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Non-Classical Polycyclic β-Lactams

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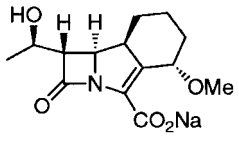
1. Introduction

Today, on the edge of the 21st century, the search for new antibacterial agents remains unabated.[1] In fact, the appearance of new types of bacteria resistant to the more commonly used β-lactam antibiotics is a problem of worldwide importance.[2] Thus, in spite of the formidable antibacterial arsenal available, someone could die today as a result of a bacterial infection, as in the dark ages prior to the discovery of penicillin. In most cases, the resistance mechanism against the β-lactam drugs involves a process of enzymatic cleavage of the β-lactam ring by β-lactamases.[3] In consequence, efforts to overcome the action of these enzymes have been undertaken on two fronts: (a) development of new β-lactam antibiotics resistant to β-lactamases and (b) use of β-lactamase inhibitors. Both approaches have produced results and a new generation of antibiotics such as trinems, **1** (formerly known as tribactams)[4] and tricyclic benzocarbapenems **2** as promising inhibitors of β-lactamases, were developed.[5] Strikingly, both classes of compounds have a tricyclic skeleton (Fig. 1).

Besides their significance as antibacterial agents, β-lactams show other interesting biological properties. They are potent inhibitors of mammalian serine proteases,[6] such as human leukocyte elastase (HLE) or thrombin and, in fact, very promising candidate compounds to fulfill this role are now under development. Another interesting property of 2-azetidinones is their role as cholesterol absorption inhibitors.[7] Furthermore, some monocyclic 2-azetidinones having diverse aromatic substituents attached to the four-membered ring have been found to be inhibitors of human cytomegalovirus (HCMV, a β-herpes virus), a serious pathogen in immunocompromised individuals.[8] These two examples of biological activity, different from the classical antibacterial action of β-lactam antibiotics, are a promising advance in finding new pharmacological uses for this family of substances.



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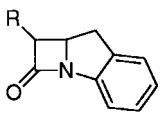

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Figure 1.

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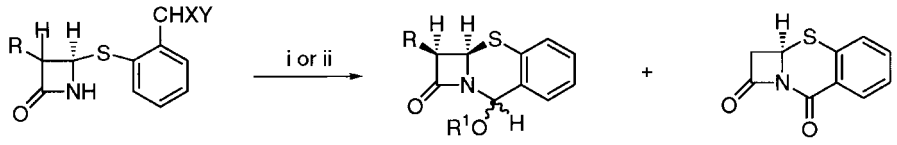


3a R = $Ph(CH_2)_2CONH$, X = H, Y = OH
3b R = H, X = H, Y = OH
3c R = H, X,Y = OCH_2CH_2O

i. DMSO/DCC or PCC oxidation
ii. TsOH, MeOH

4a (i, 20%) R = $Ph(CH_2)_2CONH$, R^1 = H **5** (20%)
4b (i, 62%) R = H, R^1 = H
4c (ii, 91%) R = H, R^1 = OMe

Scheme 1.

From a synthetic point of view, the development of a methodology based on the 2-azetidinone nucleus has reached such a level of importance as to merit its own name: 'the β-lactam synthon method'.[9] In fact, its role in the preparation of many types of non-β-lactam compounds, especially in the synthesis of non-proteinogenic amino acids, has been the subject of several reviews.[10]

This review draws attention to the diverse, and in many aspects scarcely studied, class of β-lactams having a 'non-classical' tri- or polycyclic structure. Trinems have been deliberately excluded from this work as their synthesis and chemistry has already been reviewed,[11] and they may be considered as classical β-lactam antibiotics. The different types of β-lactams with a tri- or polycyclic skeleton will be discussed in this review and it will be seen that their biological activity as well as their potential as synthetic intermediates remains mainly undiscovered.

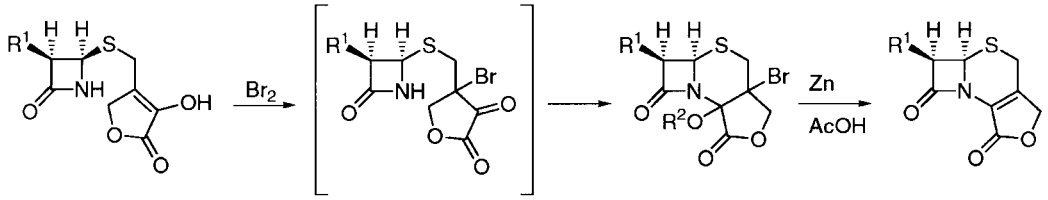
2. Building the Polycyclic Ring System on a Preformed 2-Azetidinone

Many different approaches can be devised and many have been used to achieve a ring on a preformed 2-azetidinone system. The different methods reported can be divided into two main groups: those forming an N–C bond, and those forming a C–C bond. In the first approach *NH*-2-azetidinones have been used whilst the second can be carried out in different ways, as will be described in the next section.

2.1. Ring closure on the lactam nitrogen

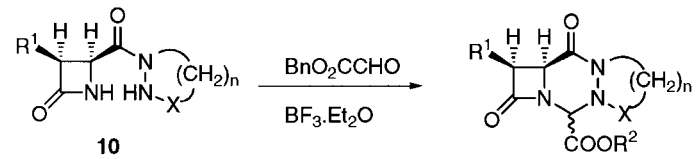
Most of the N–C bond forming processes are based on condensation reactions. One of the first examples of intramolecular condensation between the azetidinone nitrogen and a carbonyl group was reported in the early seventies by Sheehan.[12] Oxidation of the alcohol group in **3a** was followed by reaction between the 2-azetidinone nitrogen and the in situ generated aldehyde, to give the benzocepham **4a** in low yield (Scheme 1). This approach was then applied to the preparation of other compounds with different degrees of success.[13] PCC oxidation of azetidinone **3b** yielded a mixture of the expected β-lactam **4b** and its oxidation product **5**. Alternatively, compound **5** could be obtained by methanolysis of the protected aldehyde **3c** followed by hydrolysis of the resulting hemiaminal **4c**. Further transformations of compounds **4b**,**c** into their corresponding sulfoxides or sulfones, were also reported.[13]

Cephalosporin lactones **6** were obtained by transformation of the enols **7** into α-bromoketones **8**, which cyclized in situ to a mixture of *cis*/*trans* bromohydrins **9**.[14] The mixture of bromohydrins or their acetates (obtained by standard acetylation) was then reduced in the presence of Zn/acetic acid to



7 R^1 = $PhOCH_2CONH$ **8**

9a R^1 = $PhCH_2CONH$, R^2 = H **6**
9b R^1 = $PhCH_2CONH$, R^2 = OAc



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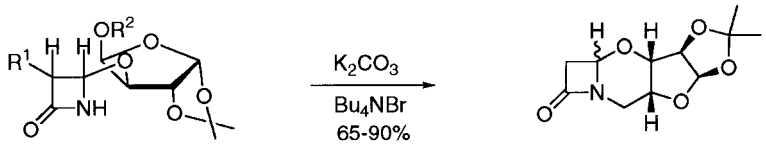
R^1 = $PhOCH_2CONH$; X = CH_2, CO;
n = 2,3

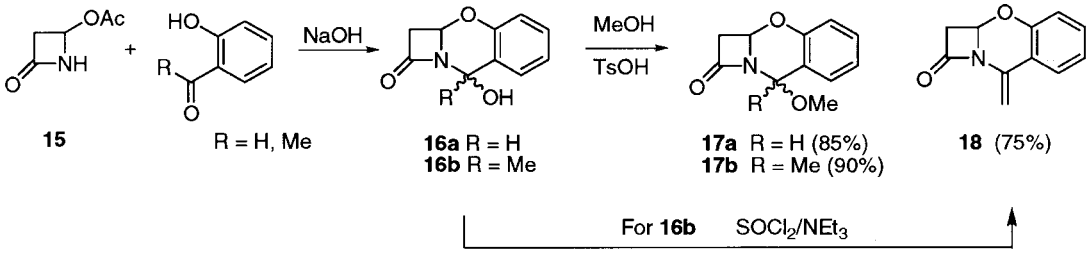
11 R^2 = Bn
12 R^2 = Na

Scheme 2.



13 R^1 = H, Me_3Si, Me_2PhSi, *t*-$BuMe_2Si$; R^2= Ts, TIBS **14**

Scheme 3.



15 R = H, Me **16a** R = H **16b** R = Me **17a** R = H (85%) **17b** R = Me (90%) **18** (75%)

Scheme 4.

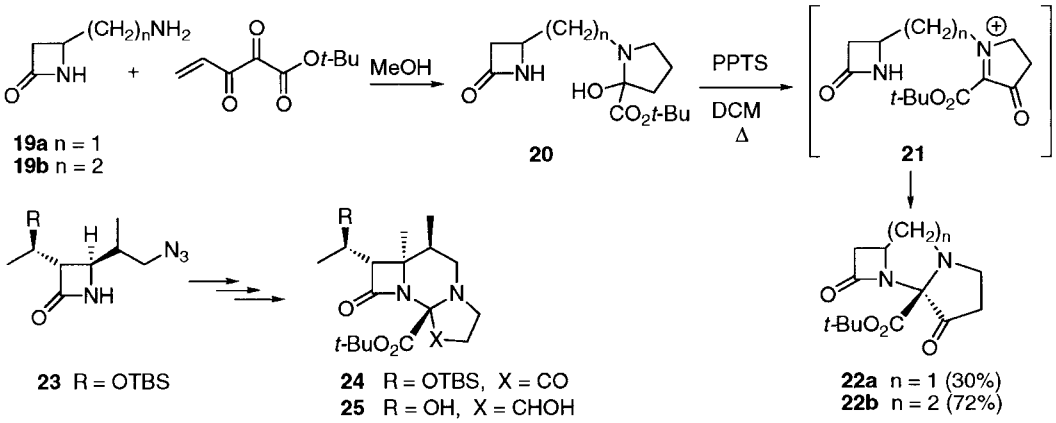
give the desired lactones **6** in 30% global yields. A related example was found in the Lewis acid promoted condensation of benzylglyoxalate with *cis*-azetidinones **10** having a hydrazone function in their structures.[15] The reaction afforded, in low yield, an epimeric mixture of tricyclic β-lactams **11** and these were subsequently transformed into their carboxylate salts **12** by treatment with H_2/Pd and $NaHCO_3$. The salts **12** showed a low antibacterial activity (Scheme 2).

The intramolecular *N*-alkylation of sugar-derived 2-azetidinones **13**, was achieved in good yields by means of a two phase system (anhydrous K_2CO_3/Bu_4NBr).[16] The cyclization process led simultaneously to desilylation and **14** was the only isolated product (except for R^1=*t*-$BuMe_2Si$) (Scheme 3).

The NH–C ring closure on a 2-azetidinone nucleus has also been effected by intermolecular condensations. A one-pot addition-condensation process was reported in the reaction of the readily available 4-acetoxyazetidin-2-one **15** with *o*-hydroxybenzaldehyde or *o*-hydroxyacetophenone, to afford the oxa-dethiabenzocephems **16a**,**b** in quantitative and 76% yield respectively.[17] Further functionalization of these compounds was achieved in good yields by methanolysis of compounds **16a**,**b** to yield **17a**,**b**, or by dehydration of the alcohol moiety in compound **16b** to form the tricyclic β-lactam **18** (Scheme 4).

Wasserman has described an analogous approach, but following a stepwise procedure. Reaction of the aminolactams **19** and vinyl vicinal tricarbonyls took place by initial addition of the primary amine to the vinyl tricarbonyl reagent, to form **20**. This intermediate in the presence of pyridinium *p*-toluenesulfonate (PPTS) was transformed into the pyrrolidinium salt **21**. The intramolecular attack by the lactam nitrogen led to the formation of the tricyclic β-lactams **22a**,**b** in 30% and 72% yield respectively (Scheme 5).[18] The β-stereochemistry of the carboxylate group was confirmed by X-ray analysis.

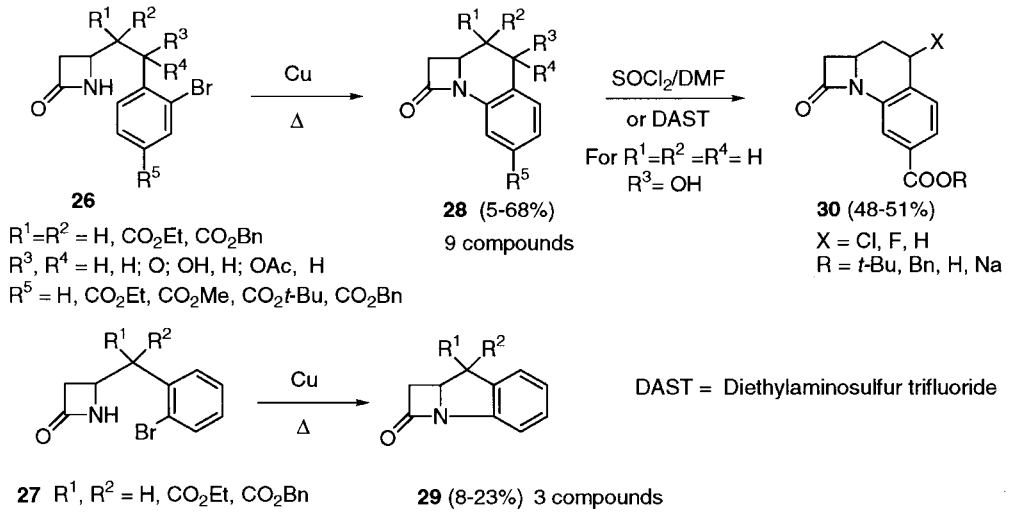
More functionalized analogs of **22** were produced by the same procedure starting from the azide **23**.[19] Reduction of the azido group followed by addition of the vinyl tricarbonyl reagent and further cyclization using PPTS, provided the tricyclic carbacepham **24**. This compound yielded the



19a n = 1 **19b** n = 2 **20** **21**

23 R = OTBS **24** R = OTBS, X = CO **25** R = OH, X = CHOH **22a** n = 1 (30%) **22b** n = 2 (72%)

Scheme 5.



Scheme 6.

tricyclic β-lactam **25** after selective reduction of the ketone group, removal of the TBS function with Bu_4NF and hydrogenolysis. The tricyclic β-lactam **25** incorporates the 3-(1-hydroxyethyl) group in its structure which is characteristic of many active bi- and tricyclic β-lactams (Scheme 5).

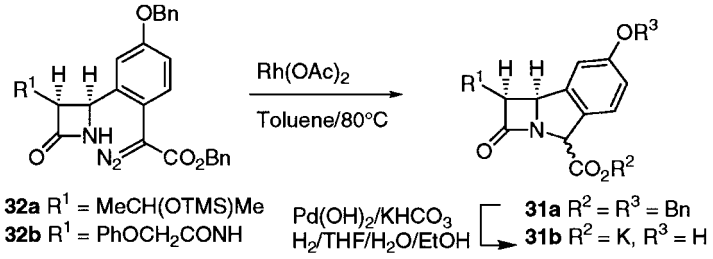
A different procedure to achieve the N1-cyclization reaction is the aromatic substitution of the azetidinone nitrogen on a halobenzene nucleus.[20] This process involves a Cu-induced intramolecular aromatic substitution on substrates **26** and **27** to yield a series of benzocarbacephems **28** and benzocarbapenems **29**, in low to moderate yields. Of particular interest were compounds **30** obtained by simple chemical transformations, after replacement of the hydroxyl group in the benzocarbacephems **28** by Cl, F, or hydrogen group. These compounds, in the form of their sodium salts, were tested as possible β-lactamase inhibitors, exhibiting in some cases good competitive inhibition results (Scheme 6).

The intramolecular insertion of in situ generated carbenes into the lactam N–H bond is an alternative route to tricyclic β-lactams. Heck designed the closure of the central five membered ring of the benzocarbapenem **31a** by reaction of the diazo compound **32** with $Rh(OAc)_2$. The compounds **31** have a norcardicine-like structure but with the additional ring strain characteristic of penicillin and thienamycin derivatives, and were obtained in 5–10% overall yield from the diazo compound precursor **32**. Hydrogenolysis of the benzyl protecting groups of **31a** gave the potassium salt **31b** which showed only low activity against a variety of microorganisms (Scheme 7).[21]

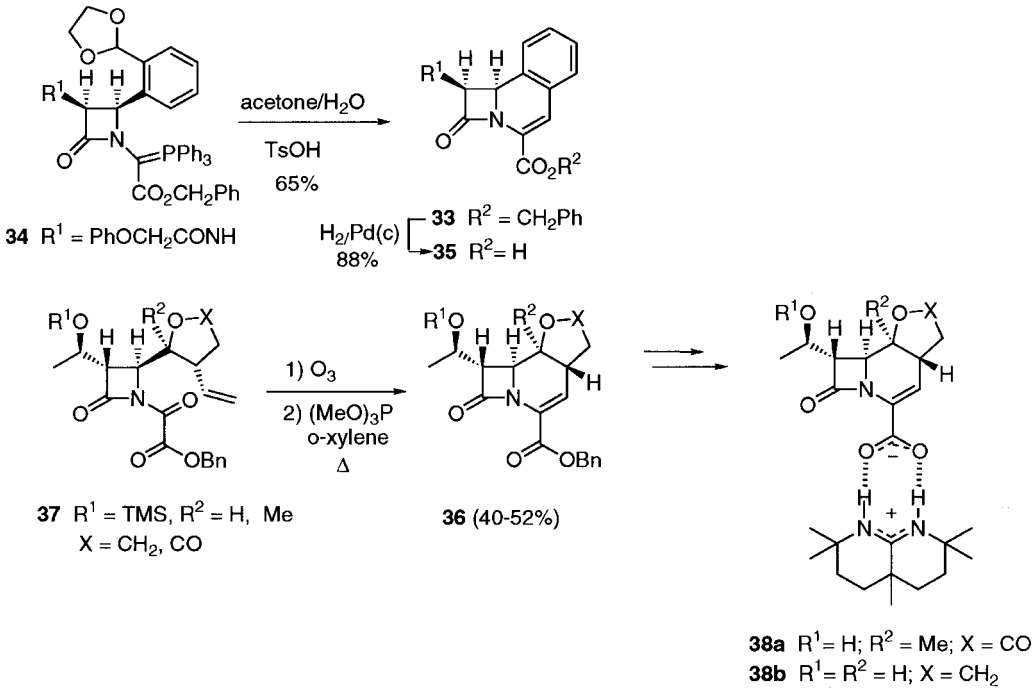
2.2. Ring closure by C–C bond formation

Wittig and related procedures. Intramolecular Wittig ring closure is one of the classical strategies of C–C bond forming that has found application in the synthesis of polycyclic β-lactams, and this methodology has been extremely useful for obtaining modified trinems.[22] One of the first polycyclic 2-azetidinones thus obtained was reported by Perchonock, who obtained the benzocarbacephem **33** after treatment of the azetidinone **34** with aqueous acetone and TsOH at room temperature. Hydrogenolysis of **33** yielded the acid **35**, that was inactive against a range of gram-positive and gram-negative bacteria.[23] The increased steric bulk, lipophilicity and/or electron density resulting from the incorporation of the fused benzene ring into the carbacephem skeleton was claimed to be responsible for the lack of antibacterial activity. Following essentially the same procedure, the tricyclic analogs of the cephalosporins **36** were prepared, by ozonolysis of compounds **37** and subsequent treatment of the corresponding aldehydes with $(MeO)_3P$ in refluxing *o*-xylene.[24] Standard protective group manipulation gave compounds **38a**,**b** as their amidine salts. In spite of their unusual structures, however, both were inactive (Scheme 8).

