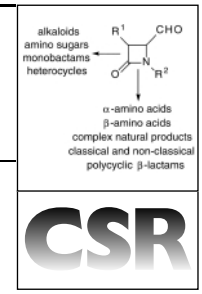
4-Oxoazetidine-2-carbaldehydes as useful building blocks in stereocontrolled synthesis



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4-Oxoazetidine-2-carbaldehydes or 4-formyl-β-lactams can be considered both as protected α-amino aldehydes and masked β-amino acids. These bifunctional compounds exhibit a valuable dual reactivity, which has been utilized in a broad range of synthetic applications. The present review is a survey of the recent salient synthetic achievements exploiting 4-oxoazetidine-2-carbaldehydes, with particular emphasis on diastereoselective processes. The usefulness of these substrates for the preparation of substances of biological interest, including α-amino acids, β-amino acids, amino sugars, polycyclic-β-lactams, alkaloids, and complex natural products is presented.

1 Introduction

The importance and structural diversity of biologically active β-lactam antibiotics, the most widely employed family of antimicrobial agents to date accounting for 50% of the world's total antibiotic market, has led to the development of efficient approaches for the stereoselective construction of appropriately substituted azetidin-2-ones.[1] The various families of β-lactam antibiotics differ in their spectrum of antibacterial activity and in their susceptibility to β-lactamase enzymes. β-Lactamases, which constitute the most common form of resistance to β-lactam antibiotics,[2] catalyze the hydrolysis of β-lactams to give ring-opened β-amino acids which are no longer active as inhibitors against their targets—bacterial membrane-bound transpeptidase enzymes. The recent discoveries of some azetidin-2-ones which display a broad range of enzyme-inhibitory activity has helped to maintain interest in this family of compounds.[3]

The phenomenal success of penicillin and related antibiotics as life-saving drugs led some time ago to extensive β-lactam research in many industrial and academic laboratories. With the discovery of the carbapenems, the penems, and the carbacephems as powerful antibacterial agents, much effort has focused on the search for novel methods for the construction of bicyclic β-lactam ring systems. The production of penicillin and cephalosporin antibiotics starts from fermented intermediates, whereas, in the total synthesis of carbapenem, monocyclic azetidinones are key intermediates. The role of the carbapenem synthetic work deserves especial mention, because it was the driving force for the development of the whole area. Besides their biological relevance, the importance of β-lactams as synthetic intermediates has been recognized in organic synthesis.[4] 4-Oxoazetidine-2-carbaldehydes (or 4-formyl-β-lactams) are now versatile synthetic intermediates. As far as we know, natural products bearing the 4-formyl-β-lactam skeleton, or structurally related bioactive unnatural compounds, have not been reported. However, a significant degree of interest has been recently focused on the synthesis and reactivity of 4-oxoazetidine-2-carbaldehydes, due to their potential use as

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viable intermediates in the synthesis of biologically active compounds. Representative examples of the latter include classical and non-classical bi- and polycyclic β-lactams, different kinds of heterocycles, alkaloids, non proteinogenic α- and β-amino acids, amino sugars, taxoids, and complex natural products.

Aspartic acid is a natural precursor of the 4-formyl-β-lactam skeleton, which could be considered as a cyclic orthogonally protected aspartic acid derivative. 4-Oxoazetidine-2-carbaldehydes exhibit a valuable dual reactivity and can be considered both as protected α-amino aldehydes as well as masked β-amino acids. The usefulness of these bifunctional compounds in stereocontrolled synthesis is based on the impressive variety of transformations which can be derived from this system, due *inter alia* to a high chirality content that can be transferred into a variety of products. The transformation of 4-oxoazetidine-2-carbaldehyde derivatives into functionalized open-chain products has been most commonly achieved by multistep protocols involving the initial conversion of the β-lactam substituents followed by ring opening. The cyclic 2-azetidinone skeleton has been extensively used as a template on which to build the carbo(hetero)cyclic structure fused to the four-membered ring, using the chirality and functionalization of the 4-oxoazetidine-2-carbaldehyde as a stereocontrolling element. Alternatively, the direct one-pot generation of fused nitrogen heterocyclic systems from the nitrogen framework of 4-formyl-β-lactam derivatives has been achieved by selective bond breakage and rearrangement.

Due to its α-amino aldehyde character, a challenge has been to evaluate diastereoselective C–C bond forming processes *via* reaction with the aldehyde. The C═C bond formation, followed by further transformations has been shown to be a versatile route to products of biological interest, while protocols involving C–O bond formation have been shown to be suitable for the preparation of fused tetrahydrofuran-β-lactams and amino sugars. Another synthetically important development concerns the stereocontrolled [2 + 2] and [3 + 2] cycloaddition reactions of 4-oxoazetidine-2-carbaldehyde-derived imines or nitrones. Because of its cyclic amide nature some rearrangements of the 2-azetidinone ring can be achieved. 4-Formyl-β-lactams are also amenable to transformations involving redox, deformylation and epimerization reactions. The various modes of reactivity of 4-oxoazetidine-2-carbaldehydes are summarized in Scheme 1.

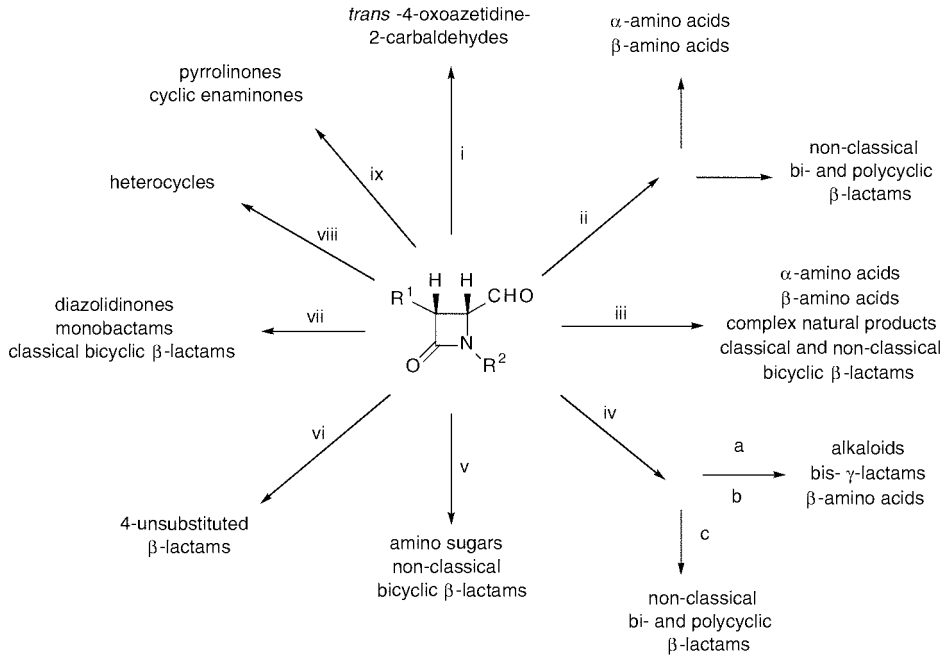
In this review we highlight some of the recent developments connected with the various modes of reactivity of 4-oxoazetidine-2-carbaldehydes and their synthetic transformations. In particular, advances in their application to the asymmetric synthesis of substances of biological interest are considered.

2 Preparation of 4-oxoazetidine-2-carbaldehydes

Optically active *N*-protected α-amino aldehydes are used as synthetic intermediates of importance in the pharmaceutical and fine chemical industries. The facility with which they undergo epimerization has been noted and strategies have been devised to minimize this propensity *via* appropriate protection of the α-amino group, *e.g.* by Rapoport's 9-(9-phenylfluorenyl) substitution of the amino group,[5] and Reetz's *N*,*N*-dibenzyl derivatization.[6] In contrast to the recurring drawbacks of the vast majority of *N*-protected α-amino aldehydes, 4-oxoazetidine-2-carbaldehydes are relatively stable both chemically and configurationally, and can be conveniently stored for long periods of times. Thus, we describe first the currently available methods for the synthesis of 4-formyl-β-lactams.

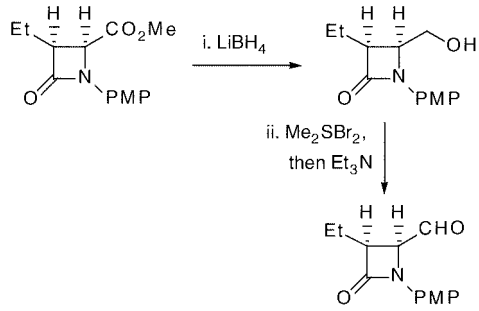
2.1 Racemic syntheses

α-Amino aldehydes have been traditionally prepared *via* oxidation of the corresponding hydroxymethyl alcohol.[7] This classical way was utilized in β-lactam chemistry *via* Swern oxidation and by means of a dimethylbromosulfonium bro-



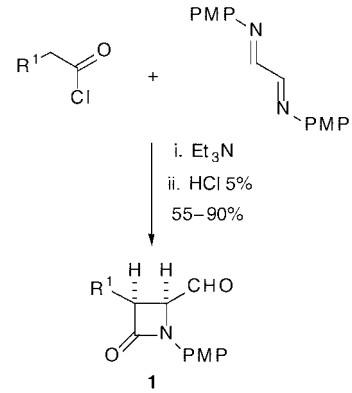
Scheme 1 i, chemoselective epimerization; ii, C–C formation; iii, C=C formation; iv, (a) intermolecular cycloaddition, (b) rearrangement, (c) intramolecular cycloaddition; v, C–O formation; vi, deformylation; vii, redox reactions; viii, (a) protection, (b) reduction, (c) rearrangement; ix, rearrangement.

mide–triethylamine system (Scheme 2).[8]† The ozonolysis of β-lactams bearing styryl groups at the C4 position, has been also probed as a straightforward preparation of these compounds.



