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A summary of the development, mechanistic features, and scope of the azomethine ylid strategy for the synthesis of a variety of bicyclic β-lactam derivatives, including carbapenams, carbapenems as well as heteroatom substituted variants, is presented.

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Since first being introduced over fifty years ago, the β-lactam antibiotics continue to represent a major class of clinically very important and commercially valuable therapeutic agents [1-4]. Over this period, the field has, of course, witnessed numerous innovations both in terms of synthetic methodology that has become available which has been combined with the discovery (usually from natural sources) of new and more potent drug candidates [5]. The isolation [6] and subsequent total synthesis [7] of thienamycin in 1978 by the Merck group represents one of the most significant advances of recent years, which has provided the lead into the carbapenem class of clinically used antibiotics, represented by imipenem (Figure 1). The carbapenems are potent antibacterial agents; the market for imipenem (Primaxin I.V.®) is currently worth about $700 million per annum. More recently, interest has focused on more highly condensed carbapenem variants, such as sanfetrinem, which is currently under investigation at GlaxoWellcome [8,9].

The sulfur-based β-lactams, such as the penams (exemplified by sulbactam) and the unsaturated penems [10-13], a synthetic β-lactam that combines key features of the penams and the carbapenems, have also attracted much interest within the pharmaceutical sector [3]. Despite the occurrence of bacterial resistance, the penams remain a very useful weapon against infection, although the penems are yet to make a significant impact in the market place.

When defining a new synthetic approach to β-lactam containing molecules, it is important to appreciate those structural features that contribute to biological activity. Clearly, the presence of the reactive β-lactam unit is critical, but so also is the C(3) carboxyl moiety. In the carbapenem area, the location of the C=C bond is critical (Δ^1 carbapenems are usually devoid of useful biological activity) [14-16] and a substituent at C(6), such as the α-hydroxyethyl residue present in thienamycin and imipenem, contributes towards stability towards β-lactamases and thereby increasing the effective lifetime of the drug [17-19].

It is also necessary to recognize that additional variation is available within this relatively simple molecular arrangement, and aza, oxa and selenium-containing analogues of the penams and/or penems have also attracted attention (Figure 2). Interest is not restricted to the 1-aza[3.2.1]heptane arrangement, and homologues, such as the cephems, and the aza-, oxa- and carbacephems, serve to extend dramatically the opportunities for structural modification that are now available [20].

An ability to generate a wide range of novel structural variants is one of the challenges facing this area, and our goal has been to focus on developing chemistry that is flexible in terms of allowing access to various substitution patterns around the central (1-aza[3.2.1]heptane) bicyclic β-lactam nucleus. However, we were also concerned to devise a synthetic strategy that would provide for a rapid and convergent entry into a variety of the different skeletal types - incorporating carbon, oxygen, sulfur, *etc.* - along the lines represented by the structures shown within Figure 2.

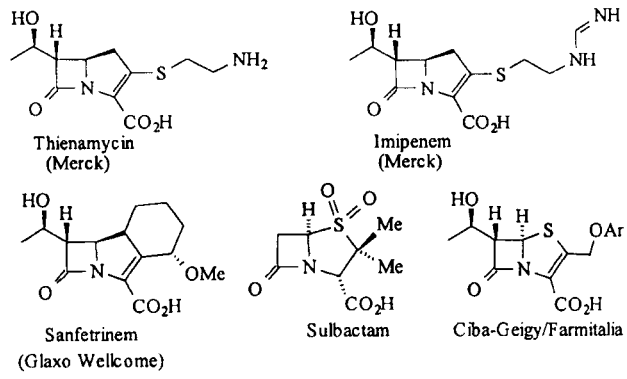


Figure 1.

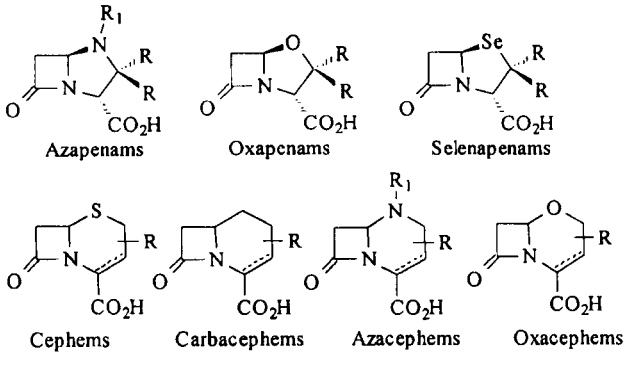
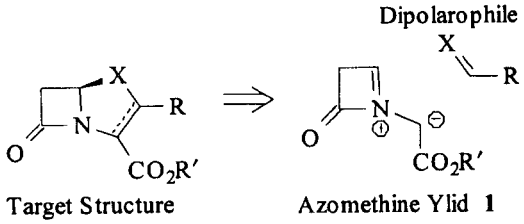


Figure 2.

