Tetrahedron 67 (2011) 1989–2012

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Tetrahedron report number 932

Synthesis and reactivity of spiro-fused β-lactams

Girija S. Singh [a,*], Matthias D'hooghe [b], Norbert De Kimpe [b,*]

[a] Chemistry Department, University of Botswana, Gaborone, Botswana
[b] Department of Sustainable Organic Chemistry and Technology, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium

ARTICLE INFO

Article history:
Received 10 December 2010
Available online 13 January 2011

Contents

1. Introduction

2-Azetidinones, commonly known as β-lactams, are the key structural motifs in the most widely used class of antibiotics, i.e., β-lactam antibiotics, such as penicillins, cephalosporins, carbapenems, etc. The development of novel synthetic methodologies for the preparation of functionalised β-lactams and the screening of their biological activity has occupied a pivotal position in medicinal chemistry for almost a century now.[1] The increasing number of resistant pathogens and the discovery of β-lactamase inhibition properties of β-lactams gave further impetus to these studies. Besides being antibacterial agents, various other biological activities, such as cholesterol absorption inhibition, inhibition of different kinds of enzymes and antitubercular, hypoglycemic and anticancer activity, have been discovered to be associated with β-lactams.[2,3] In the literature, much attention has been paid to the study of the synthesis, chemistry and biological activity of either monocyclic or condensed bicyclic β-lactams, which is evident from many review articles published in this field.[4] On the other hand, the synthesis and chemistry of C3 and C4 spiro-fused 2-azetidinones (Fig. 1) has grown steadily over the years, and significant development has been made during the last two decades.

Many new synthetic methods focussing on the construction of the spiro-fused 2-azetidinone framework have been reported, which has resulted in the synthesis of 2-azetidinones, spiro-fused

* Corresponding authors. E-mail addresses: singhgs@mopipi.ub.bw (G.S. Singh), matthias.dhooghe@UGent.be (M. D'hooghe), norbert.dekimpe@UGent.be (N. De Kimpe).

0040-4020/$ – see front matter
doi:10.1016/j.tet.2011.01.013

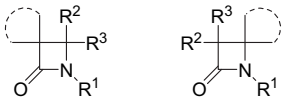


Fig. 1. General representation of C3 and C4 spiro-fused 2-azetidinones.

to diverse types of carbocyclic and heterocyclic rings. The chemistry of spiro-fused 2-azetidinones has been explored for the synthesis of many biologically important compounds, such as the marine natural products, chartellines A–C **1**–**3** (Fig. 2), in which a spiro-fused β-lactam entity is embedded in a larger architecture.[5]

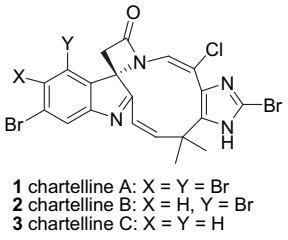


Fig. 2. Structure of chartellines A–C.

Furthermore, spiro-fused 2-azetidinones have been reported as cholesterol absorption inhibitors and poliovirus and human rhinovirus 3C-proteinase inhibitors (vide infra).

Since there is no review available in the literature focussing particularly on spiro-fused 2-azetidinones, the present report describes the synthesis, reactions and biological relevance of spiro-fused 2-azetidinones for the first time in a comprehensive way.

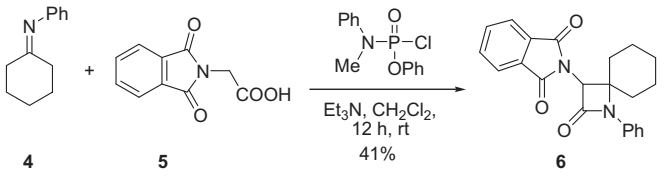
2. Synthesis of spiro-fused β-lactams

Synthetic approaches to spiro-fused 2-azetidinones can be classified mainly as ketene-imine cycloadditions, cyclisations of β-amino acids or β-functionalised amides and transformations of substituents connected to monocyclic 2-azetidinones. Many new spiro-fused 2-azetidinones are synthesised by transformation of functional groups/substituents present on other spiro-fused 2-azetidinones. Such methods are described under the section on 'Reactions of Spiro-fused β-Lactams'.

2.1. Cycloaddition reactions

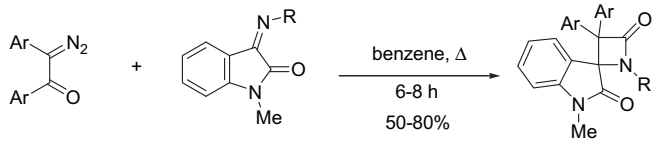
The cycloaddition of ketenes and imines, commonly known as the Staudinger [2+2] cycloaddition, is the most widely used and simple reaction for the synthesis of 2-azetidinones. Although it is often referred to as a [2+2] cycloaddition, it is now established that the reaction occurs in a stepwise manner.[6] The spiro-fused 2-azetidinone framework can be constructed by a Staudinger reaction of either a ketene in which the carbon–carbon double bond is originating from a ring structure (cyclic ketene) with a compound bearing an imino group, or a Staudinger reaction of a ketene with an imine in which the carbon–nitrogen double bond is originating from a ring structure (cyclic imine). Both alternatives have been employed in the literature, leading to two different types of spiro-fused 2-azetidinones. The reaction of a cyclic ketene with an imine affords C3 spiro-fused 2-azetidinones, whereas the reaction of an acyclic ketene with a cyclic imine forms C4 spiro-fused 2-azetidinones (Fig. 1). Furthermore, different methodologies are available for the generation of ketenes, such as the use of acid chlorides in the presence of a base, the direct use of acids in the presence of a suitable acid activator and a base, and thermal and photochemical decompositions of α-diazoketones. Recent years have also seen the application of greener technologies in the generation of ketenes. For example, the microwave-assisted, solvent-free cycloaddition reaction of chloroacetyl chloride with 3-indolylimines has been reported to form spiro-fused 2-azetidinones.[7]

2.1.1. Reactions of acyclic ketenes. The use of the Staudinger cycloaddition for synthesising spiro-fused 2-azetidinones dates back to the 1960s, when Bose and co-workers reported the reaction of *N*-phenyl imines derived from cyclohexanone, cycloheptanone and *N*-methylpiperidone with various acid chlorides, such as phenoxyacetyl chloride and azidoacetyl chloride, in the presence of tertiary amines to prepare spiro-fused 2-azetidinones.[8] Almost at the same time, Fahr and co-workers reported the reaction of fluorenone *N*-benzoyl hydrazone with diphenylketene to form a spiro-2-azetidinone.[9] In the early 1980s, *N*-cyclohexylidenebenzenamine **4** has also been used as a substrate by Shridhar and co-workers in a reaction with phthalimido acetic acid **5** to form spiro-fused 2-azetidinone **6** (Scheme 1).[10]



Scheme 1.

