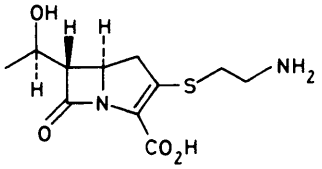
New Approaches to the Synthesis of β-Lactam Antibiotics

John Knight and Philip J. Parsons *
Department of Chemistry, The University, Southampton SO9 5NH

The selective syntheses of carbapenams and carbacephams are described from the same intermediate by application of appropriate experimental conditions using radical cyclisation techniques. The carbapenams were synthesised diastereoselectively by a 5-*exo trig* cyclisation.

Over the past decade the scope of research directed toward the synthesis of β-lactam antibiotics has increased dramatically following the discovery of thienamycin (**1**), a highly active antibiotic and fermentation product of *Streptomyces cattleya*.[1,2]



(**1**)

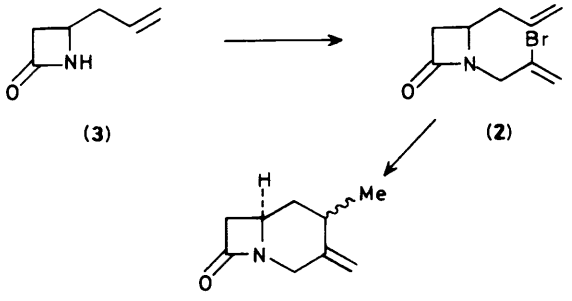
To date, the number of thienamycin derivatives and other closely related carbapenems of natural origin has risen to over 30 to include the epithienamycins, olivanic acids,[3] carpetimycins,[4] asparenomycins,[5] pluracidomycins,[6] and carbapenems of the PS group.[7] This new generation of naturally occurring β-lactam antibiotics has attracted a great deal of attention not only because of their novel chemical structures, but also owing to the fact that the majority of carbapenems are highly active broad-spectrum antibiotics with β-lactamase resistance.[8] However, owing to their strained bicyclic ring systems, the carbapenems are generally labile and only sufficiently chemically stable for study in a limited pH range around neutrality. This, coupled to the fact that, so far, efforts to optimise fermentation yields have been largely unsuccessful, puts the emphasis on totally synthetic approaches.[9]

In general, most synthetic approaches have relied upon first constructing the β-lactam ring and then completing the bicyclic nucleus by linking together appropriate substituents. For this latter bond connection three methods are commonly used: the Wittig-type reaction; the aldol-type condensation, and the carbene insertion reaction.[9] Our retrosynthetic analysis again relied upon the initial formation of the β-lactam ring, but the bond connection to generate the bicycle was to be made by a free radical annelation. The monocyclic precursors were conceptionally simple to obtain and the annelation procedure required only mild, neutral conditions.[10]

Results and Discussion

The first aim was to investigate the cyclisation of the β-lactam (**2**) in the hope of producing the carbacepham (**4**) *via* a 6-*exo trig* cyclisation[11] (Scheme 1).

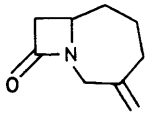
The synthesis of compound (**2**) was achieved in 61% yield by phase transfer-catalysed alkylation[12] of the 4-allylazetidinone (**3**)[13] with freshly distilled 2,3-dibromopropene. Treatment of compound (**2**) with tributyltin hydride and a catalytic amount of azoisobutyronitrile (AIBN) (8 mol%) in benzene under photolytic conditions resulted not in the carbacepham (**4**) but in the 4,7-bicyclic structure (**5**) in 77% yield *via* 7-*endo trig*



(**3**) (**2**) (**4**)

Scheme 1.

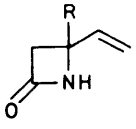
cyclisation. This product was distinguished from the carbacepham (**4**) by ^{13}C n.m.r.



(**5**)

Although in the majority of such cases the *exo* cyclisation is favoured,[11] this finding was not totally unexpected in the light of the results of Bachi *et al.*[14] who found that radical cyclisations in β-lactam systems appeared to be dominated by the stability of the intermediary radical. This was also the case when Beckwith *et al.*[15] studied the radical cyclisation reaction in β-lactam systems, suggesting that the unusual preference for *endo* ring closure was attributable to the strain imposed upon the *exo* transition structures by the azetidinonyl ring.

We next turned our attention to the vinylazetidinones (**6a**) and (**6b**) in the hope of inducing a similar *endo* cyclisation.

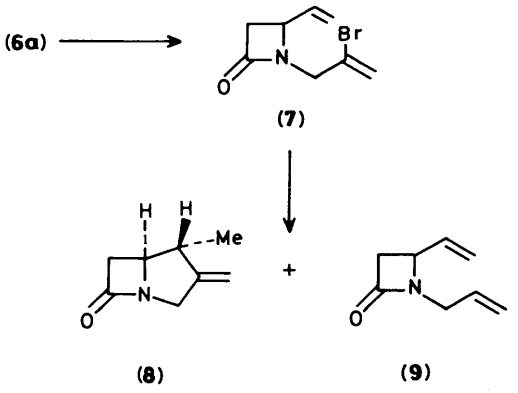


(**6**)

a; R = H

b; R = Me

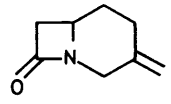
Alkylation of compound (**6a**) under phase transfer conditions[12] afforded compound (7) in 73% yield (Scheme 2). Photolysis of (7) [10mM solution of (7) in benzene] in the presence of tributyltin hydride and AIBN gave as a single diastereoisomer



Scheme 2.

the 1α-methylcarbapenam (**8**)* in 30% yield, together with about 70% of the reduction product (**9**). The relative stereochemistry of compound (**8**) was confirmed by nuclear Overhauser enhancement (n.O.e.) n.m.r. studies in which enhancements in one of the C-8 protons and the C-5 proton were observed upon irradiation at the methyl resonance together with an enhancement of the C-6β-proton upon irradiation at the C-1 resonance.