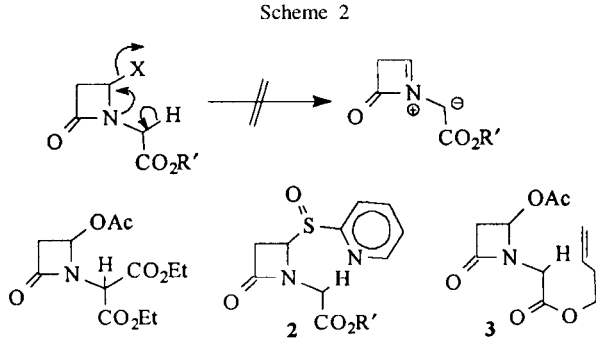
Our approach evolved from considering ways to construct the five-membered heterocyclic ring, and the opportunity to achieve this *via* a 1,3-dipolar cycloaddition reaction using an azomethine ylid [21-24] was very attractive (Scheme 1). Here the hypothetical β-lactam-based *N*-acyl azomethine ylid **1** provides the reactivity that is essential to form two new σ-bonds, but the real power of this strategy resides in being able to combine this 1,3-dipole with the wide variety of dipolarophiles that are also available. In this way, use of an alkenyl dipolarophile would provide access to the carbapenam framework, but simply switching to a thioketone would then give the penam core structure in a single step. Such an approach has a certain obvious but nevertheless elusive quality, since generating the requisite azomethine ylid reactivity proved to be a significant challenge.

Scheme 1



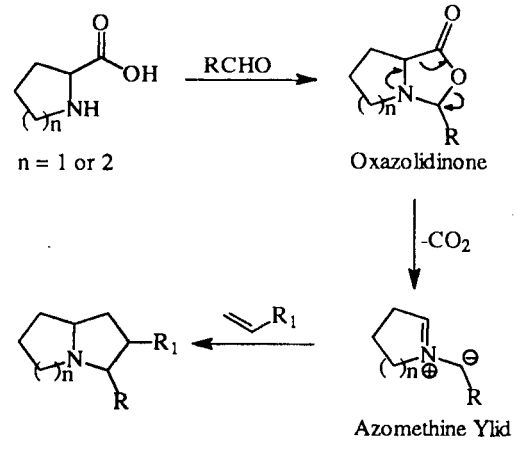
Initially, a series of β-lactam derivatives were prepared which all contained a leaving group at C(4) of the azetidinone ring and incorporated an acidic proton adjacent to nitrogen (Scheme 2). The aim was to induce an elimination of HX and trap the resulting azomethine ylid as it was formed, but this proved to be a fruitless exercise. Most substrates were thermally very stable and attempts to induce a sulfoxide (as in **2**) to fragment or capture a 1,3-dipolar intermediate *via* an intramolecular cycloaddition (as in **3**) all failed.

Scheme 2



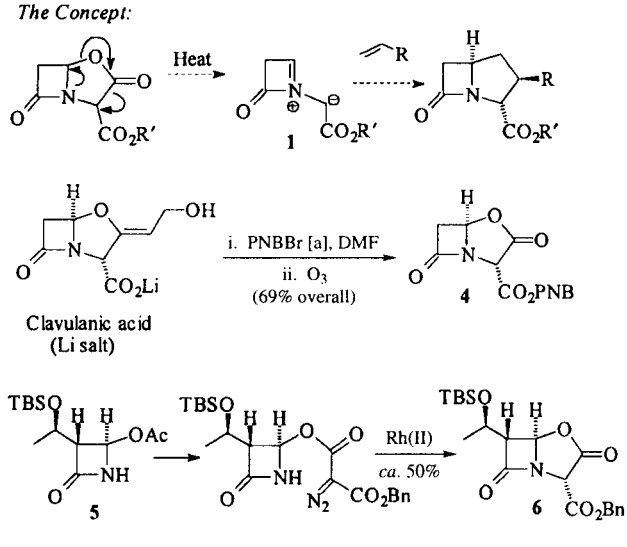
The solution to this problem lay in the use of an oxazolidinone as the azomethine ylid precursor. It has been known for some years that oxazolidinones (derived from condensation of an α-amino acid with an aldehyde) will undergo decarboxylation to give an *N*-alkyl azomethine ylid (Scheme 3). Extensive work by Grigg [25,26] and others [27-29] has provided an insight into both the mechanism of this process as well as its synthetic utility.

Scheme 3



The application of these ideas to the β-lactam area was especially attractive because two oxazolidinones **4** and **6** had in fact already been described in the literature (Scheme 4).