Furthermore, Mehrotra and Singh have reported the reaction of diphenylketene, generated from the thermal decomposition of 2-diazo-1,2-diphenylethanone, with two acenaphthaquinone imines, forming the corresponding spiro-β-lactams. This reaction established the high reactivity of an imino group, as compared to a carbonyl group (ketone) towards diphenylketene.[11] Benzil azine was isolated as a side product (3–5%) in this reaction. Later on, this reaction was extended to 3-*N*-aryliminobornan-2-ones and 3-arylimino-*N*-methylindolin-2-ones.[12] This study has been further elaborated utilising other diarylketenes, such as di-*p*-tolylketene and di-*p*-anisylketene.[13] Recently, the reactions of diarylketenes, obtained from 2-diazo-1,2-diarylethanones **7a**–**c**, with 3-alkylimino-*N*-methylindolin-2-ones **8** have been reported to yield spiro-fused 2-azetidinones **9** in good yields (Scheme 2), but with poor-to-moderate antibacterial activity.[13c]

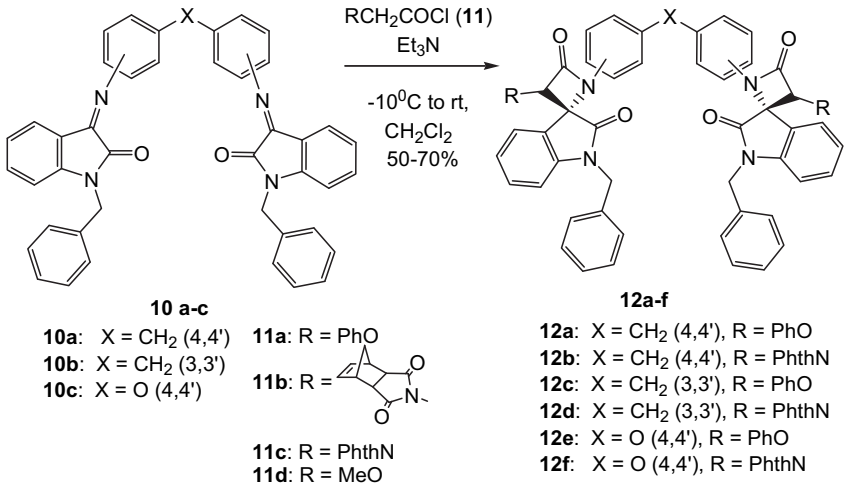


Ar = **a.** Ph, **b.** 4-MeC_6H_4, **c.** 4-$MeOC_6H_4$

R = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 4-$EtOC_6H_4$, $CHMe_2$, $CHPh_2$, CH(Me)Ph, *c*-Hex

Scheme 2.

In the recent past, the synthesis, reactivity and structure of isatin-derived, spiro-fused 2-azetidinones have been studied by many groups. For example, the synthesis of isatin-derived mono- and bis-spiroazetidinones using the Staudinger reaction has been reported by Jarrahpour and Khalili.[14] Bisimines **10a**–**c**, obtained from the reaction of *N*-benzylisatin with various diamines, were treated with different acyl chlorides **11a**–**d** in the presence of triethylamine to give spiro-fused bis-2-azetidinones **12a**–**f** in 50–70% yield (Scheme 3). 3-Arylimino-1-methyl-2-indolinones have also been reacted with dichloroketene to afford the corresponding spiro-fused 2-

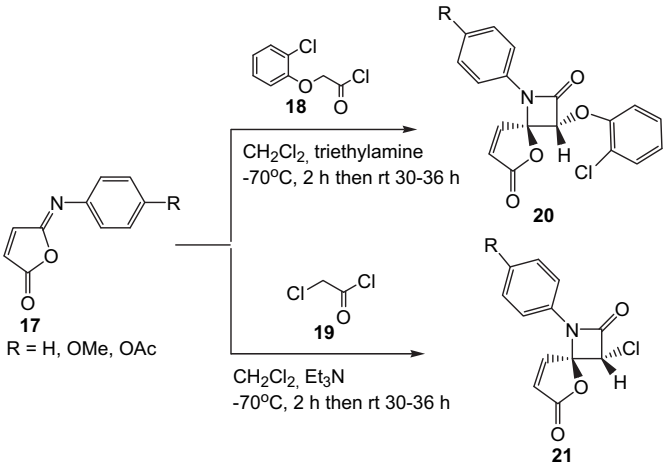


Scheme 3.

azetidinones.[15] The reaction of acyclic ketenes with cyclic imines derived from indolin-2,3-dione has been reported to form spiroazetidin-2-ones as well.[16,17]

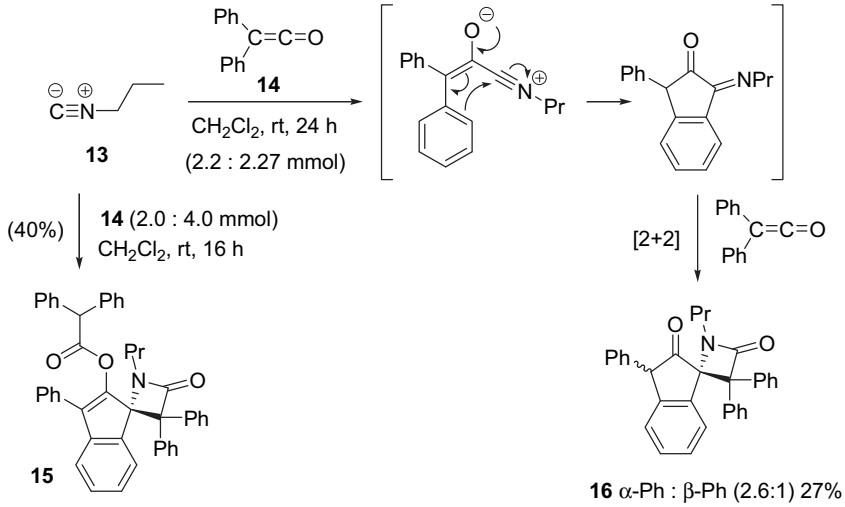
The reactions of a variety of isocyanides (such as **13**) with diphenylketene **14** have been shown to depend heavily on the concentration of diphenylketene. A high concentration of the ketene results in the formation of dioxolane derivatives, whereas the reactions follow an alternative path affording spiro-fused 2-azetidinones **15** and **16** at much lower concentrations, depending upon the molar ratios of isocyanide and diphenylketene used (Scheme 4).[18]

The Staudinger reaction of isomaleimides **17** with acid chlorides **18** and **19** has been reported by Barba and co-workers to afford spiro-fused 2-azetidinones **20** and **21**, respectively (Scheme 5).[19] The reaction, however, required a low temperature of −70 °C and a very long reaction time of over 30 h. The Staudinger reaction of *N*-substituted bicyclic imine **22** with acid chlorides **11a** and **23** led to the synthesis of spiro-fused 2-azetidinones **24** (Scheme 6). It was observed that the Staudinger reaction of imines derived from 7-oxanorbornenone with 2-alkoxyacetyl chlorides afforded the corresponding spiro-2-azetidinones with an *exo* geometry.[20] The synthesis of some sulfur-containing spiroazetidinones has been reported as well using chloroacetyl chloride and thioglycolic acid as the ketene precursor.[21]

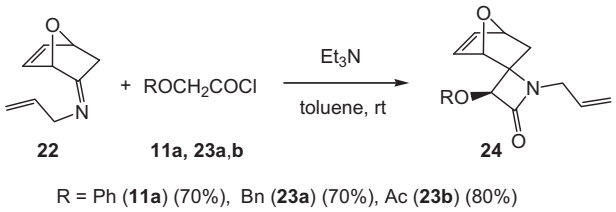


Scheme 5.