Scheme 2

Alcaide *et al.* have developed an original synthesis of 4-oxoazetidine-2-carbaldehydes by a one-pot method from *N*,*N*-di-(*p*-methoxyphenyl)glyoxal diimine. Glyoxal-derived diimines undergo a [2 + 2] cycloaddition with ketenes to give racemic 4-formyl-β-lactams **1** as single *cis*-diastereoisomers, after acidic hydrolysis (Scheme 3).[9]



Scheme 3

2.2 Enantioselective syntheses

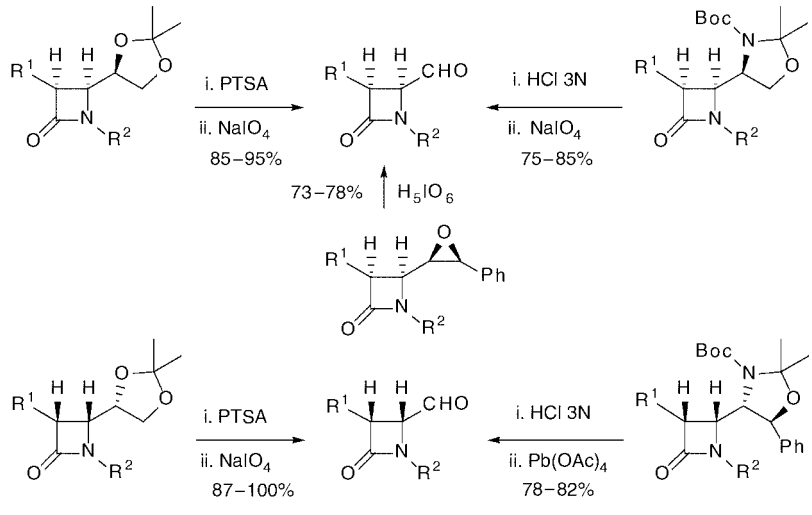
The methods outlined above for the synthesis of 4-oxoazetidine-2-carbaldehydes have also been used for their preparation in optically pure form. However, among the different strategies, the oxidative cleavage of the side chain of appropriate 4-substituted-β-lactams is usually the method of choice. Thus, the functional group yielding 4-side chain at the β-lactam ring must be a versatile building block working as an efficient chiral auxiliary in the Staudinger reaction as well as a carbaldehyde precursor. The (1*R*,2*R*)-oxazolidinyl,[10] the (1*S*,2*S*)-phenyloxazolidinyl, the *R*- and *S*-dioxolan-4–yl, and the (2*R*,3*R*)-epoxycinnamyl moieties meet this requirement and provide a convenient and widely used route of 4-formyl-β-lactams (Scheme 4).[11] A very strong preference (> 95% d.e.) for *cis*-β-lactam formation is observed. A strategy to access to *trans*-4-oxoazetidine-2-carbaldehydes has been recently reported, namely a base-promoted chemoselective C2 epimerization of *cis*-4-oxoazetidine-2-carbaldehydes to give the thermodynamically more stable *trans*-isomer (Scheme 5).[12] Aspartic acid derivatives are obvious precursors to 4-oxoazetidine-2-carbaldehydes, providing a general route to the synthesis of the functionalised core. An example of this usefulness is depicted in Scheme 6. The toluene-*p*-sulfonic acid salt of dibenzyl-D-aspartate was *N*-protected, cyclized, treated with the system sodium borohydride–lithium bromide, methylated, and reacted under Swern protocol to give a 4-oxoazetidine-2-carbaldehyde.[13]

† AIBN = 2,2′-azobis(isobutyronitrile); Ala = alanine; Bn = benzyl; Boc = *tert*-butoxycarbonyl; CAN = ceric ammonium nitrate; Cbz = carbobenzyloxy; DABCO = 1,4-diazabicyclo[2.2.2]octane; DCC = 1,3-dicyclohexylcarbodiimide; d.e. = diastereomeric excess; d.r. = diastereomeric ratio; DIBAL = diisobutylaluminium hydride; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DMSO = dimethyl sulfoxide; Im = imidazole; LDA = lithium diisopropylamide; LiHMDS = lithium bis(trimethylsilyl)-amide; MCPBA*m*-chloroperoxybenzoic acid; Ms = methanesulfonyl; Pht = phthalimido; PMB = 4-methoxybenzyl; PMP = 4-methoxyphenyl; PNB = 4-nitrobenzyl; PTSA = 4-toluenesulfonic acid; py = pyridine; TBAF = tetrabutylammonium fluoride; TBDPS = *tert*-butyldiphenylsilyl; TBS = *tert*-butyldimethylsilyl; TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy; TES = triethylsilyl; Tf = trifluoromethanesulfonyl; TFA = trifluoroacetic acid; TMS = trimethylsilyl; TTMSS = tris(trimethylsilyl)silane; Val = valine.

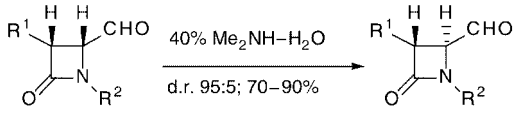
3 Applications of 4-oxoazetidine-2-carbaldehydes in stereocontrolled synthesis

3.1 Reactions involving C–C formation

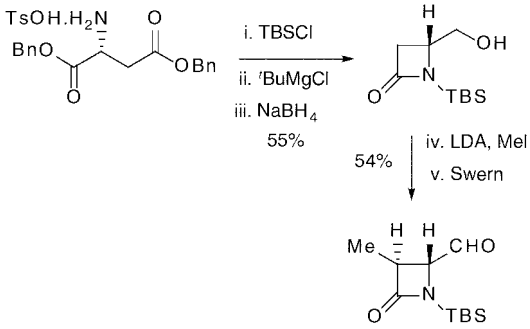
In this section, the addition reactions of common achiral organometallic reagents to the aldehyde function of 4-formyl-β-lactams are summarized. The reaction of activated vinyl systems (Baylis–Hillman reaction) with 4-oxoazetidine-2-carbaldehydes is also covered. In many studies, the corresponding alcohols are the result of non-chelation controlled addition



Scheme 4



Scheme 5

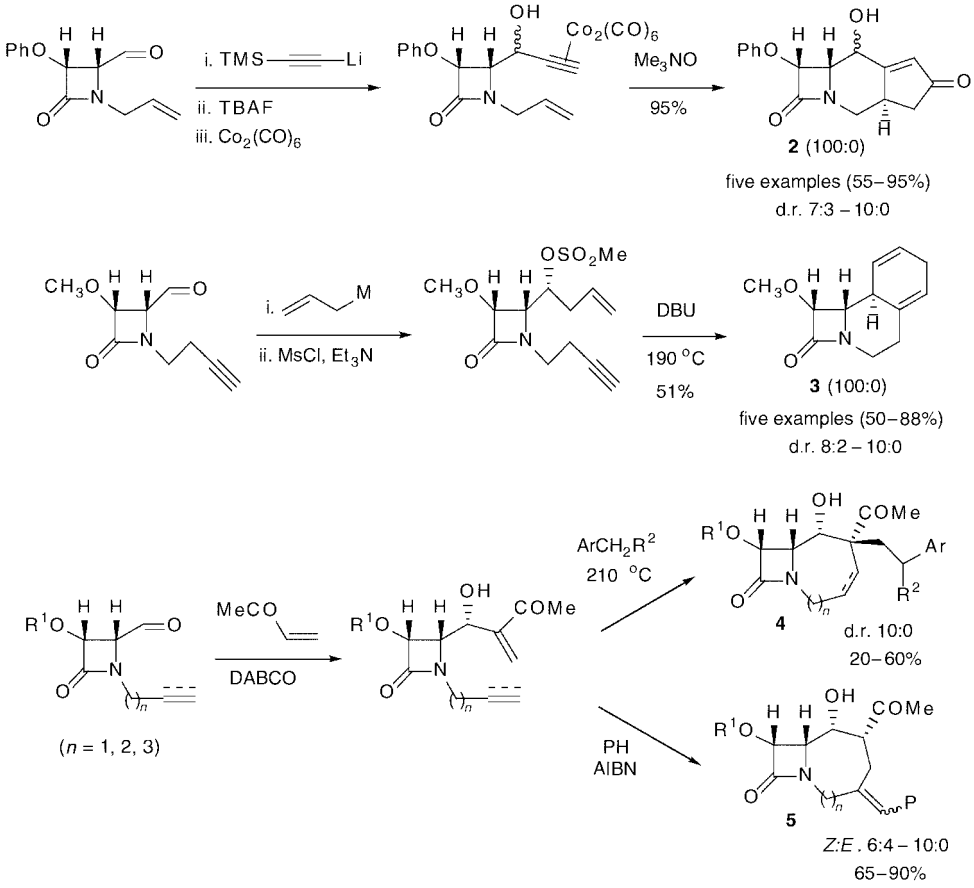


Scheme 6

which results in the *syn* adducts. These alcohols served as the starting materials for the preparation of polycyclic β-lactams and α- and β-amino acid derivatives.

3.1.1 Synthesis of non-classical bi- and tricyclic β-lactams

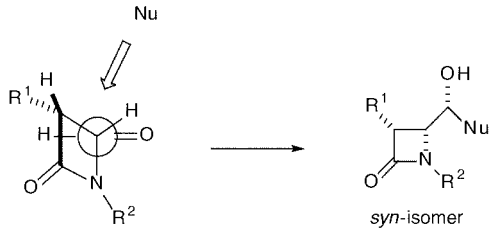
The extensive use of common β-lactam antibiotics such as penicillins and cephalosporins in medicine has resulted in an increasing number of resistant strains of bacteria through mutation and β-lactamase gene transfer. This fact has triggered a renewed interest in the building of new bi- and tricyclic β-lactam systems in an attempt to move away from the classical β-lactam antibiotic structures, which are substrates for β-lactamases. The addition of lithium (trimethylsilyl)acetylide to 4-formyl-β-lactams followed by the Pauson–Khand cyclization of the resulting enyne-2-azetidinones is a straightforward approach to tricyclic β-lactams, as shown in Scheme 7 for compound **2**.[14] A different way to obtain β-lactams of the trinem class from monocyclic β-lactam aldehydes involves the use of both stereoselective allylation of 4-oxoazetidine-2-carbaldehydes and intramolecular Diels–Alder reaction.[15] The reaction of 4-oxoazetidine-2-carbaldehydes with propenylmetal reagents in anhydrous or aqueous media yielded homoallylic alcohols with moderate to good diastereoselectivity, depending of the nature of the metal or Lewis acid. The mesylates of these homoallylic alcohols bearing an extra alkene or alkyne tether at position 1 or 3 of the β-lactam ring, on heating in the presence of DBU provided fused tricyclic 2-azetidinones, as depicted for compound **3**. In another interesting application, Baylis–Hillman adducts derived from enantiopure 1-alkenyl (or alkynyl)-4-azetidinone-2-carbaldehydes are used for the stereoselective and divergent preparation of highly functionalised β-lactams **4** and **5** fused to medium rings (Scheme 7).[16] The Baylis–Hillman reaction using non-racemic protected α-amino aldehydes has been attempted with limited success, due to partial racemisation of the chiral aldehyde by DABCO after prolongate exposure times. However, this is not the case for 4-oxoazetidine-2-carbaldehydes, because on reacting with various activated vinyl systems the corresponding adducts can be prepared almost as single diastereoisomers. Formation of bicyclic β-lactams **4** and **5** can be explained in terms of a competition between a tandem radical Michael addition–*endo*-cyclisation and a tandem radical addition–Michael addition, depending on the electronic nature of the radical promoter. It is known that nucleophilic radicals react more rapidly with electron poor alkenes than with electron rich alkenes or alkynes, and conversely, electrophilic radicals react more rapidly with electron rich alkenes than electron poor alkenes. In the above



Scheme 7

case, Baylis–Hillman adducts may react through two different pathways to give the bicyclic systems. The more nucleophilic benzylic radical would favor formation of compounds **4**, while the more electrophilic radicals, such as PhS· and Ph_3Sn·, should promote formation of compounds **5**. Alternatively, the differences in reactivity between the benzylic and the thiyl and stannyl radicals, respectively, could be explained by other considerations. Thus, for the thiyl and stannyl radicals the initial addition to the double bond is fast but reversible. Since the cyclization is a slow reaction, it cannot compete with fragmentation. However, the addition to the triple bond is irreversible and therefore only products deriving from addition to the triple bond are isolated. Addition of the benzylic radical to the double bond of course is not reversible.