Scheme 4

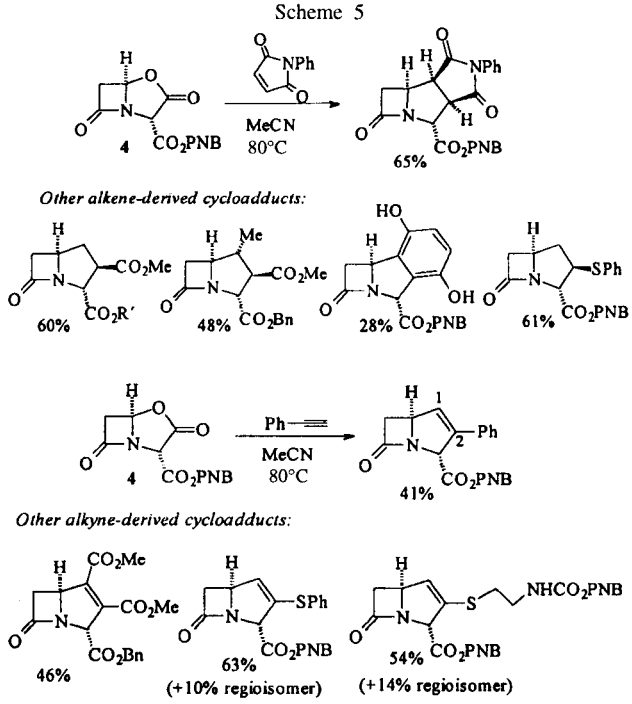


[a] PNBBr: *p*-Nitrobenzyl Bromide.

The simple variant **4**, protected as the 4-nitrobenzyl (PNB) ester, and which provides the basis of most of the reactions described here, is best prepared on a multigram scale from clavulanic acid and is obtained as an enantiomerically pure crystalline solid [30-32]. The benzyl and other alkyl esters are also available and have been used in our work. The potentially more valuable C(6) substituted oxazolidinone **6** was reported in a patent from the Merck group [33] and is prepared from the commercially available 4-acetoxylazetidinone **5**. While **6** is also a single enantiomer, the yield for the rhodium-mediated carbene insertion step is only *ca.* 50% and the sensitivity of **6** towards chromatography makes further purification difficult. Consequently, the yields reported below for cycloadducts obtained from **6** relate to the *overall* efficiency for both the carbene insertion *and* the cycloaddition step. In raw terms, these yields are lower than those obtained from **4**, but in our opinion this reflects the purity of the starting oxazolidinone **6** and not a problem connected to the presence of the bulky C(6) residue. Nevertheless, finding a solution to the purity issues associated with oxazolidinone **6** remains elusive.

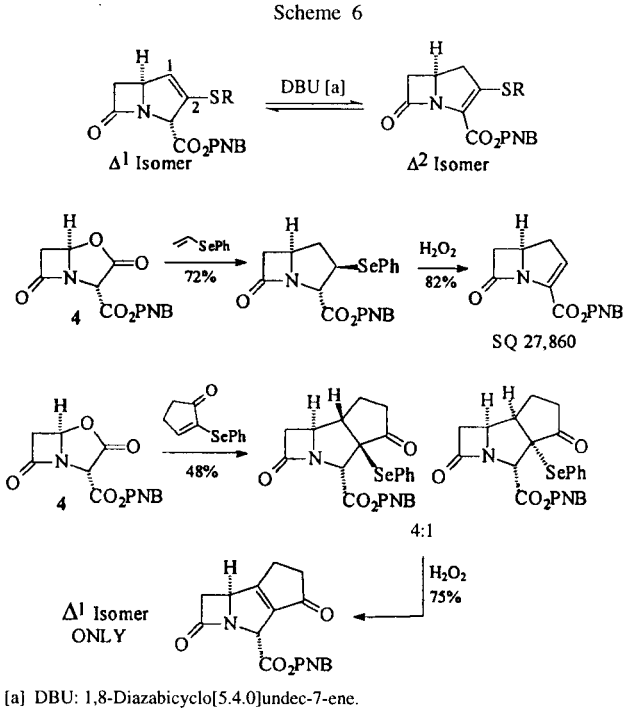
Thermolysis of **4** (or the corresponding benzyl ester) in acetonitrile at reflux (or at 100° in a sealed tube) and in the presence of an alkene or an alkyne provides a direct entry to carbapenams and Δ^1-carbapenems, respectively, in reasonable yields after chromatography (Scheme 5) [34]. It is important to appreciate that the stereochemistry shown for these cycloadducts is *relative* and not *absolute*: all cycloaddition products obtained from **4** are racemic (however, see below when **6** is employed).

Scheme 5



Stereochemical assignments for these and the other cycloadducts obtained are based on extensive nmr studies, and X-ray crystallography has also been widely used. In all cases studied to date, the C(3)/C(5) stereochemistry corresponds to the thermodynamically more favorable arrangement with the carboxyl residue on the *exo* face of the bicyclic framework [15,35,36]. Efficient access to the biologically more relevant Δ^2-carbapenems is more problematic. While base-mediated C=C isomerization can be used [15,35], this is not an efficient reaction and, as such, does not in our view represent a practical solution to this problem. Incorporating a means for introducing this important level of unsaturation within the initial dipolarophile is achievable, but the selenoxide elimination process shown in Scheme 6 is sensitive to the substrate involved.