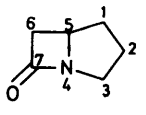
Furthermore, decoupling experiments in the n.m.r. spectrum revealed that the C-1 proton is coupled to every other proton with the exception of the C-6α-proton. When the reaction was conducted at a lower concentration (8mM) the yield of compound (**8**) increased to 50%. This sequence has provided, to our knowledge, the first example of a 5-*exo trig* radical cyclisation in β-lactam systems.[15] We next tried the experiment at 3mM concentration of compound (**7**) hoping to further enhance the cyclisation reaction to the bicycle (**8**), but to our surprise none of the carbapenam was isolated. Instead the carbacepham (**10**) was obtained in 30% yield.



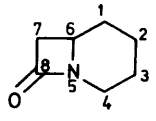
(10)

The cyclisation reaction was next tried thermally in order to investigate the product distribution. When a 10mM toluene solution of compound (**7**) was heated under reflux for 4 days with tributyltin hydride and AIBN, the carbacepham (**10**) was the only cyclised product isolated (58% yield). Repeating the thermal reaction in benzene gave again only the carbacepham (**10**) though in a lower yield (32%) and after the longer reaction time of 5.5 days. These results are very interesting as we have shown that from one readily available intermediate (**7**) it is possible to proceed regiospecifically to the carbacepham or diastereoselectively to the 1α-methylcarbapenam. Also, they pose a mechanistic problem which will be briefly considered later.†

* All compounds are racemic, for clarity only one enantiomer has been depicted. In the text a trivial naming and numbering system has been employed thus

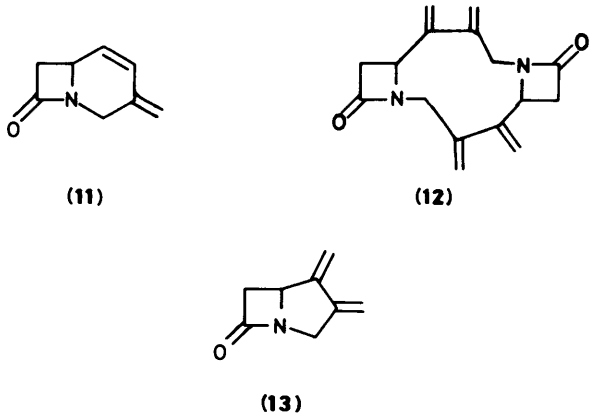


Carbapenam



Carbacepham

† See note added in proof on page 1241.

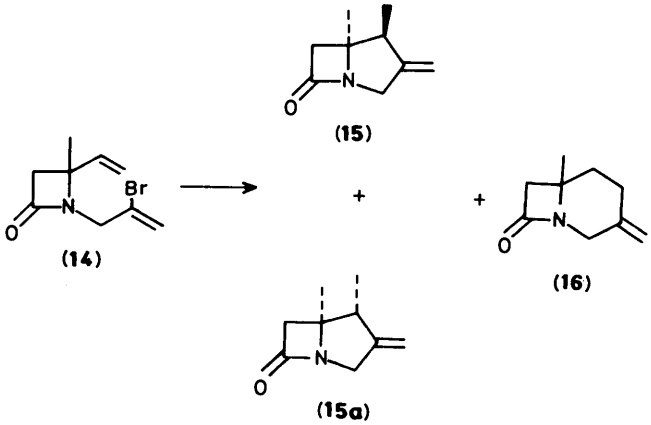


(11) (12) (13)

Besides studying the tin-mediated cyclisations of compound (**7**), we have looked at the palladium(II) catalysed cyclisation based on a recent communication by Grigg *et al.*[16a] Treatment of the azetidinone (**7**) with palladium(II) acetate (10 mol%), triphenylphosphine (20 mol%) and potassium carbonate in hot acetonitrile (80 °C) afforded two cyclised products, the carbacephem (**11**) in 35% and the unstable dimer (**12**) in 23% yield.

The dimer (**12**) was distinguished from the carbapenam (**13**) on the basis of its mass spectrum and carbonyl absorption in the i.r. region at 1 770 cm^{-1} which was considered to be too low in frequency for the strained bicycle (**13**). This was however quite surprising on the basis of Grigg's results,[16a] though a subsequent paper from the same group reports similar findings when trying to form a bicyclic system.[16b]

Returning to the tin-mediated radical cyclisations, we felt that the diastereoselectivity observed in the 5-*exo trig* cyclisation to form compound (**8**) was possibly a consequence of the preferred rotational conformation of the vinyl group in compound (**7**) such that the attacking vinyl radical was able to approach only one face of the π-system. To test this hypothesis we examined the products resulting from both the thermal and photochemical reactions of the angular methyl substituted azetidinone (**14**) which was obtained from compound (**6b**) in 67% yield.[12] The results are summarised in Scheme 3.



	(15)	(15a)	(16)
Thermally	59%	3%	30%
Photochemically	58%	10%	10%

Scheme 3.

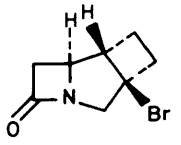
We found that in support of our hypothesis the 1β-methylcarbapenam (**15**) was the major product both from the thermal and photochemical experiments. Presumably the carbapenam products (**15**) and (**15a**) were obtained from the thermal

reaction either as a result of the angular methyl group imposing steric compression on the vinyl group, placing it closer in space to the radical site and facilitating the *exo* ring closure, or as a result of the *endo* transition structure being disfavoured through steric interactions imposed by the presence of the methyl group. The stereochemistry of compound (**15**) was assigned on the basis of its ^{1}H n.m.r., the significant feature being that the C-1 proton did not exhibit any coupling to the C-6β-proton [*cf.* product (**8**)]. The 1α-methylcarbapenam (**15a**) was inseparable from the carbacepham (**16**) and its stereochemistry was assigned on the basis of that of compound (**15**).