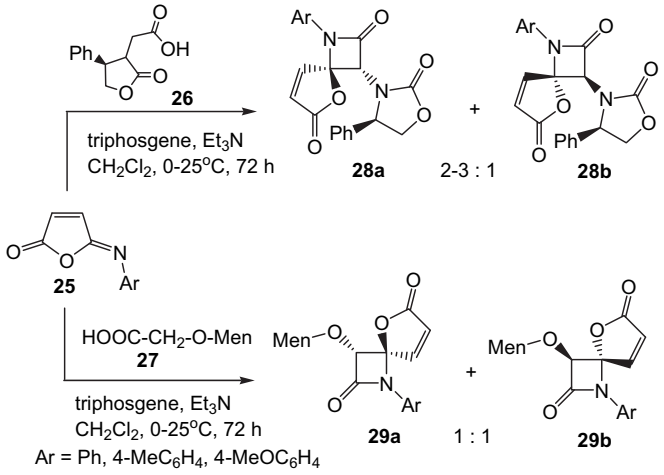
Rojas-Lima and co-workers have carried out the reactions of isomaleimides **25** with carboxylic acids **26** and **27** in the presence of triphosgene to synthesise spiro-fused 2-azetidinones **28** and **29**, respectively, as mixtures of diastereomers (Scheme 7).[22]



Scheme 4.



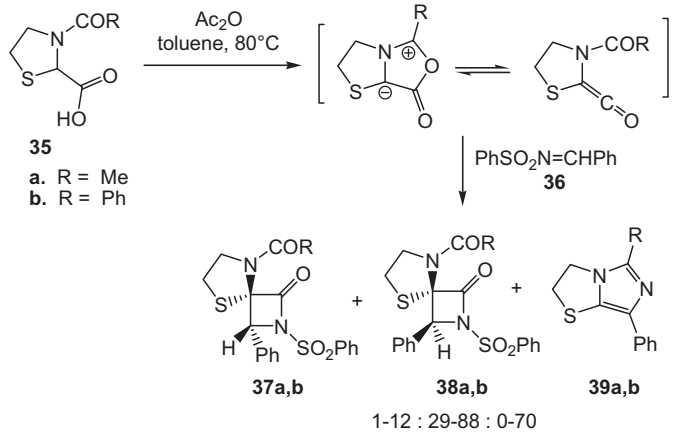
Scheme 6.



Scheme 7.

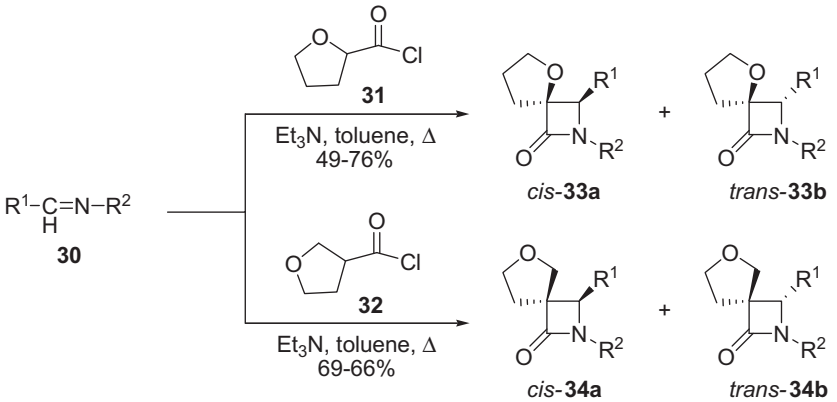
2.1.2. Reactions of cyclic ketenes. Recently, the reactions of cyclic ketenes with imines have drawn considerable interest for the synthesis of spiro-fused 2-azetidinones. L-Proline, thiazolidine-2-carboxylic acids, xanthene carboxylic acid and some other suitably substituted acetic acids have been explored as precursors of ketenes in the synthesis of C3 spiro-fused 2-azetidinones. Reactions of imines **30** with unsymmetrical cyclic ketenes, derived from 2-tetrahydrofuroyl chloride **31** and 3-tetrahydrofuroyl chloride **32**, in the presence of triethylamine afforded *cis*- and *trans*-2-azetidinones **33** and **34**, respectively (Scheme 8).[23] The nature of the substituents on the imines had a significant role in determining the stereochemical outcome of these reactions, as imines with at least one electron-withdrawing substituent favoured the formation of cis-isomers, whereas imines with at least one electron-withdrawing substituent favoured the formation of trans-isomers. According to preliminary ab initio calculations, the torquoelectronic effect was an important factor in determining the stereochemical course of the reaction. The experimental findings, however, showed steric and other electronic effects to be additionally important in determining the stereoselectivity of the reaction.

The reactions of heterocyclic carboxylic acids/chlorides, such as *N*-acylthiazolidine-2-carboxylic acids and the corresponding chlorides, oxazolidinecarboxylic acid and pyrrolidinecarboxylic acid, etc., have been explored by La Rosa and coworkers for the synthesis of spiro-fused 2-azetidinones.[24] The cyclodehydration of *N*-acylthiazolidine-2-carboxylic acids leads to the formation of *meso* ionic compounds and their tautomeric ketenes. The cycloaddition reaction of ketenes derived from *N*-acylthiazolidine-2-carboxylic acids **35a**,**b** with *N*-(phenylmethylene)benzenesulfonamide **36** led to the synthesis of diastereomeric spiro-2-azetidinones **37a**,**b** (minor) and **38a**,**b** (major) (Scheme 9).[24a] An imidazole **39a**,**b** was also formed in varying amounts when the reaction was carried out using acetic anhydride or DCC.



Scheme 9.

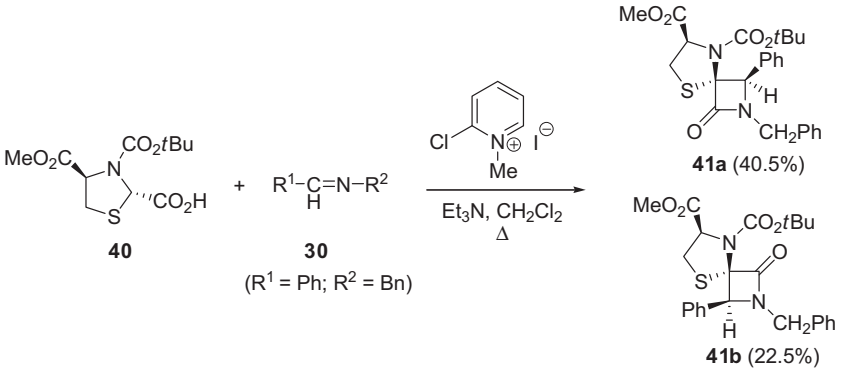
The quest for a method for exclusive formation of spiro-fused 2-azetidinones revealed Mukaiyama's reagent—in the presence of a base—as the most appropriate acid activator. The



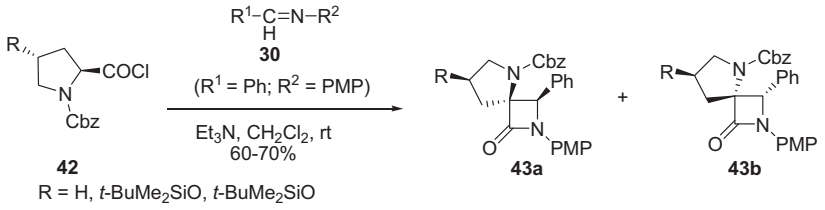
Scheme 8.

reaction of an equimolar quantity of thiazolidine carboxylic acid **40** with *N*-(benzylidene)benzylamine **30** (R^1=Ph; R^2=Bn) in the presence of 2-chloro-1-methylpyridinium iodide (Mukaiyama's reagent) and triethylamine in dichloromethane under reflux afforded spiro-2-azetidinones **41a** and **41b** as a 1.8:1 mixture of diastereomers (Scheme 10).[24e,25] The reaction proceeded with an excellent stereoselectivity, furnishing 2-azetidinones with a relative cis-disposition of the *N*-Boc group and the phenyl group (trans according to the Cahn–Ingold–Prelog priority rules).