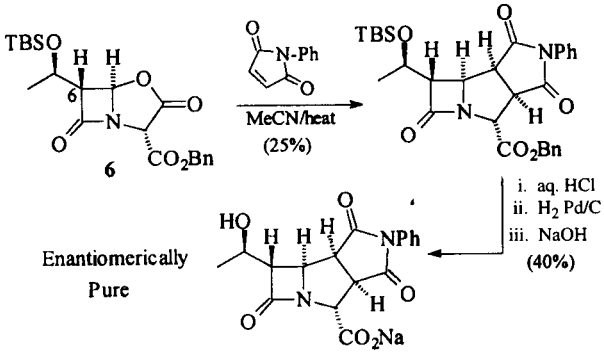
Scheme 6



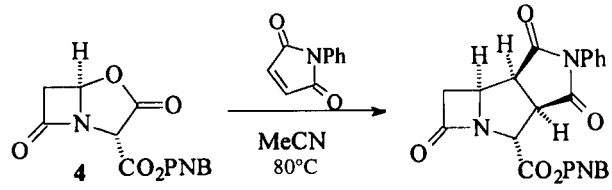
[a] DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene.

A very similar comprehensive series of cycloadducts adducts have also been produced in the α-hydroxyethyl series, and one representative example is shown in Scheme 7. Compared to the chemistry shown in Scheme 6, there are two significant differences. Firstly, lower yields of adducts are isolated (however, see above) but secondly and importantly, the cycloadducts in this series are enantiomerically pure. The C(6) substituent present in **6** serves not only to direct the facial approach of the dipolarophile but also retains the enantiomeric integrity of the starting material.

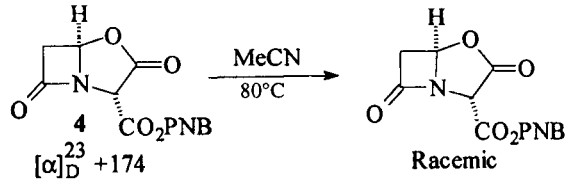
Scheme 7



Scheme 8



◊ Second order kinetics observed; first order in **4** and *N*-phenylmalimide.

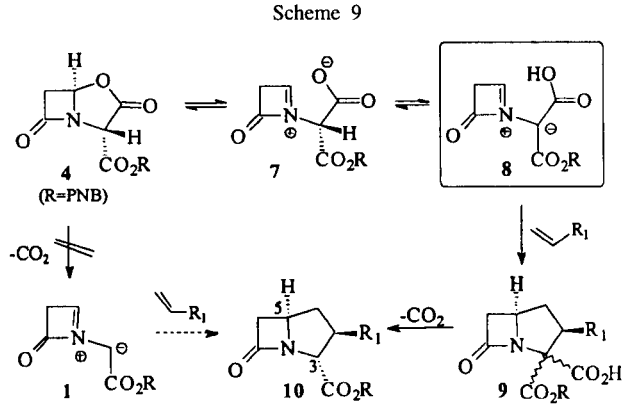


◊ Oxazolidinone **4** undergoes racemization on heating.
◊ Oxazolidinone **4** does NOT decarboxylate when heated in the absence of a dipolarophile.

It is important to consider (rather than assume) the actual structure of the azomethine ylid intermediate that is involved in this cycloaddition chemistry. Given that *N*-alkyl oxazolidinones undergo concerted decarboxylation to give an azomethine ylid (see Scheme 3), extrapolating this concept to the β-lactam variant **4** (and **6**) would suggest participation of **1** as the 1,3-dipolar species involved. However, a number of pieces of evidence were obtained suggesting that an alternative pathway was operating. The use of dimethyl fumarate and dimethyl maleate demonstrated that the cycloaddition step was indeed stereospecific, and in that sense, confirmed the operation of a concerted $4\pi + 2\pi$ process. The reaction of **4** with *N*-phenylmalimide was studied and found to show second order kinetics (first order with respect to both **4** and the dipolarophile), but more surprisingly a control experiment showed that **4** did not undergo decarboxylation when heated in the absence of a dipolarophile. This result led to further experiments, and while **4** does not undergo decarboxylation when heated (in acetonitrile at 80°), we did observe racemization of **4** under these conditions (Scheme 8); this was an unexpected result but has an important bearing on the mechanism involved.

A mechanism for the release of azomethine ylid reactivity from oxazolidinone **4** that is consistent with these observations is shown in Scheme 9 and requires a stepwise, but reversible fragmentation of **4** *via* **7** leading (after a proton transfer step) to **8**. It is this species, the carboxylated analogue of **1**, which we speculate is the key azomethine ylid intermediate involved in this chemistry [37]. When no trap is present, then participation of this two-step equilibrium would account for the recovery of racemic **4**, but when a dipolarophile is available, then the equilibrium is intercepted by a rate limiting cycloaddition step giving **9**. The final transformation requires decarboxylation of the initial adduct **9** which would be anticipated to yield the thermodynamically favored (relative) stereochemistry at C(3) that is present in **10**. It should be pointed out that at this point we cannot exclude decarboxylation of **9**, rather than the cycloaddition step, as the rate determining event, but this seems less likely and we have been unable to isolate any adducts retaining the carboxylic acid function.