These results have more significance when viewed in the light of recent findings that 1β-methylthienamycin analogues are highly resistant to renal dipeptidase-I and yet retain excellent antibacterial activity.[17] So the placement of a suitable angular group that could be removed at a later stage could be employed to selectively obtain the 1β-alkyl substitution pattern.

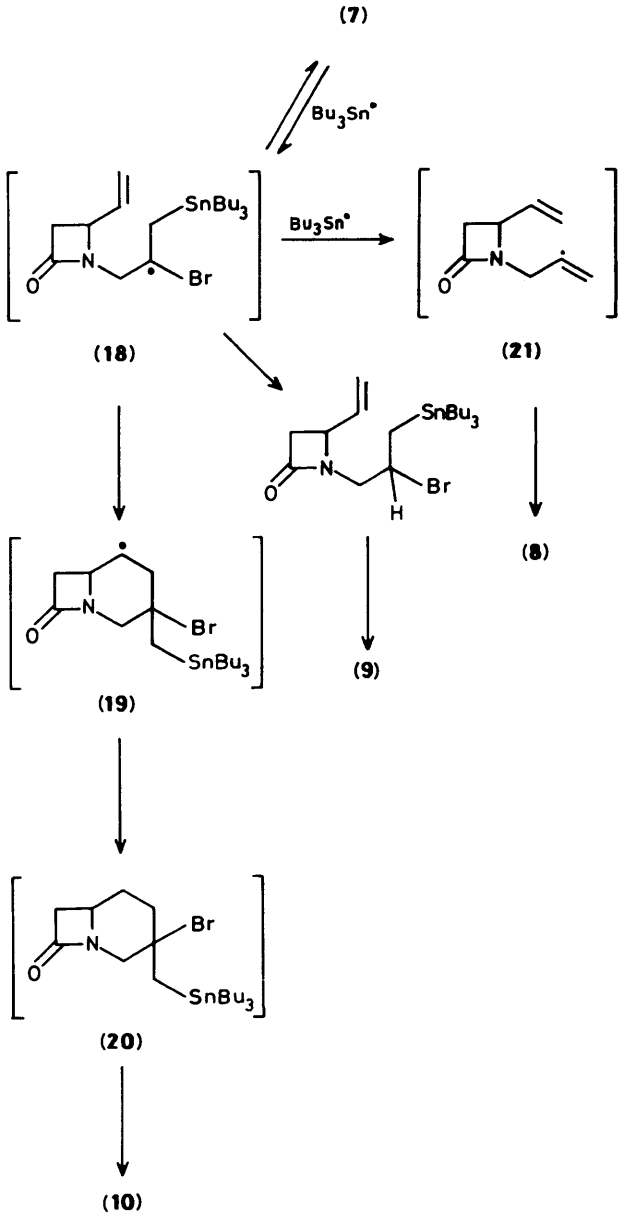
Mechanistically we feel that, in keeping with the results of Bachi *et al.*[14] and Beckwith *et al.*,[15] the thermal reactions are proceeding *via* a radical chain process and the *endo* cyclisation product is favoured as a result of the azetidinonyl ring strain disfavouring the *exo* transition structure. Bachi *et al.*[14] showed that the balance can be tipped in favour of the *exo* products by introducing a group capable of resonance stabilisation of the intermediary radical formed by *exo* ring closure. However, the differing photochemical pathway is not so straightforward.

It is well recognised that under kinetic conditions the 5-*exo* cyclisation is favoured, but reversible, so the 6-*endo* cyclisation products are favoured at higher temperatures.[11] However, we do not feel the problem is kinetic *versus* thermodynamic in origin as the uncyclised radical is not resonance stabilised, an apparent pre-requisite for the reversibility of the 5-*exo* cyclisation.[11] Also, such a rationalisation would make it difficult to explain the observation of the 6-*endo trig* product (**10**) from photolysis at low concentration. The idea of an initial $[2_\pi + 2_\pi]$ cyclisation to afford a tricyclic intermediate such as (**17**) was ruled out on two counts: first, irradiating compound (**6**)



(**17**)

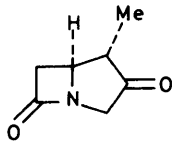
in benzene in the absence of Bu_3SnH (without AIBN, with AIBN, and also with benzophenone) resulted in 100% recovery of starting material; secondly, conducting the photochemical reaction with a low pressure lamp gave a lower product yield [32% of (**8**)] and required a longer reaction time. (This latter result may have been a consequence of lower initiator concentration.) From the results it appeared that the u.v. wavelength employed was significant and this must be taken into account when proposing a mechanism. Therefore, a possible reason for the 5-*exo trig* regioselectivity is that, as many organic compounds containing a carbonyl have end absorption in the near u.v. region, the β-lactam carbonyl was undergoing some excitation (although in the routine u.v. spectrum no chromophore was detected) and this resulted in sufficient relief of the ring strain (through bond elongation perhaps) to permit the *exo* transition structure. Furthermore, if in the case of the vinyl bromide the mechanism did not involve direct attack of the $Bu_3Sn^\bullet$ radical upon the bromide (as is the case for alkyl halides[18]) but an initial attack upon the double bond, a known process,[19] then a tertiary radical intermediate (**18**) would be formed. The demise of such a radical may then be concentration dependent as indicated in Scheme 4. At low $Bu_3Sn^\bullet$



Scheme 4.

concentration this sterically demanding tertiary radical could undergo the 6-*endo trig* cyclisation and, after reduction of compound (**19**), form (**20**), which could collapse after attack by more $Bu_3Sn^\bullet$ to form the carbacepham (**10**). However, at higher concentration the suggested tertiary radical intermediate (**18**) was attacked before the cyclisation to generate the highly reactive vinyl radical (**21**) which, being less sterically demanding, reacted *via* the 5-*exo trig* transition structure to afford the carbapenam (**8**). The thermally conducted reactions could also be said to follow such a pathway, but only afford the carbacepham (**10**) as there has been no relief in β-lactam ring strain *via* excitation in those cases.

