The azomethine ylide strategy for β-lactam synthesis. Azapenams and 1-azacephams †

David Brown,[a] Giles A. Brown,[a] Mark Andrews,[a] Jonathan M. Large,[a] Dominique Urban,[a] Craig P. Butts,[a] Neil J. Hales[b] and Timothy Gallagher*[a]

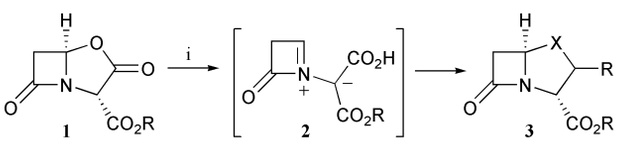
[a] *School of Chemistry, University of Bristol, Bristol, UK BS8 1TS. E-mail: T.Gallagher@bristol.ac.uk; Fax: +(44) 117 9298611; Tel: +(44) 117 9288260*
[b] *AstraZeneca, Mereside, Alderley Park, Macclesfield, Cheshire, UK SK10 4TG*

Received (in Cambridge, UK) 22nd April 2002, Accepted 6th June 2002
First published as an Advance Article on the web 31st July 2002

Reaction of the β-lactam-based oxazolidinone **5** with *N*-sulfonylimines provides the *exo* and *endo* azapenams **8** in 22–54% yield. The reactivity of 2*H*-azirines as 1,3-dipolarophiles towards β-lactam-based azomethine ylides derived from oxazolidinones **5** and **15** has also been evaluated. Azirines **11** and **12a** provide cycloadducts **13a**,**b** and **16** respectively, which incorporate the novel 2,6-diazatricyclo[4.2.0.0^{2,4}]octan-7-one ring system. These adducts were resistant towards C–N cleavage as the basis of an entry to 1-azacephams (1,5-diazabicyclo[4.2.0]octan-8-ones) **4**. The use of the 3-(4-methoxyphenyl)-2*H*-azirine **19** provides a labile initial cycloadduct, which undergoes *in situ* ring-cleavage and further reaction to give the 2 : 1 adduct 1-azacepham **22**. The initial product is stable when 3-(4-nitrophenyl)-2*H*-azirine **23** is employed, and cycloadducts **24a** and **24b** are converted under mild reducing conditions to the 1-azacepham derivatives **25** and **26**.

Introduction

The azomethine ylide strategy for β-lactam synthesis is based on the thermolysis of a β-lactam-based oxazolidinone **1**, which leads *via* a stepwise mechanism to azomethine ylide **2**.[1] This intermediate reacts with a wide range of both conventional and less conventional 1,3-dipolarophiles to give (after decarboxylation, which follows the cycloaddition event) bicyclic β-lactams **3** (Scheme 1).[2] The synthetic flexibility associated with this



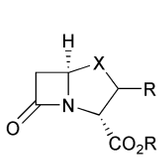
Scheme 1 *Reagents and conditions*: i, RCH(=X), MeCN, sealed tube (80 °C) or at reflux.

cycloaddition strategy is an important feature, and with alkenes and alkynes this chemistry provides carbapenams and Δ^1-carbapenems respectively.[3a]

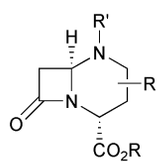
When azomethine ylide **2** is trapped by heteroatom variants (aldehydes, ketones, thio- and selenocarbonyls), this cycloaddition strategy offers entries to oxapenams,[3b] penams (and penems),[3c,e] and selenapenams,[3d,e] where X = O, S, and Se respectively.

In this paper we describe the reactivity of azomethine ylide **2** towards two distinct classes of imines. With simple imines, the process described below serves to extend the azomethine ylide strategy to the synthesis of azapenams (the 1,4-diazabicyclo-[3.2.0]heptan-7-one ring system) represented in general terms by **3** (X = NR′).[4]

However, the reactivity associated with one particular family of imines—2*H*-azirines—has provided access to the 1-azacepham skeleton **4** (*i.e.* the 1,5-diazabicyclo[4.2.0]octan-8-one ring system).[5] The net transformation formally involves a 3+3 annulation but a stepwise process *via* a novel tricyclic azapenam intermediate is implicated.



3 (X=NR')
Azapenams



4 1-Azacephams

Results

Imines as 1,3-dipolarophiles

Imines represent a synthetically useful group of dipolarophiles, and reactivity can be modulated *via* the *N*-substituent: *N*-alkyl *vs.* *N*-aryl *vs.* *N*-sulfonyl (or a variant with another electron-withdrawing *N*-substituent).[6] In addition, increased reactivity is associated with highly strained *N*-alkylimines, the most potent of which are 2*H*-azirines. With a focus on the generation of azapenams and azapenems (the $\Delta^{2,3}$ analogues), we have evaluated the ability of a range of acyclic imines to trap the azomethine ylide **6** derived from oxazolidinone **5**[7] (PNB = *p*-nitrobenzyl) (Scheme 2).

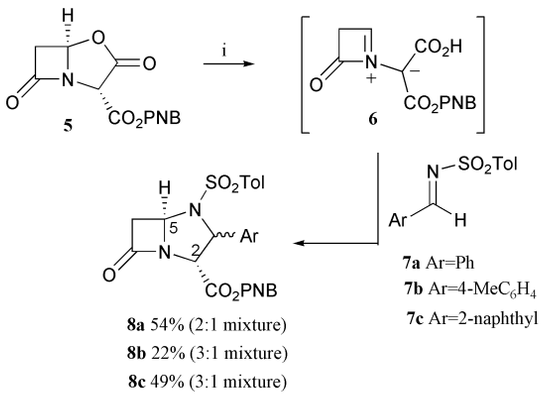
Using benzaldehyde-based imines as representative substrates, we were unable to isolate cycloadducts using imines based on the general structure PhCH=NR′, where R′ = Ph, Boc[8a] or P(O)Ph$_2$.[8b] However, the *N*-sulfonyl variant **7a** (Ar = Ph; R′=SO$_2$Tol)[8b] did react under our standard conditions (MeCN, 81 °C) to give the racemic azapenam derivative **8a** in 54% yield, and as a 2 : 1 mixture of *exo* (major) and *endo* (minor) diastereomers at C(3) ‡. The stereochemical assignment of these adducts was based on ^{1}H NMR and X-ray crystallographic analysis (see below).

Two other aryl aldehyde-derived *N*-sulfonylimines **7b** (Ar = 4-MeC$_6$H$_4$)[8b] and **7c** (Ar = 2-naphthyl)[8b] were also successfully employed as dipolarophiles to give adducts **8b** (Ar = 4-MeC$_6$H$_4$) and **8c** (Ar = 2-naphthyl) in 22 and 49% yields respectively. In both cases inseparable mixtures of *exo* and *endo* cycloadducts

† This paper is respectfully dedicated to the memory and many achievements of Professor Malcolm Campbell (1943–2001).

‡ The aryl substituent at C(3) can occupy a position on the convex or concave face of the azabicycle and these are labelled as *exo* and *endo* respectively.

 DOI: 10.1039/b203890k



Scheme 2 *Reagents and conditions*: i, **7a**–**c** (1.1. equiv.) (Tol = 4-MeC_6H_4), MeCN, sealed tube, 80 °C, 20 h (ratios correspond to the *exo*–*endo* mixture obtained).

were obtained. For each product, only the regioisomer shown was detected, which is consistent with what we have observed previously with other heteroatom-based dipolarophiles.[3] However, all attempts to achieve a cycloaddition between **6** and an imine derived from either an alkyl aldehyde or a ketone failed.

In the case of the β-naphthyl case **8c**, partial separation of the major (*exo*) isomer was achieved, and the structure (regio and relative stereochemistry) was confirmed by X-ray crystallographic analysis (Fig. 1)§. It is also significant to note that, as

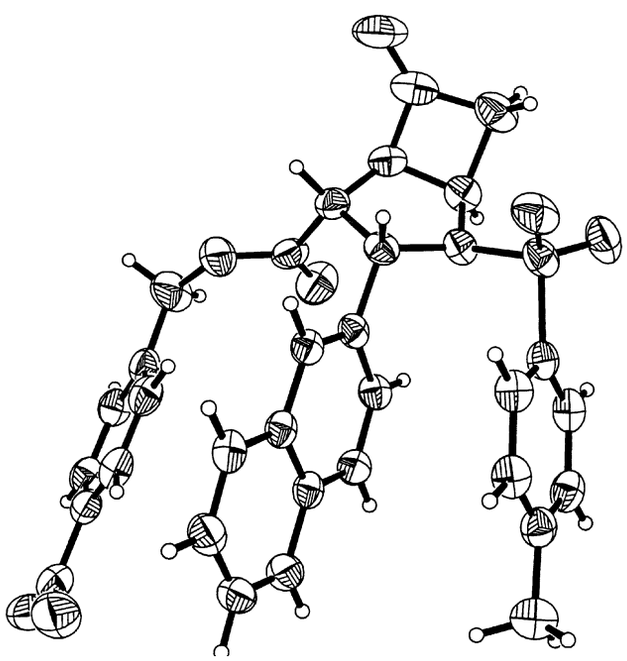
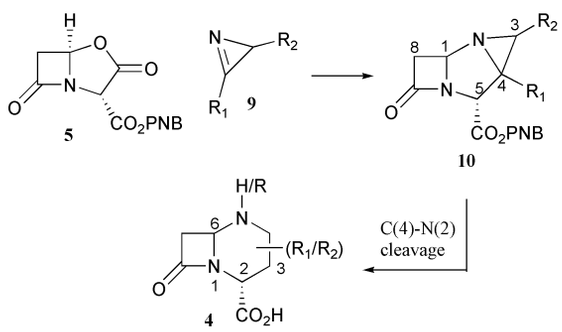


Fig. 1 Solid state structure of *exo*-**8c**.

anticipated from ^{1}H NMR analysis, the stereochemical relationship between C(2) (where the ester function is *exo*) and C(5) corresponds to the thermodynamically more stable relative configuration.[9] Again, this is a trend that has been observed with all cycloadducts derived to date from oxazolidinone **5**, regardless of the nature of the 1,3-dipolarophile.[3] Based on confirmation of *exo*-**8c**, we have assigned the major components of **8a** and **8b** as the *exo* isomer. Also, the chemical shift for H(5) in the *exo* series (δ 5.06–5.17) consistently appears at higher field than is observed for H(5) in the *endo* series (δ 5.27–5.34).