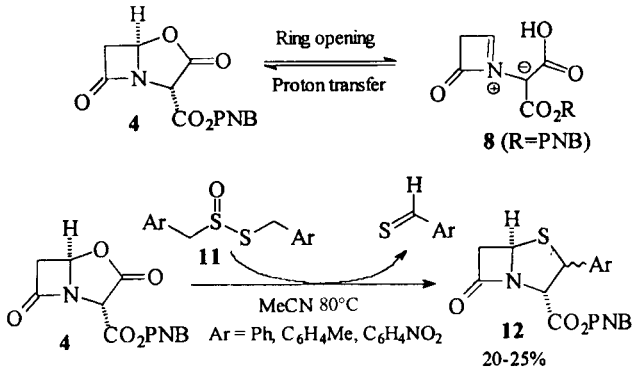
Scheme 9



This mechanistic proposal raises a number of intriguing issues. While we have not been able to detect an azomethine ylid such as **8**, our observations relating to racemization imply that some (though perhaps only low) concentration of **8** is always available in the reaction flask. In this sense, **8** may be viewed as a "persistent" 1,3-dipole, which offers an opportunity to exploit the potential of highly reactive (but also highly elusive) 1,3-dipolarophiles that can only be generated and captured *in situ*. The validity of this concept has recently been demonstrated. Slow addition of a solution of thiosulfinate **11** to **4** in acetonitrile at reflux leads to the generation [38] of a

reactive aryl thioaldehyde and to the formation of the epimeric penam cycloadducts **12** in modest (20-25%) yield (Scheme 10).

Scheme 10



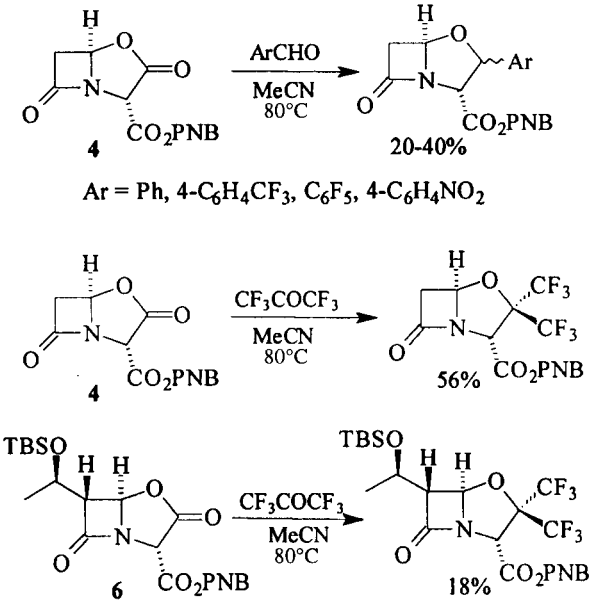
Further work is now underway to explore the scope of this process in what amounts to a reversal of what is the generally accepted profile of most 1,3-dipolar cycloaddition reactions: reactive 1,3-dipole + stable dipolarophile.

An ability to trap thiocarbonyl-based dipolarophiles provides the focus for the second part of this account. At the outset we had the goal of exploiting both C=C and C=S containing dipolarophiles to allow an entry to the carbapenam/carbapenem and penam skeletons, respectively, and to also explore other heteroatom variants of these bicyclic β-lactam frameworks. The examples discussed below serve to illustrate the range of structures that can be made available using a related set of oxygen-, sulfur and selenium-containing dipolarophiles.

Oxapenams and oxapenems represent a relatively unusual class of bicyclic β-lactam derivatives. A number of naturally-occurring examples are known, the most important of which is clavulanic acid (see Scheme 4) which is a key component of Augmentin, an antibiotic marketed by SB Pharmaceuticals which had sales in 1998 of £964 million. However, oxapenams [39-41] and oxapenems [42-49] are strained, sensitive molecules, and any synthetic entry to this system must recognize these limitations. The azomethine ylid strategy provides a very direct entry into 2-substituted (both *exo* and *endo* epimers are isolated) and 2,2-disubstituted oxapenams by using aryl aldehydes and ketones respectively (Scheme 11).

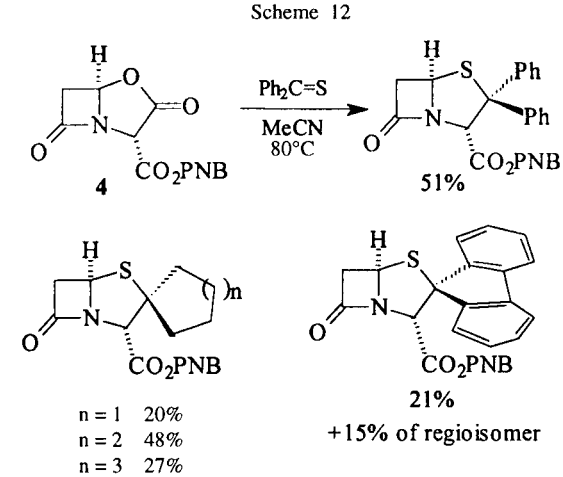
Simple ketones, such as cyclopentanone and benzophenone, failed to react but electron-deficient dipolarophiles, such as hexafluoroacetone, were viable. Other carbonyl derivatives (amides, esters and thioesters) were also examined but failed to lead to cycloadduct formation. Once again, and this also applies to the other adducts shown in this account, the complete stereochemistry of the oxapenams shown in Scheme 11 was established by a combination of extensive nmr and X-ray crystallography.