The diastereofacial preference of all these addition reaction for *syn*-addition to the aldehyde moiety was interpreted by the Felkin–Anh model, through an *anti*-Felkin addition (Scheme 8).



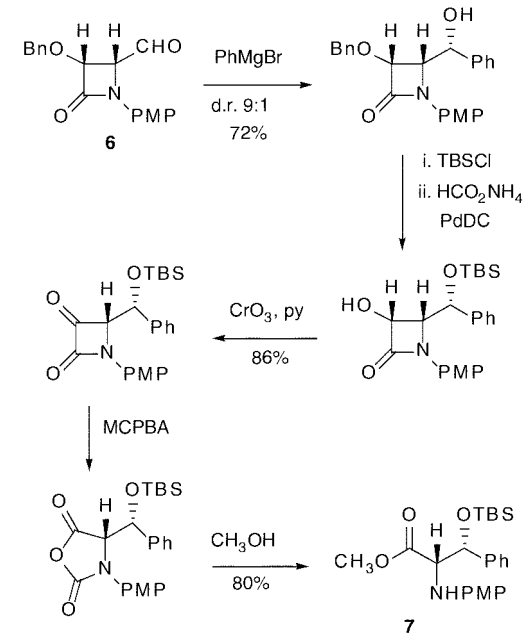
Scheme 8

3.1.2 Synthesis of α-amino acid derivatives As the defining subunit of peptides and proteins, amino acids play a central role in chemistry and biology. In addition to the need for large-scale preparation of proteinogenic amino acids, there is an ever increasing demand for nonproteinogenic amino acids. Many of these are important components of therapeutic drugs and compounds of medicinal interest such as antibiotics, decarboxylate inhibitors, aminotransferase inhibitors, protease inhibitors and anticancer agents.

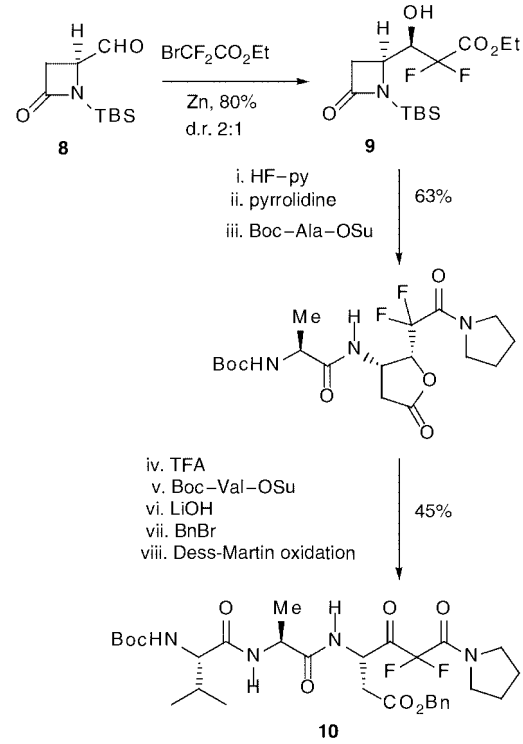
Palomo *et al*. have devised a route to an activated form of the (2*S*,3*R*)-β-hydroxyphenylalanine fragment commonly found in complex α-amino acids, starting from the 4-oxoazetidine-2-carbaldehyde **6**. Key steps were the stereoselective addition of phenylmagnesium bromide and the Baeyer–Villiger oxidation of an azetidine-2,3-dione to give a *N*-carboxy anhydride, which after coupling with methanol produced the α-amino acid derivative **7** (Scheme 9).[17]

3.1.3 Synthesis of β-amino acid derivatives The 4-oxoazetidine-2-carbaldehyde **8** has been reported to react smoothly with ethyl bromodifluoroacetate under Reformatsky reaction conditions, but with poor diastereoselectivity. The zinc-promoted reaction of this enantiomerically pure β-lactam aldehyde afforded the crystalline epimeric alcohols in a 1:2 ratio and in at least 94% enantiomeric purity. The relative stereochemistry of the major product is the same as that for the reaction of $BrZnCF_2CO_2Et$ with acyclic α-amino aldehyde derivatives (*e.g*., Boc-L-leucinal). The major isomer **9** could be separated by chromatography and was employed for the preparation of the peptide **10**, a protease inhibitor (Scheme 10).[18]

In another study, the 4-formyl-β-lactam **6** served as the starting material in the preparation of the bestatin side chain **11**. The required α-hydroxy β-amino acid derivative could be obtained by Grignard reaction, followed by conversion of the alcohol into the bromide and further radical reduction and ring opening (Scheme 11).[19]

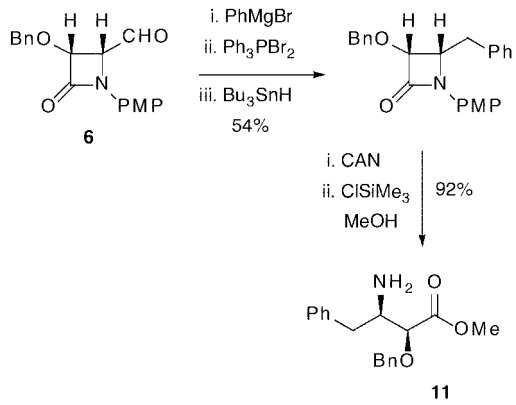


Scheme 9



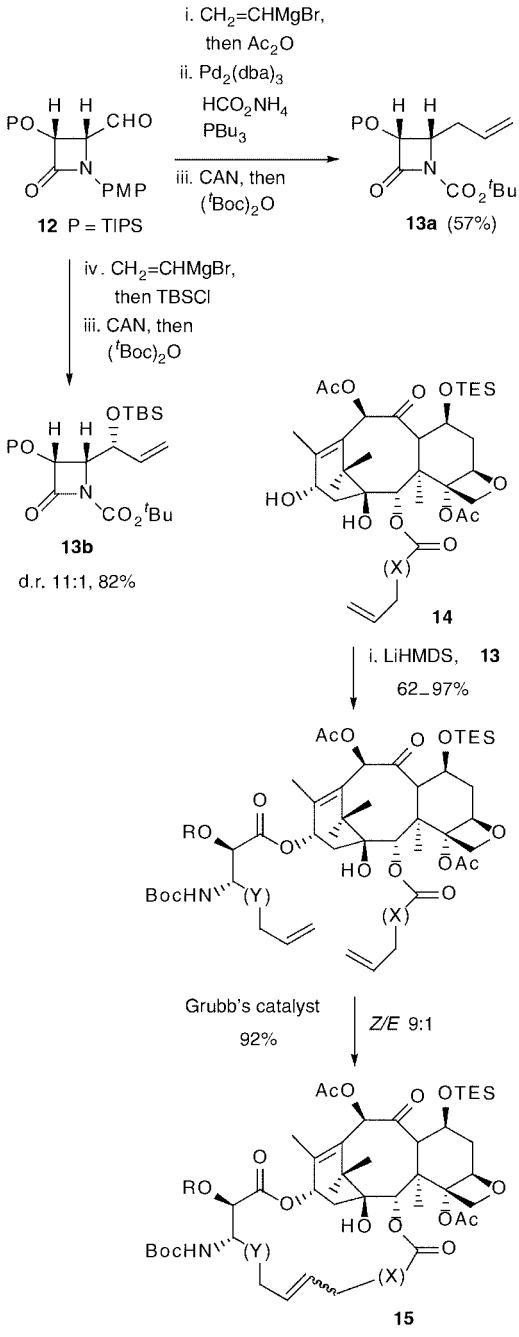
Scheme 10

Ojima *et al.* have described the use of 4-oxoazetidine-2-carbaldehydes for the syntheses of novel cytotoxic macrocyclic taxoids, according to the synthetic route illustrated in Scheme 12. Thus, the reaction of 4-formyl-β-lactam **12** with vinylmagnesium bromide followed by *in situ* protection of the resulting alcohol with acetic anhydride gave an ester, which was subjected to hydrogenolysis to achieve a 4-allyl-β-lactam. Reaction of **12** with the same Grignard reagent, followed by protection of the resulting alcohol as the TBS ether, afforded the corresponding β-lactam. After *N*-dearylation and protection of the resulting free NH with $(^tBoc)_2O$, the β-amino acid taxol side chain precursors **13** were obtained. The ring-opening coupling of alkenyl-β-lactams **13** promoted by lithium hexamethyldisilazane with C-2-alkenoylbaccatins **14** and subsequent ring-



Scheme 11

closing metathesis[20] proceeded to afford the 17-membered macrocyclic taxoids **15**.[21]