Compounds (**8**), (**10**), and (**15**) were subjected to ozonolysis, affording the respective ketones (**22**), (**23**), and (**24**) in 51, 85, and 67% respectively giving further characterisation of the bicyclic products. The relative stereochemistry of ketone (**22**) was as in the precursor (**8**), as confirmed by n.O.e. n.m.r. study which showed identical enhancement patterns with (**8**). The relative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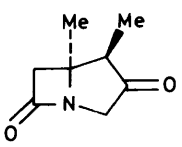
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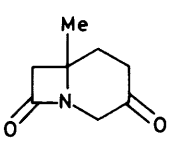
(24)

stereochemistry of compound (**23**) was assigned on the basis of the absence of a coupling between the C-1 proton and the C-6β proton, and its compatibility with that of compound (**15**).

Although attempts to introduce a carboxy group at C-3(C-4) have failed, our results show that this new approach to bicyclic β-lactams has great versatility as it is potentially tuneable with respect to both regiospecificity and diastereoselectivity, uses readily accessible intermediates, and provides quick access into the kind of bicyclic β-lactams that have become recognised as key intermediates for the synthesis of thienamycin analogues.[9]

Experimental

Where appropriate, solvents were dried before use in the following manner; tetrahydrofuran was distilled from sodium and benzophenone; acetonitrile, benzene and toluene were distilled from calcium hydride immediately prior to use. For the photolyses, the benzene was degassed with nitrogen and a Hanovia 1-l Photochemical Reactor 125 W medium pressure lamp with quartz filter was used. For the thermally conducted radical cyclisation, the toluene was degassed with nitrogen. Light petroleum refers to that fraction boiling in the range 40—60 °C. Suction flash chromatography was conducted using Merck Kieselgel 60H (Art 7736) and column chromatography with Merck Kieselgel 60 (Art 7729). Infrared (i.r.) spectra were taken on a Perkin-Elmer 298 spectrometer. The nuclear magnetic resonance (n.m.r.) spectra were run at 60 MHz on a Perkin-Elmer R12a, at 100 MHz on a Varian Associates XL100, at 250 MHz on a Bruker machine (care of Beecham Pharmaceuticals), and at 360 MHz on a Bruker AM360 instrument using tetramethylsilane (TMS δ = 0) as internal standard in deuteriochloroform. The ^{13}C n.m.r. spectrum was run on the Bruker AM360 machine at 90.556 MHz in deuteriochloroform with TMS. Mass spectra were recorded on a Kratos MS30 DS 55S instrument or care of Beecham Pharmaceuticals.

N-(2-*Bromoprop*-2-*enyl*)-4-*prop*-2-*enylazetidin*-2-*one* (**2**).—A stirred mixture of the 4-allylazetidin-2-one (**3**) (2 mmol, 0.22 g), 2,3-dibromopropene (freshly distilled, 1.2 mol equiv., 0.25 ml) and tetrabutylammonium hydrogen sulphate (10 mol%) in tetrahydrofuran (10 ml) under nitrogen at 10 °C was treated with freshly powdered potassium hydroxide (1.1 mol equiv., 0.12 g) causing an exotherm. The reaction mixture was removed from the cooling bath and stirred at room temperature for 5 h before being added to saturated aqueous ammonium chloride (30 ml) and extracted into ethyl acetate (3 × 15 ml). The combined organic extracts were washed with brine (10 ml), dried ($MgSO_4$), concentrated *in vacuo* and Kugelrohr distilled to furnish the *vinyl bromide* (**2**) (280 mg, 61%), b.p. 80 °C (0.05 mmHg) (Kugelrohr) (Found: C, 46.9; H, 5.4; Br, 35.0; N, 6.0. $C_9H_{12}BrNO$ requires C, 46.9; H, 5.3; Br, 34.7; N, 6.1%); $\nu_{max.}(CH_2Cl_2)$ 1 750 (s, C=O), 1 640 (w, C=C), and 1 630 cm^{-1} (w, C=C); δ_H (360 MHz) 2.29—2.57 (2 H, m, $HCCH_2C$=), 2.67 (1 H, dd, *J* 2.4 and 14.8 Hz, 3-H), 3.08 (1 H, dd, *J* 5.2 and 14.8 Hz, 3-H), 3.71—3.79 (1 H, m, 4-H), 3.86 [1 H, d, *J* 16.1 Hz, –N–C(*H*)H–C=], 4.28 [1 H, d, *J* 16.1 Hz, N–C(H)*H*–C=], and 5.0—6.0 (5 H, m, olefinic H) [Found: M^+ − Br (9%) 150.0888. $C_9H_{12}NO$ requires *M*, 150.0919].