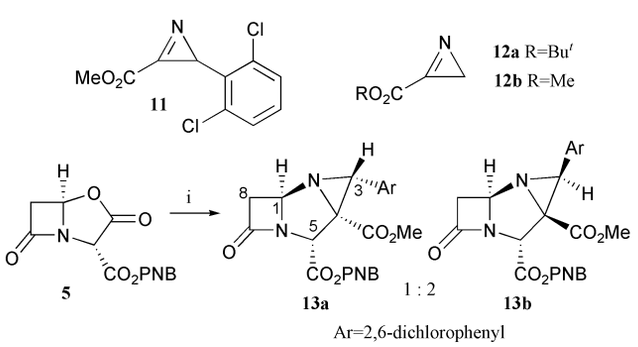
2*H*-Azirines as 1,3-dipolarophiles: synthetic access to the 1-azacepham ring system

2*H*-Azirines **9** represent an unusual group of imine-based 1,3-dipolarophiles[10] and our interest in these as substrates was prompted by two considerations. Firstly, the ring strain present within the azirine ring should provide compensation for the low reactivity normally associated with *N*-alkylimines. Secondly, cycloadducts **10** derived from azirines and an oxazolidinone (such as **5**) incorporate a highly strained C–N bond within the novel 2,6-diazatricyclo[4.2.0.0^{2,4}]octan-7-one ring system. Subsequent (and selective) cleavage of the strained C(4)–N(2) bond offers, in principle, an opportunity to generate the 1-azacepham[5] (1,5-diazabicyclo[4.2.0]octan-8-one) framework exemplified by general structure **4** (Scheme 3).



Scheme 3

A series of azirine substrates were identified that offer different options for C(4)–N(2) bond cleavage. Three azirine-3-carboxylates derivatives have been utilised: the 2-(2,6-dichlorophenyl) **11**[11] and the 2-unsubstituted variants **12a**,**b**[12] respectively. Thermolysis of **11** in the presence of oxazolidinone **5** gave a 1 : 2 mixture of cycloadducts **13a** and **13b** in 25% combined yield (Scheme 4). Structural assignments of **13a** and



Scheme 4 *Reagents and conditions*: i, **11** (1.3 equiv.), MeCN, reflux, 25 h (25%).

13b were based on NOE experiments (see Experimental section). In addition, the minor (and less polar) component **13a** provided crystals suitable for X-ray crystallographic analysis. This served to confirm the structure of **13a**, which contains the novel 2,6-diazatricyclo[4.2.0.0^{2,4}]octan-7-one ring system (Fig. 2).¶

§ Crystal data for *exo*-**8c**: $C_{30}H_{25}N_3O_7S$, M = 571.59, monoclinic, a = 43.767(8), b = 5.847(1), c = 22.777(5) Å, β = 113.78(1)°, V = 5333.9(18) Å^3, Z = 8, μ = 0.177 mm^{-1}, T = 173 K, 26690 reflections measured, 6143 unique (R_{int} = 0.0672) which were used in all calculations. Final R = 0.0491. CCDC reference number 184386. See http://www.rsc.org/suppdata/p1/b2/b203890k/ for crystallographic files in .cif or other electronic format.

¶ Crystal data for **13a**: $C_{22}H_{17}Cl_2N_3O_7$, M = 506.29, triclinic, a = 8.007(1), b = 11.908(2), c = 12.814(2) Å, α = 65.448(2), β = 80.677(3), γ = 79.668(3)°, V = 1088.1(3) Å^3, Z = 2, μ = 0.350 mm^{-1}, T = 173 K, 11461 reflections measured, 4958 unique (R_{int} = 0.0296) which were used in all calculations. Final R = 0.0382. CCDC reference number 184387. See http://www.rsc.org/suppdata/p1/b2/b203890k/ for crystallographic files in .cif or other electronic format.

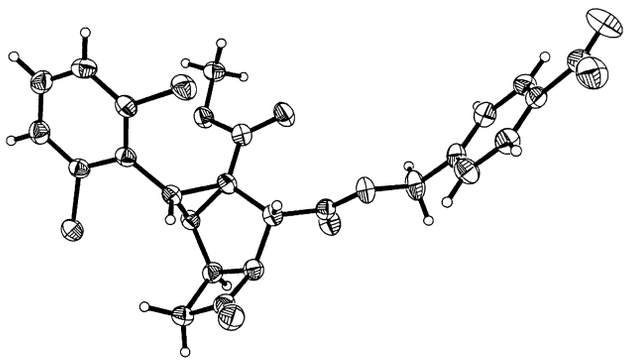
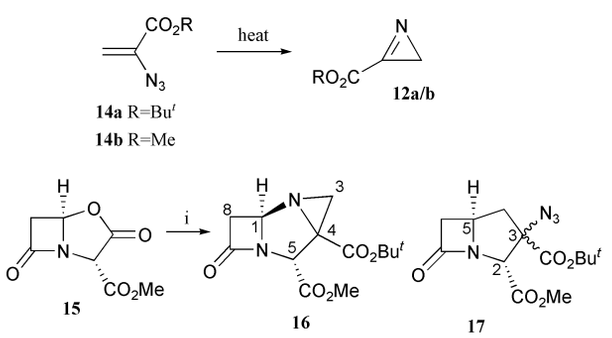


Fig. 2 Solid state structure of **13a**.

Initial attempts directed towards C(4)–N(2) cleavage of **13a** and **13b** (both separately and also as the mixture of isomers) focussed on exploiting the ring strain associated with this bond within a constrained ring system. A variety of different acid- and base-mediated reaction conditions were examined, with and without *N*-activation (*via* acylation or sulfonylation).[13,14c] However, no evidence for the desired C–N bond cleavage was observed. Indeed, **13a** and **13b** proved to be relatively both stable; **13b** underwent essentially quantitative hydrogenolysis of the PNB ester to give the corresponding carboxylic acid but even under these conditions[14c,d] the 2,6-diazatricyclo[4.2.0.0^{2,4}]-octan-7-one ring system remained intact.‖

Studies then concentrated on the simpler C(2)-unsubstituted azirine carboxylates **12a**,**b** derived from the α-azidoacrylates **14a**,**b**.[12] It was feasible to prepare the azirine prior to the 1,3-dipolar cycloaddition step, but best results were obtained when azirine **12a** was generated and used *in situ*. Indeed, Gilchrist and Alves have reported that the methyl ester **12b** (derived from vinyl azide **14b**) is both volatile and unstable.[12] Although oxazolidinone **5** reacts with **12a**, we focussed on cycloadducts derived from the methyl ester-containing oxazolidinone **15**[7]**. Azirine generation and cycloaddition were achieved by heating **14a** with oxazolidinone **15** under standard conditions (Scheme 5).

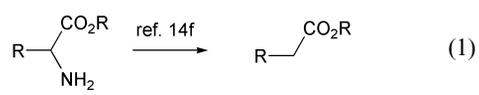


Scheme 5 *Reagents and conditions*: i, **14a** (1.1 equiv.), MeCN, reflux, 15 h (**16**: 20%; **17**: 17%).

Two azirine-derived cycloadducts were detected in the crude reaction mixture, but only the major cycloadduct **16** could be isolated in a low 20% yield. In addition, adduct **17** derived from vinyl azide **14a** was also isolated in 17% yield as a single regioisomer. Note that the stereochemistry at C(3) of **17** has not been established. Attempts to avoid this side reaction by formation of azirine **12b** prior to exposure to oxazolidinone **15** led to poor yields of the desired adducts. Diluting the cycloaddition reaction mixture (to favour the unimolecular decomposition of **14a**) did not lead to an improvement in product yield or distribution.