Scheme 11



Penams and penems continue to represent an important and topical group of bicyclic β-lactam derivatives, and the use of thiocarbonyl dipolarophiles has been briefly illustrated in Scheme 10. Again, a full range of sulfur-based traps was examined and a remarkable degree of structural/stereocontrol can be achieved. Thioketones, including simple variants such as thiocyclohexanone and thiocyclopentanone, are readily trapped to afford 2,2-disubstituted penams as single regio and stereoisomers (Scheme 12). Only in the case of thiofluorenone were

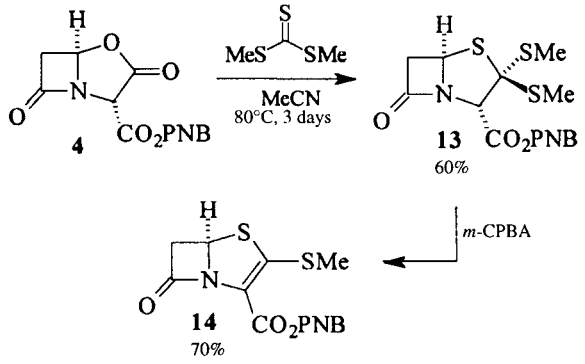
Scheme 12



both regioisomers isolated. These cycloaddition reactions are relatively slow, but the direct nature of the chemistry involved and the range of substitution patterns available remains compelling [50].

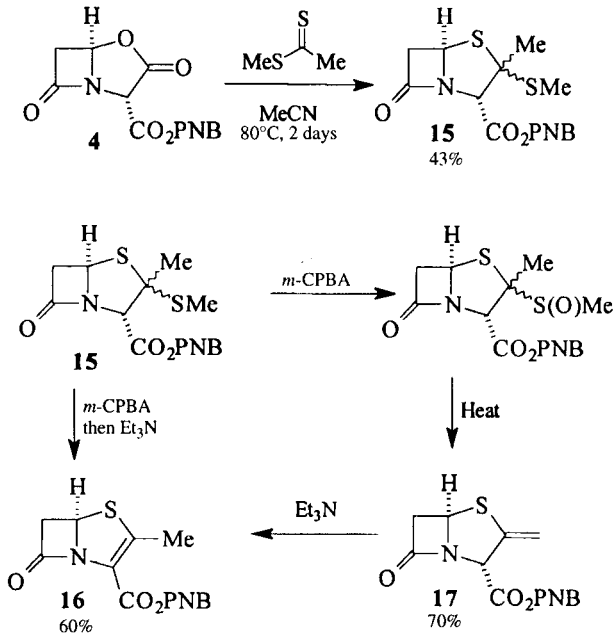
An approach to penems requires a mechanism for introducing the C(2)-C(3) double bond and we aimed to achieve this transformation by an elimination sequence. Using trithiocarbonates or dithioesters as the dipolarophile provides the corresponding cycloadducts **13** and **15**, once again as single regioisomers (Scheme 13). Treating **13** with peracid at low temperature and simply allowing the reaction mixture to warm to room temperature resulted in clean elimination to give the 2-(thiomethyl)penem **14**. Oxidation of the less reactive ring-constrained sulfur atom is easily avoided under these mild reaction conditions.

Scheme 13



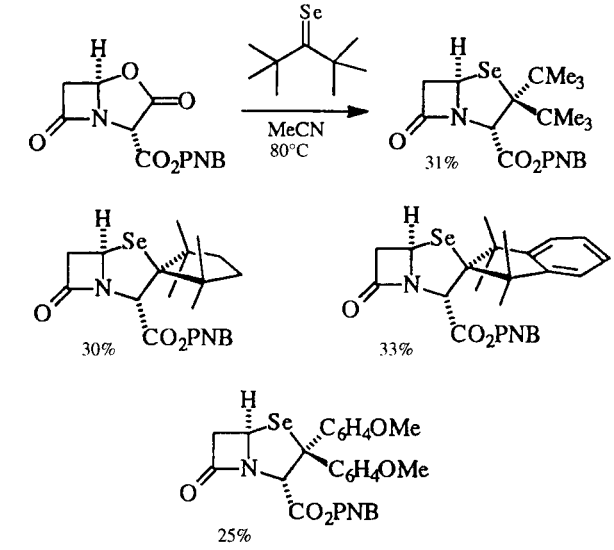
In the case of the 2-alkyl derivatives **15**, then an unexpected result was obtained (Scheme 14). Peracid oxidation of **15** gave a relatively stable, but stereochemically complex mixture of sulfoxides, which underwent smooth elimination using triethylamine. In this way the *endo* 2-alkyl penem **16** was obtained, and a similar sequence has been applied to generate the corresponding 2-aryl penem analogues. Sulfoxides are also amenable to thermally induced elimination, and heating in acetonitrile afforded the isomeric *exo* penem **17** as the sole product. This was not anticipated, but an ability to produce selectively the *endo* and *exo* penem isomers is of value, given that the position of the double bond may make a contribution to biological profile. It is also useful to recognize that the *exo* penem isomer **17** is thermodynamically less stable and does undergo facile isomerization to the *endo* isomer **16** on base treatment.