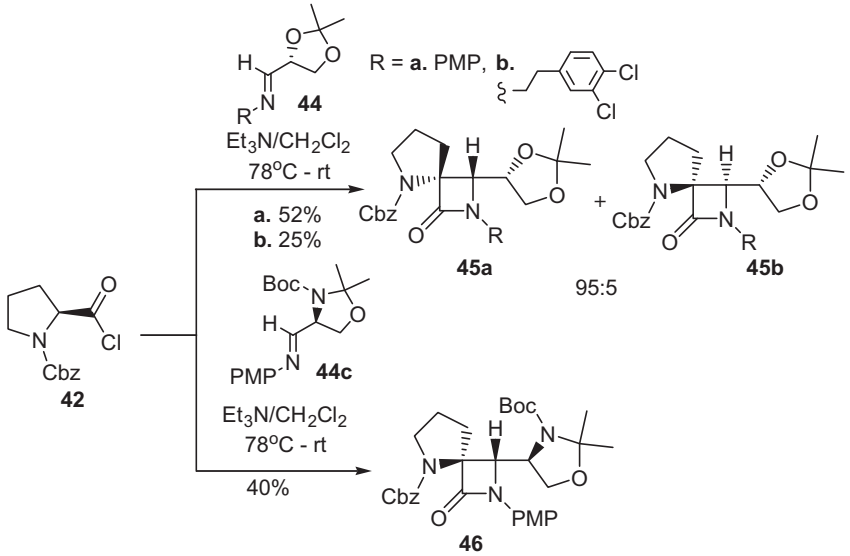
The reaction of the unsymmetrical cyclic ketenes derived from L-*N*-benzyloxycarbonylproline acid chlorides **42** with imine **30** (R^1=Ph; R^2=PMP) to form 4-phenyl spiro-2-azetidinones **43a**,**b** (Scheme 11) has been reported by Gonzalez and co-workers.[26] The products showed a cis relationship between the pyrrolidine nitrogen and the phenyl substituent at the C4-carbon of the azetidinone ring. This group then reported the reaction of acid chloride **42** with chiral imines **44a**,**b** and **44c** derived from glyceraldehyde acetonide and *N*-Boc-protected 1,3-oxazolidine-4-carbaldehyde, respectively (Scheme 12), to prepare the corresponding spiro-fused 2-azetidinones **45a**,**b** and **46** in enantiomerically pure forms.[26,27] The reaction of this acid chloride has also been performed using methyleneimines to produce spiroazetidinones.[28] *N*-Benzyloxycarbonyl-4-mesyloxylproline acid chloride **47** has been treated with *N*-(benzylidene) benzylamine **30** (R^1=Ph; R^2=Bn) to afford the spiroazetidinones **48a** and **48b** (Scheme 13).[29] The formation of these products was



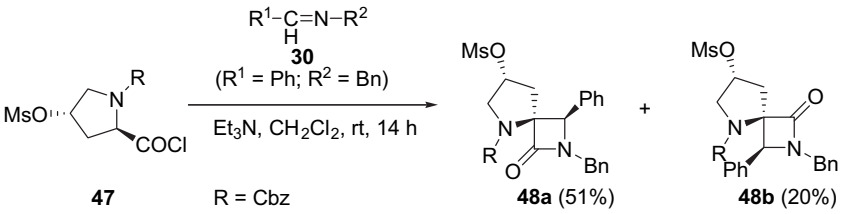
Scheme 10.



Scheme 11.



Scheme 12.

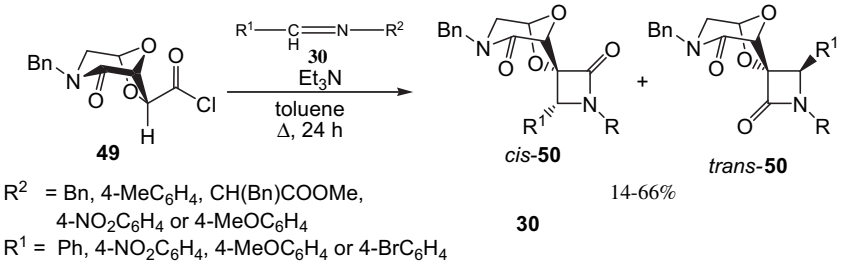


Scheme 13.

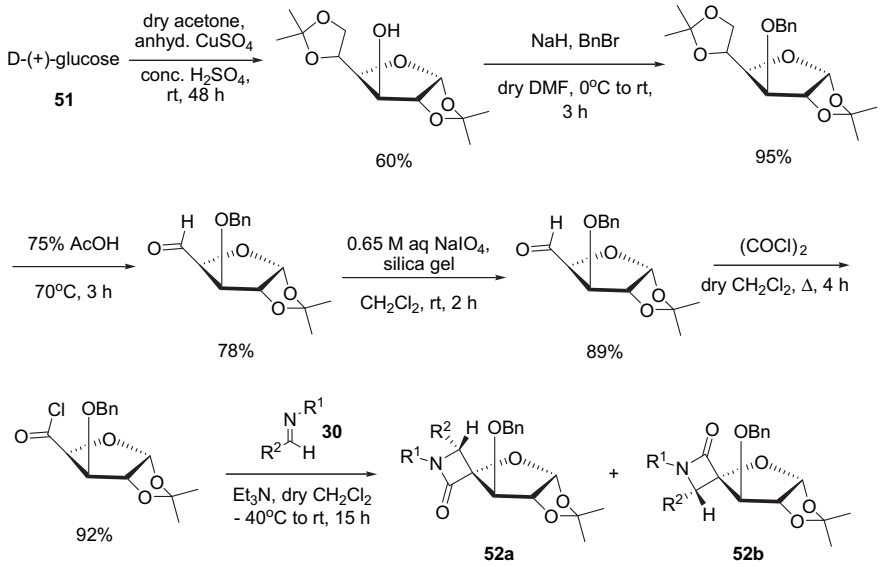
explained by attack on the less hindered side of the ketene carbonyl by the imine, either via the α- or β-face approach, followed by conrotatory ring closure. The reaction of natural *O*,*N*-protected *trans*-4-hydroxy-L-prolines with *N*-(benzylidene)benzylamine in the presence of Mukayama's reagent and triethylamine led to mixtures of diastereomeric, enantiomerically pure spiro-fused 2-azetidinones.[30] Gonzalez and co-workers performed molecular modelling calculations using ab initio methods on the spiroazetidinones synthesised from the reaction of the ketene derived from *N*-benzyloxycarbonyl L-proline acid chloride with some imines.[31] These calculations predicted that these systems could adopt a β-turn secondary structure in solution, with strong intramolecular hydrogen bonds stabilizing the U-turn conformation with a geometry that is very close to the ideal type II β-turns.