3-*Methylene*-1-*azabicyclo*[5.2.0]*nonan*-2-*one* (**5**).—The vinyl bromide (**2**) (0.56 mmol, 130 mg), tributyltin hydride (1.2 mol equiv., 0.18 ml) and AIBN (8 mol%) were stirred in dry degassed benzene and irradiated with u.v. light for 3 h. The reaction was then concentrated *in vacuo* and purified by column chromatography eluting with hexane–ethyl acetate mixtures (4:1, 3:1, and then 2:1) to provide the *bicyclic product* (**5**) (65 mg, 77%) contaminated with some organotin residues. H.p.l.c. furnished a sample for authentication (Found: M^+ + 1, 152.1076. $C_9H_{13}NO$ requires M^+ + 1, 152.1076); $\nu_{max.}(CH_2Cl_2)$ 1 740 (s, C=O) and 1 645 cm^{-1} (w, C=C); δ_H (360 MHz) 1.2—1.5 (2 H, m, $H_2CCH_2CH_2$), 1.8—2.1 (3 H, m, $HC–CH_2–$, $H_2C=C–CH–$), 2.48 (1 H, d, *J* 14.3 Hz, O=C–C*H*), 2.58 (1 H, dd, *J* 5.1 and 12.9 Hz, $H_2C=C–CH–CH_2$), 3.02 (1 H, dd, *J* 4.7 and 14.3 Hz, O=C–C*H*) 3.52—3.54 (1 H, m, NC*H*), 3.93 (2 H, ABq, *J* 13.9 Hz, $N–CH_2$), and 4.95 and 4.97 (2 H, 2 s, $C=CH_2$); δ_C (90.556 MHz) 29.6 (CH_2), 36.2 (CH_2), 36.5 (CH_2), 42.6 (CH_2), 49.4 (CH_2), 52.7 (CH), 116.1 (=CH_2), 144.7 (C=), and 199.7 p.p.m. (C=O); *m/z* (c.i.) 152 (M^+ + 1, 100%); *m/z* (e.i.) 151 (M^+, 13), 109 (*M* − 42, 8), 95 (23), and 56 (12).

N-(2-*Bromoprop*-2-*enyl*)-4-*vinylazetidin*-2-*one* (**7**).—Phase transfer alkylation of 4-vinylazetidin-2-one (16.8 mmol) as in the preparation of compound (**2**) afforded the *vinyl bromide* (**7**) (2.64 g, 73%), b.p. 80—85 °C at 0.1 mmHg (Kugelrohr) (Found: C, 44.35; H, 4.8; Br, 36.7; N, 6.6. $C_8H_{10}BrNO$ requires C, 44.45; H, 4.7; Br, 37.0 N, 6.5%); $\nu_{max.}(CH_2Cl_2)$ 1 760 (s, C=O) and 1 630 cm^{-1} (w, C=C); δ_H (60 MHz) 2.7 (1 H, dd, *J* 2 and 14 Hz, 3-H), 3.3 (1 H, dd, *J* 5 and 14 Hz, 3-H), 4.0 (2 H, ABq, *J* 16 Hz, $–N–CH_2–$), 3.9—4.3 (1 H, m, 4-H), and 5.1—6.1 (5 H, m, olefinic H) [Found: M^+ − Br (76%), 136.0734. $C_8H_{10}NO$ requires *M*, 136.0762].

4α-*Methyl*-3-*methylene*-1-*azabicyclo*[3.2.0]*heptan*-7-*one* (**8**).—A stirred solution of the vinyl bromide (**7**) (5 mmol, 1.08 g), AIBN (8 mol%), and tributyltin hydride (1.2 mol equiv., 1.61 ml) in benzene (625 ml) was irradiated with u.v. light for 6¼ h. Concentration under reduced pressure and column chromatography eluting with hexane–ethyl acetate (4:1, 3:1, and finally 2:1) afforded the *bicyclic product* (**8**) as a single diastereoisomer with slight organotin contamination (350 mg, 50%) (Found: M^+, 137.0838. $C_8H_{11}NO$ requires *M*, 137.0841); $\nu_{max.}(CH_2Cl_2)$ 3 050 (w, =CH), 1 770 (s, C=O), and 1 630 cm^{-1} (w, C=C); δ_H (250 MHz) 1.21. (3 H, d, *J* 6.6 Hz, 4-Me), 2.21—2.31 (1 H, m, 4-H), 2.66—2.74 (1 H, m, 6β-H), 3.22—3.28 (1 H, m, 5-H), 3.22—3.33 (1 H, m, 6α-H coupled to 2α-H), 3.46—3.55 (1 H, m, 2α-H), 4.21—4.29 (1 H, m, 2β-H), and 4.92—5.04 (2 H, m, $=CH_2$) (see text for n.O.e. results); *m/z* 137 (M^+, 13%), 122 (M^+ − 15, 35), 94 (63), 79 (100), 68 (95), and 42 (=C=O, 26).

3-*Methylene*-1-*azabicyclo*[4.2.0.]*octan*-1-*one* (**10**).—A solution of the vinyl bromide (**7**) (1 mmol, 216 mg), AIBN (3 mol%), and tributyltin hydride (1.2 mol equiv. 0.3 ml) in toluene (100 ml) was stirred under reflux for 3.5 days. The reaction was cooled, concentrated under reduced pressure and purified by column chromatography eluting with hexane–ethyl acetate (4:1, 3:1, and finally 2:1) to furnish the *bicyclic product* (**10**) with slight organotin contamination (80 mg, 58%) (Found: M^+, 137.0844. $C_8H_{11}NO$ requires *M*, 137.0841); $\nu_{max.}(CH_2Cl_2)$ 1 750 (s, C=O) and 1 660 cm^{-1} (w, C=C); δ_H (250 MHz) 1.3—1.5 (1 H, m, 5β-H based upon Dreiding models), 2.1—2.3 (2 H, m, 4α-H and 5α-H), 2.4—2.5 (1 H, m, 4β-H), 2.56 (1 H, dd, *J* 1.8 and 14.5 Hz, 7β-H), 3.11 (1 H, ddd, *J* 4.6, 14.5, and *ca.* 1.8 Hz, 7α-H coupled to 2α-H), 3.4 (1 H, d, *J* 14.8 Hz, 2α-H showing coupling to 9-H and 7α-H), 3.45—3.55 (1 H, m, 6-H), 4.26 (1 H, d, *J* 15.0 Hz, 2β-H), and 4.85 (2 H, apparent t, *J* about 1.8 Hz, $9-H_2$); *m/z* 137 (M^+, 100%), 94 (48), 79 (57), 77 (7), 68 (36), and 42 (=C=O, 15).