The masked aldehyde **39** has been used to prepare the carbacephem analog **40** by ozonolysis and subsequent Wittig



Scheme 7.

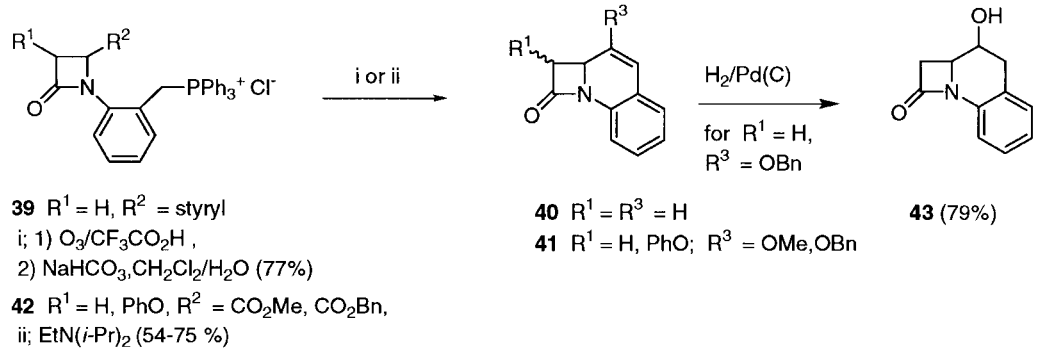


Scheme 8.

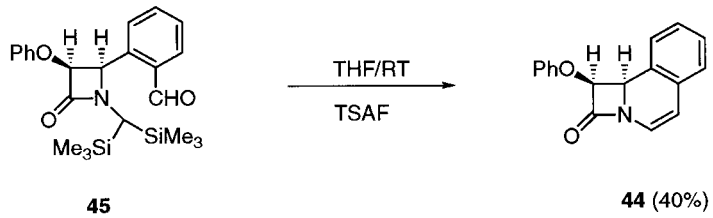
cyclization in the presence of $NaHCO_3$. Compounds **41** were obtained in moderate to good yields from the phosphonium salts **42** after treatment with *i*-Pr_2EtN. Catalytic hydrogenation of compound **41** (R^1=H; R^3=OBn) afforded the hydroxycephem **43** as a 3:1 diastereomeric mixture (Scheme 9).[25]

A related intramolecular cyclization, utilizing a Peterson olefination, has been reported by Palomo.[26] Preparation of the tricyclic benzocarbapenem **44** was achieved, at room temperature, by desilylative cyclization of the aldehyde **45**. The reaction was catalyzed by tris(dimethylamino)sulfonium difluorotrimethylsiliconate (TSAF) and the product was obtained in 40% yield (Scheme 10).

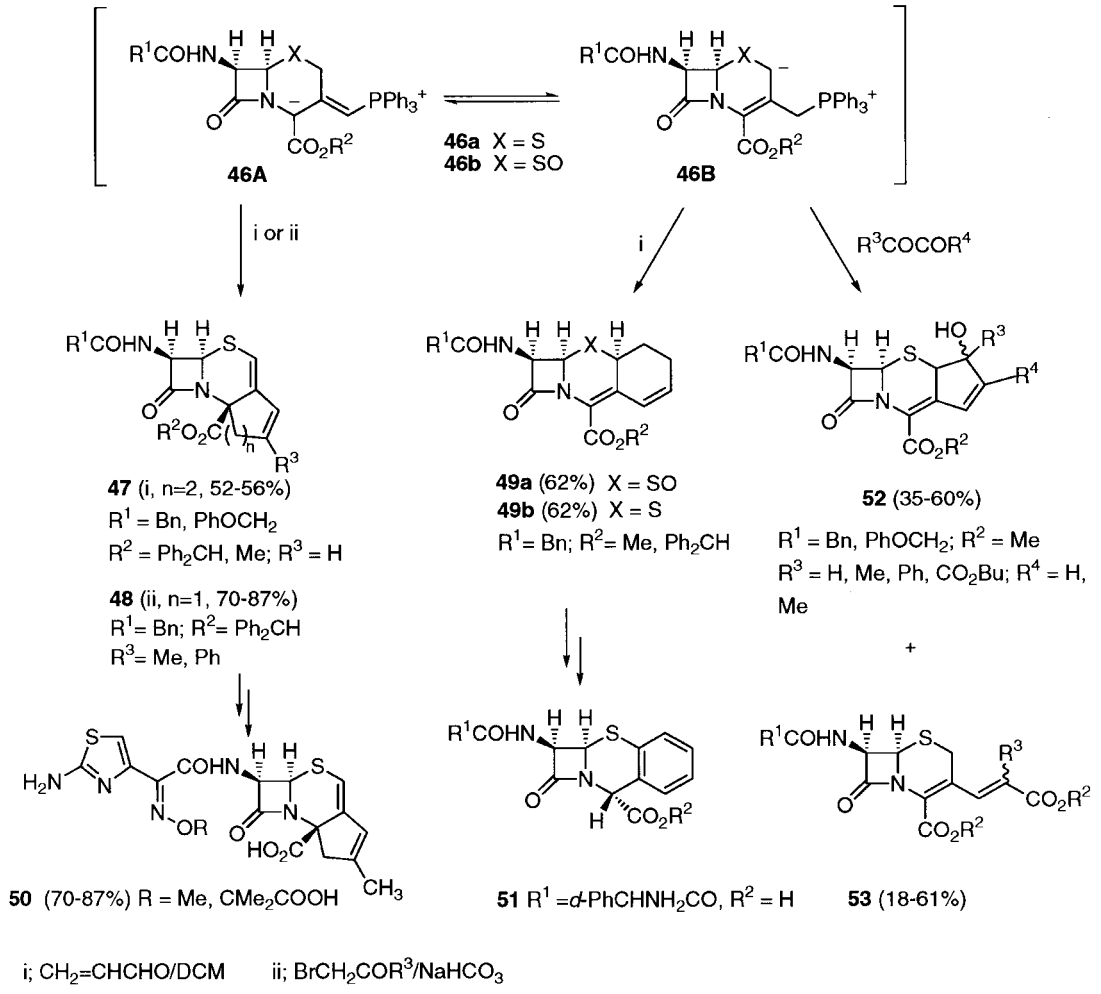
In all of the previous examples the central ring of the tricyclic system was built up from a 2-azetidinone skeleton. An alternative method is the formation of the new ring on a bicyclic β-lactam system, an approach that has been used to prepare tricyclic cephalosphorins. Thus, by treatment of the



Scheme 9.

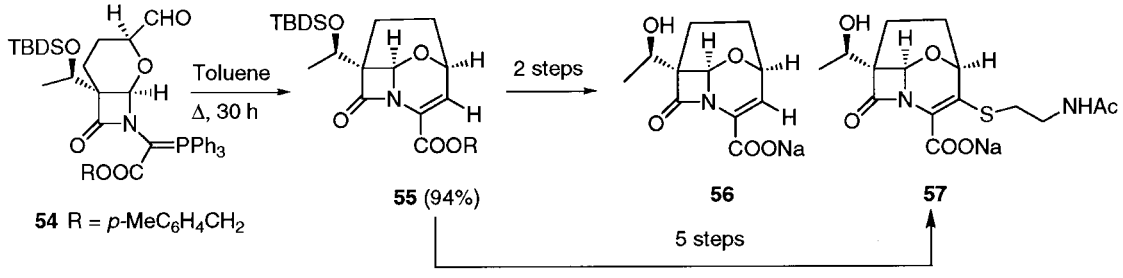


Scheme 10.

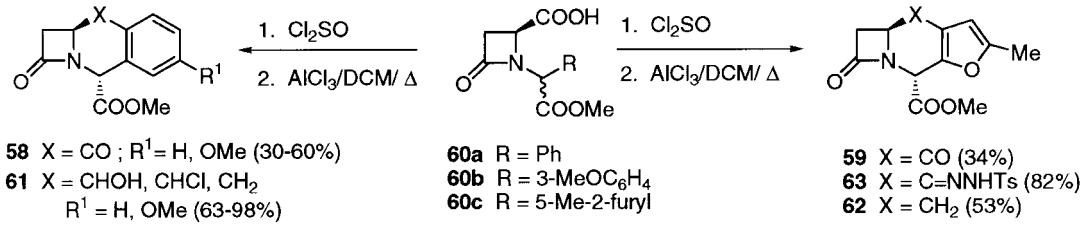


Scheme 11.

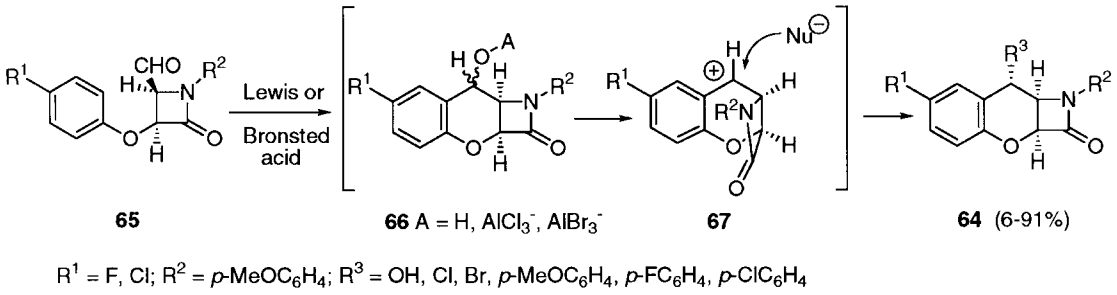
cephalosporin ylide **46a** with an excess of acrolein, the fused C3–C4 cephalosphorins **47** were obtained in moderate yields (Scheme 11).[27,28] When α-bromoketones were employed, cephalosporins fused to a cyclopentene ring, **48**, were isolated in good yields.[29] The formation of these products appears to arise exclusively from the resonance stabilized tautomer **46A**, by initial incorporation of the reagent in C4 and subsequent intramolecular Wittig reaction.[27] A total reversal of the reaction outcome, however, was observed when the starting material was the sulfoxide **46b**. Reaction of **46b** with acrolein exclusively formed the cephalosporin **49a**. Stabilization of the ylide tautomer **46B** by the sulfoxide group should favour the Michael addition onto C2 in this case. Compounds **48** were converted into the aminothiazole oximino derivatives **50** in several steps, and both **48** and **50** exhibited significant activity against gram-negative organisms. Reduction of the sulfoxide **49a** yielded **49b**, a precursor of the weakly active norcardicin analog **51**.[27] The preference for the C2–C3 ring closure was also observed in the reactions of the cephalosporin phosphorous ylides **46** with 1,2-dicarbonylic compounds, to yield a mixture of the tricyclic β-lactams **52** and the alkenyl cephems **53** in moderate yields.[30,31] The ratio **52/53** was dependent on the substituents on the carbonyl group. The cephalosporins **52** were isolated as a diastereomeric mixture, the major isomer showing H2 and H11 in a *cis* arrangement (Scheme 11).



Scheme 12.



Scheme 13.



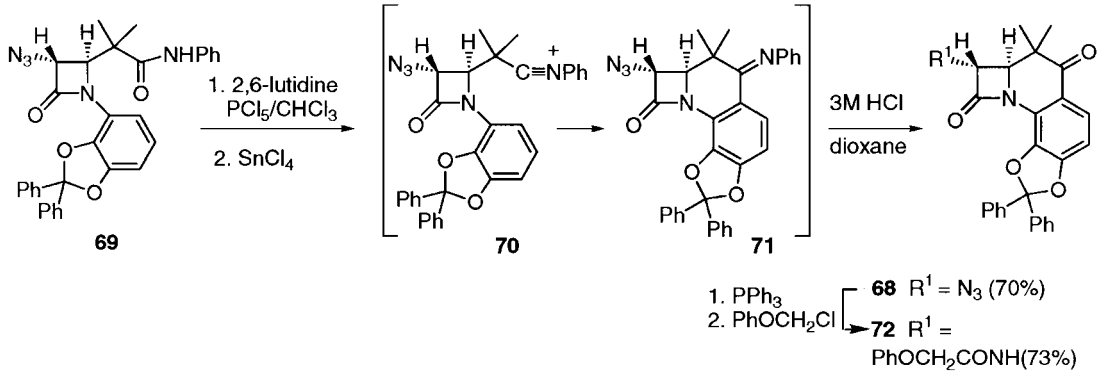
Scheme 14.

Bridged oxacephems have also been obtained by intramolecular Wittig reaction.[32] Thus, internal Wittig condensation on the aldehyde **54** gave the strained oxacephem **55**. This reaction required 30 h reflux in toluene, but despite the forcing conditions the yield was high (94%). This compound was then transformed in several steps into the potentially active sodium salts **56** and **57**. When tested for antibacterial activity, however, **56** was virtually inactive and **57**, the side chain of which resembles that present in thienamycin, showed only very low activity levels (Scheme 12).

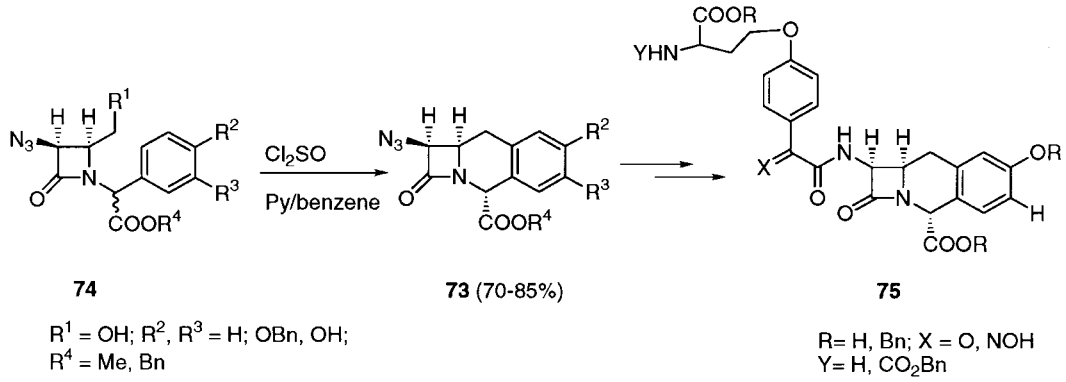
Friedel–Crafts and related processes. The intramolecular Friedel–Crafts (FC) ring closure has been frequently used to prepare tricyclic β-lactams. The fused benzo and furocarbacephems, **58** and **59**, were prepared as single isomers, in low to moderate yields, by treatment of the acid chloride derivatives of **60** with an excess of $AlCl_3$.[33] These compounds were then transformed into the corresponding carbacephem derivatives **61** and **62**. In the case of **62**, direct reduction of the ketone failed and the desired methylene group was achieved by reduction of the ketone tosylhydrazone **63** with $NaHB(CN)_3$. Although the biological activity of all of the compounds was tested, none were found to be active (Scheme 13).

Fetter reported the formation of tricyclic β-lactams **64** by treatment of the azetidinone carbaldehydes **65** with Lewis or Brönsted acids ($AlCl_3$, $AlBr_3$ or H_2SO_4) (Scheme 14).[34] When halobenzenes or toluene were employed as solvents, one molecule of the solvent was incorporated into the product. The high diastereoselectivity of the process was interpreted by the formation of the intermediates **66** and **67** in the reaction media. Hydroxyl derivatives could be derived from the intermediate **66**, from which the formation of the two epimers was possible. In these cases the selectivity decreases by up to 5:1. When the nucleophilic attack takes place at the cation **67**, however, the complete diastereoselectivity of the reaction was explained by assuming that these species existed in a folded conformation, which was expected to be attacked by the nucleophiles from outside. The entering ligand should therefore approach by the α-face, forcing H8 into the β-position.

Bachi and Klein employed a modified Bischler–Napieralsky reaction to obtain the cephalosporin analog



Scheme 15.