A rigid bicyclic ketene derived from a bicyclic acyl chloride **49** and imines **30** has been used to synthesise highly constrained polycyclic spiro-2-azetidinones **50** (Scheme 14).[32] Depending on the imine component, high diastereoselectivity was observed in the process, leading mainly to the cis diastereomer in the case of aromatic imines. This observation was attributed to an *anti* addition of the imine to the ketene, followed by a conrotatory ring closure in which the heteroatom at the 6-position of the scaffold rotates outwards because of torquoelectronic effects. The substituents on the imine nitrogen had a significant effect on the yields of products. The imine with an *N*-benzyl group afforded the highest yield of 66%, whereas the imine with a *p*-tolyl group afforded the minimum yield of 14%. The imine with a 4-nitrophenyl group on the nitrogen did not react.

The reaction of the chiral ketene, derived from D-(+)-glucose **51**, with imines **30** led to the diastereoselective synthesis of spiro-2-azetidinones **52** (Scheme 15).[33] From the four possible diastereoisomers, the reaction afforded only two diastereoisomers, with **52a** being the major isomer and **52b** the minor isomer. The formation of these stereoisomers led to the assumption that the



Scheme 14.

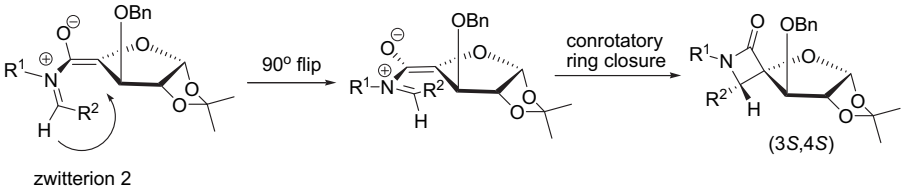


Scheme 15.

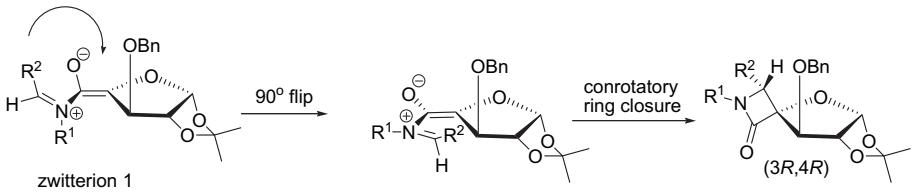
Table 1
Synthesis of spiro-fused β-lactams **52a**,**b**

Entry	R^1	R^2	Yield (%)	dr (**52a**/**52b**)
1	PMP	PMP	65	70:30
2	Ph	PMP	71	72:28
3	Ph	Ph	62	70:30
4	PMP	Ph	62	68:32
5	4-ClC_6H_4	Ph	59	65:35
6	Ph	Styryl	69	71:39
7	PMP	Styryl	67	68:32
8	4-MeC_6H_4	Ph	72	64:36
9	Ph	4-MeC_6H_4	70	64:36

proposed spiro configuration at C3 was confirmed by X-ray crystallography of β-lactam **55** bearing a 4-methoxyphenyl group. The X-ray crystallography also showed that the 2-azetidinone ring was planar and perpendicular to the xanthene ring. The anthracene ring was observed to have a dihedral angle of 51.8° with respect to the 2-azetidinone ring. Two imines derived from the reaction of 2-naphthaldehyde with *p*-anisidine and with 1-naphthylamine also yielded the corresponding spiroazetidinones in 40 and 50% yields, respectively.[34] The reaction of 9*H*-xanthene-9-carboxylic acid **53** was extended to some bis-imines, derived from treatment of anthracene-9-carbaldehyde with diamines, forming novel bis-spiro-fused 2-azetidinones **56a**–**e** (Fig. 3).[34]



Scheme 16.



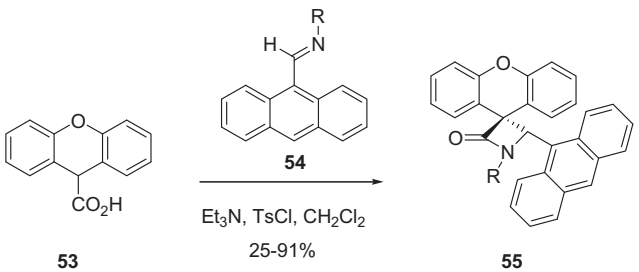
Scheme 17.

torquoelectronic effect dominated the steric constraints. The diastereoselectivity was only moderate (Table 1), which was rationalised by proposing that the bulky 6,7-*O*-isopropylidene moiety, to some extent, prevented the attack of the imine from the bottom face, so that the zwitterionic intermediate **2** (Scheme 16) was formed to a lesser extent than the zwitterion **1** (Scheme 17), resulting in the observed proportion of diastereoisomers. A similar mechanism was proposed earlier by Khasanov and co-workers for explaining the formation of spiro-fused 2-azetidinones.[29]

The reactions of 9*H*-xanthene-9-carboxylic acid **53** with imines **54**, derived from the treatment of anthracene-9-carbaldehyde with several amines, in the presence of tosyl chloride and triethylamine have been reported recently to afford polycyclic spiro-fused 2-azetidinones **55** as single diastereomers (Scheme 18).[34] The

The α-oxoketenes, generated by pyrolysis of 2-aryl-substituted 1,5,7-trioxaspiro[2,5]octane-4,8-diones **57**, reacted with imines **30** to give diastereomeric 2-azetidinones, spiro-fused to 1,3-dioxolan-4-ones **59** and **60** (Table 2).[35] The proposed mechanism for the generation of ketenes involves an intramolecular rearrangement between the oxirane ring and the carbonyl group in compounds **57** forming bicycles **58**, which undergo another intramolecular rearrangement under anhydrous conditions forming α-oxoketenes (Scheme 19).

2.1.3. Reaction of isocyanates with ketene-N,S-acetals. An example of isocyanate–alkene cycloadditions leading to spiro-fused 2-azetidinones has been reported by Zhou and co-workers. *N*-Methyl cyclic ketene-*N*,*S*-acetal **61** reacted with (*E*)-1-isocyanato-2-phenylethene **62** (R=Ph) or (*E*)-1-isocyanato-1-butene **62** (R=Et) to



R = 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 2-$MeOC_6H_4$, Ph, 4-ClC_6H_4, 3-$NO_2C_6H_4$, 2-Et, 3-BrC_6H_4, 2,4-di-$MeOC_6H_3$, 3,4-di-$MeOC_6H_3$, *c*-Hex, 1-naphthyl

Scheme 18.