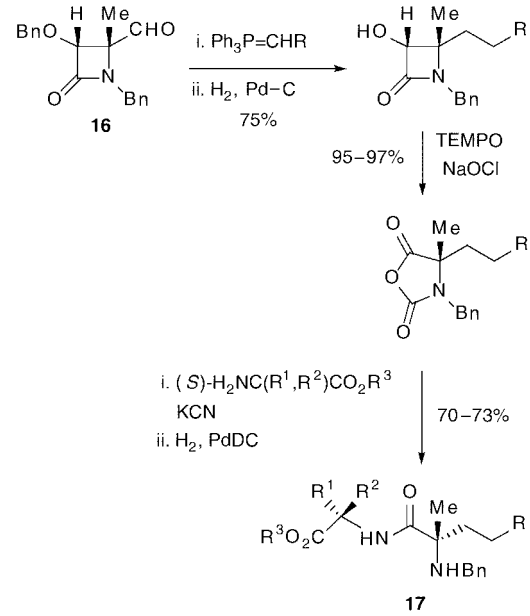


Scheme 12

3.2 Reactions involving C=C formation

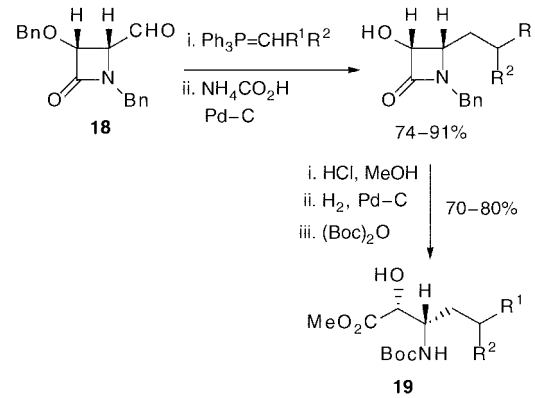
The relatively high stability of 4-oxoazetidine-2-carbaldehydes and their ability to undergo reactions with ylides under very mild conditions, in combination with another of their modes of reactivity has led to their application to the synthesis of important building blocks and natural products.

3.2.1 Synthesis of α-amino acid derivatives The 4-oxoazetidine-2-carbaldehyde **16** has been used as a synthetic intermediate for the preparation of dipeptide segments containing α,α-disubstituted α-amino acids.[22] The synthesis starts by using the Wittig reaction followed by hydrogenation of the corresponding olefinic products with concomitant debenzylation. The treatment of the resulting α-hydroxy β-lactams with sodium hypochlorite and a catalytic amount of TEMPO, leads to the formation of *N*-carboxy anhydrides (NCAs) in a straightforward manner. The ring opening of NCAs by α-amino acid esters catalyzed by potassium cyanide, gave after hydrogenation the dipeptides **17** (Scheme 13).



Scheme 13

3.2.2 Synthesis of β-amino acid derivatives The preparation of β-alkyl isoserines, constituents of biologically significant compounds, was accomplished by Palomo *et al.* in five-steps from the 4-formyl-β-lactam **18** as outlined in Scheme 14. The

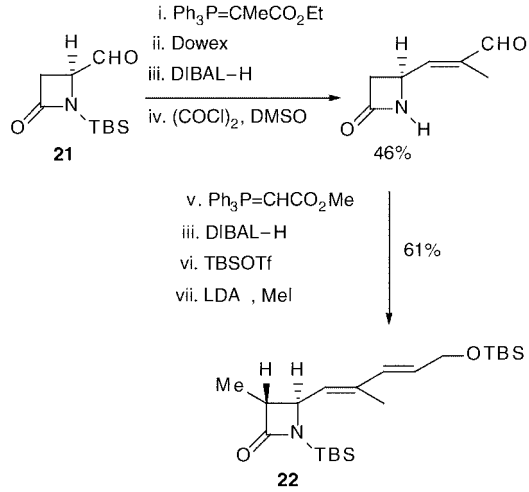


Scheme 14

carbaldehyde moiety can be transformed into alkyl chains *via* Wittig reaction. One-pot double bond reduction and *O*-

deprotection with subsequent ring opening of the resulting β-lactams provided β-amino acid derivatives **19**.

3.2.3 Synthesis of natural products bearing β-amino acid units A good example of the synthetic potential of the 4-oxoazetidine-2-carbaldehyde moiety is the preparation of advanced intermediates of the antitumor antibiotic lankacidin C described by Thomas *et al.*[23] The enantioselective total synthesis of (−)-lankacidin C **20**, reported by Kende *et al.*, further illustrates the usefulness of the 4-formyl-β-lactam framework for the construction of complex molecules.[24] The C(1)–C(8) segment of lankacidin C was in turn available from 4-oxoazetidine-2-carbaldehyde **21** as shown in Scheme 15. Two



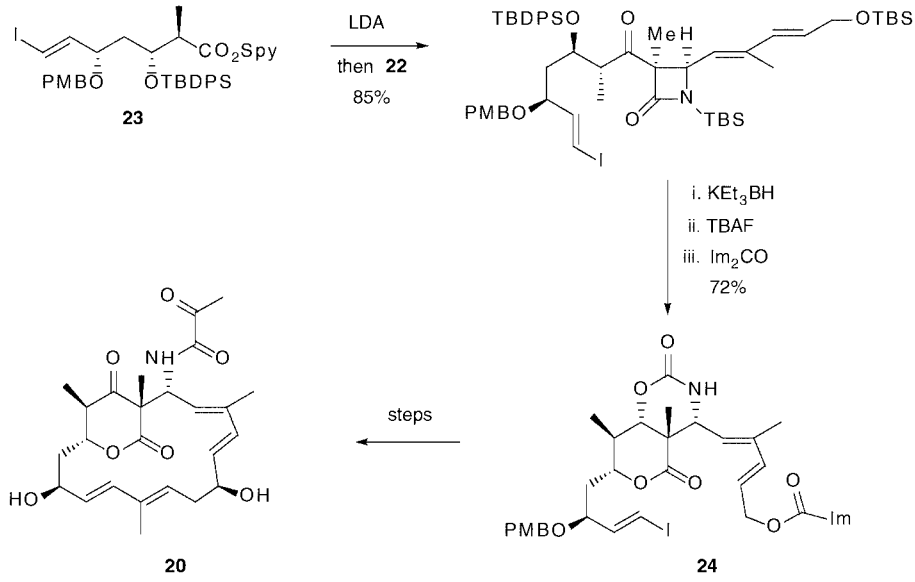
Scheme 15

successive modified Wittig sequences,[25] reduction, silylation, and finally *C*-methylation produced the C(1)–C(8) synthon **22**, which was coupled with the C(12)–C(18) fragment **23** to give a β-ketolactam. This β-lactam afforded compound **24** after diastereoselective reduction, deprotection, *N*-to-*O* transacylation, and subsequent protection of the hydroxy amine. The total synthesis was accomplished after a few more steps including a key macrocyclization (Scheme 16).

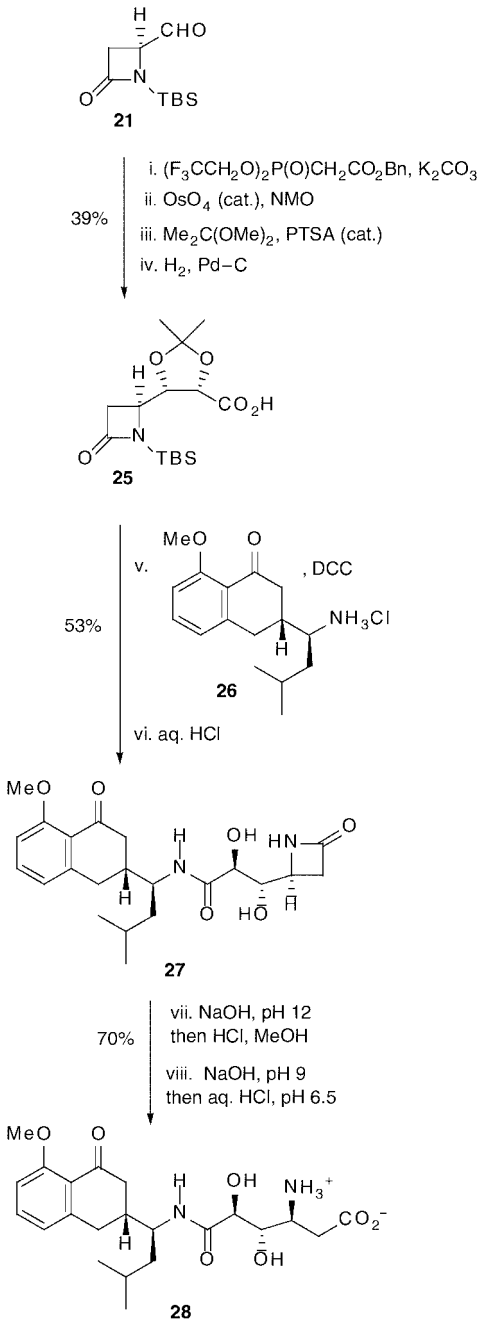
Work in Thomas' laboratory has shown that the aldehyde **21** could also be transformed into the natural dipeptide AI-77,[26] which displays activity against stress ulcers in rats yet is also non-central suppressive, non-anticholinergic and non-antihistaminergic. The synthesis starts with a phosphonate condensation, followed by stereoselective *cis*-dihydroxylation, protection and hydrogenolysis, achieving the acetonide β-lactam **25**. The 3,4-dihydroisocoumarin fragment **26**, obtained by chelation controlled addition of a lithiated 2-alkoxy-6-methylbenzoate heterocyclic synthetic equivalent to a protected leucinal, was coupled with the acid **25** which was deprotected to give the dihydroxyalkylazetidinone **27**. β-Lactam ring cleavage with concomitant lactonisation, followed by selective hydrolysis of the γ-lactone ring gave AI-77-B methyl ether **28** (Scheme 17).