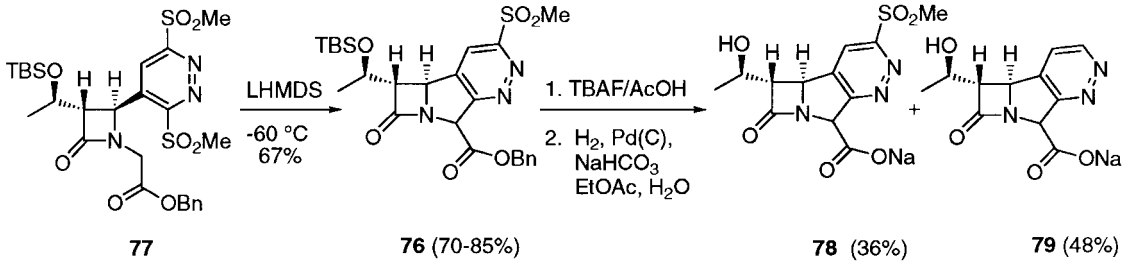
Scheme 16.

68 (Scheme 15).[35] Annelation of the *trans*-β-lactams **69** was performed by addition of 2,6-lutidine and PCl_5, followed by addition of $SnCl_4$. The electrophilic nitrilium ion **70**, which initially formed, cyclized to **71**. Acid hydrolysis of the C=N bond gave the azido β-lactam **70** which was subsequently transformed into the corresponding acylamino β-lactam **72** in 73% yield. The product resulting from deprotection of compound **72** was inactive.

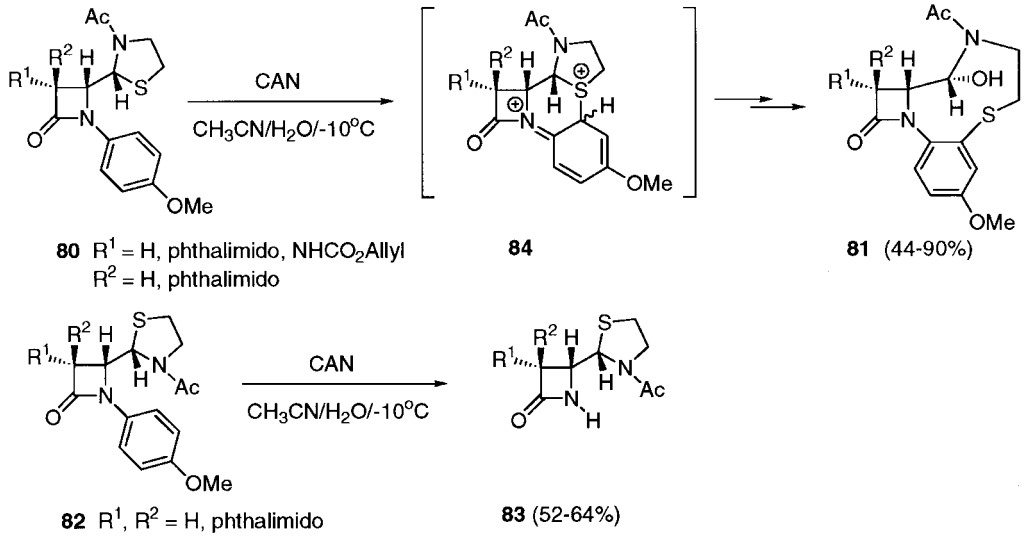
Analogs of Norcardicin A, **73**, have been prepared in good yields by treatment of the 2-azetidinones **74** with Cl_2SO. The cyclization reaction was totally diastereoselective. Further modifications of the azido group in **73** allowed the synthesis of compounds **75** that were found to be totally inactive (Scheme 16).[36]

The tricyclic diazocarbapenem **76** was obtained as a single diastereomer by cyclization of the pyridazinyl sulfone **77** with 2 equiv. of LHMDS.[37] Removal of the TBS-protecting group, followed by hydrogenolysis gave the desulfonated compound **78** together with the expected **79**. Both compounds were inactive in in vitro antibacterial assays (Scheme 17).

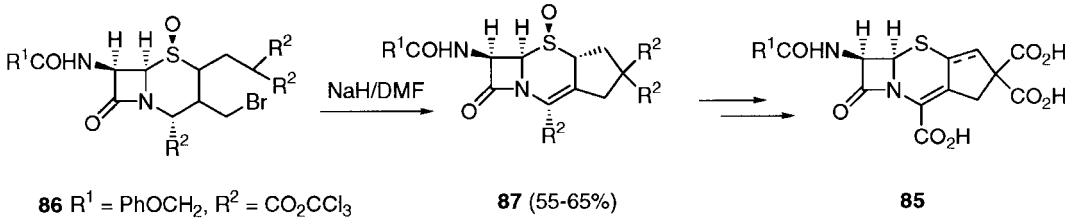
In the following example an S–C rather than a C–C bond is formed by direct cyclization of a sulfur atom on an aromatic



Scheme 17.



Scheme 18.

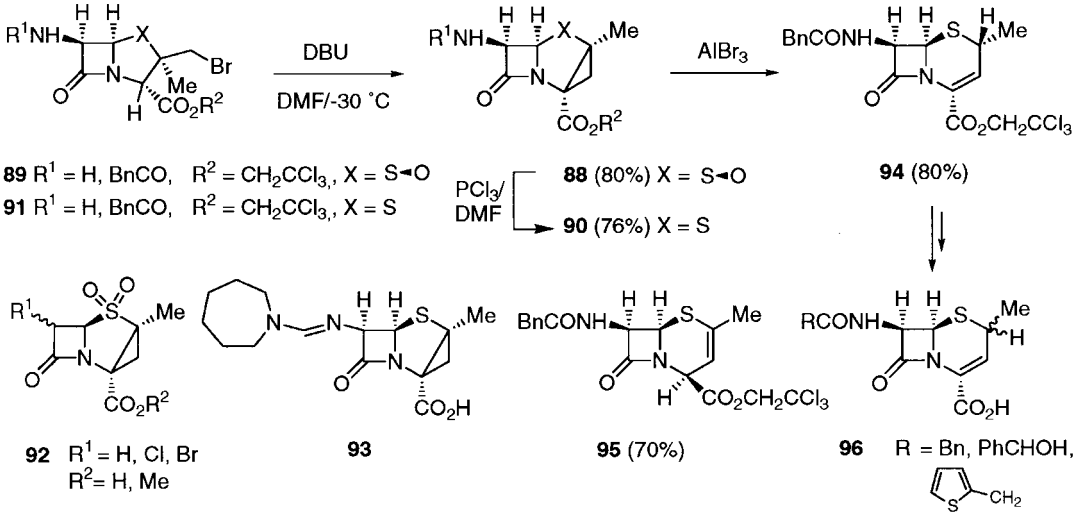


Scheme 19.

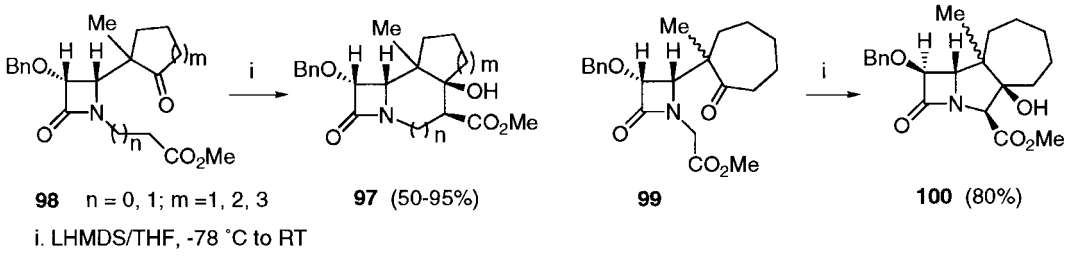
ring. In an attempt to deprotect the *cis*-2-azetidinones **80** with ceric ammonium nitrate (CAN), the tricyclic β-lactams **81** were obtained in good yields as the sole reaction products.[38] Interestingly, the azetidinones **82**, the epimers of **80** at the thiazolidine ring, afforded exclusively the desired *NH*-2-azetidinones **83** when treated under the same conditions. The cyclization products **81** were isolated in a lower yield when the starting 2-azetidinone had a *trans*-stereochemistry. The process was interpreted by initial attack of the nucleophilic thiazolidine sulfur atom on the aromatic ring, to give the intermediate **84** which evolved to the observed ring transformation products. On the other hand, molecular mechanics calculations suggest that the restricted rotation across the C–C bond that links the two heterocyclic rings is responsible for the different behaviour of the two epimers in the presence of the oxidising agent (Scheme 18).[38b]

Intramolecular alkylation processes and aldol condensations. An alternative strategy for building a tricyclic β-lactam system starting from a bicyclic system involves the creation of a new ring by means of an intramolecular alkylation process leading to C–C bond formation. This approach was originally reported from Lilly laboratories to synthesize the C2,C3-tricyclic cephalosporins **85** (Scheme 19).[39] Treatment of the bromo sulfoxide **86** with NaH/DMF yielded the tricyclic lactam **87**, which was converted into the tricyclic cephalosporins **85** by further synthetic manipulations. The biological activity of compounds **85** and **87** was tested and both displayed a significantly reduced microbiological activity, in comparison to the well known and structurally related 3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylic acid.

The intramolecular alkylation reaction has also been employed to obtain 2,3-β-methylenepenams **88** starting from the sulfoxides **89**.[40] The cyclization was best achieved with DBU in DMF at low temperature and the yields were high. Removal of the sulfoxide function was readily accomplished by treatment with PCl_3 in DMF,[40] or TFA/KI/acetone,[41] giving the tricyclic sulfides **90** in good yields. These compounds could additionally be obtained in one step, starting from the sulfides **91**. Biological tests carried out on a series of the β-lactams **90** (R^2=H) showed that they possessed gram-positive bacterial activity (Scheme 20). β-Methylene penams of structure **90**, have been used as precursors for other derivatives **92–93**, the activity of which has been evaluated and compared to that of penicillins.[42] Despite their close structural relationship, these tricyclic penams **92**,**93** showed a clear reduction of antibacterial potency compared to their penicillin counterparts, although they acted as β-lactamase inhibitors. The presence of a cyclopropyl methylene in the compounds could prevent the activation of the β-lactam carbonyl group, thereby rendering a loss in activity. Apart from their antibacterial properties, the tricyclic β-lactams **90** are interesting as precursors of 2-methyl-3-cephem derivatives **94**. Cyclopropane ring opening of compound **90** by $AlBr_3$ gave the 3-cephem **94** in 80% yield, while **95** was isolated when the reaction was carried out with $TiCl_4$.[43] Further modifications



Scheme 20.



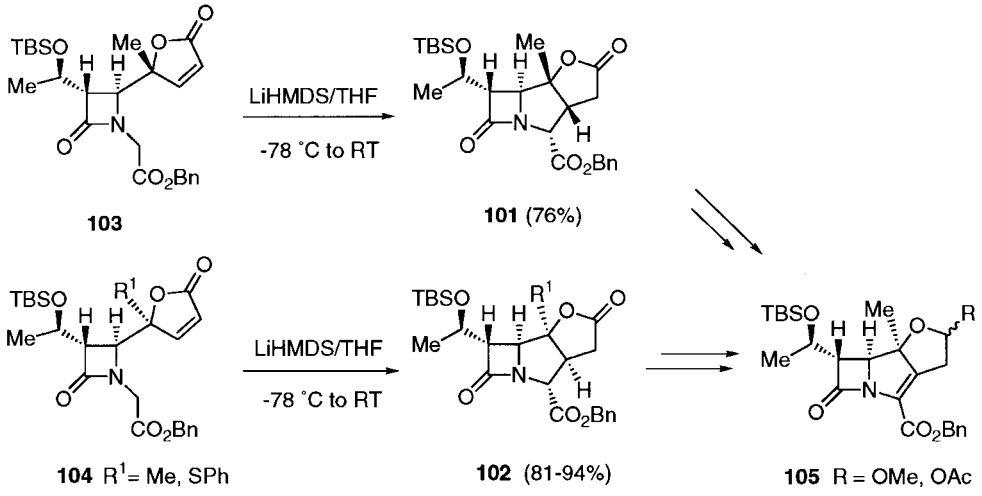
Scheme 21.

were carried out on **94** to obtain a series of substituted cephalosporins **96** that showed a low antibacterial activity (Scheme 20).

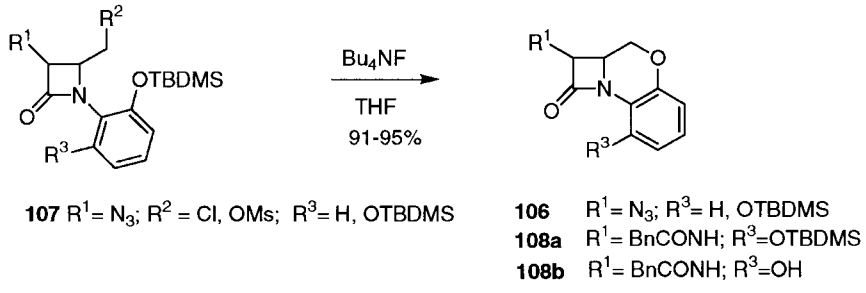
A series of [4, *n*, *m*] (*n*=5, 6; *m*=5, 6, 7) tricyclic 2-azetidinones **97** has been obtained by LHMDS promoted intramolecular aldol condensation of the azetidinones **98**.[44] The yields ranged from good to moderate and the conditions required to promote the reaction depended on the structure of the system to be obtained (configuration of the angular methyl group, size of the ring etc.). All of the products retained the *cis*-stereochemistry of the starting 2-azetidinone rings, with the sole exception of the inseparable mixture of *cis*-epimers **99**, which after cyclization were transformed into a mixture of *trans* β-lactams **100**. It is known[45] that *cis-trans* isomerization at the 2-azetidinone nucleus occurs in the presence of a base, and possibly the longer reaction times required in this case could have promoted both, cyclization and isomerization processes (Scheme 21).

Hanessian and coworkers have recently reported the use of an intramolecular Michael addition to obtain the tricyclic carbapenams **101** and **102** in high yields. The cyclization was carried out upon treatment of the azetidinones **103** and **104** with LHMDS at −78°C to give the carbapenams **101** and **102** as single isomers. (Scheme 22).[46] Some derivatives of these compounds were prepared by removal of the TBS group and deprotection of the ester function, but all were found to be inactive. On the other hand, compounds **101** and **102** were used as precursors for the unstable tricyclic carbapenems **105**.

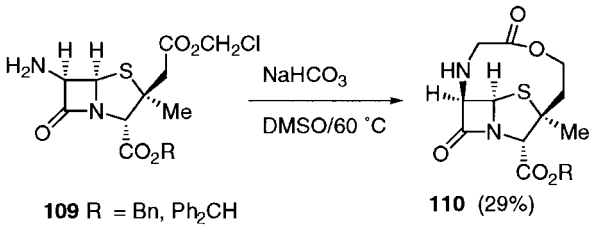
Other cyclizations leading to the formation of a *C*-heteroatom bond have been reported. Ugolini described the formation of a C–O bond through an intramolecular condensation



Scheme 22.



Scheme 23.



Scheme 24.

to yield the *O*-2-isocephems **106** in quantitative yields by cyclization of the mesylates or chlorides **107** in the presence of freshly prepared Bu_4NF.[47] Reduction of the azide function, followed by acylation with phenylacetyl chloride afforded **108a** which was transformed into the tricyclic amide **108b** by removal of the silyl group. This compound was found to be moderately active as an antibacterial agent (Scheme 23).