Scheme 14



The final set of Group VI based dipolarophiles are those incorporating the C=Se moiety, but unlike the penams and penems, very little is known about the synthesis of the corresponding selenium-containing bicyclic β-lactams. While selenoketones are very reactive and difficult to isolate (which places some limitations on the methods employed and the range of substrates available), these molecules are effective dipolarophiles and a series of (novel) selenapenams have been obtained (Scheme 15).

Scheme 15



Selenocarbonyl derivatives, such as selenoamides and selenourea, proved to be insufficiently reactive towards 1,3-dipolar cycloaddition, and an entry to selenapenems [51] is being studied along similar lines to that shown in Scheme 13.

Clearly, the azomethine ylid strategy provides a versatile entry to a range of different bicyclic β-lactam structures, and a selection of those skeletons now available using this approach have been demonstrated in this account. A number of issues do remain to be solved. For example, an efficient solution is needed to the challenge presented by the Δ^2-carbapenems, but new directions also need to be explored. The reactivity associated with both **4** and **8** offers potential for alternative annulation strategies to be developed, and this is being examined with a view towards producing significantly different and synthetically useful molecular frameworks.

It remains for me to express my lasting gratitude to all of the postgraduate and postdoctoral students who have all worked so hard on this and the other areas of research that we have been involved in since 1983. Without these people, nothing would have been possible. I must also thank the funding agencies (EPSRC and BBSRC), the many companies and especially the individuals within these organizations who provided the financial support to fuel the effort.

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REFERENCES AND NOTES

[1] W. Dürckheimer, J. Blumbach, R. Lattrell and K. H. Scheunemann, *Angew. Chem., Int. Ed. Engl.*, **24**, 180 (1985).

[2] A. H. Berko, *Tetrahedron*, **52**, 331 (1996).

[3] G. I. Georg, Recent Advances in the Chemistry and Biology of β-Lactam and β-Lactam Antibiotics, *Bioorg. Med. Chem. Letters* (Symposia in Print No 8), **3**, 2159 (1993).

[4] R. B. Morin and M. Gorman, in Chemistry and Biology of β-Lactam Antibiotics, Academic Press, New York, 1982.

[5] D. Niccolai, L. Tarsi and R. J. Thomas, *J. Chem. Soc., Chem. Commun.*, 2333 (1997).

[6] G. Albers-Schönberg, B. H. Arison, O. D. Hensens, J. Hirschfield, K. Hoogsteen, E. A. Kaczka, R. E. Rhodes, J. S. Kahan, F. M. Kahan, R. W. Ratcliffe, E. Walton, L. J. Ruswinkle, R. B. Morin and B. G. Christensen, *J. Am. Chem. Soc.*, **100**, 6491 (1978).

[7] K. C. Nicolaou and E. J. Sorensen, in Classics in Total Synthesis, VCH, Weinheim, Chapter 16, p 249, 1996.

[8] E. Dimodugno, I. Erbetti, L. Ferrari, G. Galassi, S. M. Hammond and L. Xerri, *Antimicrob. Agents Chemother.*, **38**, 2362 (1994).

[9] A. Padova, S. M. Roberts, D. Donati, A. Perboni and T. Rossi, *J. Chem. Soc., Chem. Commun.*, 441 (1994).

[10] I. Ernest, J. Gosteli, C. W. Greengrass, W. Holick, D. E. Jackman, H. P. Pfaendler and R. B. Woodward, *J. Am. Chem. Soc.*, **100**, 8214 (1978).

[11] I. Ernest, J. Gosteli and R. B. Woodward, *J. Am. Chem. Soc.*, **101**, 6301 (1979).

[12] M. Lang, K. Prasad, W. Holick, J. Gosteli, I. Ernest and R. B. Woodward, *J. Am. Chem. Soc.*, **101**, 6296 (1979).

[13] H. R. Pfaendler, J. Gosteli and R. B. Woodward, *J. Am. Chem. Soc.*, **101**, 6306 (1979).

[14] G. H. Hakimelahi, *Helv. Chim. Acta*, **65**, 1378 (1982).

[15] R. Sharva, R. J. Stoodley and A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 2361 (1987).

[16] C. L. Branch and M. J. Pearson, *J. Chem. Soc., Perkin Trans. 1*, 2123 (1982).