3.2.4 Synthesis of an analogue of the cephalosporins The effect of nuclear substitution of the cephalosporin ring system has been widely investigated and a carbacephalosporin (*Lorabide* or *Loracarbef*) is used medicinally.[27] Accordingly, the development of practical asymmetric synthesis of the carbacephalosporin nucleus is a worthwhile objective. A route for the synthesis of the carbacephem nucleus starting from the 4-oxoazetidine-2-carbaldehyde **29** has been reported. 4-Formyl-β-lactam **29** was converted into the valuable β-keto ester intermediate **30**. The steps used in this transformation were homologation with a phosphorane, hydrogenation, oxidative *N*-protecting group cleavage, and dioxenone opening. By simply combining the dioxenone-β-lactam with an equivalent of benzyl alcohol in refluxing toluene, the product **30** was obtained.[28] Monocyclic **30**, after diazo transfer with tosyl azide, was submitted to the key cyclization step. The rhodium-catalyzed carbene insertion proved to be a sensitive reaction, but satisfactory results were obtained in refluxing alcohol-free chloroform using 1% $Rh_2(OAc)_4$. The resulting 3-hydroxycarbacephem was not isolated, but trapped *in situ* with triflic anhydride to give the compound **31**. Replacement of the triflate group by treatment with the *p*-nitrobenzyl carbamate of cysteamine provides an efficient way of incorporating the desired substituent. The synthesis of the carbacephem **32** was completed by cleavage of the benzyl moiety with aluminium trichloride and hydrogenolysis of the *p*-nitrobenzyl group (Scheme 18).[29]

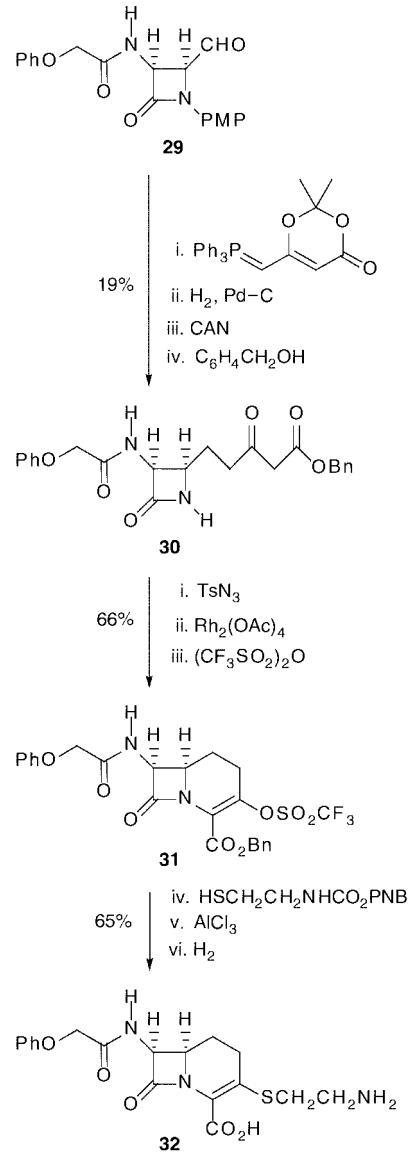
3.2.5 Synthesis of non-classical bicyclic β-lactams A stereoselective entry to fused bicyclic β-lactams **33** and **34** involving radical-mediated cycloisomerization of enyne-β-lactams has been developed (Scheme 19).[16] The double bond of these monocyclic 2-azetidinone precursors works as a radical



Scheme 16



Scheme 17



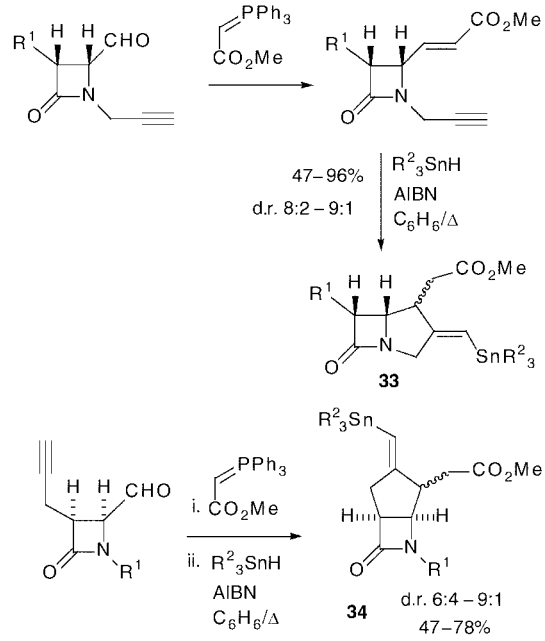
Scheme 18

acceptor and was obtained in some cases *via* Wittig olefination of the appropriate 4-oxoazetidine-2-carbaldehyde.

3.3 Cycloaddition reactions of C═N bonds derived from 4-oxoazetidine-2-carbaldehydes

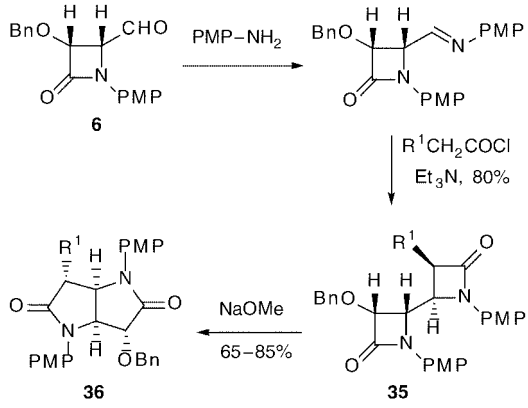
The high asymmetric induction observed for [2 + 2] and [3 + 2] cycloaddition reactions coupled with the possibility of further synthetic transformations has prompted a detailed investigation of imines and nitrones derived from 4-oxoazetidine-2-carbaldehydes.

3.3.1 Synthesis of fused bis-γ-lactams Interest in bis-γ-lactams arises because of the possibility of their cage-shaped structure which may make them receptors for metal cations.[30] Starting from enantiomerically pure 4-oxoazetidine-2-carbaldehyde **6**, sequential imine formation and ketene cycloaddition allowed the synthesis of differently substituted *cis,cis*-C4,C4′-



Scheme 19

bis-β-lactams **35**, which were obtained in all cases as a single diastereoisomer. Bis-lactams **35** smoothly rearranged to fused *trans,trans*-bis-γ-lactams **36** upon basic treatment (NaOMe–MeOH) in a totally stereoselective process (Scheme 20).[31] The

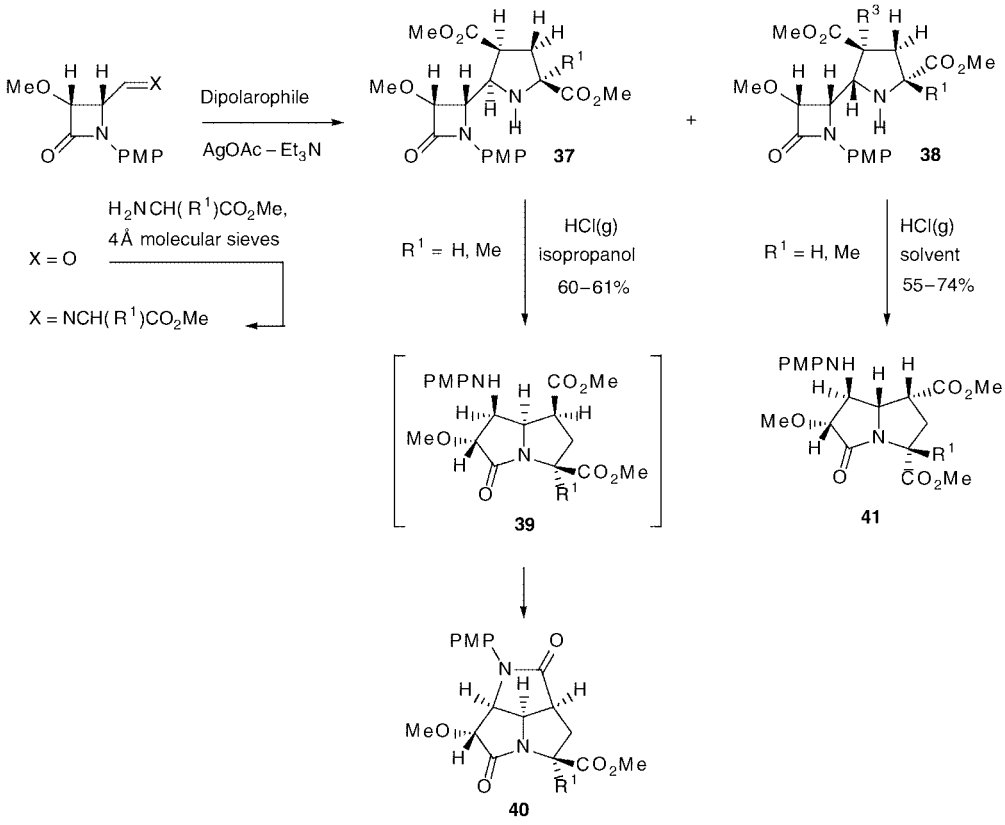


Scheme 20

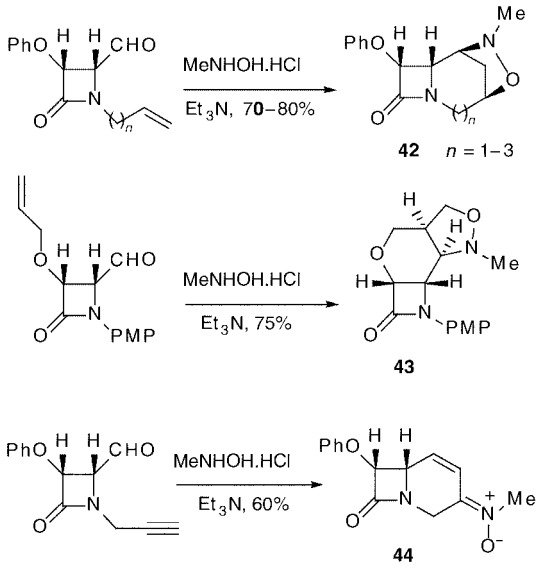
most likely pathway for the formation of bis-γ-lactams is the ring opening of bis-β-lactams **35**, by MeO^- to form an intermediate monocyclic 2-azetidinone anion, which cyclizes to the final products **36** by intramolecular ring opening followed by ring closure.