The intramolecular *N*-alkylation reaction of the bicyclic derivatives **109** was the key step in the synthesis of one of the few reported anti-Bredt β-lactam systems **110**.[48] Despite their strain, the compounds **110** were thermally stable, and could be transformed to the corresponding *N*-acyl derivatives, and oxidized to sulfoxides or sulfones (Scheme 24).[49]

Bromination of the azetidinones **111** in methanol formed the bromonium cations **112** that were intramolecularly quenched by the pyridine nitrogen. The cation **112b** was more susceptible to solvolysis than to intramolecular nucleophilic attack, giving **113**, while **112a** cyclized to **114**. Both compounds were evolved further to the salts **115** and **116**, respectively (Scheme 25).[50] Other tricyclic penams have been obtained through a Bamford–Stevens-like process.[51,52]

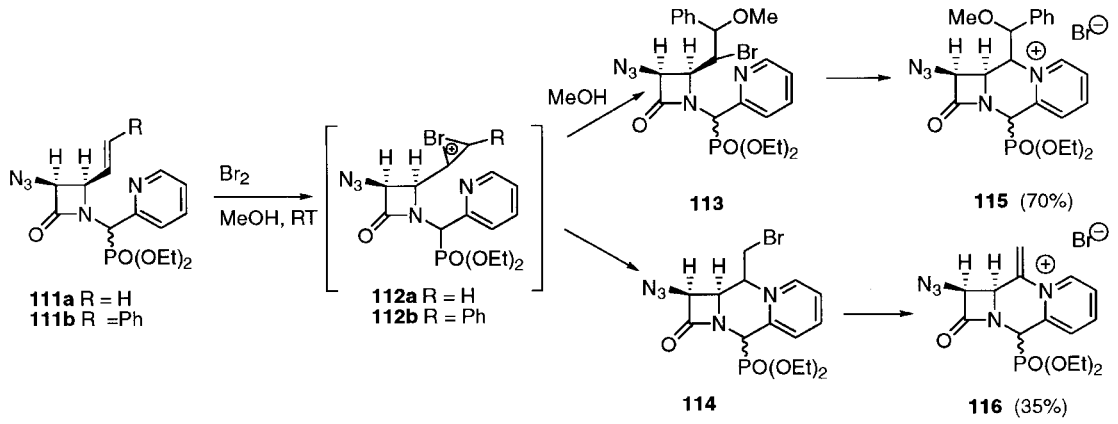
Metal mediated cyclizations. Except for some examples of Pd-induced [2+2] cycloadditions of cephem triflates discussed below, the building of polycyclic 2-azetidinones from monocyclic compounds using transition metal reagents or catalysts has been scarcely investigated. The synthesis of the novel tricyclic β-lactams **117–120** has been carried out through a Heck reaction of 2-azetidinones **121–123** generated in situ by the ketene-imine method.[53] An analogous reaction on compound **124** led to the benzocarbacephem **125** in acceptable yield (Scheme 26).[54] In other cases, the use of Pd catalysts yields the expected products together with dimers in comparable yields.[55]

A conceptually different synthetic approach to polycyclic β-lactams is the simultaneous building of two of the three rings on a 2-azetidinone nucleus. This has been achieved by a Pauson–Khand (P–K)[56] reaction on the monocyclic enyne-azetidinones **126–130**. These compounds formed the alkyne-$Co_2(CO)_6$ complexes in quantitatively yield. Treatment of the complexes derived from **126**, **127** and **128a** with trimethylamine *N*-oxide (TMNO), gave the desired tricyclic products **131**, **132** and **133a** as single diasteromers, and for compound **131** as a single enantiomer. When the reaction was extended to compounds **128b**,**c**, **129** and **130** having an hydroxypropargyl moiety, however, lower yields and selectivities were obtained in the formation of compounds **133c**, **134** and **135**. These results show that the P–K reaction is a simple and most by efficient entry to different tricyclic 2-azetidinones with a five- or six-membered ring fused to the β-lactam nucleus (Scheme 27).[57]

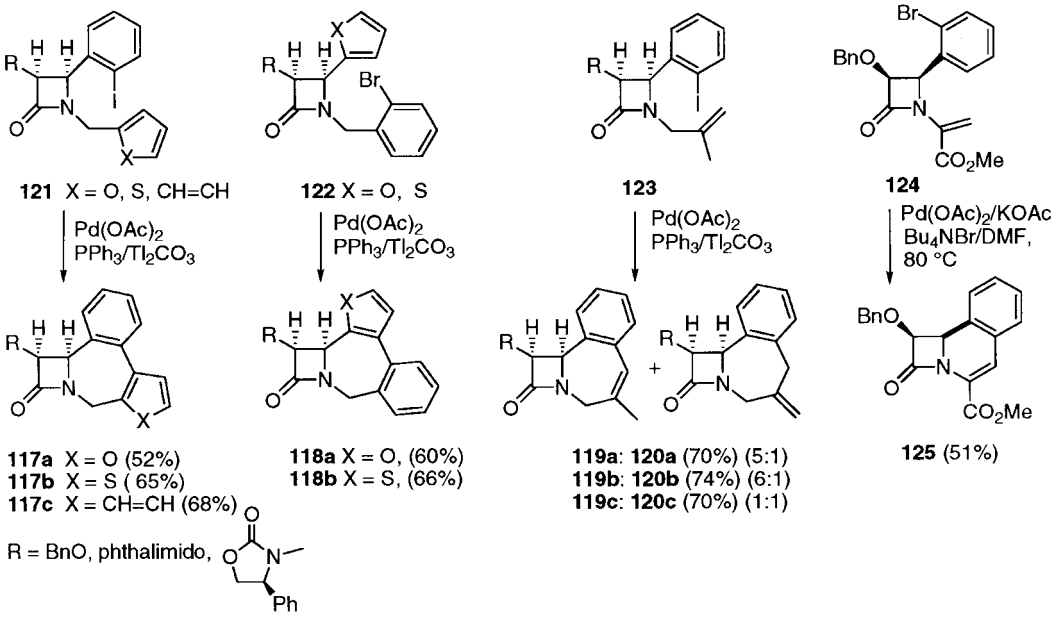
2.3. Cycloaddition processes

The synthesis of tri- or polycyclic β-lactams by means of a cycloaddition process on a preformed 2-azetidinone has been widely investigated, especially 1,3-cycloadditions and Diels–Alder reactions. Although both inter- and intramolecular processes have been reported, most of the work has been done on intermolecular cycloadditions. For intramolecular processes, monocyclic 2-azetidinones have been employed as the substrates, whereas bicyclic β-lactams were required for intermolecular reactions.

1,3-Dipolar cycloadditions. Most of the methods used to prepare bi- and polycyclic 2-azetidinones by an intramolecular 1,3-dipolar cycloaddition start from monocyclic 2-azetidinones with an azido group as the 1,3-dipolar reagent. The synthesis of two different classes of tricyclic β-lactams having fused triazole rings has been reported from monocyclic 2-azetidinones differing exclusively in the relative position of the dipole and the dipolarophile



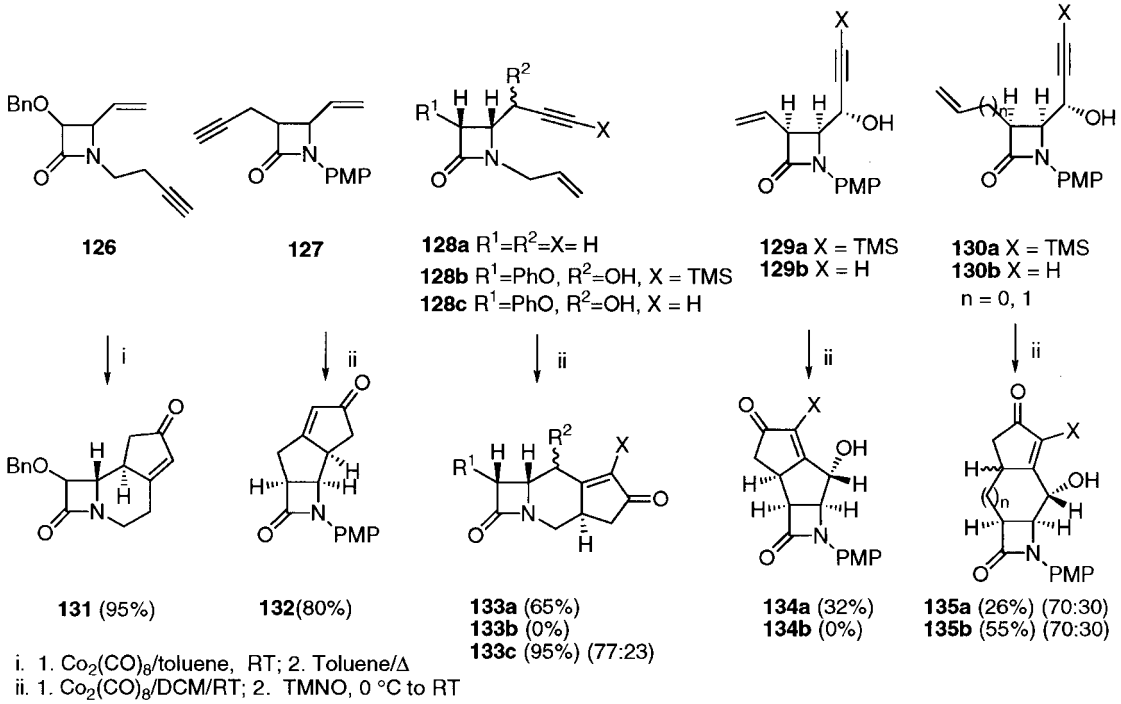
Scheme 25.



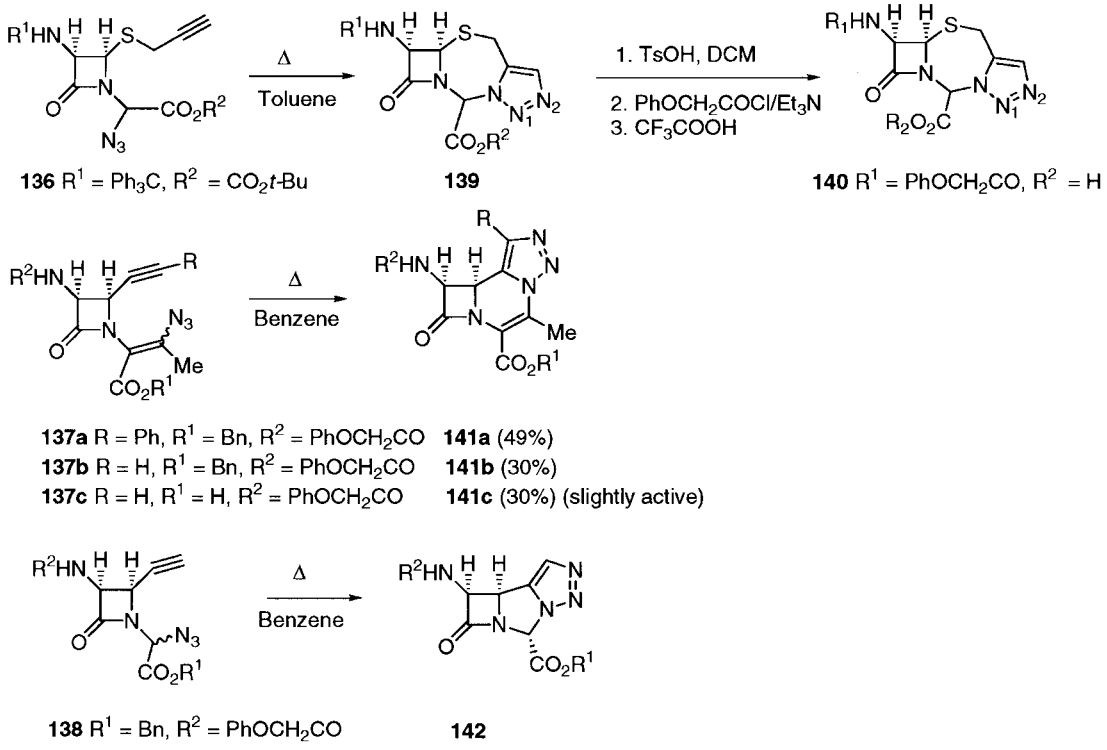
Scheme 26.

moieties. Based on the behaviour of azides as 1,3-dipoles, the monocyclic 2-azetidinones **136**–**138** having the azido group at the lactam nitrogen side-chain and the acceptor at the ring C4 position were chosen as starting materials in the preparation of tricyclic fused [4,*n*,5]-2-azetidinones (*n*=5, 6, 7) **139**–**142**. The free acids were prepared from the corresponding tricyclic systems but, except for **141c**, that was slightly active against gram-positive organisms, the compounds were inactive (Scheme 28).[58]

The alternative ring closure was effected by locating the azido group on the C4 position of the 2-azetidinone ring. The compounds **143** reacted as expected to produce the tricyclic [4,5,5] triazolo derivatives **144**, although for a successful intramolecular cycloaddition, high dilution conditions (1 mg/ml) were required, otherwise the intermolecular dimers **145** were obtained.[58c] Interestingly, substitution of the triple bond with alkyl or aryl groups inhibited the cycloaddition process and the best results were achieved when small, strongly electron-withdrawing groups (such as a formyl group) were incorporated into the triple bond. The formation of a six-membered ring also favoured the reaction, as in the acetylene **146** which cyclized to provide the triazolocepham **147** (Scheme 29).[58b]



Scheme 27.



136 $R^1 = Ph_3C$, $R^2 = CO_2t\text{-Bu}$ **139** **140** $R^1 = PhOCH_2CO$, $R^2 = H$

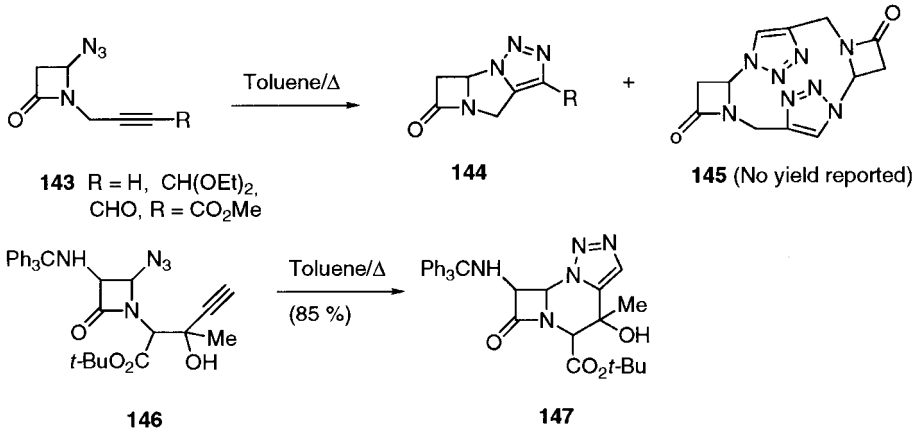
137a R = Ph, R^1 = Bn, $R^2 = PhOCH_2CO$ **141a** (49%)
137b R = H, R^1 = Bn, $R^2 = PhOCH_2CO$ **141b** (30%)
137c R = H, R^1 = H, $R^2 = PhOCH_2CO$ **141c** (30%) (slightly active)

138 R^1 = Bn, $R^2 = PhOCH_2CO$ **142**

Scheme 28.

The 1,3-dipolar cycloaddition of diazoalkanes and azides to the C=C double bond of cephalosporins has been used to modify these classical β-lactam antibiotics in the search for more active compounds. Both Δ^2, Δ^3, and exocyclic vinyl cephalosporins have been investigated as dipolarophiles. In the case of Δ^2-carbapenems **148** the reaction with diazomethane led to the adducts **149** or **150** depending on the reaction conditions, but Δ^3-cephems were unreactive. For vinyl Δ^2-carbapenems **151a** both double bonds were reactive towards diazomethane, and mixtures of mono **152** and bisadducts **153** were obtained. In the case of **153**, the process was totally stereo- (only one of the two possible C3′ steroisomers was formed) and regioselective (the molecule is a 'β-adduct', the new bond being formed at the β-position to carbon C3). The vinyl cephalosporin sulfoxide **151b** underwent cycloaddition with diazomethane to give a single product **154** in a stereo- and regioselective reaction. The double adduct was not formed in this case (Scheme 30).[59]

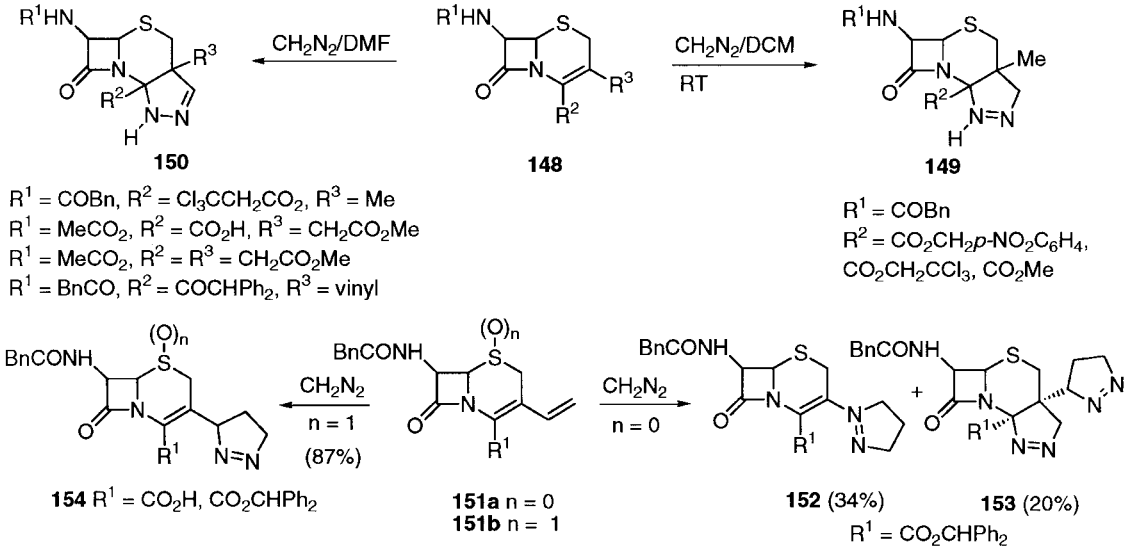
Penems and carbapenems have been used to prepare polycyclic 2-azetidinones. One example comparing the reactivity of the exocyclic 6-alkylidene and the endocyclic double bond towards diazomethane has been reported.[60] The exocyclic double bond of *E*-furylmethylene penem *E*-**155** reacted with diazomethane to give a mixture of the pyrazolines **156**, resulting respectively from α and β attack at the exocyclic double bond, with the same regiochemistry of addition. When the *Z*-furylmethylene compound *Z*-**155** was similarly exposed to diazomethane, however, the products obtained arose from the addition of diazomethane only to the exocyclic (**156**) C=C bond and to both the endo- and exocyclic double bonds (**157**) (Scheme 31).



143 R = H, $CH(OEt)_2$, CHO, $R = CO_2Me$ **144** **145** (No yield reported)

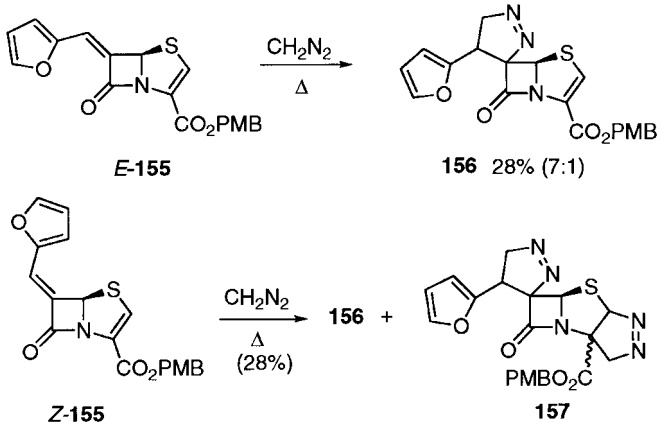
146 **147**

Scheme 29.