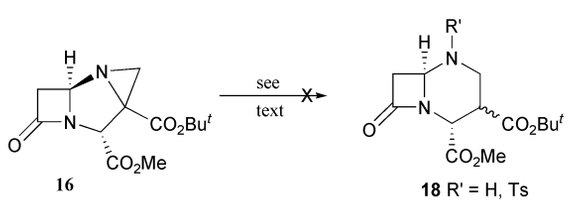
The stereochemistry of cycloadduct **16** has not been rigorously determined. We anticipate that the C(1)/C(5) stereochemistry is as shown, which corresponds to the thermodynamically more stable relative configuration and matches that observed with the imine cycloadducts (see **8c** above); the presence of a small (W) coupling (^4J 1 Hz) between one of the H(3) methylene protons and H(5) within this rigid framework together with the lack of a ^5J coupling between H(5) and H(8α)[15] is consistent with the C(1)/C(5) stereochemistry shown. The relative stereochemistry at C(4) has not, however, been determined. Again, a wide variety of reaction conditions were examined in order to achieve aziridine ring cleavage and provide the 1-azacepham framework, but cycloadduct **16** proved to be stable towards acid- and base-mediated fragmentation.‖

Based on the known propensity of α-amino esters to undergo reductive C–N cleavage [*e.g.* eqn. (1)[14f]], the ability of cyclo-



(1)

adducts **13a**,**b** and **16** to react with a range of reducing agents was also evaluated (Scheme 6). Our exploratory studies focused



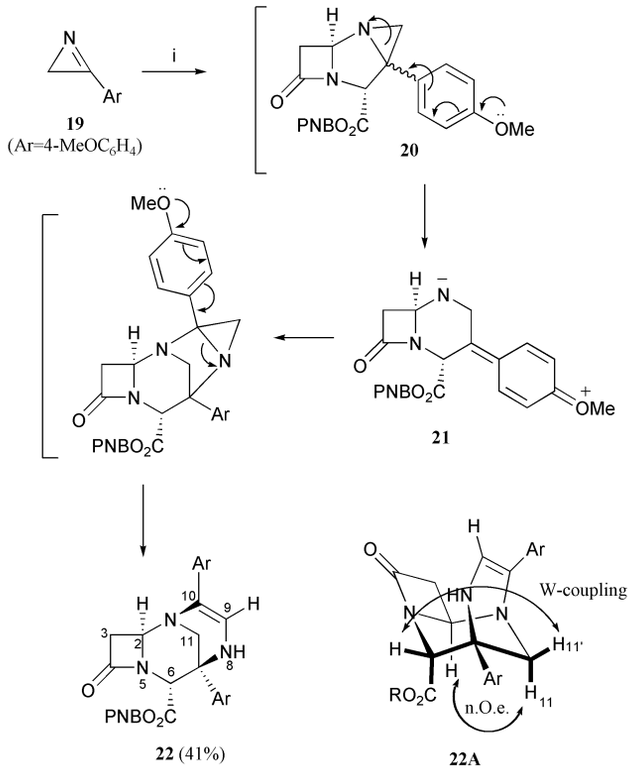
Scheme 6

on the mixture of the simpler cycloadduct **16**, but exposure to Riecke zinc, $CrCl_2$,[14b] or SmI_2 (in THF, with MeOH or $Me_2NCH_2CH_2OH$, and in the presence of DMPU or HMPA)[14e,f] failed to give the desired product, although starting material was consumed. Some evidence (^{1}H NMR) for the desired C(4)–N(2) cleavage was obtained, but the corresponding 1-azacepham **18**, if formed, appeared to be unstable and proved impossible to isolate cleanly.‖ Furthermore, exposure of **16** to SmI_2 in the presence of methanol proved to be an exceptionally efficient method for methanolysis of the β-lactam ring resulting in cleavage to give the corresponding β-amino ester.

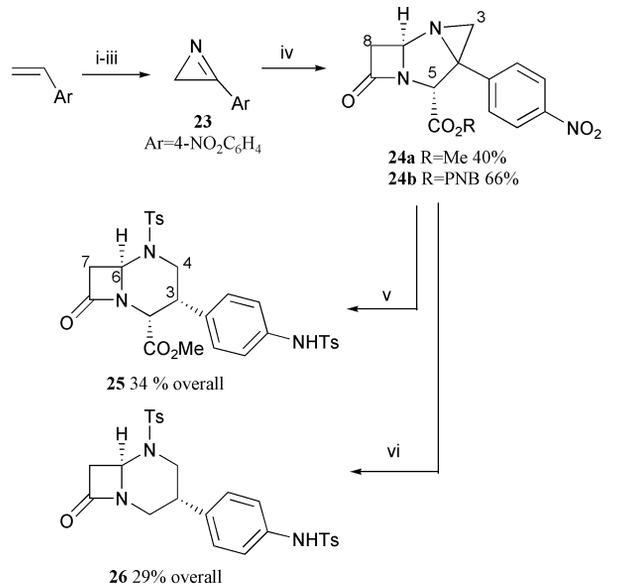
Given the difficulties encountered with reductive cleavage of the α-amino ester moiety embodied within **16**, an alternative mode of C–N bond cleavage has been pursued. This is based on positioning an electron-rich arene at C(4) of the 2,6-diazatricyclo[4.2.0.0^{2,4}]octan-7-one scaffold. Reaction of the known azirine **19**[16] (Ar = 4-MeOC$_6$H$_4$) with oxazolidinone **5** did not afford the expected cycloadduct **20**. Rather, the major product, which was isolated in 41% yield when two equivalents of **19** were used, has been assigned as the 2 : 1 cycloadduct **22** (Scheme 7). This assignment is based primarily on ^{1}H (COSY and NOE) and ^{13}C NMR spectroscopy, and a key feature is the NOE observed between H(2) (δ 5.10) and H(11) (δ 4.44). In addition a small W-coupling (^4J 2 Hz) between H(6) (δ 4.74) and H(11′) (δ 2.95) was also observed (see **22A**). A plausible mechanism to account for **22** is shown in Scheme 7. Ring cleavage of the initial cycloadduct **20** must take place under the

‖ Use of both basic and acidic conditions to mediate the cleavage of aziridines has precedent in the literature.[13,14c] We also evaluated reductive cleavage methods for cycloadducts **13a**,**b** and **16** based on literature precedents,[14] although we did not examine the use of Li in liquid ammonia[14a] because of the lability of the β-lactam ring. A number of these reactions did consume the starting material but the products appeared to be unstable and decomposed on attempted isolation. Efforts to avoid this by *N*-acetylation or *N*-sulfonylation also failed. There is a report[5b] that the *N*-unsubstituted 1-azacephams are unstable, but this may be substrate specific.

** The use of the methyl ester oxazolidinone variant **15** was dictated by the lability of the PNB moiety in the presence of strong reductants. Oxazolidinone **5** did react with azirines **12a** and **12b**, and cycloadducts analogous to **16** and **17** were isolated and characterised.



Scheme 7 *Reagents and conditions*: i, **5**, **19** (2.3 equiv.), MeCN, 100 °C, sealed tube, 15 h.



Scheme 8 *Reagents and conditions*: i, NaN_3, ICl, MeCN; ii, *t*-BuOK, Et_2O; iii, PhMe, reflux (36% overall yield); iv, **5** or **15**, MeCN, sealed tube, 80 °C, 18 h (**24a**; 40%; **24b**: 66%); v, (from **24a**) H_2, Pd/C, EtOAc, 8 h, then TsCl, py, CH_2Cl_2 (34% overall yield); vi, (from **24b**) H_2, Pd/C, EtOAc, 18 h, then TsCl, py, CH_2Cl_2 (29% overall yield).

reaction conditions and the resulting zwitterion **21** can capture another equivalent of azirine **19**. A second methoxy-assisted[17] C–N cleavage followed by proton transfer would account for the formation of the observed product **22**. Interestingly, reducing the amount of azirine **19** to one equivalent still led to the 2 : 1 adduct **22**, but in lower yield.

This was a significant observation, and this facile fragmentation pathway can be controlled by appropriate choice of the aryl moiety, and a nitro-substituted arene would provide a suitable 'safety catch' unit. The nitro group would render the cycloadduct stable towards further fragmentation under the initial cycloaddition conditions, but this is then easily converted to a potent electron-donating residue which then would be anticipated to trigger C–N bond cleavage (Scheme 8). ††

3-(4-Nitrophenyl)-2*H*-azirine **23** was prepared in 36% overall yield starting from 4-nitrostyrene. Thermolysis of **23** in the presence of oxazolidinone **15** gave a single cycloadduct **24a** in 40% isolated yield. Using oxazolidinone **5**, the corresponding PNB ester **24b** was isolated in 66% yield, as a single diastereomer. Again, the structure of cycloadducts **24a** and **24b** has not been completely assigned, but the C(4) stereochemistry is lost in the next step in any event.

Hydrogenation of **24a**, followed by double *N*-sulfonylation (to aid isolation) gave the 2,3-disubstituted azacepham **25** in 34% overall yield for two steps. Reduction of **24b** led to a more extensive reaction and resulted in PNB ester cleavage, nitro group reduction as well as decarboxylation (and alkene reduction) to give, after *N*-sulfonylation, **26** in 29% overall yield (Scheme 8). ‡‡ In neither case were we able to obtain crystals suitable for crystallographic analysis and the stereochemical assignments of both **25** and **26** are based primarily on extensive NOE studies. These data are presented in the Experimental section. Based on the coupling constants observed in the ^1H NMR spectra, the six-membered ring of both **25** and **26** appears to adopt a chair conformation, which is expected to be flattened slightly adjacent to the β-lactam ring.