3.3.2 Synthesis of pyrrolizidines The structural and stereochemical complexity of natural products having the 1-azabicyclo[3.3.0]octane skeleton (pyrrolizidine alkaloids), coupled with their diverse and potent biological activities, make pyrrolizidine alkaloids as well as structurally related unnatural compounds attractive synthetic targets. The use of 4-oxoazetidine-2-carbaldehydes as substrates for addition reactions and cyclization processes, prompted Alcaide *et al.* to evaluate the combination of the 1,3-dipolar cycloaddition of 2-azetidinone-tethered azomethine ylides with rearrangement reactions on the 2-azetidinone ring as a route to complex pyrrolizidine alkaloids.[32] The 1,3-dipolar cycloaddition was achieved *via* metal ion catalysis at room temperature. Treatment of the aldimines with the appropriate dipolarophile in the presence of AgOAc–Et_3N, gave, in reasonable diastereoselectivity (30–90% d.e.), mixtures of cycloadducts **37** and **38**, which could be easily separated by gravity flow chromatography. The methodology capitalizes on a HCl(g) promoted reaction of pyrrolidinyl-β-lactams **37** and **38**, which after selective bond cleavage of the four-membered ring, followed by a rearrangement under the reaction conditions afforded bi- and tricyclic pyrrolizidine systems **40** or **41** (Scheme 21). The overall transformation must be driven by relief of the strain associated with the four-membered ring, on forming more stable polycyclic systems. The relative *anti*-disposition of the ester and amine moieties in bicycles **41** must be responsible for the failure of the third cyclization to occur, preventing the formation of a highly strained tricyclic system. By contrast, the initially formed bicyclic pyrrolizidines **39**, bearing a *syn*-disposition of the ester and amine moieties, evolves to the more stable tricycles **40**.

3.3.3 Synthesis of bi- and polycyclic β-lactams The intramolecular nitrone–alkene cycloaddition reaction using 2-azetidinone-tethered alkenylaldehydes as starting materials has been recently introduced as an efficient route to prepare tricyclic β-lactams **42** and **43**. The regioselectivity of this cycloaddition deserves special mention, because depending on the alkene substituent position at the tethered alkenylaldehyde, the regioselectivity was tuned from bridged (**42**) to fused (**43**) tricyclic compounds (Scheme 22). Within this context the same authors reported that the reaction between 2-azetidinone-tethered alkynyl aldehydes and *N*-methylhydroxylamine is a direct access to bicyclic β-lactams such as **44** (Scheme 22).[33] The formation of compound **44** is the result of a formal reverse-Cope elimination reaction of the intermediate α-hydroxyhydroxylamine as shown in Scheme 23. Retro-Cope cyclization of the initially formed carbinolamine gives a bicyclic *N*-oxide



Scheme 21



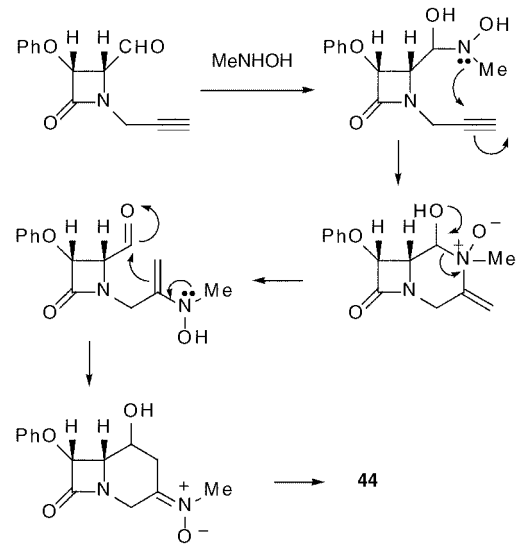
Scheme 22

which ring opens to a *N*-hydroxyenamine aldehyde. Reacting as a *C*-nucleophile, the above compound provides a bicyclic hydroxynitrone, and finally, the α,β-unsaturated nitrone **44** by dehydration.

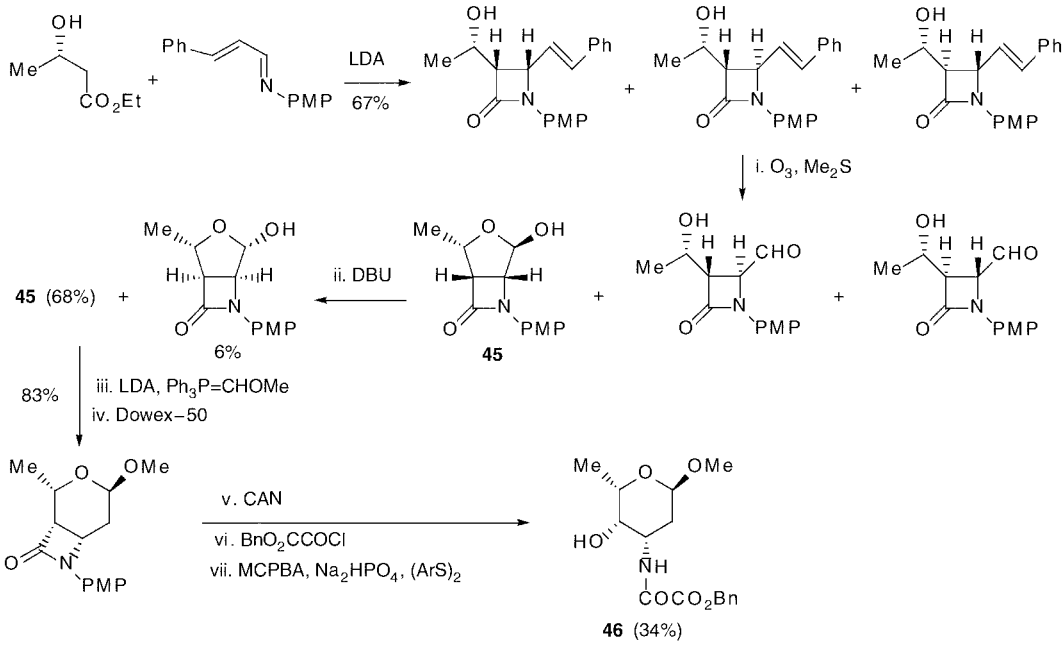
3.4 Reactions involving C–O formation

The preparation of aminosugars from β-lactams is a little explored process. Hart *et al*. have accomplished the enantioselective syntheses of aminosaccharides, analogs of daunosamine.[34] This strategy involves a key compound, the lactol **45**,as outlined in Scheme 24. The ester–imine condensation provided a mixture of *cis*- and *trans*-β-lactams. Although the *cis*-isomer could be separated from the *trans*-compounds, it was more convenient to continue with the mixture. Sequential treatment of the mixture of *cis*- and *trans*-β-lactams with ozone and dimethyl sulfide gave hemiacetal **45** and a mixture of *trans*-4-oxoazetidine-2-carbaldehydes. By treatment with DBU the above mixture was converted mainly into compound **45**. The use of DBU serves to epimerise the chiral centre α to the aldehyde in addition to forming the hemiacetal. Subsequent Wittig reaction, cyclization of the resulting vinyl ether, oxidative removal of the *p*-methoxyphenyl group, acylation and buffered peracid treatment completed the synthesis of the aminosaccharide **46** (Scheme 24).

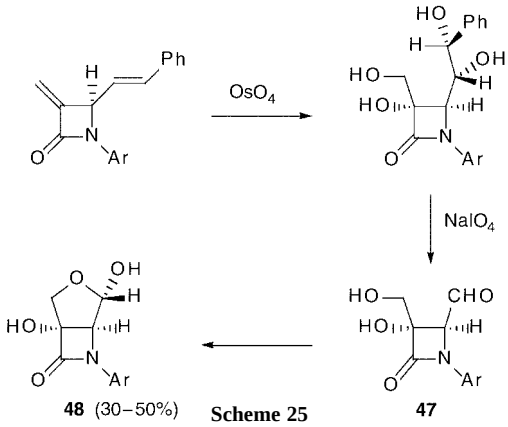
In another study, new bicyclic β-lactams were obtained *via* a dihydroxylation–oxidation process from α-alkylidene derivatives, 4-oxoazetidine-2-carbaldehydes **47** being key intermediates.[35] The authors deduced that: (i) the methylene group is hydroxylated faster than the styryl group; (ii) the dihydroxylation of both olefinic groups can be achieved in large part at longer hydroxylation time; (iii) cleavage of the diol moiety derived from styryl group on C4 is faster than that from the methylene group on C3. Attack of OsO_4 on the methylene group at the less hindered side of the double bond give an intermediate diol derivative. This diol functionality directs hydroxylation of the styryl group in a later stage to form stereoselectively a tetraol. After cleavage of one of these diol groups, the corresponding hemiacetal could be formed by intramolecular attack of the γ-hydroxy group on the aldehyde function in compound **47**. Scheme 25 summarizes this procedure for making β-lactam–furan hybrids **48**.



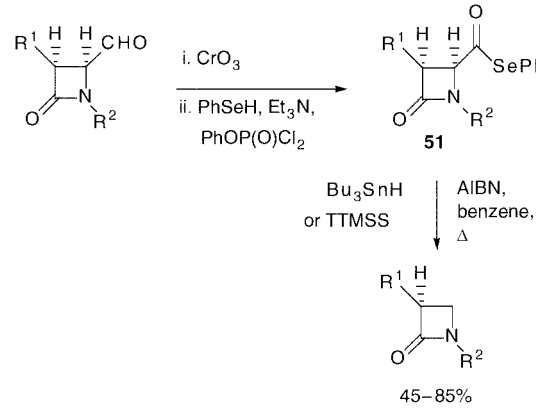
Scheme 23



Scheme 24



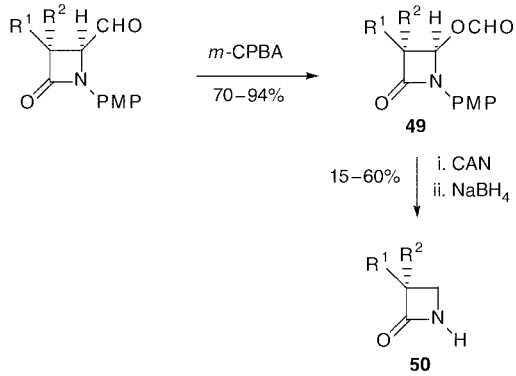
Scheme 25



Scheme 27

3.5 Synthesis of 4-unsubstituted β-lactams

The biological activity of nocardicins and monobactams against Gram negative organisms has highlighted the importance of developing efficient methods for the preparation of monocyclic 4-unsubstituted β-lactams. Additionally, other relevant monocyclic β-lactams lacking substituents at position 4 of the 2-azetidinone ring such as tabtoxin, and pachystermines have been isolated from natural sources. Among the different methods for the synthesis of this particular type of monocyclic β-lactam, the use of 4-formyl-β-lactams has resulted in two different entries to C4-unsubstituted β-lactams.[36] The first route is based on the Baeyer–Villiger oxidation of 4-oxoazetidine-2-carbaldehydes followed by *N*-deprotection and reduction of the resulting 4-(formyloxy)-2-azetidinones **49**, to give *NH*-β-lactams **50** (Scheme 26). The second strategy uses the reductive radical decarbonylation of 4-phenylselenocarbonyl-β-lactams **51**, easily available from 4-oxoazetidine-2-carbaldehydes (Scheme 27).