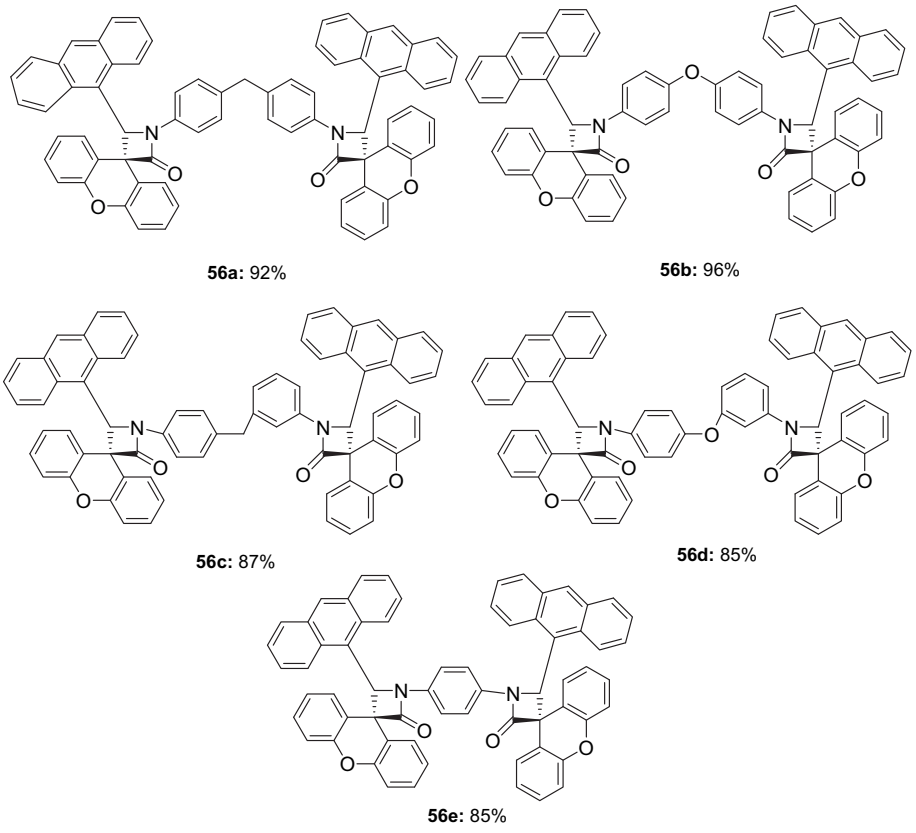


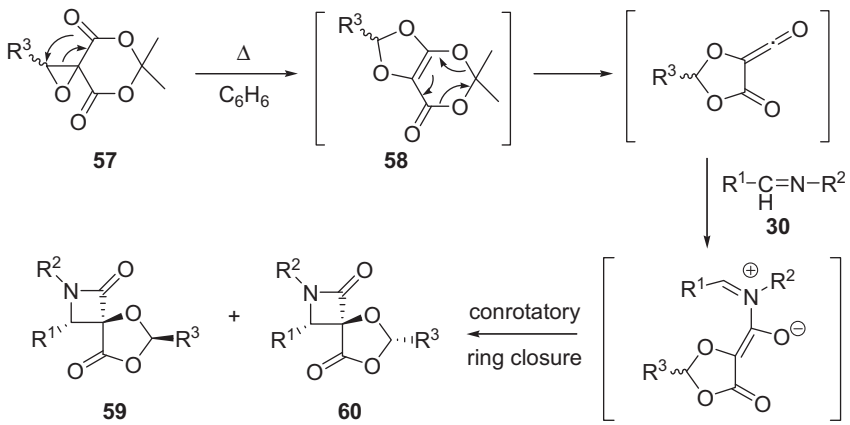
Fig. 3. Structures and yields of bis-spiro-fused 2-azetidinones.

Table 2
Synthesis of spiro-fused β-lactams **59** and **60**

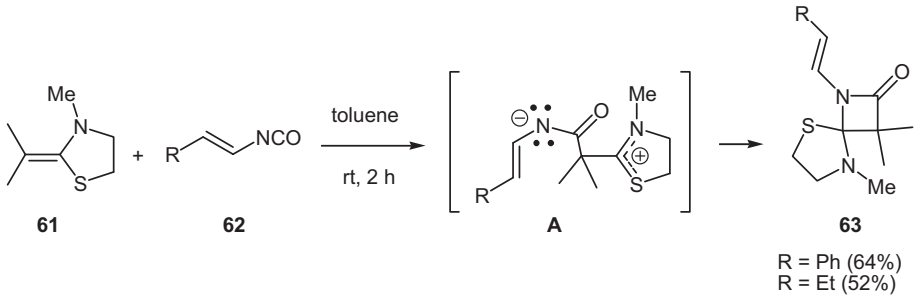
R^3	R^2	R^1	Yield **59** (%)	Yield **60** (%)
Ph	Ph	Ph	17	24
4-BrC_6H_4	Ph	Ph	16	16
4-ClC_6H_4	Ph	Ph	13	21
3-MeC_6H_4	Ph	Ph	22	37
3-$MeOC_6H_4$	Ph	Ph	31	40
Ph	Ph	4-ClC_6H_4	13	12
4-BrC_6H_4	Ph	4-ClC_6H_4	41	37
3-MeC_6H_4	Ph	4-ClC_6H_4	29	36
3-$MeOC_6H_4$	Ph	4-ClC_6H_4	32	40
Ph	Ph	4-$MeOC_6H_4$	17	21
3-MeC_6H_4	Ph	4-$MeOC_6H_4$	26	32
4-BrC_6H_4	4-MeC_6H_4	4-MeC_6H_4	20	27
3-MeC_6H_4	4-MeC_6H_4	4-MeC_6H_4	22	32

form the corresponding spiro-fused 2-azetidinones **63** through zwitterionic intermediates **A** (Scheme 20). The highly nucleophilic nitrogen atom of the isocyanate moiety in the latter intermediates induced cyclisation at the ring carbon to furnish the observed products.[36]

Cycloaddition reactions of ketenes and imines have been widely employed in the synthesis of spiro-fused 2-azetidinones, and diverse types of imines and ketene precursors have been used to accomplish this reaction. In recent years, heterocyclic ketene precursors have drawn considerable interest. For example, an equimolar reaction of diphenylketene with isocyanides afforded the [4+2] cycloaddition product, whereas a 2:1 M reaction afforded 2-azetidinones as the [2+2] cycloaddition products.[18] In one case, theoretical calculations indicated torquoelectronic effects

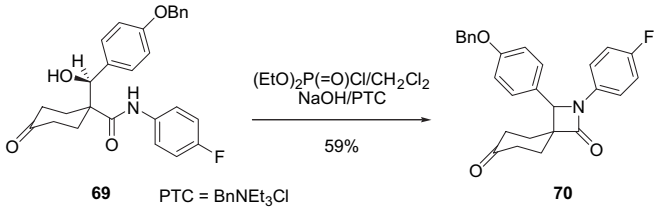


Scheme 19.



Scheme 20.

dominating, but the experimental findings suggested steric and other electronic factors determining the course of the reactions.[23] The experimental findings of Deshmukh and co-workers showed that the torquoelectronic effects dominated the steric constraints.[33] It is thus evident that the product and stereochemical outcome of the Staudinger reaction depends on the nature of the substrates. Isatin-based spiro-2-azetidinones have drawn wide attention, probably due to biological activity associated with the indolinone ring,[37] and also its presence in the naturally occurring chartellines.



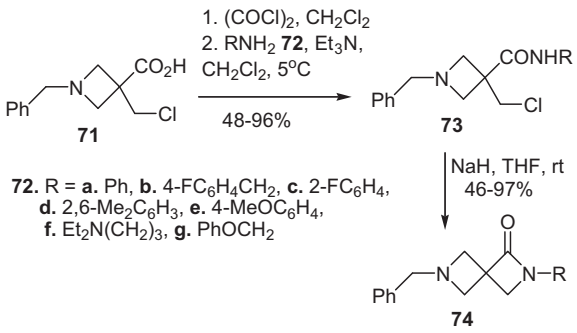
Scheme 22.