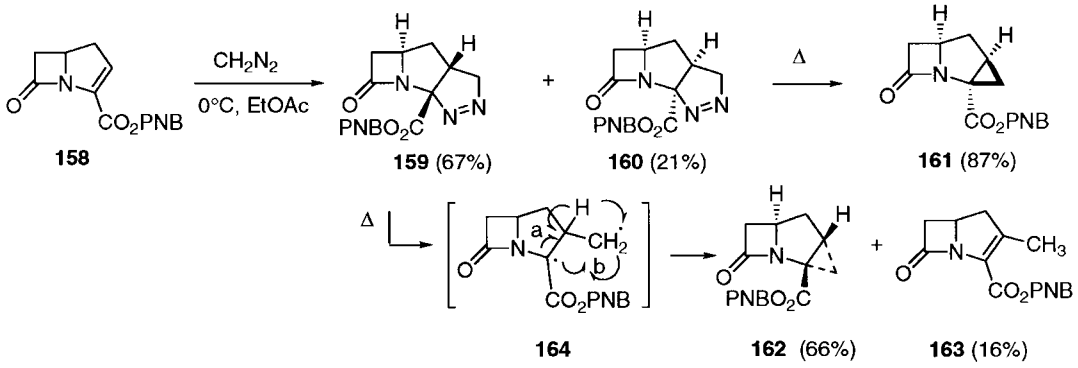


Scheme 30.

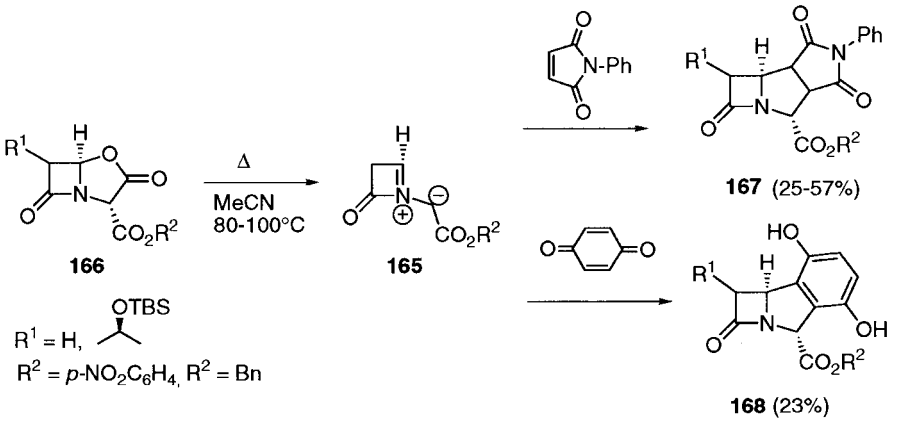
The fate of the pyrazoline rings in the above polycyclic 2-azetidinones and other similar compounds is to be used as precursors for fused cyclopropanes. In fact several cephalosporins, penams, and carbapenams having a fused cyclopropane ring have been prepared by thermolysis of these pyrazoline derivatives.[61] As an example of this rich chemistry, reaction of the ester **158** and N_2CH_2 under mild conditions gave two separable, diastereomeric, tricyclic pyrazolines **159** and **160** (67% and 21% yields, respectively). These compounds produced by thermolysis the fused cyclopropane systems **161** and **162** in good yields. The adduct **159** led to the *anti*-fused-ring-system **161** (66%), accompanied by a small amount of the Δ^2-3-methyl isomer **163** (16%), whereas the isomer **160** gave the cyclopropane having a *syn*-ring fusion **162** (87%) as a single product. These results may be explained by the initial



Scheme 31.



Scheme 32.



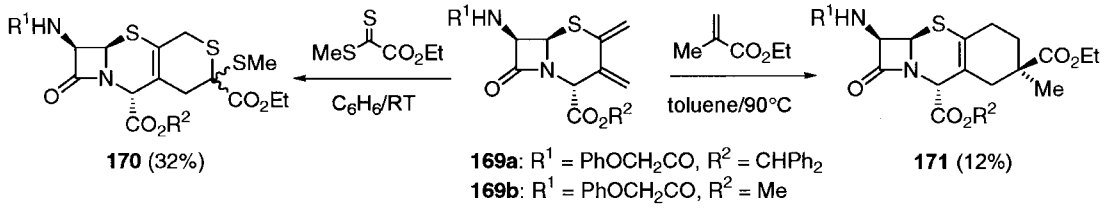
Scheme 33.

formation of the biradical **164** which may evolve by competition between a 1,2-hydrogen shift mechanism (path a) that provides **163** or by ring closure to provide the fused cyclopropanes (path b) (Scheme 32). Many other related systems have been obtained employing the same methodology.[60]

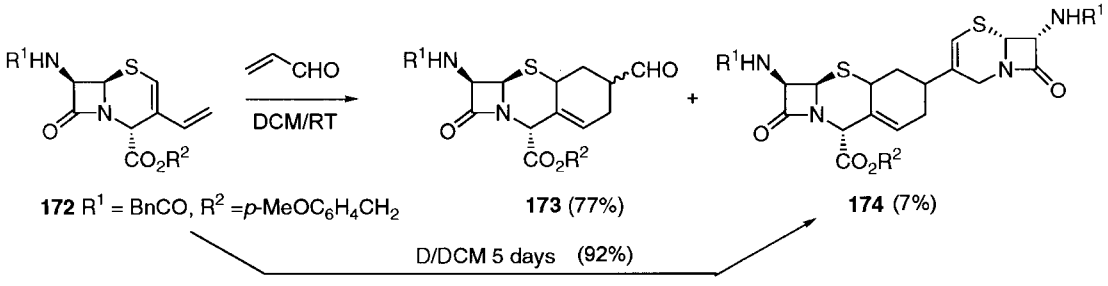
An alternative approach to the building of a polycyclic 2-azetidinone is the use of a monolactam as the precursor of the 1,3-dipole.[62] Generation of the azomethine ylides **165** by decarboxylation of the β-lactam-based oxazolidinone **166**, followed by cycloaddition with different dipolarophiles, led to the corresponding fused tricyclic β-lactams in moderate yields, provided that the dipolarophile had a cyclic structure. Several aspects of this reaction merit specific comments. *endo* Cycloadducts predominate and the cycloaddition step (which exhibits a high degree of regioselectivity for unsymmetrical 1,3-dipolarophiles) is also stereospecific. Many tricyclic structures have been prepared in this way and some examples are shown in Scheme 33.

Diels–Alder and [2+2] cycloadditions. One of the first approaches to the building of a polycyclic 2-azetidinone system by means of a Diels–Alder reaction, used a diene system supported on the 2-azetidinone component. The 2-methylenecephems **169** ('exomethylene' cephems) have been employed as dienes in Diels–Alder reactions with homo or heterodienophiles, acting as useful starting materials for the synthesis of new tricyclic β-lactams.[63] Treatment of **169a** with *O*-ethyl *S*-methyldithioxolate afforded the crystalline cycloadduct **170** as a diastereomeric mixture. The analogous reaction with ethyl methacrylate yielded the cycloadduct **171** in low yield. Other dienophiles such as maleic anhydride and diethyl azodicarboxylate reacted very slowly with **169a** affording a large number of byproducts under forced thermal conditions (Scheme 34).[63]

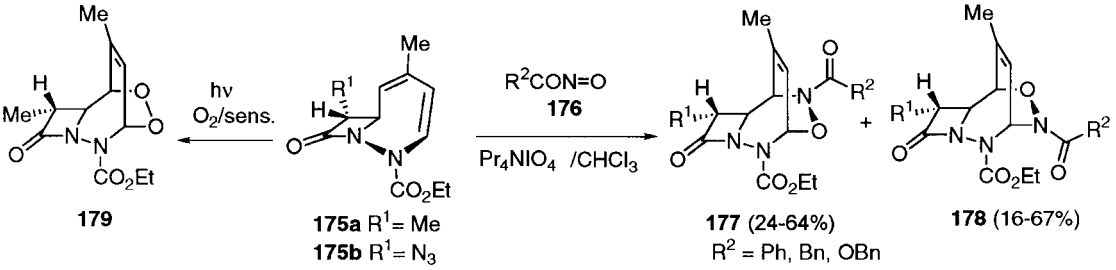
Vinyl cephems have been used as dienes in Diels–Alder cycloadditions. The compound **172** reacted with acrolein (4 equiv.) to afford the tricyclic cephalosporin **173** and the dimer **174** (7%).[64] The formation of the dimer was more effective (92%) by heating **172** in DCM for five days. It is



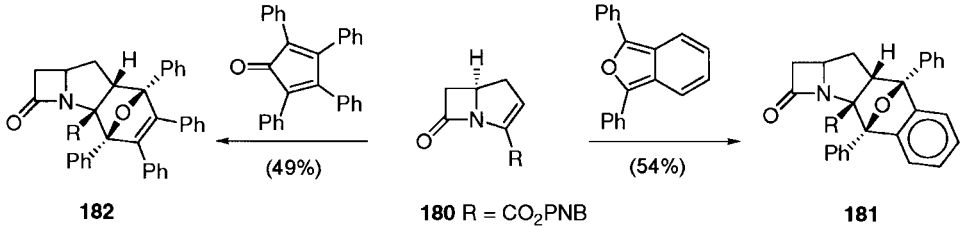
Scheme 34.



Scheme 35.



Scheme 36.



Scheme 37.

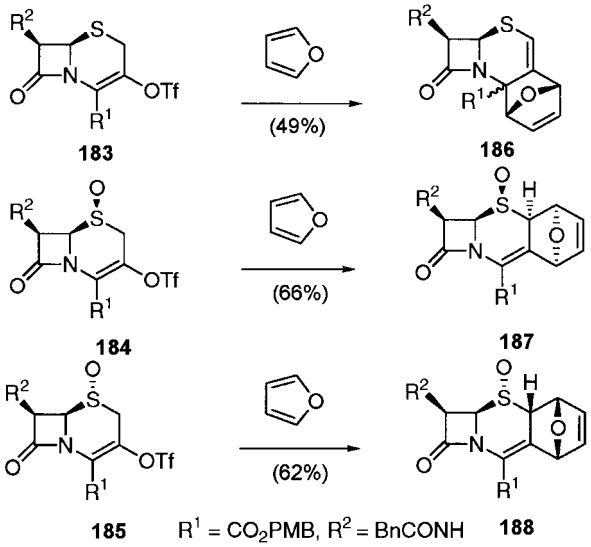
clear that the role of the starting material is not only as a diene but also as a dienophile in this Diels–Alder reaction (Scheme 35).

Bicyclic 2-azetidinones having an endocyclic diene array have been used to prepare polycyclic 2-azetidinones through a Diels–Alder reaction. The azetidinodiazepines **175a**,**b** reacted with the acylnitroso dienophiles **176**, from their convex α-side. The reaction was non-regiospecific, however leading stereospecifically to mixtures of regioisomers **177** and **178** in good overall yields. Singlet molecular oxygen has also been used as a dienophile and the unstable endoperoxide **179** was obtained by UV irradiation of an oxygenated solution of compound **175b** with *meso*-tetraphenylphorphyrin as photosensitizer. There is no mention in the original paper of the biological activity of any of these compounds (Scheme 36).[65]

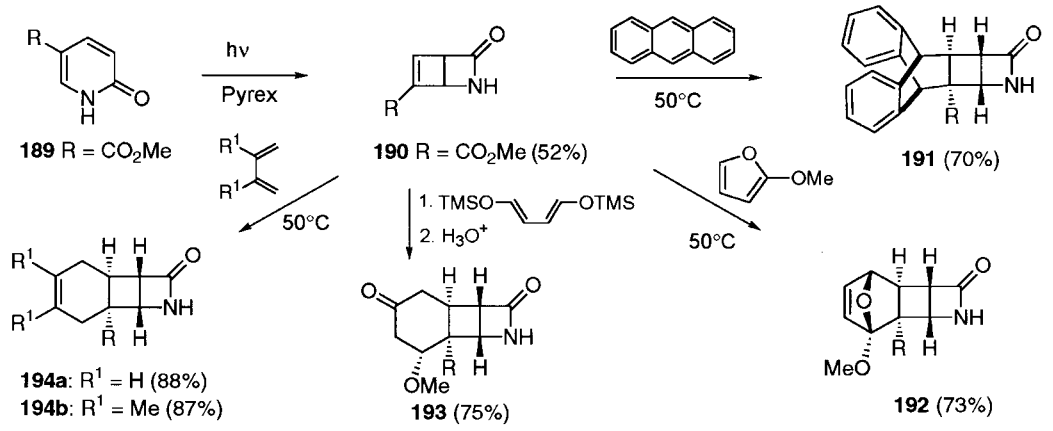
The double bonds of the cephem, penem and carbapenem systems are suitable dienophiles for Diels–Alder and [2+2] reactions but relatively few polycyclic 2-azetidinones have been constructed using these compounds as substrates. The strained acrylate component in the ester **180** acted as a dienophile with reactive dienes such as diphenylisobenzofuran or benzoisofuran to yield the tetra- **181** or penta- **182** cyclic 2-azetidinones as single adducts, respectively. The stereochemistry of these processes was explained by an *exo* approach of the diene to the less hindered α-face of the dienophile double bond. The instability of the ester **180** towards acids and heat precluded the use of Lewis acid catalysts or elevated temperatures to increase the yield of the reaction (Scheme 37).[66]

Allenes generated in situ from the triflate **183** and the *S*- and *R*- sulfoxides **184** and **185** reacted with dienophiles giving the tetracyclic 2-azetidinones **186**–**188** in excellent yields. The reaction involves a formal elimination of trifluoromethanesulfonic acid to form an allene intermediate in the six-membered ring, followed by the [4+2] cycloaddition reaction. The chemoselectivity of the cycloaddition is determined by the oxidation state of the sulfur atom in the starting cephalosporin triflate. The addition takes place across the 2,3 positions in the sulfoxides **184** and **185**, but across the 3,4 position in the sulfide **183**. Furthermore, the two sulfoxide isomers gave rise to opposite stereochemistries at the three newly-formed chiral centers. The results were explained by [4+2] cycloaddition to the more electron deficient double bond of the allene intermediate (Scheme 38).[67]

The well known photoisomerization of 2(1*H*)-pyridones **189** to the photopyridones **190** (a β-lactam ring fused to a cyclobutene), has been used by many authors in designing the syntheses of polycyclic 2-azetidinones, since the latter



Scheme 38.



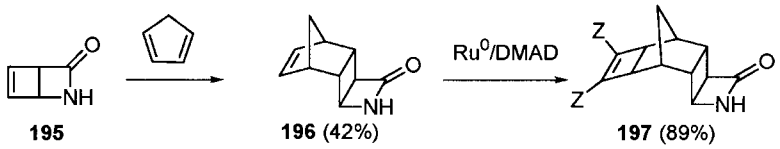
Scheme 39.

compounds are highly reactive towards cycloaddition processes. Hongo and Nakano employed the photopyridone **190** as the precursor for a series of tricyclic β-lactams **191**–**194** by Diels–Alder cycloaddition with different dienes using high pressure conditions.[68] These reactions always produced the corresponding *cis-anti-cis*-adducts in good yields (Scheme 39).

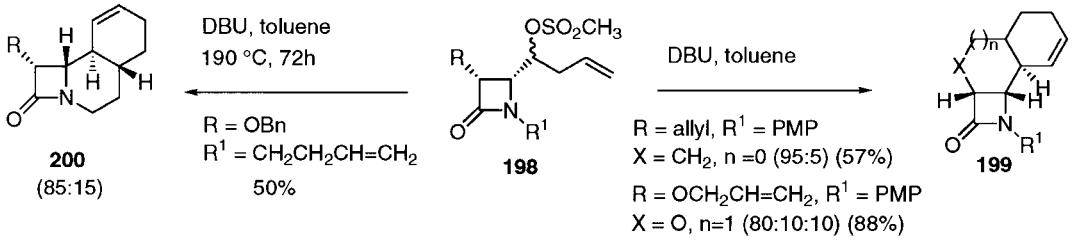
Photopyridones have also been used as the starting compounds to prepare ladderanes. The Diels–Alder cycloaddition of **195** with cyclopentadiene gave **196** as a 10:1 mixture of the *endo* and the *exo* adducts. Further extension of compound **196** was achieved by reaction with dimethylacetylene dicarboxylate (DMAD) yielding the pentacyclic 2-azetidinone **197** (Scheme 40).[69]

Finally, there is only one example to date of an intramolecular Diels–Alder reaction to build a tricyclic 2-azetidinone. The mesylates **198** were used as in situ precursors of 4-dienyl-2-azetidinones by heating at high temperatures in the presence of DBU as base. The corresponding cycloadducts were obtained as mixtures of diastereomers with medium to low selectivity. The C3–C4 and C4–N1 fused systems **199** and **200** were available by this approach (Scheme 41).[70]

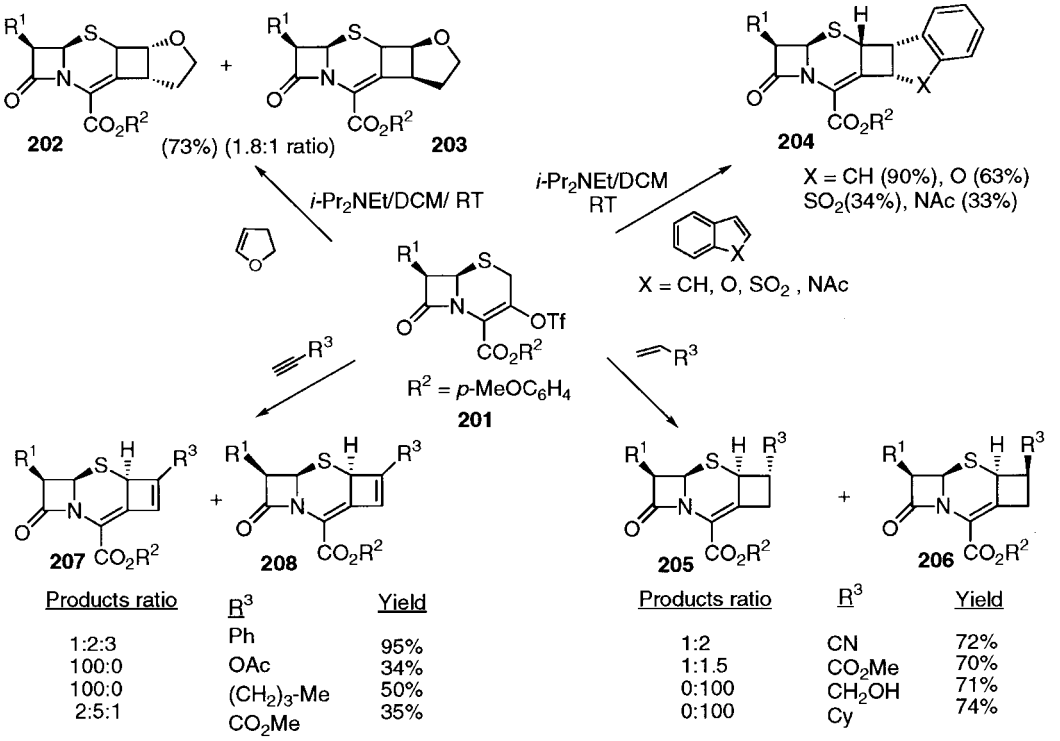
[2+2] Cycloaddition processes have been used to build tricyclic-β-lactams bearing a wide range of funcionalities. Starting from the cephalosporin triflate **201**, which has been used previously in [4+2] cycloadditions, a wide array of tri-, tetra-, and pentacyclic-2-azetidinones **202**–**208** have been constructed.[67,71] For example, treatment of the bicycle **201** with 2,3-dihydrofuran and $NEt(i\text{-}Pr)_2$, in the presence or absence of $Pd(OAc)_2$ and (*R*)-BINAP, gave a mixture of two isomeric tetracyclic products **202** and **203** (1.8:1 ratio, 73% isolated yield). This reaction has proved to be extremely general for different olefins, although in some cases a large excess of alkene was required to obtain acceptable yields. For terminal double bonds, the substituent was always placed adjacent to the C2 position of the cephalosporin nucleus and, when only one isomer was observed, the substituent was on the β-face and the proton at C2 at the α-face of the molecule. The most facile cycloadditions in terms of yield occurred with electron-rich olefins and styrene. In general the monosubstituted olefins with conjugated π-systems gave mixtures of isomers with substituents in the 5α and 5β positions, whereas the monosubstituted olefins with no π-extended systems gave isomers with the substituent in the 5β position. The same considerations can be applied for the reaction with acetylenes to give fused cyclobutenes (Scheme 42).