Carbacephem (**11**) *and Tricyclic Compound* (**12**).—The vinyl bromide (**7**) (1 mmol, 216 mg), palladium(II) acetate (10 mol%, 22 mg) and triphenylphosphine (20 mol%, 52 mg) were mixed with acetonitrile (5 ml) at room temperature and degassed with nitrogen before being treated with potassium carbonate (1 mmol, 140 mg) and stirred in an oil bath at 80 °C for 5.5 h. The reaction was cooled, filtered, and concentrated *in vacuo*. Purification by suction flash chromatography with diethyl ether as eluant afforded the unstable 3,4,10,11-*tetramethylene*-1,8-*diazatricyclo*[10.2.0.0^{5,8}]*tetradecane*-7,14-*dione* (**12**) (32 mg, 23%) (Found: M^+, 270.1367. $C_{16}H_{18}N_2O_2$ requires M, 270.1368); $\nu_{max.}$(CH_2Cl_2) 1 770 cm^{-1} (s, C=O); δ_H (100 MHz) 2.8 [2 H, dd, J 2 and 16 Hz, O=C–C(H)H–], 3.4—3.8 (4 H, m, O=C–(*H*)H–, –N–C(H)*H*], 4.2—4.5 [4 H, m, *H*C–N–C(H)*H*–C=], 5.0—6.7 (8 H, m, olefinic H); m/z 270 (M^+, 48%), 242 (M^+ − CO, 28), 228 (M^+ − 42, 15), 186 (M^+ − 84, 15), 135 (M^+ − ½M, 24), and 42 (=C=O, 100).

Further elution of the column with diethyl ether furnished the 3-*methylene*-1-*azabicyclo*[4.2.0]*oct*-4-*en*-8-*one* (**11**) (49 mg, 35%) (Found: M^+, 135.0649. C_8H_9NO requires M, 135.0684); $\nu_{max.}$(CH_2Cl_2) 1 760 cm^{-1} (s, C=O); δ_H (100 MHz) 2.6 [1 H, dd, J 2 and 15 Hz, O=C–CH(H)], 3.3 [1 H, dd (broadened), J 7 and 15 Hz, O=C–CH–], 3.6 [1 H, d (broadened), J 16 Hz, –N–C(H)H–C=], 3.9—4.2 (1 H, m, N–CH–), 4.5 [1 H, d, J 16 Hz, –N–C(*H*)H–C=], 4.94 and 5.06 (2 H, 2 × s, =CH_2), 6.0 (1 H, d, J 11 Hz, HC–CH=C–), 6.3 (1 H, d, J 11 Hz, HC–C=CH–); m/z 135 (M^+, 25%), 93 (M^+ − 42, 50), and 42 (=C=O, 34).

N-(2-*Bromoprop*-2-*enyl*)-4-*methyl*-4-*vinylazetidin*-2-*one* (**14**).—Freshly powdered potassium hydroxide (1.1 mol equiv., 0.12 g) was added to a well stirred mixture of the azetidinone (**6b**) (2 mmol, 0.22 g), 2,3-dibromopropene (freshly distilled, 2 mmol, 0.2 ml) and tetrabutylammonium hydrogen sulphate (10 mol%, 0.07 g) in tetrahydrofuran (10 ml) under nitrogen at room temperature. After being stirred for 5 h, the mixture was added to saturated aqueous ammonium chloride (30 ml) and extracted into diethyl ether (3 × 20 ml). The combined organic extracts were washed with brine (30 ml) and dried ($MgSO_4$). Concentration under reduced pressure followed by suction flash chromatography (eluting with light petroleum–ethyl acetate, 10% polarity gradient, 0—60% ethyl acetate) afforded the *vinyl bromide* (**14**) (310 mg, 67%), b.p. 56—66 °C at 0.1 mmHg (Kugelrohr) (Found: C, 46.5; H, 5.4; N, 6.1. $C_9H_{12}BrNO$ requires C, 47.0; H, 5.3; N, 6.1%); $\nu_{max.}$(CH_2Cl_2) 1 760 (s, C=O), 1 645 (w, C=C) and 1 635 cm^{-1} (w, C=C); δ_H (100 MHz) 1.58 (3 H, s, 4-Me), 2.94 (2 H, s, O=C–CH_2), 3.96 (2 H, ABq, J 15 Hz, –N–CH_2–), and 5.18—6.30 (5 H, m, olefinic H) [Found: M^+ − Br, 150.0908 (67%). $C_9H_{12}NO$ requires M, 150.0918].

Carbapenams (**15**) *and* (**15a**) *and Carbacepham* (**16**).—The thermal reaction was conducted as in the preparation of carbacepham (**10**) but required only 2 days of refluxing. Column chromatography as before afforded the 4β,5α-*dimethyl*-3-*methylene*-1-*azabicyclo*[3.2.0]*heptan*-7-*one* (**15**) (90 mg, 59%) (Found: M^+, 151.1000. $C_9H_{13}NO$ requires M, 151.0997); $\nu_{max.}$(CH_2Cl_2) 1 755 cm^{-1} (s, C=O); δ_H (250 MHz) 1.11 (3 H, d, J 6.7 Hz, 4-Me), 1.16 (3 H, s, 5-Me), 2.30—2.38 (1 H, m, 4-H), 2.79 (1 H, d, J 15.2 Hz, 6β-H), 2.92 (1 H, dd, J 1.05 and 15.2 Hz, 6α-H coupled to 2α-H), 3.42—3.51 (1 H, m, 2α-H), 4.20 (1 H, ddd, J 2.5, 4.3 and 14.8 Hz, 2β-H), 4.93 (1 H, apparent dt, J 2.7 and 1.9 Hz, 8-H), and 5.04 (1 H, apparent dt, J 2.6 and 1.6 Hz, 8-H); m/z 151 (M^+, 37%), 108 (50), 68 (45), and 42 (=C=O, 54).