Scheme 26

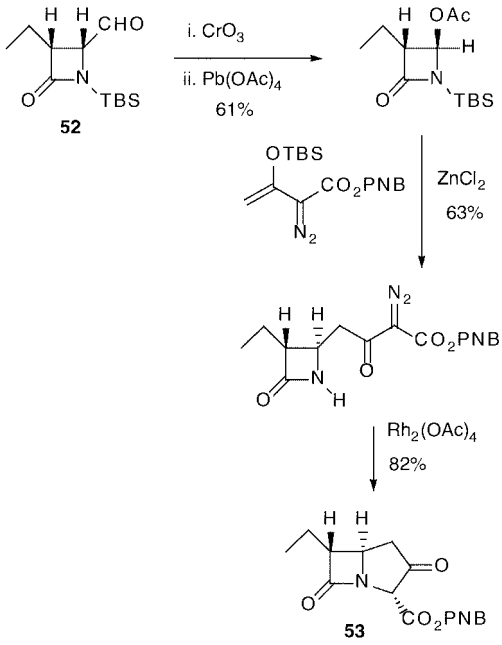
3.6 Oxidation and reduction reactions

3.6.1 Synthesis of carbapenems PS-5 and thienamycin Here we highlight some of the efforts that have been devoted towards developing this classical β-lactam antibiotic structure starting from 4-oxoazetidine-2-carbaldehydes. Within this context, the formal total synthesis of carbapenem (+)-PS-5 developed by Hart and Lee is notable. Thus, 4-oxoazetidine-2-carbaldehyde **52** was submitted to Jones and lead tetraacetate oxidations. Treatment of the obtained β-lactam with a diazo enol ether resulted in addition to the *in situ* formed acylimminium ion. Formation of the rhodium carbene and insertion into the N–H bond was promoted by $Rh_2(OAc)_4$, to afford the bicyclic compound **53**, an immediate precursor of carbapenem (+)-PS-5 (Scheme 28).[37] George *et al.* have described a formal total synthesis of (+)-thienamycin by preparing the key precursor 4-acetoxy-β-lactam **54** from a 4-oxoazetidine-2-carbaldehyde, as outlined in Scheme 29.[38]

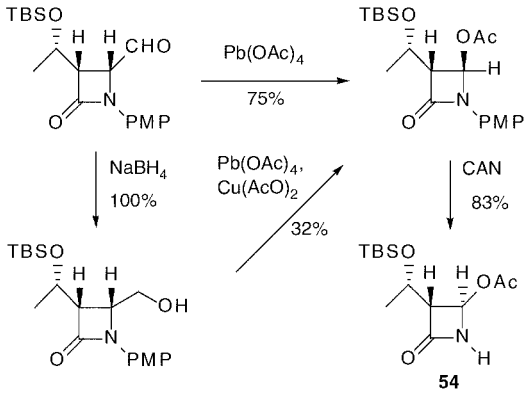
3.6.2 Synthesis of monobactams Since the discovery of the penicillin, the minimum structural features believed to be essential for antimicrobial activity in the β-lactams antibiotics have undergone considerable revision. Several natural monocyclic β-lactams have been shown to exhibit high anti-bacterial activity, and now it appears that the minimum requirement for biological activity is a suitable β-lactam ring or even γ-lactam ring.[39] Aldehyde **55** has been found to be a practical precursor to the protected amino azetidinone **56** that has been used for the synthesis of the monobactam Ro 17-2301 **57** (Scheme 30).[40] After sodium borohydride reduction of the formyl moiety in 4-oxoazetidine-2-carbaldehyde **55** and upon subjecting the resulting azetidinone to dissolving metal reduction, two significant events were facilitated, namely, the 4-phenyloxazolidinone auxiliary removal and the *N*-benzyl bond cleavage. Subsequent benzoylation of the free amine group achieved the key compound **56**. In a similar fashion, the 4-formyl-β-lactam **58** after reduction and oxidative dearylation yielded compound **59** which is an intermediate of the antibiotic carumonan **60** (Scheme 31).[41]

3.6.3 Synthesis of 2-oxaisocephems and 2-isocephems Starting from 4-oxoazetidine-2-carbaldehyde **61** the 2-oxaisocephem **62** has been prepared by standard chemistry, and positively evaluated for antimicrobial activity against *Staphylococcus aureus* (Scheme 32).[42] The key step in the above sequence is the formation of the dihydropyran ring fused to the 2-azetidinone. This transformation was achieved *via* allylic bromination with concomitant ring closure across the hydroxy and methanosulfonate moieties. Similarly, the 2-isocephem **64** which displayed *in vitro* and *in vivo* activity against *Pseudomonas aeruginosa* was obtained from an intermediate β-lactam aldehyde **63** (Scheme 33).[43]

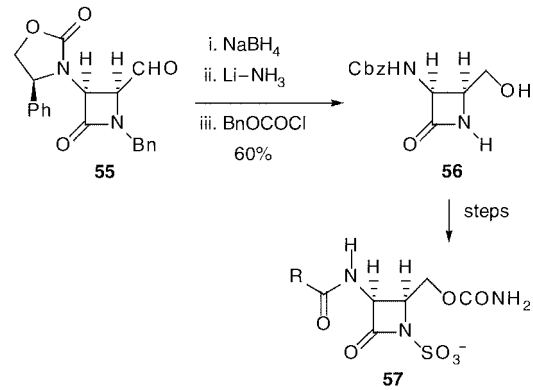
3.6.4 Synthesis of diazolidinones A new example demonstrating that 4-oxoazetidine-2-carbaldehydes are useful chiral precursors for the asymmetric synthesis of heterocycles is indicated in Scheme 34 by the transformation of a 4-formyl-β-lactam into the azaoxabicyclo[4.3.0]system.[44] First, the aldehyde **65** was converted to the corresponding 4-hydroxymethyl-β-lactam **66** by sodium borohydride reduction. Next, compound **66** was treated with excess sodium methoxide in methanol at refluxing temperature, obtaining the diazolidinone **67** as a single stereoisomer. A likely mechanism must involve the initial intramolecular attack of the alkoxide derived from 4-hydroxymethyl-β-lactam **66** onto the β-lactam carbonyl to cleave the four-membered ring, forming stereospecifically a



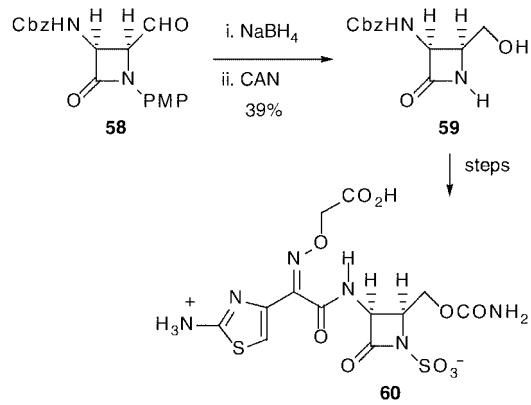
Scheme 28



Scheme 29



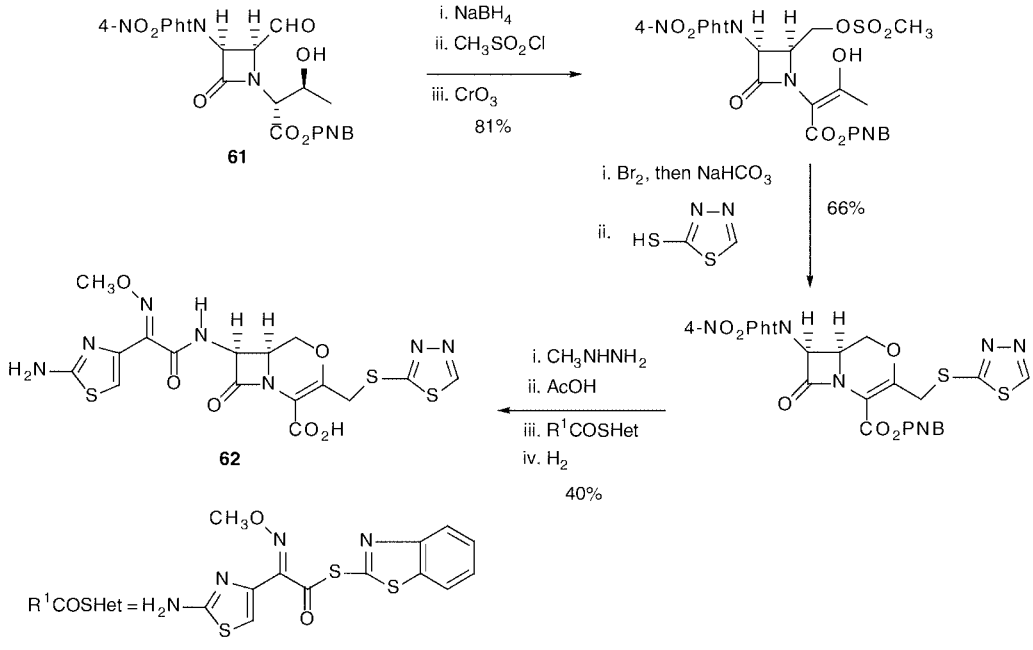
Scheme 30



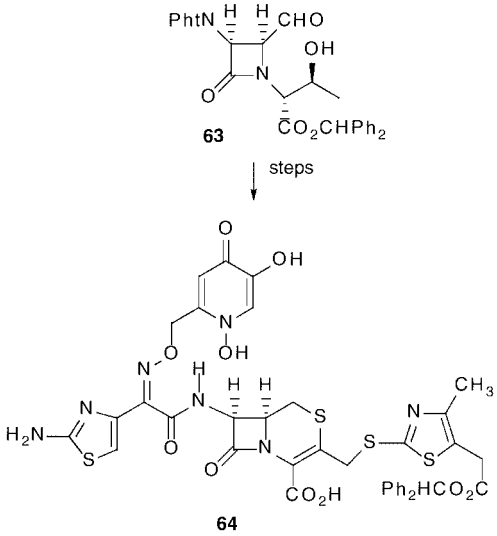
Scheme 31

lactone intermediate. Because the base is used in excess, the methoxide anion attacks the chiral oxazolidinone moiety to open the five-membered ring, generating a methyl carbamate. This intermediate compound undergoes lactone exchange to form a morpholinone, which finally gave bicyclic diazolidinone **67**.