Scheme 40.



Scheme 41.

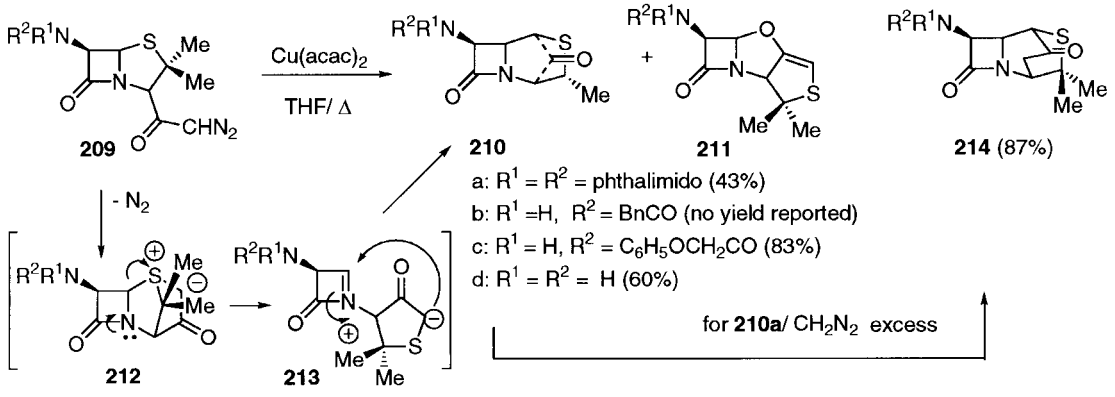


Scheme 42.

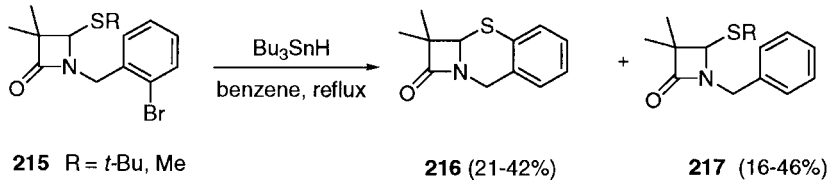
2.4. Intramolecular carbene insertion

Penicillin derived diazoketones **209** were prepared for the first time as intermediates in the synthesis of homopenicillins.[72] The synthetic potential of these systems as precursors of tricyclic β-lactams was recognized as early as 1977, when their Cu(II) catalyzed decomposition in aprotic media was reported to yield the tricyclic compounds **210** and **211**, the latter being formed in very low yields. The compounds **210** are formally derived from the skeleton of the starting diazoketones by a backside insertion of an intermediate acylcarbene into the C5–S bond. The formation of these products was explained by an intramolecular interaction of the acylcarbene with the S-atom of the thiazolidine ring, resulting in the formation of a strained ylide **212**. Breaking of the C5–S^+ bond with participation of the non-bonding electrons of the azetidinone nitrogen and, finally, reclosure by a backside attack of the carbanion **213** on C5 yields the bridged penicillins **210**. These compounds can experience a further enlargement of the ketone bridge by reaction with an excess of diazomethane to yield a new tricyclic compound **214** (Scheme 43).[73–75]

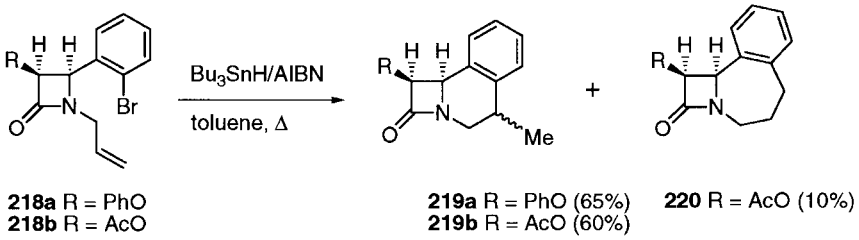
Bacteriological bioassays of all of these compounds showed that they were inactive in vitro against *S. aureus*, penicillin-resistant *S. aureus* and *E. coli*. Nevertheless, the synthesis of these unusually bridged tricyclic ketones became of interest since they possessed a carbon skeleton similar to that found in thienamycin and olivianic acids. Consequently the reaction was extended to C6 unsubstituted compounds (designed as analogs or hybrids of these natural products) and further transformations of these systems, as reductions of the ketone bridge and further oxidation to tricyclic sulfoxides were undertaken, but none showed any bacteriological activity.[75a]



Scheme 43.



Scheme 44.



Scheme 45.

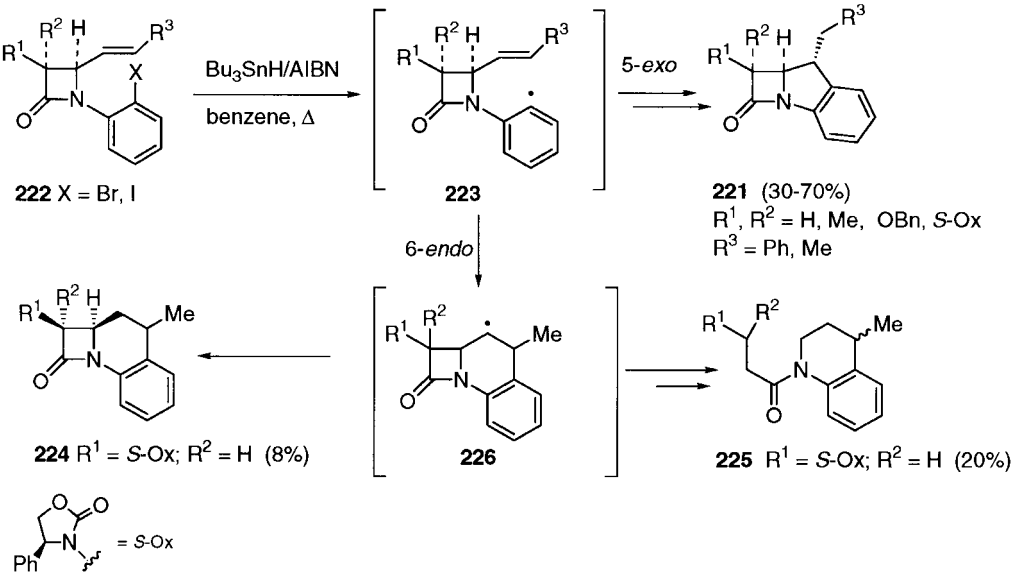
The analogous intramolecular cyclization of diazosulfoxides has also been reported.[76]

2.5. Other cyclization methods

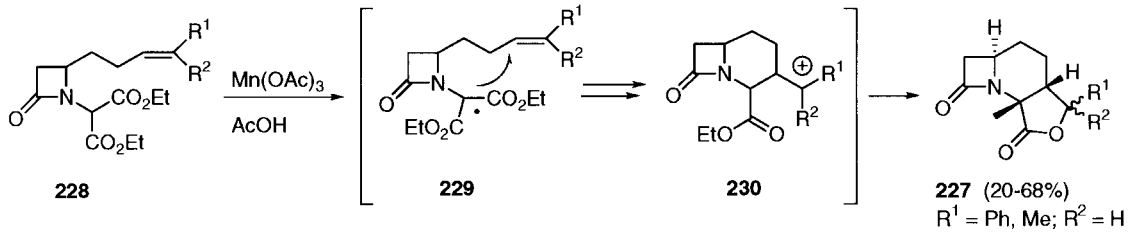
Radical cyclizations. Free radical cyclization reactions have emerged as a powerful synthetic tool for the construction of tricyclic β-lactams and in particular for the preparation of benzo-fused six-membered rings. One of the first examples was reported by Beckwith and Boate,[77] who, after treatment of the bromoazetidinones **215** with Bu_3SnH (0.03 M) and a catalytic amount of 2,2′-azobisisobutyronitrile (AIBN) in refluxing benzene, obtained the benzopenams **216** (21 and 42% yields) together with the reduction products **217** (16 and 46%) (Scheme 44).

Cyclization of the compounds **218** having a C=C double bond as the radical acceptor was initially reported by Bose.[78] Due to the presence of an allyl group linked to the nitrogen, the two possible cyclization modes, 6-*exo* and 7-*endo*, could be observed (Scheme 45). Only *exo*-cyclization was detected in the case of the *cis*-azetidinone **218a**, and this gave a diastereomeric mixture of the benzocarbacephams **219a**. The structurally related compound **218b** however, yielded the 6-*exo* product **219b** (60%) together with the seven-membered ring fused β-lactam **220** (10%). Similarly, a clear preference for the 6-*exo* cyclization pathway was observed for the *trans*-isomer of azetidinone **218a**, which afforded *trans*-7-*endo* products with only 5% yield. The formation of the competitive 7-*endo* product can be inhibited by the presence of an aromatic ring in the allylic position, and only the more stable radical was observed.[79]

Taking advantage of this stabilization, the intramolecular aryl radical cyclization reaction was employed to synthesize the 2,3-benzocarbapenems **221**.[80] The 2-azetidinones **222** (R^3=Ph) underwent 5-*exo* radical cyclization to afford exclusively the benzocarbapenems **221** in moderate yields. The presence of a phenyl group in the allylic moiety



Scheme 46.



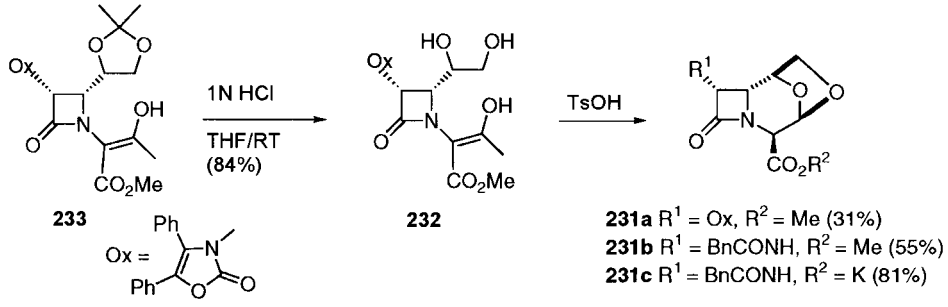
Scheme 47.

controlled the cyclization mode. The role of the stabilizing group in determining the regiochemistry was clear, since when the phenyl group attached to the acceptor double bond was replaced by a methyl group, a mixture of the benzocarbapenem **221** (R=Me) (30%), benzocarbacephem **224** (8%) and 1,4-dihydroquinoline **225** (20%) was obtained. The benzocarbacephem **224** was formed through a 6-*endo* cyclization leading to intermediate **226**. Homolytic C3–C4 bond cleavage in the azetidinone nucleus of species **226** followed by hydrogen abstraction, led to **225** (Scheme 46).

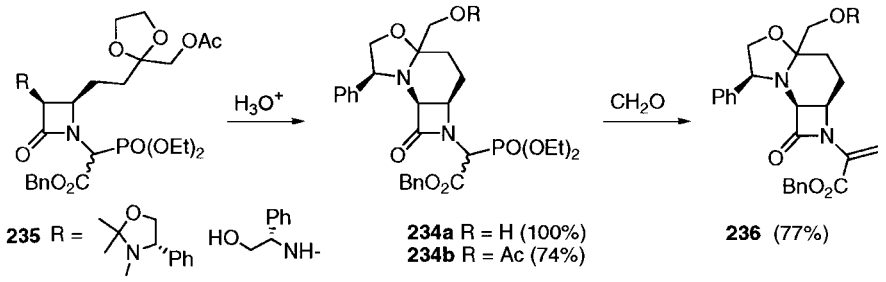
Snider-type Mn(III) oxidative cyclizations have also been used to prepare tricyclic 2-azetidinones. Miller prepared the tricyclic carbacepham ring systems **227** by $Mn(OAc)_3$ promoted cyclization starting from the *N*-malonyl-2-azetidinones **228**. The yields reported were low to moderate and several by-products were obtained with the desired compound **227**. The process was explained by cyclization of the malonyl radical **229** followed by Mn(III) oxidation to form the cationic intermediate **230**. Lactonization of this species by intramolecular trapping of the ester carbonyl oxygen gave the tricyclic lactams **227** (Scheme 47).[81]

Intramolecular acetal formation. Miller and coworkers have described a versatile and enantioselective method for the synthesis of the polycyclic β-lactams **231**, in which the key part of the cyclization step is the intramolecular formation of an acetal.[82] Cyclization of the enol **232** (easily obtained by deprotection of the acetal **233**) to the tricyclic *O*-2-isocepham **231a** was achieved with TsOH in refluxing benzene or, alternatively, by refluxing the acetal **233** with one equivalent of $FeCl_3$. In the same way, the enantiomer of enol **232** afforded the cyclization products in comparable yield. Standard modifications were carried out on **231a** to transform these tricyclic structures into compounds **231b** and **231c** which exhibited significant antibacterial activity (Scheme 48).

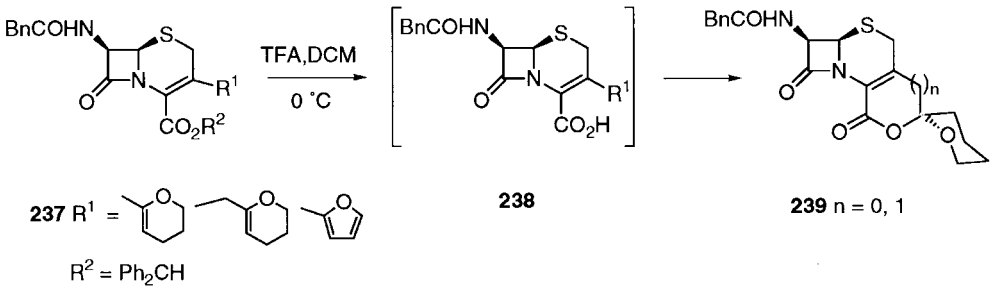
Other tricyclic β-lactams **234** were obtained by Hegedus while trying to remove both the chiral auxiliary and the ketal protecting group in 2-azetidinones **235**.[83] Acid treatment of these compounds afforded, either directly or in a two step process, the tricyclic β-lactams **234** in good yields and as a mixture of two diastereoisomers, epimeric solely at the racemic phosphonate center. This was confirmed by transformation of compound **234b** into compound **236** by olefination with formaldehyde (Scheme 49).



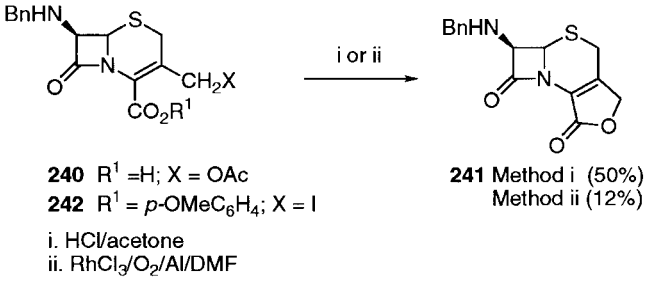
Scheme 48.



Scheme 49.



Scheme 50.

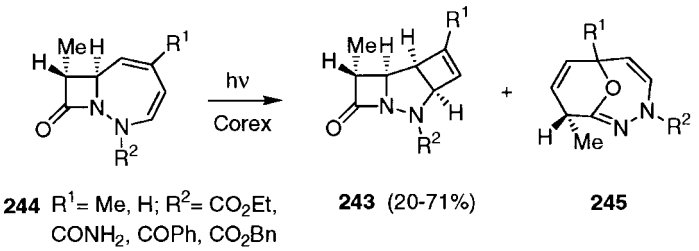


Scheme 51.