In summary, activated imines may be trapped by β-lactam-based azomethine ylide **6** to provide racemic azapenams as mixtures of C(3) epimers. Azirines also provide a versatile and effective group of 1,3-dipolarophiles. The ester-based cycloadducts **13a**,**b** and **16** are stable with respect to C–N bond cleavage within the 2,6-diazatricyclo[4.2.0.$0^{2,4}$]octan-7-one framework, even under strongly reducing conditions. Cycloaddition with the electron-rich aryl-substituted azirine **19** leads to an adduct which does result in C–N bond cleavage, but this takes place spontaneously under the cycloaddition conditions, and is followed by further reaction to give the 2 : 1 adduct **22**. By using a nitroaryl moiety, the initial cycloadduct **24a**,**b** is prevented from undergoing further fragmentation. Subsequent release (by nitro group reduction) of the corresponding aniline then triggers the desired C–N bond cleavage. Depending on the nature of the ester-protecting group (**24a** *vs.* **24b**), these conditions lead to either **25** or **26**, both of which are novel azacepham derivatives.

The results described in this paper extend the scope of viable dipolarophiles associated with the azomethine ylide strategy to include imines, but more significantly, use of azirines provides a novel entry to azacephams. At this time the range of 1-azacephams available is limited, but the chemistry reported in this paper represents the first entry to the 2-carboxy derivatives of this class of bicyclic β-lactam.

Experimental

General experimental procedures have recently been described.[1b] All solvents were dried and deoxygenated prior to use. All compounds reported are racemic. Where shown, proton and carbon assignments were made using a combination of ^1H–^1H and ^1H–^{13}C correlation spectroscopy, and any

†† A competition experiment was also carried out to compare the reactivity of the methoxyphenylazirine **19** and the nitrophenyl analogue **23** towards azomethine ylide **6** derived from oxazolidinone **5**. Only cycloadduct **24b** derived from the electron-deficient azirine **23** was observed.

‡‡ The timing of the different steps leading to **26** is open to further investigation and the possibility that a decarboxylative fragmentation may be involved in the crucial C–N bond cleavage cannot be ruled out. However, it should be noted that in the case of **13b**, hydrogenolysis of the PNB ester is not complicated by decarboxylation or C–N bond rupture.

ambiguities associated with assignments are indicated. Details of NOE experiments are provided with the other spectroscopic data.

4-Nitrobenzyl (2*R**,3*R**,5*R**)- and (2*R**,3*S**,5*R**)-4-*N*-(4-methylphenylsulfonyl)-3-phenyl-7-oxo-1,4-diazabicyclo[3.2.0]-heptane-2-carboxylate 8a

A solution of oxazolidinone **5** (70 mg, 0.23 mmol) and *N*-tosylimine **7a** (65 mg, 0.25 mmol) in MeCN (3 cm^3) was heated at 80 °C for 20 h in a sealed tube. Removal of solvent *in vacuo* and purification by flash chromatography (petrol–EtOAc, 4 : 1) gave azapenam **8a** (64 mg, 54%) as a colourless solid and as an inseparable 2 : 1 mixture of *exo* and *endo* isomers (Found: M + H^+, 522.1330. $C_{26}H_{24}N_3O_7S$ requires 522.1335); ν_{max}/cm^{-1} (CH_2Cl_2) 1793, 1753; δ_H (300 MHz, C_6D_6, signals corresponding to the major and minor isomers are indicated) 7.79–7.30 (16 H, m, 9 × Ar major, 7 × Ar minor), 7.06–6.29 (10 H, m, 4 × Ar major, 6 × Ar minor), 5.41 (1 H, d, *J* 3.5, H-2 minor or H-3 minor), 5.30 (1 H, m, H-5 minor), 5.26 (1 H, d, *J* 8.5, H-2 major or H-3 major), 5.11 (1 H, dd, *J* 3.5, 1.0, H-5 major), 4.96 (1 H, d, *J* 8.5, H-2 major or H-3 major), 4.72 (1 H, d, *J* 3.5, H-2 minor or H-3 minor), 4.54 (1 H, d, *J* 13.5, CH_AH_BAr minor), 4.46 (1 H, d, *J* 13.5, CH_AH_BAr minor), 4.18 (1 H, d, *J* 13.0, CH_AH_BAr major), 4.08 (1 H, d, *J* 13.0, CH_AH_BAr major), 3.64 (1 H, dd, *J* 17.0, 1.0, H-6β major), 3.15 (1 H, dd, *J* 17.0, 3.5, H-6α major), 3.11 (1 H, dd, *J* 16.5, 1.0, H-6β minor), 3.07 (1 H, dd, *J* 16.5, 3.0, H-6α minor), 1.86 (3 H, s, CH_3 minor) 1.84 (3 H, s, CH_3 major); δ_C (75.5 MHz, C_6D_6, signals for the aromatic carbons were not completely resolved) 174.9, 173.1, 168.0, 167.0 (2 × N*C*O, 2 × *C*O_2PNB), 148.0, 147.8, 144.3, 143.3, 141.9, 141.5, 139.3, 136.9, 135.2, 134.1 (5 × C-quat. major, 5 × C-quat. minor), 129.9, 129.7, 129.3, 129.2, 128.8, 127.5, 127.0, 126.8, 123.8, 123.4 (5 × Ar major, 5 × Ar minor), 71.4 (C-5 minor), 71.2 (C-2 minor or C-3 minor), 70.4 (C-5 major), 69.1 (C-2 major or C-3 major), 66.8 (C-2 minor or C-3 minor), 65.8 (CH_2Ar minor), 65.3 (CH_2Ar major), 63.7 (C-2 major or C-3 major), 47.2 (C-6 minor), 46.4 (C-6 major), 21.2, 21.1 (2 × CH_3); *m*/*z* (CI, NH_3) 522 (M + H^+, 25%).

4-Nitrobenzyl (2*R**,3*R**,5*R**)- and (2*R**,3*S**,5*R**)-4-*N*-(4-methylphenylsulfonyl)-3-(4-methylphenyl)-7-oxo-1,4-diaza-bicyclo[3.2.0]heptane-2-carboxylate 8b

Using the same procedure as described for **7a**, reaction of oxazolidinone **5** with imine **7b** gave azapenam **8b** in 22% yield as a colourless oil and as an inseparable 3 : 1 mixture of isomers (Found: M^+, 535.1409. $C_{27}H_{25}N_3O_7S$ requires 535.1413); ν_{max}/cm^{-1} (CH_2Cl_2) 1793, 1751; δ_H (300 MHz, C_6D_6, signals corresponding to the major and minor isomers are indicated) 7.75 (2 H, d, part of AA′BB′, *J* 9.0, Ar minor), 7.64 (2 H, d, part of AA′BB′, *J* 9.0, Ar major), 7.50 (2 H, d, part of AA′BB′, *J* 8.0, Ar minor), 7.22 (2 H, d, part of AA′BB′, *J* 8.0, Ar minor), 7.04 (2 H, d, part of AA′BB′, *J* 8.0, Ar major), 6.85 (2 H, d, part of AA′BB′, *J* 8.0, Ar minor), 6.66 (2 H, d, part of AA′BB′, *J* 9.0, Ar minor), 6.65 (2 H, d, part of AA′BB′, *J* 8.0, Ar minor), 6.51 (2 H, d, part of AA′BB′, *J* 8.0, Ar major), 6.43 (2 H, d, part of AA′BB′, *J* 8.0, Ar major), 6.31 (2 H, d, part of AA′BB′, *J* 8.0, Ar major), 6.29 (2 H, d, part of AA′BB′, *J* 9.0, Ar major), 5.39 (1 H, d, *J* 4.0, H-2 minor or H-3 minor), 5.27 (1 H, dd, *J* 3.0, 1.0, H-5 minor), 5.19 (1 H, d, *J* 8.5, H-2 major or H-3 major), 5.06 (1 H, dd, *J* 3.5, 1.5, H-5 major), 4.89 (1 H, d, *J* 8.5, H-2 major or H-3 major), 4.72 (1 H, d, *J* 4.0, H-2 minor or H-3 minor), 4.50 (1 H, d, *J* 13.5, CH_AH_BAr minor), 4.42 (1 H, d, *J* 13.5, CH_AH_BAr minor), 4.23 (1 H, d, *J* 13.0, CH_AH_BAr major), 4.09 (1 H, d, *J* 13.0, CH_AH_BAr major), 3.60 (1 H, dd, *J* 17.0, 1.5, H-6β major), 3.11–3.04 (2 H, m, H-6α major and H-6β minor), 2.99 (1 H, dd, *J* 16.5, 3.0, H-6α minor), 2.00 (3 H, s, CH_3 minor), 1.85 (3 H, s, CH_3 major), 1.84 (3 H, s, CH_3 minor), 1.81 (3 H, s, CH_3 major); δ_C (75.5 MHz, C_6D_6, a signal due to one aromatic C-quat. was not observed) 174.7, 173.0, 168.0, 167.0 (2 × NCO, 2 × CO_2PNB), 148.0, 147.7, 144.0, 143.0, 141.7, 141.5, 138.5, 138.4, 137.0, 136.2, 135.3 (11 × *C*-quat.), 131.0, 129.9, 129.7, 129.0, 128.7, 128.6, 128.1, 127.9, 127.5, 126.9, 123.7, 123.2 (12 × Ar), 71.5 (C-5 minor), 71.4 (C-2 minor or C-3 minor), 70.5 (C-5 major), 69.1 (C-2 major or C-3 major), 67.2 (C-2 minor or C-3 minor), 66.0 (CH_2Ar minor), 65.4 (CH_2Ar major), 63.9 (C-2 major or C-3 major), 47.5 (C-6 minor), 46.4 (C-6 major), 21.4, 21.3, 21.2, 21.1 (4 × CH_3); *m*/*z* (EI) 535 (M^+, 7%).