2.2. Cyclisation reactions

Cyclisations of β-amino acids and β-functionalised amides are old and classical methods to synthesise 2-azetidinones and these approaches have been employed as well to prepare 2-azetidinones bearing a spiro framework. Ikeda and co-workers have reported the photocyclisation of 2-(*N*-acyl-*N*-alkylamino)cyclohex-2-enones leading to the formation of spiro-fused 2-azetidinones in 1986.[38] Cyclisation reactions mostly afford 2-azetidinones with the C3 carbon as the spiro atom. Examples are known, however, of some oxidative cyclisations and radical reactions, which lead to the formation of C4 spiro-fused 2-azetidinones.

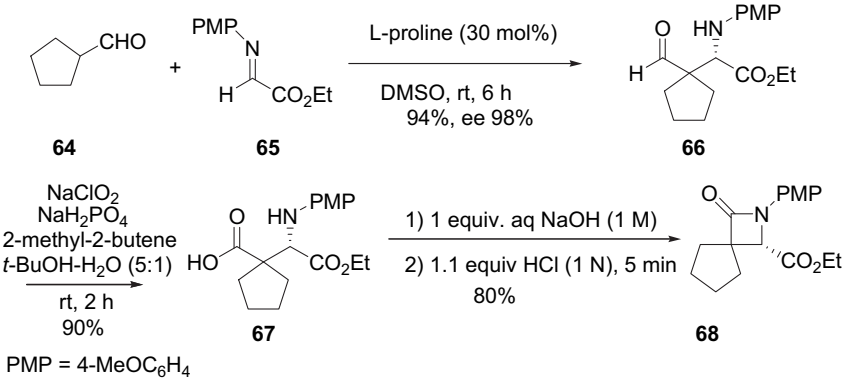
An L-proline-catalysed Mannich reaction of cyclopentane carbaldehyde **64** with α-iminoester **65** furnished β-formyl amino ester **66**, which underwent oxidation to the carboxylic acid **67**. The cyclodehydration of the latter compound with sodium hydroxide yielded the cyclopentane-spiro-fused azetidin-2-one **68** (Scheme 21).[39]

Activation of the hydroxyl group in 3-hydroxy-3-arylpropanamide **69** by transformation into a phosphonate followed by cyclisation yielded spiroazetidin-2-one **70** (Scheme 22).[40] The β-chloro amides **73**, formed from chlorination and subsequent reaction of 1-benzyl-3-(chloromethyl)azetidine-3-carboxylic acid **71** with amines **72**, cyclised on treatment with sodium hydride in tetrahydrofuran to afford the spiro-fused 2-azetidinone **74** (Scheme 23).[41]

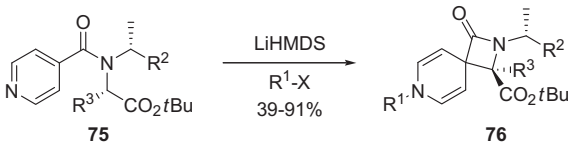


Scheme 23.

The cyclisation of enolates from glycine derivatives **75** (R^3=H), generated from *N*-nicotinoyl and *N*-isonicotinoyl glycine, and the corresponding alanine derivatives (R^3=Me) took place with dearomatisation of the pyridine ring forming 2-azetidinones **76** spiro-fused to a dihydropyridine moiety (Scheme 24).[42] These reactions occur with a benzylic group at the amide nitrogen as well.[43]



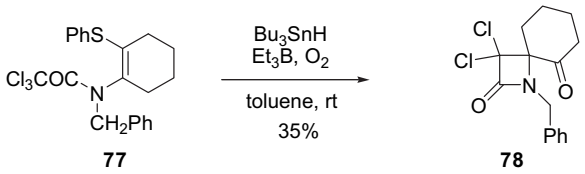
Scheme 21.



a. $R^1 = CO_2Me$, $R^2 = tBu$, $R^3 = H$; **b.** $R^1 = CO_2Me$, $R^2 = CH_2Ph$, $R^3 = H$; **c.** $R^1 = CO_2Me$, $R^2 = C(Me)_2Ph$, $R^3 = H$; **d.** $R^1 = CO_2Me$, $R^2 = 4\text{-}MeOC_6H_4$, $R^3 = H$; **e.** $R^1 = CO_2Me$, $R^2 = 4\text{-}MeOC_6H_4CH_2$, $R^3 = H$; **f.** $R^1 = CO_2Me$, $R^2 = 4\text{-}MeOC_6H_4CH_2$, $R^3 = Me$

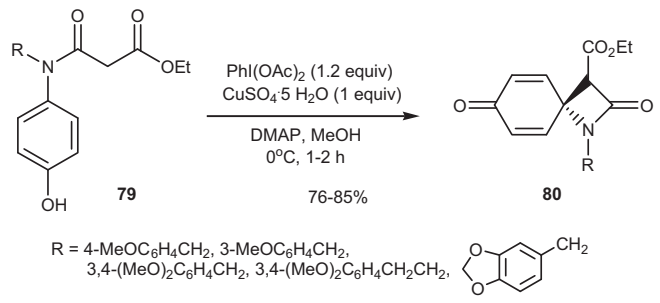
Scheme 24.

The radical-initiated 4-*exo*-*trig* cyclisation of *N*,*N*-disubstituted trichloroacetamide **77** upon treatment with tributyltin hydride in toluene at room temperature yielded an azetidin-2-one **78** in 35% yield (Scheme 25).[44]



Scheme 25.

4-Aminophenol-derived amides **79** have been reported to undergo oxidative dearomatisation upon treatment with iodobenzene diacetate and copper(II) sulfate pentahydrate, followed by cyclisation to form the spiro-fused 2-azetidinones **80** (Scheme 26).[45] This reaction represents an example of carbon–carbon bond formation during the cyclisation step.



Scheme 26.

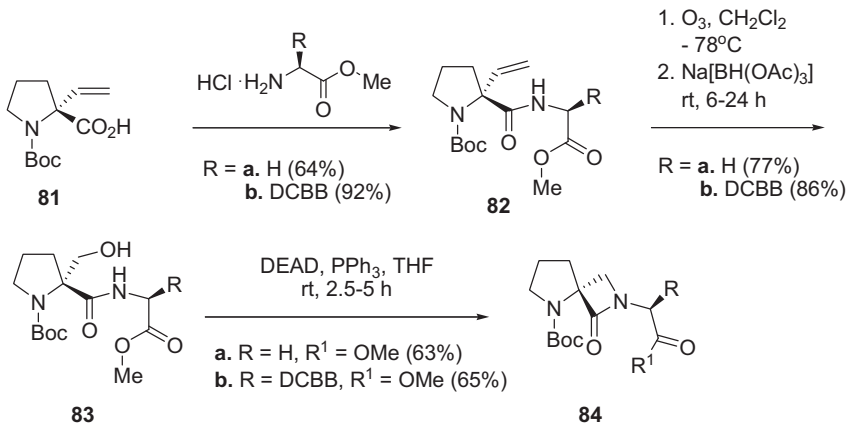
Gmeiner and co-workers have devised a methodology to synthesise spiro-fused 2-azetidinones starting from natural prolines by using Seebach's self-reproduction of a chiral methodology in combination with a peptide-coupling reaction and Grubbs' ring-closing metathesis.[46,47] Thus, α-vinyl-*N*-Boc proline **81** has been converted via amides **82** and β-hydroxy amides **83** into spiro-fused 2-azetidinones **84** (Scheme 27).