3.6.5 Synthesis of pyrroles and pyrrolidines Recently, the usefulness of 4-oxoazetidine-2-carbaldehydes in the stereocon-

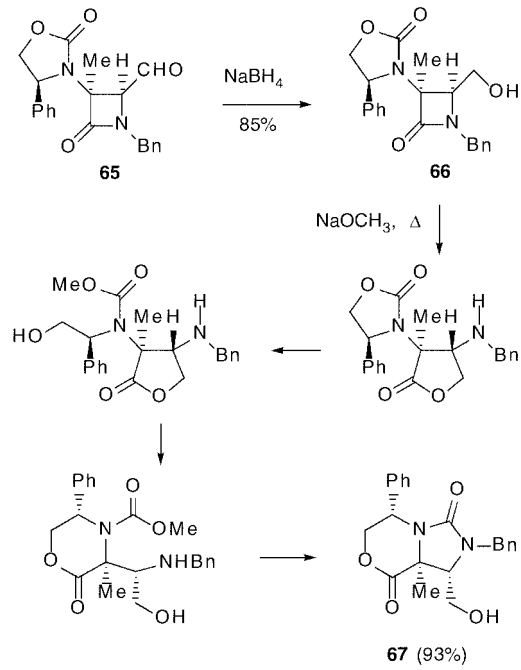


Scheme 32



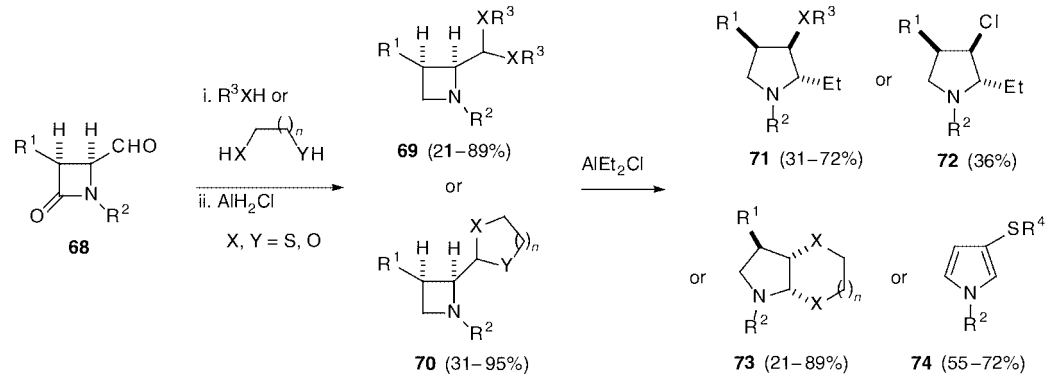
Scheme 33

trolled synthesis of aza-heterocycles has been demostrated. The starting 4-formyl-β-lactams **68** were converted by standard chemistry to the corresponding acetal azetidines **69** or **70**, which undergo rearrangement reactions promoted by diethylaluminium chloride. This Lewis acid promoted process can be used to prepare different types of functionalized heterocycles such as monocyclic pyrrolidines **71** and **72**, fused bicyclic pyrrolidines **73**, and pyrroles **74** (Scheme 35).[45] Formation of fused pyrrolidines **73** can be rationalized through initial coordination of the lone electron pair of nitrogen to $AlEt_2Cl$ to give a coordinate species. This coordination should promote the C2–N1 bond breakage to form a zwitterion. The acetal moiety promotes the conversion of this intermediate to a new carbocation, which is, in turn, trapped intramolecularly by the

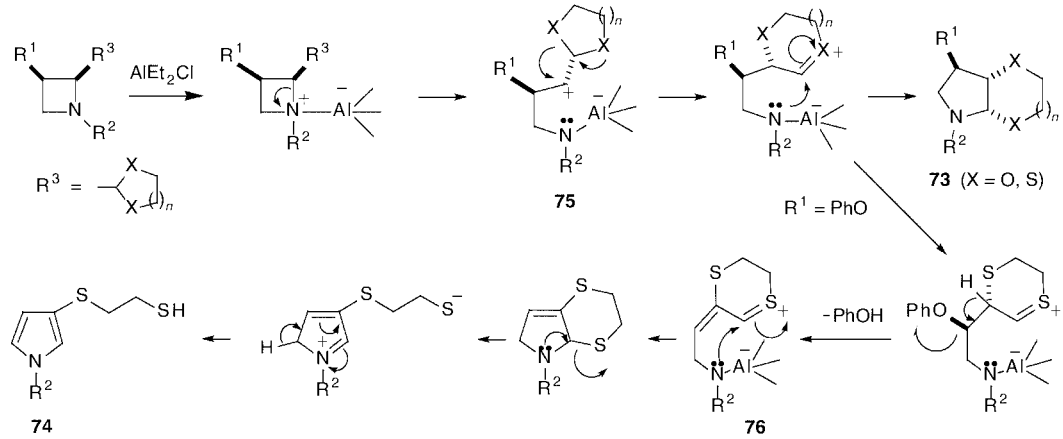


Scheme 34

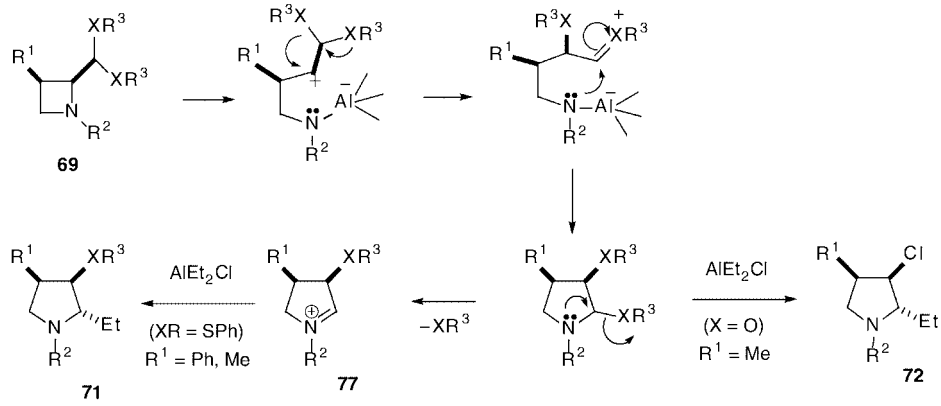
nitrogen atom, to yield the double rearranged product **73**. The stereochemical result can be tentatively interpreted through species **75**, which suffers a rearrangement, and the nucleophilic moiety being delivered from the less hindered face (Scheme 36). The strong preference for the rearrangement of the five membered ring in compounds **70** may be due to the increased stability of the new carbocation formed. The formation of pyrroles **74** can be illustrated following Scheme 36. The main



Scheme 35



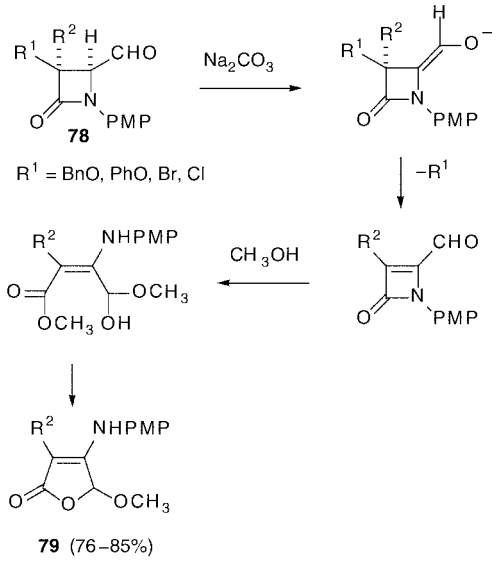
Scheme 36



Scheme 37

difference from the mechanistic proposal for the formation of fused pyrrolidines **73** is the elimination of a molecule of phenol to give an intermediate **76**. The carbocation **76** evolves to give pyrroles **74**. For monocyclic compounds **71** and **72** the XR^3 group at C2 in the former pyrrolidine is eliminated to give an iminium salt **77**, the alkyl moiety being delivered from the organometallic reagent on the less hindered face at the iminium cation (Scheme 37). Azetidines **69** should evolve into an intermediate bearing an oxygenated substituent at C3. This intermediate should be coordinated by another molecule of $AlEt_2Cl$ with further substitution for a chlorine atom, yielding the chloropyrrolidine **72**.

3.6.6 Rearrangement processes on 4-oxoazetidine-2-carbaldehydes The examples to date accounting for a direct rearrangement reaction on 4-oxoazetidine-2-carbaldehydes were observed under basic treatment. The use of sodium carbonate in methanol has been described for the smooth conversion of 4-oxoazetidine-2-carbaldehydes **78** bearing alkoxy substituents at position C3 to cyclic enaminones **79**, related to enaminones derived from tetronic acid (Scheme 38). The



Scheme 38

formation of compounds **79** was rationalized through a tandem E1cB-elimination–rearrangement process of the initially generated enolate, followed by ring opening of the resulting strained 2-azetinone. Further intramolecular transesterification of the resulting hemiacetal enaminoester gives the final enamine lactones.[12] The above results showed that a carbonyl group able to stabilize a negative charge at C4 position, and a good leaving group on C3, are necessary for the process to occur.

4 Conclusion

The chemistry summarized in this review shows that 4-oxoazetidine-2-carbaldehydes, prepared in enantiomerically pure form from readily available precursors, are useful chiral building blocks for a wide variety of diastereoselective C–C, C–O and C–N bond forming reactions. Besides, the direct one-pot generation of fused nitrogen heterocyclic systems from the nitrogen framework of 4-formyl-β-lactam derivatives has been achieved by selective bond breakage and rearrangement. Alternatively, the conversion of 4-oxoazetidine-2-carbaldehyde derivatives into functionalized open-chain products has been achieved by ring opening of the β-lactam.

The versatile reactivity of the 4-oxoazetidine-2-carbaldehyde moiety has resulted in their continued use in the synthesis of a wide range of substances of biological interest. In this context, classical and non-classical bi- and polycyclic β-lactams, different kinds of heterocycles, alkaloids, nonproteinogenic α- and β-amino acids, amino sugars, taxoids, and complex natural products are representative examples.

Further developments in the area of 4-oxoazetidine-2-carbaldehydes at an academic as well as industrial level are likely, and we believe that the interest in these valuable synthetic intermediates will continue to increase.

5 Acknowledgements

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6 References

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