4-Nitrobenzyl (2*R**,3*R**,5*R**)- and (2*R**,3*S**,5*R**)-4-*N*-(4-methylphenylsulfonyl)-3-(2-naphthyl)-7-oxo-1,4-diazabicyclo-[3.2.0]heptane-2-carboxylate 8c

Using the same procedure as described for **7a**, reaction of oxazolidinone **5** with imine **7c** gave azapenam **8c** in 49% yield as a colourless solid and as a 3 : 1 mixture of isomers. The major isomer has been assigned as *exo*-**8c** (see below) (Found: M^+, 571.1427. $C_{30}H_{25}N_3O_7S$ requires 571.1413). ν_{max}/cm^{-1} (CH_2Cl_2) 1795, 1754; δ_H (300 MHz, C_6D_6) 7.72–7.17 (8 H, m, 4 × Ar major and 4 × Ar minor), 7.13–6.47 (18 H, m, 7 × Ar major and 11 × Ar minor), 6.05 (2 H, d, part of AA′BB′, *J* 8.5, Ar major), 5.95 (2 H, d, part of AA′BB′, *J* 8.5, Ar major), 5.54 (1 H, d, *J* 4.5, H-2 minor or H-3 minor), 5.34 (1 H, m, H-5 minor), 5.33 (1 H, d, *J* 8.5, H-2 major or H-3 major), 5.17 (1 H, dd, *J* 3.5, 1.5, H-5 major), 4.98 (1 H, d, *J* 8.5, H-2 major or H-3 major), 4.80 (1 H, d, *J* 4.5, H-2 minor or H-3 minor), 4.56 (1 H, d, *J* 13.5, CH_AH_BAr minor), 4.43 (1 H, d, *J* 13.5, CH_AH_BAr minor), 4.24 (1 H, d, *J* 13.0, CH_AH_BAr major), 3.81 (1 H, d, *J* 13.0, CH_AH_BAr major), 3.69 (1 H, dd, *J* 17.0, 1.5, H-6β major), 3.15 (1 H, d, *J* 16.5, H-6β minor), 3.12 (1 H, dd, *J* 17.0, 3.5, H-6α major), 3.02 (1 H, dd, *J* 16.5, 3.0, H-6α minor), 1.72 (3H, s, CH_3 minor), 1.55 (3 H, s, CH_3 major); δ_C (75.5 MHz, C_6D_6, signals due to two aromatic C-quat. were not observed and the aromatic carbons were not completely resolved) 174.7, 173.2, 168.0, 167.0 (2 × NCO, 2 × CO_2PNB), 147.7, 147.4, 144.1, 143.1, 141.6, 140.7, 136.7, 135.7, 133.6, 133.4, 133.1, 132.5 (12 × C-quat.), 131.0, 129.5, 128.8, 128.7, 128.6, 128.5, 128.4, 128.2, 127.6, 127.3, 127.2, 126.9, 126.8, 126.4, 123.7, 122.9, 122.8 (17 × Ar), 71.6 (C-5 minor), 71.3 (C-2 minor or C-3 minor), 70.6 (C-5 major), 69.0 (C-2 major or C-3 major), 66.7 (C-2 minor or C-3 minor), 65.8 (CH_2Ar minor), 65.0 (CH_2Ar major), 63.6 (C-2 major or C-3 major), 47.0 (C-6 minor), 46.7 (C-6 major), 21.6, 21.3, 21.1, 21.0 (4 × CH_3); *m*/*z* (EI) 571 (M^+, 29%).

Although the minor isomer could not be obtained in pure form, partial separation of the major component (*exo*-**8c**) was achieved by flash chromatography and crystallisation from CH_2Cl_2 (slow evaporation) gave crystals suitable for X-ray crystallographic analysis.

4-Nitrobenzyl (1*S**,3*R**,4*S**,5*R**)-4-methoxycarbonyl-3-(2,6-dichlorophenyl)-7-oxo-2,6-diazatricyclo[4.2.0.$0^{2,4}$]octane-5-carboxylate 13a and 4-nitrobenzyl (1*S**,3*S**,4*R**,5*R**)-4-methoxycarbonyl-3-(2,6-dichlorophenyl)-7-oxo-2,6-diazatricyclo-[4.2.0.$0^{2,4}$]octane-5-carboxylate 13b

A solution of oxazolidinone **5** (215 mg, 0.70 mmol) and azirine **11** (220 mg, 0.90 mmol) in MeCN (6 cm^3) was heated at reflux for 25 h. Removal of solvent *in vacuo* and purification by flash chromatography (CH_2Cl_2–Et_2O, 49 : 1) gave cycloadduct **13a** (31 mg, 8%) as a colourless solid. Continued elution gave **13b** (59 mg, 17%) as a colourless solid.

Data for 13a. R_f 0.20 (CH_2Cl_2–Et_2O, 49 : 1) (Found: M + H^+, 506.0530. $C_{22}H_{18}{}^{35}Cl_2N_3O_7$ requires 506.0522); ν_{max}/cm^{-1} (CH_2Cl_2) 2960, 1785; δ_H (400 MHz, $CDCl_3$) 8.24 (2 H, d, part of AA′BB′, *J* 8.5, Ar), 7.56 (2 H, d, part of AA′BB′, *J* 8.5, Ar), 7.19–7.33 (3 H, m, Ar), 5.38 (1 H, dd, *J* 4.0, 1.0, H-1), 5.29 (2 H, s, CH_2Ar), 5.17 (1 H, s, H-5), 3.44 (1 H, dd, *J* 16.5, 4.0, H-8α), 3.39 (3 H, s, CO_2CH_3), 3.28 (1 H, dd, *J* 16.5, 1.0, H-8β), 3.03

(1 H, s, H-3); δ_C (100 MHz, $CDCl_3$) 172.3, 166.8, 166.4 (NCO, 2 × CO_2), 147.9, 142.0, 135.7 (3 × C-quat.), 129.8 (Ar), 129.1 (C-quat.), 128.8, 128.6, 123.9 (3 × Ar), 73.5 (C-5), 65.9 (CH_2Ar), 64.3 (C-4), 61.9 (C-1), 52.7 (CO_2CH_3), 41.2 (C-8), 40.7 (C-3); *m*/*z* (CI) 510, 508, 506 ($M + H^+$, 68%).

NOE experiments: irradiation of H-3 (δ 3.03) showed enhancements of H-5 (δ 5.17) and H-8β (δ 3.28). Irradiation of H-8β showed enhancements of H-3 and H-8α (δ 3.44). Irradiation of H-5 showed enhancement of H-3. Crystallisation from CH_2Cl_2–pentane gave crystals of **13a** suitable for X-ray crystallographic analysis.

Data for 13b. R_f 0.14 (CH_2Cl_2–Et_2O, 49 : 1) (Found: $M + H^+$, 506.0516. $C_{22}H_{18}{}^{35}Cl_2N_3O_7$ requires 506.0522); ν_{max}/cm^{-1} (CH_2Cl_2) 2955, 1750; δ_H (300 MHz, $CDCl_3$) 8.25 (2 H, d, part of AA′BB′, *J* 8.5, Ar), 7.59 (2 H, d, part of AA′BB′, *J* 8.5, Ar), 7.30–7.16 (3 H, m, Ar), 5.69 (1 H, s, H-5), 5.41 (1 H, d, *J* 13.5, CH_AH_BAr), 5.30 (1 H, d, *J* 13.5, CH_AH_BAr), 5.17 (1 H, dd, *J* 4.5, 2.0, H-1), 3.63 (3 H, s, CO_2CH_3), 3.62 (1 H, s, H-3), 3.56 (1 H, dd, *J* 17.0, 4.5, H-8α), 3.34 (1 H, dd, *J* 17.0, 2.0, H-8β); δ_C (75.5 MHz, $CDCl_3$) 175.7, 168.2, 167.1 (NCO, 2 × CO_2), 141.8, 135.5, 130.1 (3 × C-quat.), 129.8, 128.4, 128.3, 123.9 (4 × Ar), 80.3 (C-5), 66.2 (C-4), 66.0 (CH_2Ar), 60.9 (C-1), 53.3 (CO_2CH_3), 51.3 (C-3), 45.4 (C-8); *m*/*z* (CI) 510, 508, 506 ($M + H^+$, 3%).

NOE experiments: irradiation of H-1 (δ 5.17) showed enhancements of H-8a (δ 3.56) and H-3 (δ 3.62). Irradiation of H-3 showed enhancement of H-1. Irradiation of H-5 (δ 5.69) showed no enhancements to any of the tricyclic ring protons.