[17] I. Massova and S. Mobashery, *Acc. Chem. Res.*, **30**, 162 (1997).

[18] L. Maveyraud, I. Massova, C. Birck, K. Miyashita, J.-P. Samama and S. Mobashery, *J. Am. Chem. Soc.*, **118**, 7435 (1996).

[19] L. Maveyraud, L. Mourey, L. P. Kotra, J.-D. Pedelacq, V. Guillet, S. Mobashery and J.-P. Samama, *J. Am. Chem. Soc.*, **120**, 9748 (1998).

[20] G. I. Georg, in the Organic Chemistry of β-Lactams, VCH, New York, 1992.

[21] J. W. Lown, 1,3-Dipolar Cycloadditions, A. Padwa, ed, New York, Vol **1**, 1984, p 653.

[22] R. Grigg, *Chem. Soc. Rev.*, **16**, 89 (1987).

[23] O. Tsuge and S. Kanemasa, Adv. Heterocyclic Chem., A. R. Katritzky, ed, Academic Press, San Diego, Vol **45**, 1989, p 231.

[24] W. H. Pearson, Studies in Natural Product Chemistry, Atta-ur-Rahman, ed, Elsevier, Amsterdam, Vol **1**, 1988.

[25] R. Grigg, S. Surendrakumar, S. Thianpatanagul and D. Vipond, *J. Chem. Soc., Perkin Trans. 1*, 2693 (1988).

[26] R. Grigg, J. Idle, P. McMeekin, S. Surendrakumar and D. Vipond, *J. Chem. Soc., Perkin Trans. 1*, 2703 (1988).

[27] S. Kanemasa, K. Sakamoto and O. Tsuge, *Bull. Chem. Soc. Japan*, **62**, 1960 (1989).

[28] A. Echenmoser, *Chem. Soc. Rev.*, **5**, 377 (1976).

[29] K. Burger, A. Meffert and S. Bauer, *J. Fluorine Chem.*, **10**, 57 (1977).

[30] T. T. Howarth and I. Stirling, German Offen 2,655,675; *Chem. Abstr.* **87**, 102 313 (1977).

[31] 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*, 635 (1984).

[32] M. M. Campbell and V. J. Jasys, *Heterocycles*, **16**, 1487 (1981).

[33] E. J. J. Grabowski and P. J. Reider, European Patent. 78 026; *Chem. Abstr.*, **99**, 122171 (1983).

[34] S. R. Martel, R. Wisedale, T. Gallagher, L. D. Hall, M. F. Mahon, R. H. Bradbury and N. J. Hales, *J. Am. Chem. Soc.*, **119**, 2309 (1997).

[35] S. M. Schmitt, D. B. R. Johnston and B. G. Christensen, *J. Org. Chem.*, **45**, 1135 (1980).

[36] A. G. Brown, D. F. Corbett and T. T. Howarth, *J. Chem. Soc., Chem. Commun.*, 359 (1977).

[37] S. R. Martel, D. Planchenault, R. Wisedale, T. Gallagher and N. J. Hales, *J. Chem Soc., Chem. Commun.*, 1897 (1997).

[38] J. E. Baldwin and R. C. G. Lopez, *Tetrahedron*, **39**, 1487 (1983).

[39] M. Wanning, H. Zahner, B. Krone and A. Zeeck, *Tetrahedron Letters*, **22**, 2539 (1981).

[40] D. L. Pruess and M. Kellett, *J. Antibiotics*, **36**, 208 (1983).

[41] J. E. Baldwin, R. M. Adlington, J. S. Bryans, A. O. Bringhen, J. B. Coates, N. P. Crouch, M. D. Lloyd, C. J. Schofield, S. W. Elson, K. H. Baggaley, R. Cassels and N. Nicholson, *Tetrahedron*, **47**, 4089 (1991).

[42] W. Nagata, *Pure Appl. Chem.*, **61**, 325 (1989).

[43] H. R. Pfaendler, W. Hendel and U. Nagel, *Z. Naturforsch. Teil B*, **47**, 1037 (1992).

[44] H. Wild, *Tetrahedron Letters*, **34**, 285 (1993).

[45] H. Wild and W. Hartwig, *Synthesis*, 1099 (1992).

[46] H. R. Pfaendler, F. Weisner and K. Metzger, *Bioorg. Med. Chem. Letters*, **3**, 2211 (1993).

[47] M. Botta, M. Crucianelli, R. Saladino, C. Mozzetti and R. Nicoletti, *Tetrahedron*, **52**, 10205 (1996).

[48] H. R. Pfaendler and C. Medicus, *Bioorg. Med. Chem. Letters*, **7**, 623 (1997).

[49] P. Couture and J. Warkentin, *Can. J. Chem.*, **76**, 241 (1998).

[50] D. Planchenault, R. Wisedale, T. Gallagher and N. J. Hales, *J. Org. Chem.*, **62**, 3438 (1997).

[51] M. Alpegiani, A. Bedeschi, E. Perrone and G. Franceschi, *Tetrahedron Letters*, **27**, 3041 (1986).