.5 Hz), 4.03 (1 H, m), 6.4 (1 H, ddd, *J* 2.5, 2.8, and 48 Hz), and 7.42—7.76 (3 H, ArH); $\delta_F(D_2O)$ (as sodium salt) −14.3 p.p.m. (ddd, *J* 12.5, 41.5, and 48 Hz); *m/z* 235 (M^+), 194, 193, 148, 69, 57, 55, 45, 44, 43, and 41.

2-Acetoxybenzocarbacephem-4'-carboxylic Acid (**18d**).—The acid was obtained from the ester (**14i**) *via* the procedure used for the preparation of acid (**18a**), as a solid (8.4 mg), m.p. 173—175 °C; $\nu_{max.}$(KBr) 1 755, 1 730, and 1 710 cm^{-1}; $\delta_H(D_2O)$ [as a sodium salt by taking up the acid in D_2O with $NaHCO_3$ (1.1 mol equiv.)] [diastereoisomeric ratio 1:2.3 and the axial isomer (major product) only was described] 1.83 (1 H, ddd, *J* 2.5, 12.5, and 14.5 Hz), 2.60 (1 H, ddd, *J* 3.3 and 14.5 Hz), 2.12 (3 H, s), 3.01 (1 H, dd, *J* 2.5 and 15.5 Hz), 3.49 (1 H, dd, *J* 4.5 and 15.5 Hz), 4.18 (1 H, m), 6.15 (1 H, dd, *J* 2.5 and 3 Hz), and 7.5—7.96 (3 H, ArH); *m/z* 275 (M^+), 173, 156, 60, and 43.

Acknowledgements

One of us (L. D. S. Yadav) on leave from M. G. Degree College (Gorakhpur, India) thanks the CNRS for its financial support.

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Received 10*th March* 1986; *Paper* 6/468