Methyl (1*S**,5*R**)-4-*tert*-butoxycarbonyl-7-oxo-2,6-diazatricyclo[4.2.0.0^{2,4}]octane-5-carboxylate 16 and methyl (1*S**,5*R**)-3-azido-3-*tert*-butoxycarbonyl-7-oxo-1-azabicyclo[3.2.0]heptane-2-carboxylate 17

A solution of oxazolidinone **15** (494 mg, 2.67 mmol) and vinyl azide (945 mg, 5.59 mmol) in MeCN (50 cm^3) was heated under reflux for 15 h. Removal of solvent *in vacuo* and purification by flash chromatography (CH_2Cl_2–Et_2O, 9 : 1) gave the bicyclic cycloadduct **17** (132 mg, 17%) as pale yellow oil. ν_{max}/cm^{-1} (CH_2Cl_2) 2127; δ_H (270 MHz, $CDCl_3$) 4.94 (1 H, s, H-2), 4.25 (1 H, m, H-5), 3.78 (3 H, s, CO_2CH_3), 3.37 (1 H, dd, *J* 5.0 and 16.0, H-6α), 2.80 (1 H, dd, *J* 2.0 and 16.0, H-6β), 2.55 (1 H, dd, *J* 5.5 and 13.5, H-4), 2.09 (1 H, dd, *J* 9.0 and 13.5, H-4), 1.55 (9 H, s, $C(CH_3)_3$); δ_C (67.5 MHz, $CDCl_3$) 175.1, 167.4, 167.0, 85.1, 79.9, 66.3, 53.1, 42.6, 42.1, 27.7. We were unable to obtain satisfactory high resolution or microanalytical data for this compound.

Continued elution gave cycloadduct **16** (149 mg, 20%) as a colourless oil (Found: M^+, 282.1219. $C_{13}H_8N_4O_5$ requires 282.1216); ν_{max}/cm^{-1} (CH_2Cl_2) 1750; δ_H (270 MHz, $CDCl_3$) 5.38 (1 H, d, *J* 1.0, H-5), 4.62 (1 H, dd, *J* 2.0 and 4.5, H-1), 3.78 (3 H, s, CO_2CH_3), 3.39 (1 H, dd, *J* 4.5 and 16.5, H-8α), 3.21 (1 H, dd, *J* 2.0 and 16.5, H-8β), 2.74 (1 H, d, *J* 1.0, H-3), 2.20 (1 H, s, H-3), 1.50 (9 H, s, $C(CH_3)_3$); δ_C (67.5 MHz, $CDCl_3$) 176.1, 169.2, 166.6, 83.5, 79.2, 60.2, 59.7, 52.8, 45.4, 41.5, 27.8; *m*/*z* (EI) 282 (M^+, 20%).

4-Nitrobenzyl (2*S**,6*R**,7*R**)-7,10-bis(4-methoxyphenyl)-4-oxo-1,5,8-triazatricyclo[5.3.1.0^{2,5}]undec-9-ene-6-carboxylate 22

A solution of the oxazolidinone **5** (70 mg, 0.23 mmol) and azirine **19**[16] (77 mg, 0.53 mmol) in MeCN (3 cm^3) was heated at 100 °C in a sealed tube for 15 h. Removal of solvent *in vacuo* and purification by flash chromatography (CH_2Cl_2–Et_2O, 49 : 1) gave the title compound **22** (52 mg, 41%) as a pale yellow oil (Found: M^+, 556.1950. $C_{30}H_{28}N_4O_7$ requires 556.1958). ν_{max}/cm^{-1} ($CHCl_3$) 3426, 1753, 1644, 1609; δ_H (400 MHz, $CDCl_3$) 8.06 (2 H, d, part of AA′BB′, *J* 8.0, Ar), 7.35 (2 H, d, part of AA′BB′, *J* 8.0, Ar), 7.19 (2 H, d, part of AA′BB′, *J* 8.0, Ar), 7.02 (2 H, d, part of AA′BB′, *J* 8.0, Ar), 6.82 (2 H, d, part of AA′BB′, *J* 8.0, Ar), 6.75 (2 H, d, part of AA′BB′, *J* 8.0, Ar), 6.71 (1 H, d, *J* 5.3, H-9), 5.10 (1 H, dd, *J* 4.5, 1.5, H-2), 4.88 (1 H, d, *J* 13.0, CH_AH_BAr), 4.74 (1 H, d, *J* 2.0, H-6), 4.72 (1 H, d, *J* 13.0, CH_AH_BAr), 4.44 (1 H, d, *J* 12.5, H-11), 4.05 (1 H, d, *J* 5.5, NH), 3.78 (3 H, s, OCH_3), 3.71 (3 H, s, OCH_3), 2.95 (1 H, dd, *J* 12.5, 2.0, H-11′), 2.80 (1 H, dd, *J* 15.5, 4.5, H-3α), 2.77 (1 H, dd, *J* 15.5, 1.5, H-3β); δ_C (67.9 MHz, $CDCl_3$) 168.4, 167.1 (NCO, CO_2PNB), 159.4, 157.4, 147.5, 141.6, 132.2, 132.1 (6 × C-quat.), 128.7, 125.8 (2 × Ar), 123.7 (C-9), 123.5, 114.2, 114.0 (3 × Ar), 66.3 (C-2), 65.0 (CO_2CH_2Ar), 61.9 (C-6), 55.2 (OCH_3), 55.0 (OCH_3), 51.5 (C-7), 48.8 (C-11), 40.8 (C-3); *m*/*z* (EI) 556 (M^+, 21%).

NOE experiments: irradiation of H-2 (δ 5.10) showed enhancement of H-11 (δ 4.44).

3-(4-Nitrophenyl)-2*H*-azirine 23

(i) 1-Azido-1-(4-nitrophenyl)ethene. A stirred suspension of sodium azide (236 mg, 3.69 mmol,) in dry MeCN (6 cm^3) at 0 °C was treated over 15 minutes with iodine monochloride (0.18 cm^3, 3.69 mmol) and then stirred for 20 minutes. A solution of 4-nitrostyrene (500 mg, 3.35 mmol) in MeCN (2 cm^3) was added dropwise and the reaction mixture was allowed to warm to room temperature and stirred for 2 h [TLC analysis (petrol–EtOAc, 4 : 1) indicated that two products had been formed]. The reaction mixture was poured into water (20 cm^3) and extracted with Et_2O (3 × 20 cm^3). The combined extracts were washed with 5% aqueous $Na_2S_2O_3$ (20 cm^3) followed by water (20 cm^3), then dried ($MgSO_4$) and concentrated *in vacuo* to give a mixture of the diazide and the desired vinyl azide. This mixture was redissolved in Et_2O (10 cm^3) at 0 °C and treated with ^{t}BuOK (452 mg, 4.02 mmol) and stirred for 30 minutes, after which time TLC analysis indicated complete conversion to the vinyl azide. The mixture was washed with water (10 cm^3), brine (10 cm^3), dried ($MgSO_4$) and concentrated *in vacuo* to give 1-azido-1-(4-nitrophenyl)ethene as a colourless oil, which was not purified further. δ_H (270 MHz, $CDCl_3$) 8.21 (2 H, d, part of AA′BB′, *J* 8.0, Ar), 7.73 (2 H, d, part of AA′BB′, *J* 8.0, Ar), 5.64 (1 H, d, *J* 3.0, C=CH_AH_B), 5.16 (1 H, d, *J* 3.0, C=CH_AH_B). This material was not characterised further but was used directly in the next step.

(ii) 3-(4-Nitrophenyl)-2*H*-azirine 23. Crude 1-azido-1-(4-nitrophenyl)ethene prepared above was redissolved in toluene (50 cm^3) and heated at reflux for 6 h. Removal of solvent *in vacuo* and purification by flash chromatography (petrol–Et_2O, 4 : 1) gave 23 (196 mg, 36% over 3 steps) as a colourless solid (Found: M^+, 162.0429. $C_8H_6N_2O_2$ requires 162.0429). ν_{max}/cm^{-1} ($CHCl_3$) 1605; δ_H (400 MHz, $CDCl_3$) 8.44 (2 H, d, part of AA′BB′, *J* 8.0, Ar), 8.11 (2 H, d, part of AA′BB′, *J* 8.0, Ar), 1.94 (2 H, s, CH_2); δ_C (100 MHz, $CDCl_3$) 165.5 (C-NO_2), 131.4 (C-quat.), 130.4, 124.4 (Ar), 20.9 (N*C*H_2); *m*/*z* (EI) 162 (M^+, 9%).

Methyl (1*S**,5*R**)-4-(4-nitrophenyl)-7-oxo-2,6-diazatricyclo[4.2.0.0^{2,4}]octane-5-carboxylate 24a

A solution of oxazolidinone **15** (75 mg, 0.40 mmol) and azirine **23** (72 mg, 0.45 mmol) in MeCN (3 cm^3) was heated at 80 °C in a sealed tube for 18 h. Removal of solvent *in vacuo* and purification by flash chromatography (CH_2Cl_2–Et_2O, 2 : 1) gave cycloadduct **24a** (49 mg, 40%) as a single diastereoisomer and as a foam (Found: M^+, 303.0855. $C_{14}H_{13}N_3O_5$ requires 303.0855); ν_{max}/cm^{-1} ($CHCl_3$) 1779, 1751, 1605; δ_H (270 MHz, $CDCl_3$) 8.18 (2 H, d, part of AA′BB′, *J* 8.5, Ar), 7.56 (2 H, d, part of AA′BB′, *J* 8.5, Ar), 5.31 (1 H, s, H-5), 5.10 (1 H, s, H-1), 3.42 (3 H, s, CO_2CH_3), 3.35 (1 H, dd, *J* 16.5, 4.0, H-8α), 2.86 (1 H, dd, *J* 16.5, 1.5, H-8β), 2.04–2.01 (2 H, m, 2 × H-3); δ_C (100 MHz, $CDCl_3$) 173.1, 167.6 (NCO, CO_2Me), 147.7, 142.5 (2 × C-quat.), 128.5, 123.7 (2 × Ar), 76.8 (C-5), 63.8 (C-1), 61.6

(C-4), 52.4 (CO_2CH_3), 41.1 (C-8), 32.3 (C-3); *m*/*z* (EI) 303 (M^+, 62%).