Further elution of the column provided the 4α,5α-*dimethyl*-3-*methylene*-1-*azabicyclo*[3.2.0]*heptan*-7-*one* (**15a**) and 6-*methyl*-3-*methylene*-1-*azabicyclo*[4.2.0]*octan*-8-*one* (**16**) as an inseparable mixture (1:10 respectively) (50 mg combined yield, 33%) (Found: M^+, 151.0993. $C_9H_{13}NO$ requires M, 151.0997); $\nu_{max.}$(CH_2Cl_2) 1 740 cm^{-1} (s, C=O); δ_H (250 MHz) *carbacepham*: 1.44 (3 H, s, 6-Me), 1.68 (1 H, apparent dt, J 8.7 and 12.9 Hz, 5-H), 2.02 (1 H, apparent dt, J 3.8 and 12.9 Hz, 5-H), 2.3—2.37 (2 H, dd, J 3.7 and about 8.1 Hz, 4-H_2), 2.77 (2 H, ABq, J 14.5 Hz, 7-H_2; fine structure was apparent on the left branch of the signal showing J 1.4 Hz, 7α-H coupled to 2α-H), 3.36 [1 H, d br, J 14.8 Hz, 2α-H], 4.21 (1 H, d, J 14.8 Hz, 2β-H), 4.81—4.83 (2 H, m, 9-H_2); *carbapenam:* 1.03 (3 H, d, J 7.4 Hz, 4-Me), 1.20 (3 H, s, 5-Me), 1.60—1.70 (1 H, m, 4-H), 2.62—2.86 (2 H, m, 6-H_2), 3.33—3.46 (1 H, m, 2α-H), 4.07 (1 H, d, J 18.3 Hz with further fine coupling of J 3.2 Hz, 2β-H), 5.53—5.62 (2 H, m, 8-H_2); m/z 151 (M^+, 48%), 136 (M^+ − 15, 13), 108 (100), 93 (61), and 42 (=C=O, 16).

The photolytic reaction was conducted in a similar manner to that for the vinyl bromide (**7**) yielding after chromatography the 4β-methylbicycle (**15**) (125 mg, 58%) and the 4α-methylbicycle (**15a**) and carbacepham (**16**), the latter two again as an inseparable mixture (1:1) (40 mg, 19%). N.m.r. and i.r. data were exactly as for the thermally derived products.

4α-*Methyl*-1-*azabicyclo*[3.2.0]*heptane*-3,7-*dione* (**22**).—A solution of the carbapenam (**8**) (1 mmol, 137 mg) in ethyl acetate (15 ml) was stirred at −60 °C and saturated with ozone. After the solution had been degassed with argon, triphenylphosphine (1.5 mol equiv., 393 mg), in ethyl acetate (2 ml) solution was added and the reaction stirred while being slowly warmed to 10 °C. Concentration under reduced pressure and column chromatography of the residue eluting with hexane–ethyl acetate (2:1) provided the *ketone* (**22**) (70 mg, 51%), m.p. 44—45 °C (Found: C, 60.35; H, 6.3; N, 9.9%; M^+, 139.0632. $C_7H_9NO_2$ requires C, 60.4; H, 6.5; N, 10.1%; M, 139.0633); $\nu_{max.}$(CH_2Cl_2) 1 760 cm^{-1} (s, C=O), high resolution KBr disc failed to show a second C=O; δ_H (250 MHz) 1.25 (3 H, d, J 7.0 Hz, 4-Me), 2.13—2.25 (1 H, apparent quintet with further coupling, largest J 7.3 Hz, 4-H coupled to 4-Me, 2β-H and 6β-H), 2.90—2.99 (1 H, m, 6β-H), 3.22 (1 H, dd, J 1.2 and 18.2 Hz, 2α-H), 3.52—3.64 (2 H, m, 5-H and 6α-H), and 4.12 (1 H, dd, J 1 and 18.2 Hz, 2β-H); m/z 139 (M^+, 8%), 95 (23), 83 (20), 55 (100), and 42 (=C=O, 11).

4β,5α-*Dimethyl*-1-*azabicyclo*[3.2.0]*heptane*-3,7-*dione* (**23**).—Ozonolysis of compound (**15**) as before gave the *ketone* (**23**) (174 mg, 85%), m.p. 52—53 °C (Found: C, 63.2; H, 7.1; N, 9.2%; M^+, 153.0793. $C_8H_{11}NO_2$ requires C, 62.7; H, 7.2; N, 9.15%; M, 153.0790); $\nu_{max.}$(CH_2Cl_2) 1 760 cm^{-1} (s, C=O); δ_H (250 MHz) 1.15 (3 H, d, J 7.05 Hz, 4-Me), 1.30 (3 H, s, 5-Me), 2.33 (1, q with slight broadening, J 7.04 Hz, 4-H), 3.04 (1 H, d, J 15.64 Hz, 6β-H), 3.18 (1 H, dd, J 1.2 and 18.1 Hz, 2α-H), 3.21 (1 H, dd, J 1.1 and 15.7 Hz, 6α-H), and 4.11 (1 H, dd, J 0.8 and 18.1 Hz, 2β-H); m/z 153 (M^+, 11%), 125 (M^+ − CO, 17), 97 (M^+ − 2CO, 19), and 69 (100).

1-*Azabicyclo*[4.2.0]*octane*-3,8-*dione* (**24**).—Ozonolysis as before afforded the *ketone* (**24**) (278 mg, 67%) (Found: M^+, 139.0621. $C_7H_9NO_2$ requires M, 139.0633); $\nu_{max.}$($CDCl_3$) 1 755 cm^{-1} (s, C=O) with a shoulder at 1 740 cm^{-1}; δ_H (360 MHz) 1.91—2.03 (1 H, m, 5-H), 2.36—2.44 (1 H, m, 5-H), 2.46—2.52 (1 H, m, 4-H), 2.60—2.67 (1 H, m, 4-H), 2.71 (1 H, dd, J 1.7 and 15.0 Hz, 7β-H), 3.25 (1 H, ddd, J 1.6, 5.1 and 15.0 Hz, 7α-H), 3.52 (1 H, dd, J 1.15 and 18.6 Hz, 2α-H), 3.81—3.86 (1 H, m, 6-H), and 4.26 (1 H, d, J 18.6 Hz, 2β-H); m/z 139 (M^+, 2%), 111 (M^+ − CO, 13), 69 (5), 68 (12), 55 (74), and 42 (=C=O, 100).