Intramolecular lactonizacion. Tricyclic β-lactams have been obtained by diverse lactonization methods starting from bicyclic azetidinones. The synthesis of some spiro-acetal-lactones from benzhydryl esters has been reported by Bateson.[84] Deprotection (TFA, DCM, 0°C) of the benzhydryl esters **237** released the respective carboxylic acids **238** which cyclised spontaneously to the highly stable crystalline oxaspirolactones **239** as a mixture of two diastereomers differing only in the stereochemistry at the spirocenter. None of these oxaspirolactones were found to exhibit significant levels of antimicrobial activity (Scheme 50).

Conversion of the aminocephalosporanic acid **240** into the lactone **241** occurred on treatment with aqueous acetone (1:1 v/v) and concentrated HCl.[85] The lactone **241** has been obtained in low yield, as a secondary product of the oxidation of the iodocephems **242** in DMF in the presence of $RuCl_3.3H_2O$/Al (Scheme 51).[86]

Photocyclizations. Azetidinodiazepines, which are easily obtained by cycloaddition of ketenes and 1,2-diazepines, undergo photochemical ring closure leading to tricyclic systems the partial structure of which, azetidinone and five-membered ring, is similar to that of the penicillin and thienamycin skeletons. A series of tricyclic β-lactams **243** was obtained by photoisomerization of the azetidinodiazepines **244**.[87] The stereochemistry of these compounds was defined by the photochemical disrotatory ring closure between positions 3 and 6 of the starting bicyclic system. It was confirmed that the preferred conformation for the seven-membered ring of azetidinodiazepines was boat-shaped and that the H3 and H6 hydrogens were *syn*, pointing towards the backside of the cycle. A minor product **245** was obtained in all cases with the β-lactams **243**. The mechanism for the formation of these compounds was not determined, although when the irradiations were carried out in the presence of a triplet sensitizer, the β-lactams **243** were no longer formed. These results might indicate that the by-products **245** were formed from an excited triplet state, and thus they become the sole products when a sensitizer was used. The reactivity of the tricyclic β-lactams of structure **243** has been extensively studied (Scheme 52).[88] Other unexpected photochemical reactions leading to tricyclic 2-azetidinones in very low yields have been reported.[89]



Scheme 52.

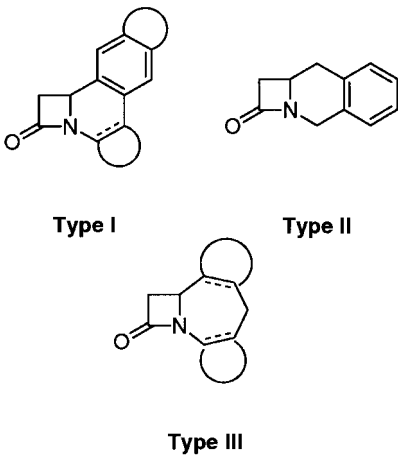


Figure 2.

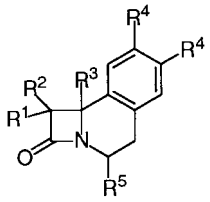
3. Building the β-Lactam Ring on a Preformed Bi- or Polycyclic System

3.1. Cycloaddition reactions

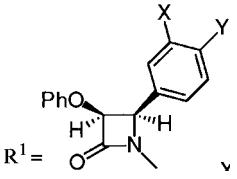
The Staudinger reaction. The cycloaddition between a ketene or a ketene precursor and an imine (the venerable Staudinger reaction)[90] is one of the more commonly employed procedures for the preparation of 2-azetidinone rings. When the imine is part of a bicyclic or polycyclic ring system, this method would lead to polycyclic β-lactams. A large number of tri- and polycyclic β-lactams with diverse substitution patterns have been prepared through this methodology but, in general, they could be classified in three fundamental types according to the structure of the imine precursors: type I, derived from 3,4-dihydroisoquinolines, type II, derived from 1,4-dihydroisoquinolines and

Table 1.

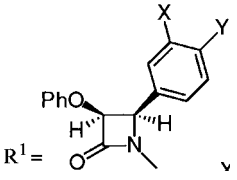
Type I polycylic 2-azetidinones



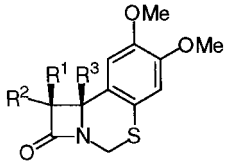
R^1=OPh, OCH_2Ph, O^{t}Bu, OH, $OCOCH_2OPh$, $OCOCH_2p$-C_6H_4–NO_2, $OCOCH_2p$-C_6H_4–NH_2, $OCOCH_2p$-C_6H_4–$N(CH_2CH_2OH)_2$, $OCOCH_2p$-C_6H_4–$N(CH_2CH_2Cl)_2$; R^2=R^4=R^5=H; R^3=Ph, p-C_6H_4–NO_2, p-C_6H_4–$N(CH_2CH_2OH)_2$, p-C_6H_4–$N(CH_2CH_2Cl)_2$ (Ref. 91)
R^1=N_3, NH_2, $NHCOCH_2Ph$; R^2=H; R^3=Ph, p-C_6H_4–NO_2; R^4=R^5=H, OCH_3 (Ref. 92)
R^1=OPh, OCH_3, N_3, NH_2, $NHCOCH_2Ph$, $NHCOCHCl_2$; R^2=H; R^3=Ph, p-C_6H_4–NO_2, p-C_6H_4–NH_2, p-C_6H_4–CN, p-C_6H_4–OCH_3, p-C_6H_4–CH_3, p-C_6H_4–CO_2H, p-C_6H_4–Br, p-C_6H_4–Cl; R^4=H, OCH_3; R^5=H, CO_2CH_3 (Ref. 93)
R^1=N_3; R^2=R^5=H; R^3=Ph; R^4=OCH_3 (Ref. 94)
R^1=OCH_2Ph; R^2=R^5=H; R^3=p-C_6H_4–NO_2, p-C_6H_4–NH_2, p-C_6H_4–Br; R^4=H, OCH_3 (Ref. 95)
R^1=O-p-C_6H_4–Cl, phthalimido; R^2=R^4=R^5=H; R^3=Ph, p-C_6H_4–NO_2, m-C_6H_4–NO_2 (Ref. 96)
R^1=OCH_3, N_3, NH_2, $NHCOCH_2OPh$; R^2=R^4=R^5=H; R=SCH_3, H(*cis*) (Ref. 97)
R^1=OPh; R^2=R^5=H; R^3=SCH_3, H(cis); R^4=OCH_3, OCH_2O (Ref. 98)
R^1=NH_2, $NHCOCH_2Ph$; $NHC(CH_3)CHCO_2CH_2CH_3$; R^2=R^5=H; R^3=SCH_3, H; R^4=OCH_3 (Ref. 99)
R^1=OPh; R^2=R^4=R^5=H; R^3=p-C_6H_4–CH_3, p-C_6H_4–OCH_3 (Ref. 100)
R^1=OPh, *O*-β-naphthyl, *O*-2,4-dichlorophenyl; R^2=R^4=R^5=H; R^3=SCH_3, H(*cis*) (Ref. 101)
R^1=R^2=OCH_3; R^3=R^5=H; R^4=OCH_3 (Ref. 102)



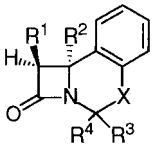
X=Y=H, OCH_3, OCH_2O, R^2=R^5=H; R^3=H, SCH_3, Ph, p-C_6H_4–CH_3, p-C_6H_4–OCH_3; R^4=R^5=H, OCH_3 (Ref. 103)



X=Y=OCH_3, OCH_2O, R^2=R^4=R^5=H; R^3=H; SCH_3, Ph, p-C_6H_4–CH_3, p-C_6H_4–OCH_3 (Ref. 101)



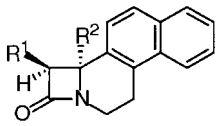
R^1=MeO; R^2=Ph, CH_3; R^3=Ph, CH_3, H (Ref. 102)
R^1=Cl, Ph, PhO, R^2=H, Cl; R^3=Ph (Ref. 104)



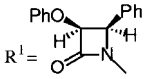
R^1=OPh, O-2,4-dichlorophenyl; R^2=SCH_3, H; R^3=CH_3; R^4=CH_2CH_3; R^3, R^4=$(CH_2)_4$, $(CH_2)_5$; X=O (Ref. 105)
R^1=OPh, *O*-2,4-dichlorophenyl, *O*-α-naphthyl; R^2=SCH_3, H; R^3=CH_3; R^4=CH_2CH_3; R^3, R^4=$(CH_2)_5$; X=NH (Ref. 105)
R^1=OPh; R^2=SCH_3, H; R^3=CH_3, Ph, CH=CHPh,; R^4=CH_3, H; X=NCH_3 (Ref. 106)

Table 1 (*continued*)

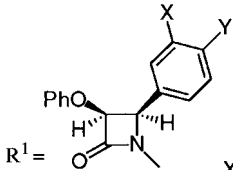
Type I polycylic 2-azetidinones



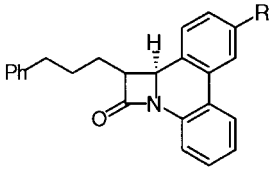
R^1=OPh; R^2=Ph, *p*-C_6H_4–CH_3, *p*-C_6H_4–OCH_3 (Ref. 100)
R^1=OPh, NH_2, $NHCOCH_2OPh$, $NHC(CH_3)CHCO_2CH_2CH_3$; R^2=H, SCH_3 (Ref. 101)



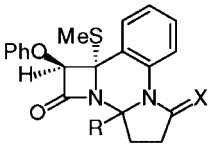
R^2=H, SCH_3 (Ref. 101)



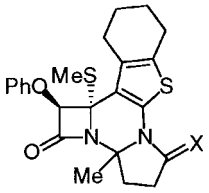
X=Y=H, OCH_3, OCH_2O, R^2=Ph, *p*-C_6H_4–CH_3 (Ref. 103)



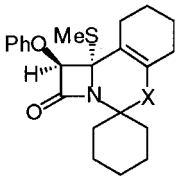
R=H, OMe (Ref. 107)



R=Me, α-naphthyl; X=O,S (Ref. 105)

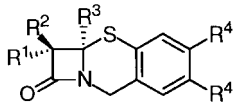


X=O,S (Ref. 105)



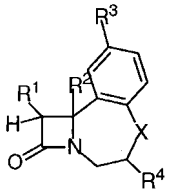
X=NH, $NCOCH_2O$ Ph (Ref. 106)

Type II polycylic 2-azetidinones

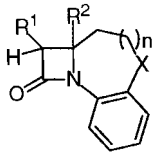


R^1=OCH_3; R^2=Ph, CH_3; R^3=Ph; R^4=OCH_3 (Ref. 102)
R^1=Ph, OPh, Cl; R^2=H, Cl; R^3=Ph; R^4=OCH_3 (Ref. 104)

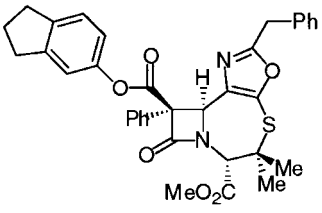
Type III polycylic 2-azetidinones



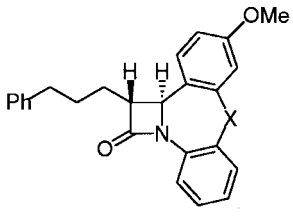
R^1=N_3, OMe, OPh; R^2=SMe, SEt, S^{i}Pr, OMe; R^3=H, Cl; R^4=H; X=O (Ref. 108)
R^1=N_3, OMe, OPh; R^2=SMe, S^{i}Pr; R^3=H; R^4=H, OMe; X=S (Ref. 108)



R^1=H, OMe, OPh, OCH_2Ph, Cl; R^2=SMe; n=0,1; X=O,S,CH_2 (Ref. 109)



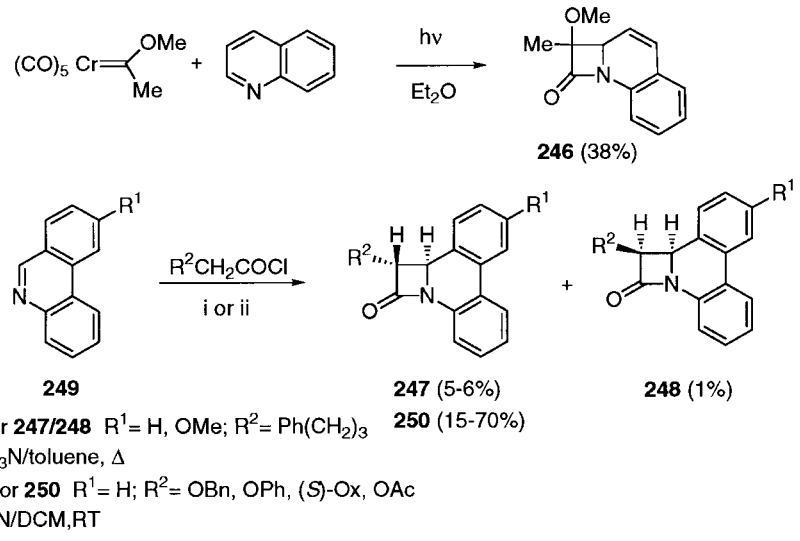
(Ref. 110)



X=O, CH_2 (Ref. 107)

type III, derived from bi- or polycyclic imines with the C=N double bond included on a seven-membered ring (Fig. 2). These basic skeletons could also incorporate other heteroatoms (N, O, S). The tri- and polycyclic 2-azetidinones of type I constitute the main group of compounds reported in the literature. A more detailed list is compiled in Table 1.

Although the ketene-imine method has been widely

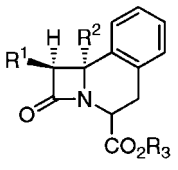


Scheme 53.

employed to prepare tri- and polycyclic-2-azetidinones of types I–III, it should be noted that there are only a few examples in which the C=N double bond of the imine precursor is part of a fused aromatic heterocycle. One of these cases was reported by Hegedus,[102] in which the irradiation (visible light) of [methoxymethylcarbene]pentacarbonylchromium(0) in the presence of quinoline gave the β-lactam **246** in 38% yield (Scheme 53).

The tetracyclic azetidinones **247** and **248**, on the other hand, were obtained from the phenanthridines **249** in very low yield. Even though the compounds **247** and **248** were rigid analogs of a novel cholesterol absorption inhibitor,[111] both were found to be essentially inactive agents.[107] Interestingly, the synthesis of phenanthridine-derived 2-azetidinones **250** as single *trans*-isomers and in moderate to good yields, has been reported recently.[112] The presence of electron withdrawing substituents in the acid chlorides and the smooth reaction conditions employed, appear to be the cause of the successful outcome of the reaction in this case (Scheme 53).

The chemical reactivity of the compounds in Table 1 has not been extensively studied, except for the standard functional group transformations. The facile conversion of the azido group to the amino function under mild conditions (such as catalytic hydrogenation) has been particularly useful, allowing the synthesis of amino β-lactams and their derivatives.[91–93,97] An example, is the cephalosporin analog



252 R^1= N_3 R^2= SMe; R^3= Me
251 R^1= $PhOCH_2CONH$; R^2 = R^3= H

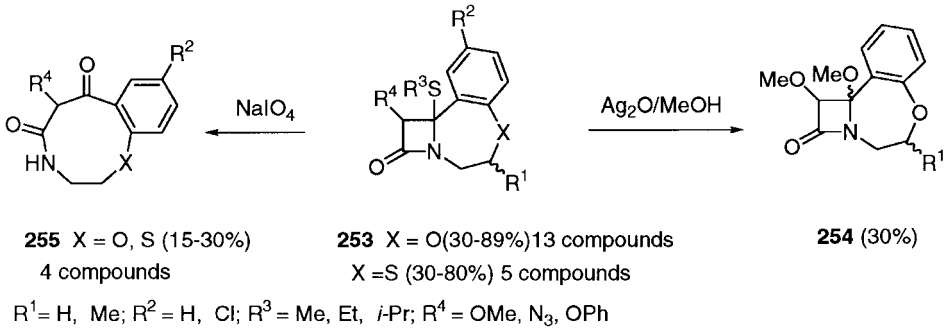
Figure 3.