4-Nitrobenzyl (1*S**,5*R**)-4-(4-nitrophenyl)-7-oxo-2,6-diazatricyclo[4.2.0.0^{2,4}]octane-5-carboxylate 24b

A solution of oxazolidinone **5** (77 mg, 0.25 mmol) and azirine **23** (45 mg, 0.28 mmol) in MeCN (3 cm^3) was heated at 80 °C in a sealed tube for 18 h. Removal of solvent *in vacuo* and purification by flash chromatography (CH_2Cl_2–Et_2O, 3 : 1) gave cycloadduct **24b** (70 mg, 66%) as a single diastereoisomer and as a colourless solid (Found: M^+, 424.1020. $C_{20}H_{16}N_4O_7$ requires 424.1019); ν_{max}/cm^{-1} ($CHCl_3$) 1781, 1753; δ_H (270 MHz, $CDCl_3$) 8.13 (2 H, d, part of AA′BB′, *J* 8.0, Ar), 8.05 (2 H, d, part of AA′BB′, *J* 8.0, Ar), 7.49 (2 H, d, part of AA′BB′, *J* 9.0, Ar), 7.24 (2 H, d, part of AA′BB′, *J* 9.0, Ar), 5.30 (1 H, s, H-5), 5.15 (1 H, s, H-1), 4.94 (1 H, d, *J* 13.0, CH_AH_BAr), 4.87 (1 H, d, *J* 13.0, CH_AH_BAr), 3.38 (1 H, dd, *J* 16.5, 4.5, H-8α), 2.89 (1 H, dd, *J* 16.5, 1.0, H-8β), 2.05 (1 H, br s, H-3), 2.01 (1 H, br s, H-3′); δ_C (100 MHz, $CDCl_3$) 173.3, 167.2 (NCO, CO_2PNB), 142.2, 141.7 (2 × C-quat.), 129.1, 128.4, 123.8, 123.6 (4 × Ar), 72.5 (C-5), 65.8 (CH_2Ar), 63.9 (C-1), 61.8 (C-4), 41.2 (C-8), 32.4 (C-3); *m*/*z* (EI) 424 (M^+, 4%).

Methyl (2*R**,3*S**,6*R**)-3-{4-[*N*-(4-methylphenylsulfonyl)amino]phenyl}-5-(4-methylphenylsulfonyl)-8-oxo-1,5-diazabicyclo[4.2.0]octane-2-carboxylate 25

A solution of cycloadduct **24a** (80 mg, 0.26 mmol) in EtOAc (4 cm^3) containing 10% Pd on carbon (30 mg) was stirred vigorously under one atmosphere of hydrogen for 8 h. The catalyst was removed by filtration through Celite and the solution was concentrated *in vacuo*. The residue was immediately redissolved in dry CH_2Cl_2 (2 cm^3), cooled to 0 °C and treated with dry pyridine (0.07 cm^3, 0.84 mmol) and toluenesulfonyl chloride (301 mg, 1.58 mmol). The mixture was stirred for 30 minutes at 0 °C, then warmed to room temperature and stirred for a further 3 h. Removal of solvent *in vacuo* and purification by flash chromatography (CH_2Cl_2–Et_2O, 2 : 1) gave 1-azacepham **25** (52 mg, 34% for two steps) as a colourless solid (Found: M^+, 583.1447. $C_{28}H_{29}N_3O_7S_2$ requires 583.1447); ν_{max}/cm^{-1} ($CHCl_3$) 3372, 1771, 1737; δ_H (400 MHz, $CDCl_3$) 7.68 (2 H, d, part of AA′BB′, *J* 8.0, Ar), 7.65 (2 H, d, part of AA′BB′, *J* 8.0, Ar), 7.41 (2 H, d, part of AA′BB′, *J* 8.5, Ar), 7.24 (2 H, d, part of AA′BB′, *J* 8.5, Ar), 7.01 (2 H, d, part of AA′BB′, *J* 8.5, Ar), 6.89 (2 H, d, part of AA′BB′, *J* 8.5, Ar), 6.52 (1 H, br, NH), 4.64 (1 H, dd, *J* 3.5, 1.1, H-6), 4.60 (1 H, d, *J* 6.4, H-2), 3.74 (1 H, dd, *J* 11.6, 3.3, H-4β), 3.58 (1 H, dd, *J* 15.8, 1.1, H-7β), 3.48–3.41 (1 H, m, H-3), 3.38 (1 H, dd, *J* 15.8, 3.5, H-7α), 3.18 (1 H, app. t, *J* 11.7, H-4α), 3.17 (3 H, s, CO_2CH_3), 2.50 (3 H, s, Ar-CH_3), 2.40 (3 H, s, Ar-CH_3); δ_C (100 MHz, $CDCl_3$) 168.9, 165.4 (NCO, CO_2Me), 145.0, 144.2 (2 × SO_2-C-quat.), 136.6, 136.0, 132.6, 132.2 (4 × C-quat.), 130.3, 129.8, 128.2, 128.0, 127.3, 121.5 (6 × Ar), 61.5 (C-2), 53.4 (C-6), 51.7 (CO_2CH_3), 46.3, 44.9 (C-4, C-7), 43.4 (C-3), 21.8, 21.6 (2 × Ar-CH_3); *m*/*z* (EI) 583 (M^+, 14%).

NOE experiments: irradiation of H-2 (δ 4.60) gave an enhancement of H-3β (δ 3.41). Irradiation of H-3β gave enhancements of H-2 (δ 4.60) and H-4β (δ 3.74). Irradiation of H-4α (δ 3.18) gave enhancements of H-4β, H-6 (δ 4.64) and the *ortho* protons of the C-3 aryl substituent.

(3*S**,6*R**)-3-{4-[*N*-(4-Methylphenylsulfonyl)amino]phenyl}-5-(4-methylphenylsulfonyl)-8-oxo-1,5-diazabicyclo[4.2.0]octane 26

A solution of cycloadduct **24b** (99 mg, 0.23 mmol) in EtOAc (4 cm^3) containing 10% Pd on carbon (35 mg) was stirred vigorously under an atmosphere of hydrogen for 18 h. The catalyst was removed by filtration through Celite and the solvent removed *in vacuo* to give a solid which was immediately redissolved in dry CH_2Cl_2 (3 cm^3), cooled to 0 °C, treated with dry pyridine (0.08 cm^3, 0.98 mmol) and toluenesulfonyl chloride (266 mg, 1.40 mmol) and stirred at 0 °C for 2 h. Removal of solvent *in vacuo* and purification by flash chromatography (EtOAc–petrol, 2 : 1) gave **26** (36 mg, 29%) as a colourless foam (Found: M^+, 525.1381. $C_{26}H_{27}N_3O_5S_2$ requires 525.1392). ν_{max}/cm^{-1} ($CHCl_3$) 3374, 1763; δ_H (300 MHz, $CDCl_3$) 7.66 (2 H, d, part of AA′BB′, *J* 8.5, Ar), 7.65 (2 H, d, part of AA′BB′, *J* 8.5, Ar), 7.39 (2 H, d, part of AA′BB′, *J* 8.5, Ar), 7.25 (2 H, d, part of AA′BB′, *J* 8.5, Ar), 7.11 (1 H, br, N*H*), 7.04 (2 H, d, part of AA′BB′, *J* 6.5, Ar), 6.97 (2 H, d, part of AA′BB′, *J* 6.5, Ar), 4.22 (1 H, dd, *J* 3.3, 1.0, H-6), 3.90 (1 H, dd, *J* 13.5, 4.5, either H-2β or H-4β), 3.80 (1 H, dd, *J* 12.0, 2.5, either of H-2β or H-4β), 3.50 (1 H, dd, *J* 15.5, 1.0, *H*-7β), 3.39 (1 H, ddd, *J* 15.6, 3.3, 1.5, *H*-7α), 3.05 (1 H, m, H-3), 2.61 (1 H, t, *J* 12.0, either H-2α or H-4α), 2.47 (3 H, s, Ar-CH_3), 2.41 (1 H, t, *J* 12.0, either H-2α or H-4α), 2.40 (3 H, s, Ar-CH_3); δ_C (75.5 MHz, $CDCl_3$) 171.2 (NCO), 144.9, 144.1 (2 × SO_2-C-quat.), 136.3, 136.1, 134.6, 131.9 (4 × C-quat.), 130.1, 129.7, 128.1, 128.0, 127.1, 121.7 (6 × Ar), 61.8 (C-6), 50.4 (C-2 or C-4), 46.6 (C-7), 43.4 (C-2 or C-4), 41.5 (C-3), 21.7, 21.6 (2 × Ar-CH_3); *m*/*z* (EI) 525 (M^+, 25%).