Note added in proof. Since completion of this work two relevant publications have appeared; G. Stork, *Tetrahedron Lett.*, 1986, **27**, 4529; A. L. J. Beckwith, *ibid.*, 1986, **27**, 4525.

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References

1 (*a*) 16th Interscience Conference on Antimicrobial Agents and Chemotherapy (16th ICAC), Chicago, 1976; (*b*) J. S. Kahan, F. M. Kahan, R. Goegelman, S. A. Currie, M. Jackson, F. O. Stapley, T. W. Miller, A. K. Miller, D. Hendlin, S. Mochales, S. Hernandez, and H. B. Woodruff in 1a, Abstr. No. 227.

2 J. S. Kahan, F. M. Kahan, R. Goegelman, S. A. Currie, M. Jackson, E. O. Stapley, T. W. Miller, A. K. Miller, D. Hendlin, S. Mochales, S. Hernandez, H. B. Woodruff, and J. Birnbaum, *J. Antibiot.*, 1979, **32**, 1.

3 (*a*) A. G. Birnbaum, D. Butterworth, M. Cole, G. Hanscomb, J. D. Hood, C. Reading, and G. N. Reading, *J. Antibiot.*, 1976, **29**, 668; (*b*) A. G. Brown, D. F. Corbett, A. J. Eglington, and T. T. Howarth, *J. Chem. Soc., Chem. Commun.*, 1977, 523; (*c*) D. F. Corbett, A. J. Eglington, and T. T. Howarth, *ibid.*, 1977, 953; (*d*) J. D. Hood, S. J. Box, and M. S. Verrall, *J. Antibiot.*, 1979, **32**, 295; (*e*) A. G. Brown, D. F. Corbett, A. J. Eglington, and T. T. Howarth, *ibid.*, 1979, **32**, 961; (*f*) S. J. Box, J. D. Hood, and S. R. Spear, *ibid.*, 1979, **32**, 1239.

4 (*a*) M. Nakayama, A. Iwasaki, S. Kimura, T. Mizoguchi, S. Tanabe, A. Murakami, I. Watnanabe, M. Okuchi, H. Itoh, Y. Saino, F. Kobayashi, and T. Mori, *J. Antibiot.*, 1980, **33**, 1388; (*b*) Y. Nozaki, S. Harada, and K. Kitano, *ibid.*, 1984, **37**, 218.

5 (*a*) K. Tanaka, J. Shoji, Y. Terui, N. Tsuji, E. Kondo, M. Mayama, Y. Kawamura, T. Hattori, K. Matsumoto, and T. Yoshida, *J. Antibiot.*, 1981, **34** 909; (*b*) J. Shoji, H. Hinoo, R. Sakazaki, N. Tsuji, K. Nagashima, K. Matsumoto, Y. Takahashi, S. Kozuki, T. Hattori, E. Kondo, and K. Tanaka, *ibid.*, 1982, **35**, 15.

6 N. Tsuji, K. Nagashimo, M. Kobayashi, Y. Terui, K. Matsumoto, and E. Kondo, *J. Antibiot.*, 1982, **35**, 536.

7 K. Okamura, S. Hirata, Y. Okumura, Y. Fukagawa, Y. Shimauchi, K. Kouno, and T. Ishikura, *J. Antibiot.*, 1978, **31**, 480.

8 W. Dürckheimer, J. Blumbach, R. Lattrell, and K. H. Scheunemann, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 180.

9 T. Kametani, *Heterocycles*, 1982, **17**, 463.

10 (*a*) A. L. J. Beckwith and C. H. Schiesser, *Tetrahedron*, 1985, **41**, 3925; (*b*) B. Giese, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 553.

11 A. L. J. Beckwith, *Tetrahedron*, 1981, 37 , 3073.

12 D. Reuschling, H. Pietsch, and A. Linkies, *Tetrahedron Lett.*, 1978, 615.

13 J. H. Bateson, A. J. G. Baxter, P. M. Roberts, T. C. Smale, and R. Southgate, *J. Chem. Soc., Perkin Trans. 1*, 1981, 3242.

14 M. D. Bachi, F. Frolow, and C. Hoornaert, *J. Org. Chem.*, 1983, **48**, 1841.

15 A. L. J. Beckwith and D. R. Boate, *Tetrahedron Lett.*, 1985, **26**, 1761.

16 (*a*) R. Grigg, P. Stevenson, and T. Worakun, *J. Chem. Soc., Chem. Commun.*, 1984, 1073; (*b*) R. Grigg, P. Stevenson, and T. Worakun, *ibid.*, 1985, 971.

17 (*a*) D. H. Shih, F. Baker, L. Cama, and B. G. Christensen, *Heterocycles*, 1984, **21**, 29; (*b*) D. H. Shih, J. A. Fayter, L. D. Cama, B. G. Christensen, and J. Hirshfield, *Tetrahedron Lett.*, 1985, **26**, 583; (*c*) D. H. Shih, L. Cama, and B. G. Christensen, *ibid.*, 1985, **26**, 587; (*d*) T. Shibata, K. Iino, T. Tanaka, T. Hasimoto, Y. Kameyama, and Y. Sugimura, *ibid.*, 1985, **26**, 4739.

18 H. O. House, 'Modern Synthetic Reactions,' Benjamin/Cummings, London, 2nd edn, p. 100.

19 Y. Ueno, S. Aoki, and M. Okawara, *J. Am. Chem. Soc.*, 1979, **101**, 5414.

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