251, which is obtained after reduction of the azido group in **252**, followed by treatment with phenoxyacetyl chloride, desulfurization and ester hydrolysis (Fig. 3).[97] Additionally, removal of the SMe group by Raney Ni has been used in other cases to confirm the stereochemistry of the 2-azetidinone ring by measuring the $J_{6,7}$ coupling constants, which for the *cis* isomer, were in the range 4–5 Hz.[97,98]

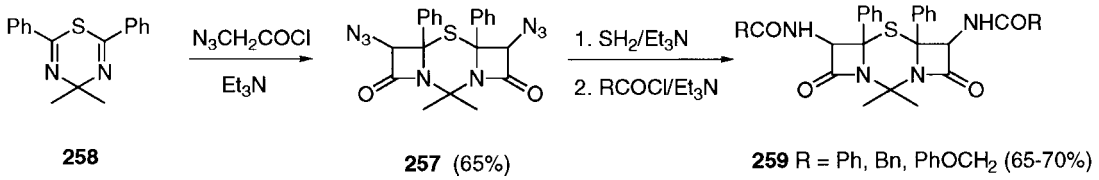
The standard reaction conditions can sometimes lead to unexpected results. Thus, removal of the SMe group in compound **253** (R^1=R^2=H, R^3=Me, R^4=OMe) was accomplished with Ag_2O or Ag_2CO_3 in refluxing dry MeOH, in the dark, to give the β-lactam **254** in 30% yield. When the reaction was carried out with $NaIO_4$ in aqueous propanol, however, the benzoxazoninediones **255** were isolated in low yields. The initial formation of a hydroxy β-lactam as a possible intermediate that rearranged to the observed ring expansion products was suggested (Scheme 54).[113] Other analogous ring expansion processes have been observed.[113,114]

Finally, compounds with a bis-β-lactam structure incorporated in a fused tricyclic system are also available by the ketene-imine cycloaddition. This is exemplified for compound **256** which is obtained from the thiadiazine **257** and azidoacetyl chloride. Reduction of the azide group and acylation with acid chlorides gave the compounds **258** in good yields (Scheme 55).[115]

The isocyanate-olefin cycloaddition. The formation of a 2-azetidinone ring in a polycyclic system can be alternatively achieved by addition of an isocyanate to a C=C bond, an approach that has been frequently used to prepare mono- and bicyclic 2-azetidinones.[116] The β-amino-β-lactams **259** were prepared by the reaction of phenyl isocyanate with the corresponding bicyclic enamines **260** (Scheme 56).[117] The reactivity of compounds **259** towards different reagents has been studied and, depending on the nature of the reagents used, products of diverse structures have been formed. In the presence of water or aniline, for



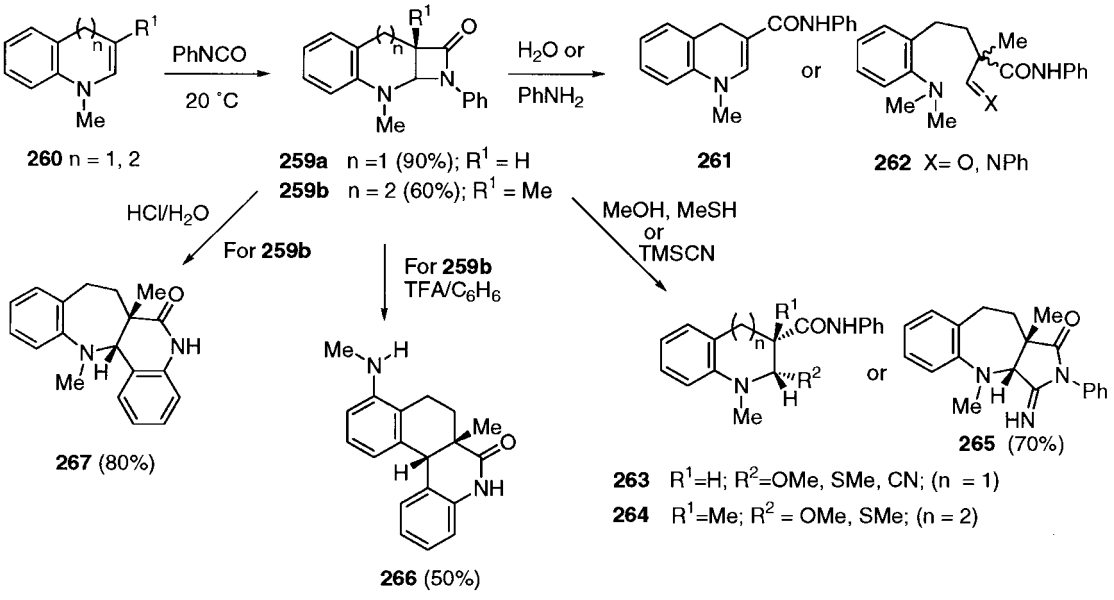
Scheme 54.



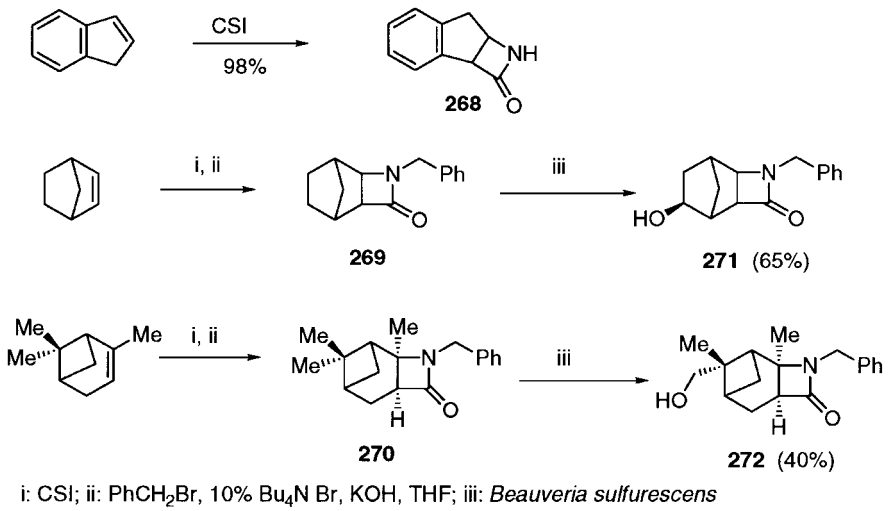
Scheme 55.

example, the compound **259a** isomerized spontaneously to the dihydroquinoline **261**, whereas the solvolysis products **262** were isolated when starting from **259b**. When treated with other nucleophilic reagents such as MeOH, MeSH or TMSCN, the compounds **259a** were transformed into the *cis*-dihydroquinolines **263**. The same type of behaviour was observed when the β-amino-β-lactams **259b** were treated with MeOH or MeSH in DCM, to afford the benzoazepines **264**, although in this case, the iminopyrrolidionones **265** were obtained with TMSCN in the presence of $AlCl_3$.[118] In strong biphasic acidic media, such as $HCl/CHCl_3$ or TFA/benzene, the benzazepinoquinolines **266** were isolated in good yields, while in a homogeneous phase, the tetracyclic aminonaphthoquinolines **267** were obtained in 50% average yield (Scheme 56).[119]

The more reactive chlorosulfonyl isocyanate (CSI)[116] has also been employed to produce tri- and polycyclic 2-azetidinone systems from bi- or polycyclic alkenes and dienes.[120–123] The reported yields for this type of reaction are good in the case of alkenes, although complex mixtures of different products were frequently obtained when starting from polyenes. Once the 2-azetidinone ring has been formed through this procedure, as in **268**, further functionalization can be achieved without difficulty by alkylation of the nitrogen in the β-lactam ring,[124] as exemplified for



Scheme 56.



Scheme 57.

compounds **269** and **270** (Scheme 57).[125] These compounds were regioselectively transformed into the alcohols **271** and **272** by an interesting biohydroxylation process using the fungus *Beauveria sulfurescens*.

3.2. Cyclization of β-amino acids

The creation of the 2-azetidinone ring by cyclization of a bi- or polycyclic β-amino acid is another strategy commonly used in the preparation of mono- and bicyclic 2-azetidinones[126] that have been employed in the synthesis of polycyclic β-lactams. The bi- or polycyclic framework is constructed initially and the building of the sensitive four-membered ring is delayed to the final steps, thereby avoiding reaction conditions that might be incompatible with the labile 2-azetidinone moiety. The cyclization step can be carried out either from the free amino acid or by means of a derivative, such as an acid chloride or an amine salt and, generally, it is necessary to use a cyclizing agent.

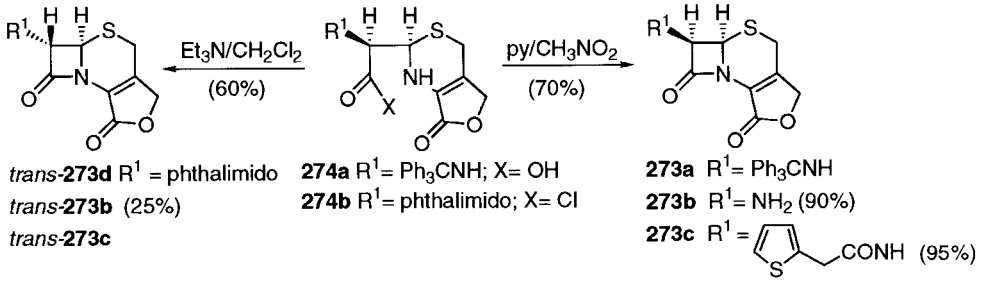
This type of methodology was applied to obtain the cephalosporin C analogs **273** starting from the *cis*-aminolactones **274**.[127] When the cyclization step was carried out from the free amino acid **274a** in nitromethane and in the presence of pyridine, the *cis*-β-lactam **273a** was obtained in 70% yield. Detritylation in an acidic medium afforded the free amine **273b**, which was subsequently acylated to give the racemic tricyclic 2-azetidinone having a cephalosporin nucleus **273c**. Interestingly, *trans*-**273d** was obtained when the cyclization step was carried out starting from the acid chloride **274b** in the presence of Et_3N (Scheme 58).

The indole **275**, tetrahydroquinoline **276**, dihydrobenzothiazole **277** and tri- or polycyclic thiazole β-lactams **278** and **279**, were successfully obtained by cyclization of the corresponding β-amino acids using different condensation agents, e.g. tris(2-oxobenzoxazolin-3-yl)phosphine oxide,[128] methanesulfonyl chloride,[129] dipyridyl disulfide/PPh_3[130] or 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride in the presence of Et_3N (Fig. 4).[131]

Other carbapenam and carbacepham analogs having fused cyclic ketals have been obtained by β-amino acid cyclization. The bicyclic skeleton was built starting from biomolecules such as carbohydrates or amino acids. Thus, starting from 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose and in four steps, the pyrrolidine **280** was obtained in 45% average yield. Cyclization in the presence of 2,2′-dipyridyl disulfide/PPh_3 afforded the β-lactam **281** that was isolated in 62% yield.[132] Tricyclic carbacepham derivatives having a fused cyclic ketal have also been obtained from D-serine in 26% average yield using a multistep synthesis (Scheme 59).[133]

3.3. Other methods

The synthesis of the tricyclic β-lactams **282** by reaction of the acetoacetyl enamides **283** with two equivalents of Mn(III) has been recently reported. The compounds **282** were obtained in low yields with monocyclic 2-azetidinones



Scheme 58.

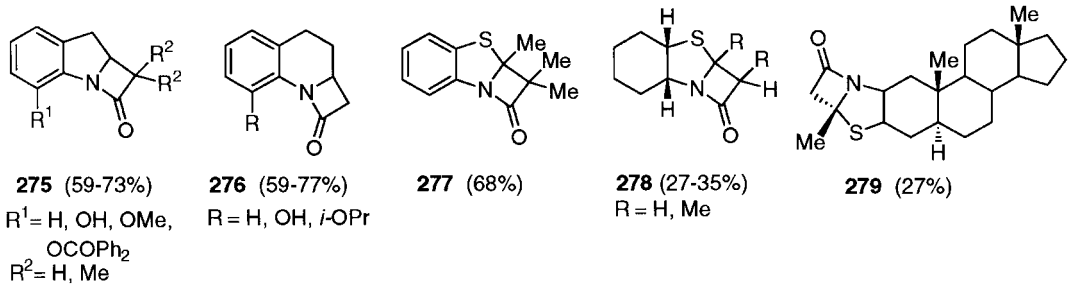
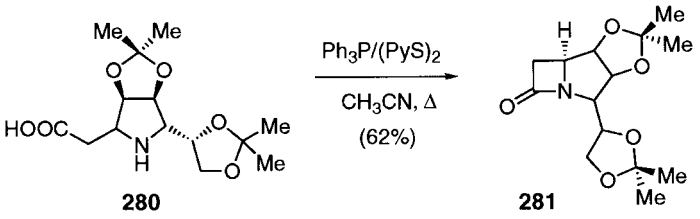


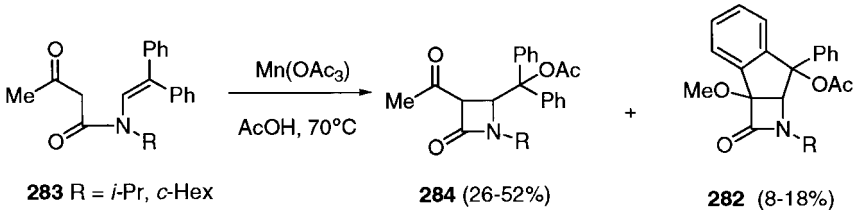
Figure 4.



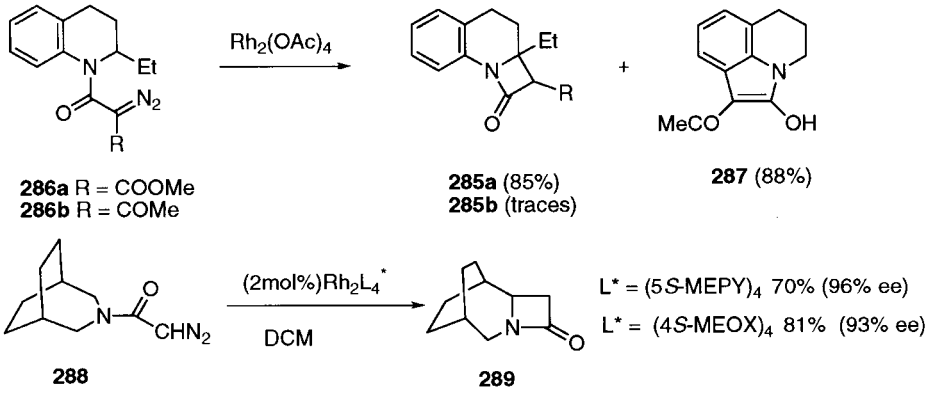
Scheme 59.

284 being the main reaction products.[134] The formation of the compounds **282** was certainly due to a further oxidation of the C3 carbon in the initially formed **284**, followed by attack of the resulting radical on the phenyl group. This hypothesis was demonstrated by reacting the pure compound **284** (R=*c*-Hex) with an excess of Mn(III) at 70°C. This reaction yielded **282** (R=*c*-Hex) in 80% yield (Scheme 60).

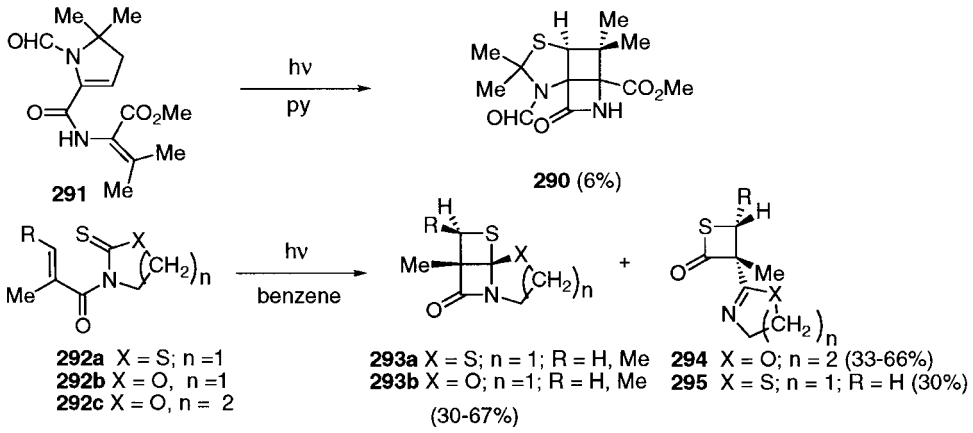
Other procedures for 2-azetidininone ring construction, such as Rh(II) catalyzed intramolecular C–H insertion of diazoamides, have been applied to obtain polycyclic β-lactams. The synthesis of the benzocarbacepham **285a** from the carbomethoxy diazoamide **286a** and $Rh_2(OAc)_4$ occurred in excellent yield, as a 1:1 mixture of diastereomers.[135] The acetyl-substituted amide **286b** gave compound **287** resulting from a C–H insertion reaction and only traces of the β-lactam **285b** were isolated. The results suggest that the α-substituent in the rhodium carbenoid determines the chemoselectivity of the insertion reaction observed. Another interesting example described by Doyle and Kalinin,[136] is the intramolecular C–H insertion of the diazoacetamide **288** catalyzed by chiral dirhodium(II) carboxamidates. The reaction showed high enantiocontrol in both cases, affording the β-lactam **289** in good yields (Scheme 61).



Scheme 60.



Scheme 61.



Scheme 62.

Other tricyclic 2-azetidinones have been prepared by an isoxazolidine to 2-azetidinone ring contraction.[137] The tricyclic β-lactam **290** was isolated in very low yield after 70 h irradiation in pyridine of the dehydropeptide **291**. The authors considered this compound as a *seco*-pyridone and interpreted its photochemical transformation as a special case of the general pyridone-photopyridone reaction.[138] Better results were obtained in the irradiation of the unstable *N*-acyl dithiocarbamates **292a** and thionocarbamates **292b,c**. These compounds were transformed by an intramolecular [2+2] cyclization into the thietane fused penams and oxapenams **293** with yields ranging from 33 to 67%. In the case of the six-membered compounds **292c** the expected β-lactams **293** were not observed, and the β-thiolactone **294** was isolated. The authors confirmed that the formation of such compound was due to a thermal transformation of the corresponding β-lactams **293**, the primary photoproduct of the reaction. In the case of dithiocarbamate **292a**, the β-lactam **293a** and the thiolactone **295** were both obtained (Scheme 62).[139]

4. Conclusions

In this article many different approaches to polycyclic β-lactams that use mainly the synthetic methodology previously refined for the preparation of bicyclic 2-azetidinones are described. The array of structures prepared is impressive, but in terms of both antibacterial activity and synthetic potential, these have resulted in little utility. The synthesis of polycyclic 2-azetidinones is a mature field, but the true potential of these compounds as therapeutic agents as well as synthetic intermediates is still unknown. The need for new antibiotics will continue because bacteria have a remarkable ability to overcome each new agent synthesized. Perhaps the clues for the new generation of new pathogen-killers are to be found in the pages above. Meanwhile, polycyclic β-lactams are especially attractive structures to fulfill other pharmacological goals, an aspect of these compounds which remains essentially unexplored.

Acknowledgements

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