NOE experiments: irradiation of H-3 (δ 3.05) showed enhancements of the signals at δ 3.90 and δ 3.80 (which have been assigned as H-2β and H-4β, but we cannot distinguish between these signals), but no enhancement of H-6 (δ 4.22) was observed. Irradiation of H-6 showed an enhancement of H-7α (δ 3.39) only.

Acknowledgements

We thank Drs Martin Murray and Ian Fairlamb for extensive NMR (NOE and NOESY) work, and EPSRC and AstraZeneca for generous financial support.

References

1 (*a*) S. R. Martel, D. Planchenault, R. Wisedale, T. Gallagher and N. J. Hales, *Chem. Commun.*, 1997, 1897; (*b*) D. Brown, G. A. Brown, S. R. Martel, D. Planchenault, E. Turmes, K. E. Walsh, R. Wisedale, N. J. Hales, C. W. G. Fishwick and T. Gallagher, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1270.
2 T. Gallagher, *J. Heterocycl. Chem.*, 1999, **36**, 1365.
3 (*a*) S. R. Martel, R. Wisedale, T. Gallagher, L. D. Hall, M. F. Mahon, R. H. Bradbury and N. J. Hales, *J. Am. Chem. Soc.*, 1997, **119**, 2309; (*b*) D. Planchenault, R. Wisedale, T. Gallagher and N. J. Hales, *J. Org. Chem.*, 1997, **62**, 3438; (*c*) M. D. Andrews, G. A. Brown, J. P. H. Charmant, T. M. Peakman, A. Rebello, K. E. Walsh, T. Gallagher and N. J. Hales, *Chem. Commun.*, 1999, 249; (*d*) G. A. Brown, K. M. Anderson, M. Murray, T. Gallagher and N. J. Hales, *Tetrahedron*, 2000, **56**, 5579; (*e*) G. A. Brown, K. M. Anderson, J. M. Large, D. Planchenault, D. Urban, N. J. Hales and T. Gallagher, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1897.
4 (*a*) G. Johnson and B. C. Ross, *J. Chem. Soc., Chem. Commun.*, 1981, 1269; (*b*) G. Johnson, P. M. Rees and B. C. Ross, *J. Chem. Soc., Chem. Commun.*, 1984, 970; (*c*) T. Shibata, Y. Sugimura, S. Sato and K. Kawazoe, *Heterocycles*, 1985, **23**, 3069; (*d*) M. Es-Sayed, T. Heiner and A. de Meijere, *Synlett*, 1993, 57; (*e*) Y. Hsiao and L. S. Hegedus, *J. Org. Chem.*, 1997, **62**, 3586; (*f*) E. Kuester and L. S. Hegedus, *Organometallics*, 1999, **18**, 5318.
5 (*a*) S. Wolfe, J. B. Ducep, G. Kannengiesser and W. S. Lee, *Can. J. Chem.*, 1972, **50**, 2902; (*b*) A. K. Bose, J. C. Kapur, J. L. Fahey and M. S. Manhas, *J. Org. Chem.*, 1973, **38**, 3437; (*c*) D. Davies and M. J. Pearson, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2539; (*d*) M. J. Pearson, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2544; (*e*) S. D. Sharma and U. Mehra, *Tetrahedron Lett.*, 1984, **25**, 1849; (*f*) S. D. Sharma, S. K. Arora and U. Mehra, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 1985, **24**, 895; (*g*) S. D. Sharma, U. Mehra and V. Kaur, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 1986, **25**, 1061; (*h*) H. H. Wasserman, M. D. Xia, A. J. Carr, W. T. Han and M. G. Siegel, *Tetrahedron*, 2000, **56**, 5621.
6 (*a*) J.-P. Anselme, in *The chemistry of the carbon–nitrogen double bond*, ed. S Patai, Interscience, London, 1970, ch. 7, p. 299; (*b*) G. Tennant, *Comprehensive Organic Chemistry*, ed. I. O. Sutherland, Pergamon Press, Oxford, 1979, vol. 2, p. 385;

(*c*) W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*, eds. J. E. Baldwin and P. D. Magnus, Pergamon Press, Oxford, 1990.

7 (*a*) T. T. Howarth and I. Stirling, Ger. Offen. 2,655,675 (*Chem. Abstr.*, 1977, **87**, 102313); (*b*) A. G. Brown, D. F. Corbett, J. Goodacre, J. B. Harbridge, T. T. Howarth, R. J. Ponsford, I. Stirling and T. J. King, *J. Chem. Soc., Perkin Trans. 1*, 1984, 635.

8 (*a*) A. M. Kanazawa, J.-N. Denis and A. E. Greene, *J. Org. Chem.*, 1994, **59**, 1238; (*b*) W. B. Jennings and C. J. Lovely, *Tetrahedron Lett.*, 1988, **29**, 3725.

9 (*a*) A. G. Brown, D. F. Corbett and T. T. Howarth, *J. Chem. Soc., Chem. Commun.*, 1977, 359; (*b*) S. M. Schmitt, D. B. R. Johnston and B. G. Christensen, *J. Org. Chem.*, 1980, **45**, 1135; (*c*) R. Sharva, R. J. Stoodley and A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 1987, 2361; (*d*) W. Maison, M. Kosten, A. Charpy, J. Kintscher-Langenhagen, I. Schlemminger, A. Lutzen, O. Westerhoff and J. Martens, *Eur. J. Org. Chem.*, 1999, 2433.

10 F. W. Fowler, *Adv. Heterocycl. Chem.*, 1971, **13**, 45 . For reactions specifically involving azirines and azomethine ylides, see Z. Bende, I. Bitter, L. Toke, L. Weber, G. Toth and F. Janke, *Liebigs Ann. Chem.*, 1982, 2146; D. M. B. Hickey, C. J. Moody and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1119 . See also: O. Meth-Cohn, N. J. R. Williams, A. MacKinnon and J. A. K. Howard, *Tetrahedron*, 1998, **54**, 9837.

11 (*a*) D. Knittel, *Synthesis*, 1985, 186; (*b*) M. J. Alves and T. L. Gilchrist, *J. Chem. Soc., Perkin Trans. 1*, 1998, 299.

12 M. J. Alves and T. L. Gilchrist, *Tetrahedron Lett.*, 1998, **39**, 7579.

13 (*a*) Aziridine C–N cleavage α to a carbonyl group can be achieved by β-elimination reactions: A. Laurent, P. Mison, A. Nafti and N. Pellissier, *Tetrahedron*, 1979, **35**, 2285; (*b*) A. Padwa and Y. Kulkarni, *Tetrahedron Lett.*, 1979, 107; (*c*) M. J. Alves, T. L. Gilchrist and J. H. Sousa, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1305.

14 For the cleavage of aziridine C–N bond cleavage α to a carbonyl group, see the following (*a*) cleavage based on Li in liquid NH_3: E. J. Corey and R. D. Balanson, *Heterocycles*, 1976, **5**, 445; (*b*) use of $CrCl_2$: K. Sha, S. L. Ouyang, D. Y. Hsieh, R. C. Chang and S. C. Chang, *J. Org. Chem.*, 1986, **51**, 1490; (*c*) transfer hydrogenation and acid-mediated cleavage: D. A. Evans, M. M. Faul, M. T. Bilodeau, B. A. Anderson and D. M. Barnes, *J. Am. Chem. Soc.*, 1993, **115**, 5328; (*d*) hydrogenolysis: Y. H. Lim and W. K. Lee, *Tetrahedron Lett.*, 1995, **36**, 8431; (*e*) use of SmI_2: G. A. Molander and P. J. Stengel, *J. Org. Chem.*, 1995, **60**, 6660; G. A. Molander and P. J. Stengel, *Tetrahedron*, 1997, **53**, 8887; (*f*) reduction of α-amino acids using SmI_2: T. Honda and F. Ishikawa, *Chem. Commun.*, 1999, 1065.

15 In related bicyclic systems, the *cis* isomer shows a small (*ca.* 1 Hz) ^5J coupling between the proton adjacent to the ester (equivalent to H-5 in 16) and one proton (α) of the methylene unit adjacent to the β-lactam carbonyl (equivalent to H-8α in **16**). See (*a*) P. H. Crackett, C. M. Pant and R. J. Stoodley, *J. Chem. Soc., Perkin Trans. 1*, 1984, 2785; (*b*) M. D. Bachi, R. Breiman and H. Meshulam, *J. Org. Chem.*, 1983, **48**, 1439 . See also ref. 9*d*.

16 A. G. Hortmann, D. A. Robertson and B. K. Gillard, *J. Org. Chem.*, 1972, **37**, 322.

17 (*a*) V. N. Belov and M. A. Kuznetsov, *Zh. Org. Khim.*, 1988, **24**, 1288 (*Chem. Abstr.*, 1989, **110**, 75232a); (*b*) R. Muller, R. Gust, U. Klement and H. Schonenberger, *Chem. Ber.*, 1991, **124**, 2381; (*c*) J. Legters, L. Thijs and B. Zwanenburg, *Recl. Trav. Chim. Pays-Bas*, 1992, **111**, 16; (*d*) S. Chandrasekhar and M. Ahmed, *Tetrahedron Lett.*, 1999, **40**, 9325.