The cyclisation of alkyl hydroxamates **85**, mediated by phenyliodine(III) bis(trifluoroacetate), has been described to lead to the formation of spirodienone 2-azetidinones **86** (Scheme 28).[48] Oxidative dearomatisation occurred in this case, resulting in the formation of a carbon–nitrogen bond. When the reaction was carried out in dichloromethane and methanol, a minor amount (26%) of spiroazetidinone **87** was also obtained by conjugate addition of methanol to the dienone system. The formation of this product was eliminated by carrying out the reaction in dichloromethane only. Benzylic strain in the nitrenium ion intermediate was responsible for the selective formation of *anti*-2-azetidinones.

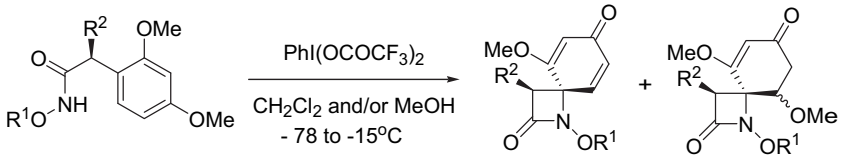
Baran's approach to synthesise chartelline started from a simple α-amino ester **88**, which was transformed into a complex amide **89** through a number of steps.[49] The bromination of the latter amide **89** with *N*-bromosuccinimide, followed by intramolecular cyclisation of the resulting β-bromo amide **90**, led to the formation of spiro-fused 2-azetidinone **91** (Scheme 29). In the total synthesis of chartelline C by the same group, β-bromo amide **89** was cyclised using potassium carbonate in the presence of 18-crown-6.[5] It is worth mentioning that chartellines A–C **1**–**3** (Fig. 2) have been isolated in the 1980s from the marine bryozoans, *Chartella papyracea*, collected from the North sea.[50] Although the chartellines lacked biological activity, they remained targets of interest, due to their novel and complex structure. The 2-azetidinone ring in chartellines is spiro-fused to the indoline ring and fused to the 10-membered imidazoazacyclodecadiene ring. The structure of chartelline A was confirmed by X-ray crystallography, showing the 10-membered ring to adopt a rigid tube-like conformation and the indoline ring to reside perpendicularly to the azetidinone ring and almost parallel to the imidazole ring.

2.3. Transformations of substituents connected to monocyclic 2-azetidinones

The chemistry of substituents at monocyclic 2-azetidinone rings has been explored frequently for the construction of spiro-fused frameworks. One of the first reports of such a strategy has been published by Bose and co-workers and consisted of the reaction of 4-oxo-1-phenylazetidine-2,2-dicarboxylic acid with different carbodiimides to form spiro-fused 2-azetidinones.[51] More recently, Alcaide and co-workers have explored a metal-catalysed, ring-



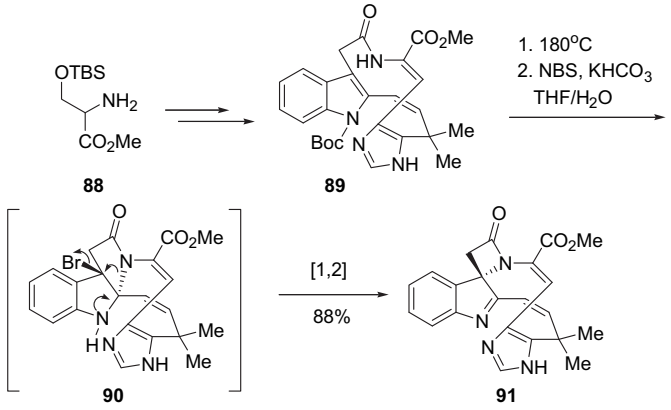
Scheme 27.



85 **86** **87**

86. a. R^1 = Me, R^2 = H (67%; 53% in CH_2Cl_2 + MeOH)
b. R^1 = Bn, R^2 = H (86%)
87. R^1 = Me, R^2 = H (26%)

Scheme 28.



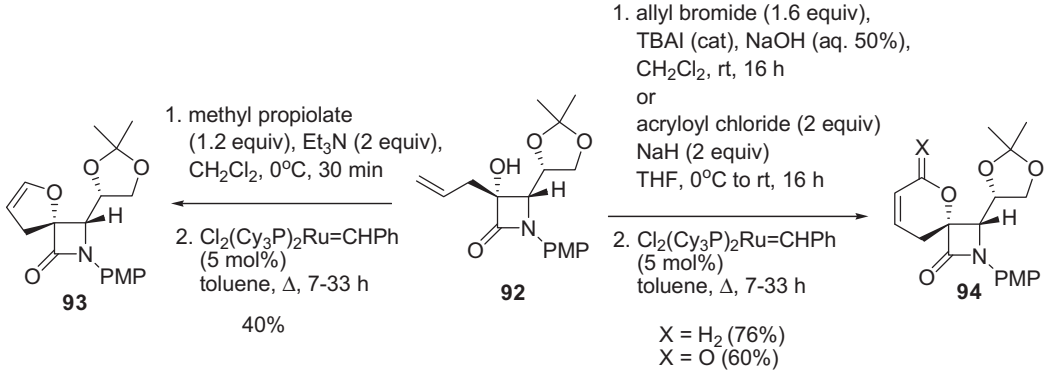
88 **89** **90** **91**

Scheme 29.

closing metathesis of 2-azetidinone-tethered α-allenol **92** for the synthesis of spiroheterocycles including spiro-fused 2-azetidinones **93** and **94** (Scheme 30).[52] In a different approach, the palladium-catalysed reaction of 2-azetidinone-tethered α-allenols **95a**,**b** with Baylis–Hillman acetates **96a**,**b** furnished enantiopure spiroazetidinones **97a**–**d** in moderate-to-good yields (Scheme 31).[53] When α-allenol **95a** and acetate **98** containing a cyano group were subjected to this palladium-catalysed protocol, the reaction did not yield the expected adduct **99**, which would have resulted from S_N2 substitution by attack at the methylene position remote from the leaving group, followed by migration of the double bond (Scheme 32). In contrast, the reaction exclusively led to spiroazetidinone **100**, which was explained considering a regio- and diastereo-specific S_N1 substitution protocol.

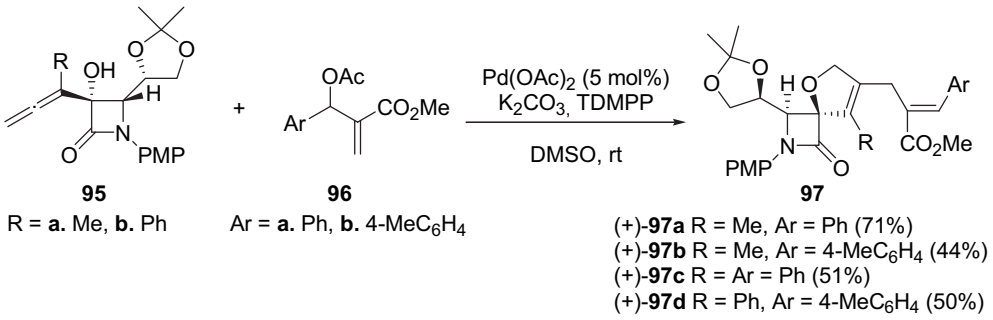
Furthermore, the same group has recently disclosed a novel methodology for the metal-catalysed cycloetherification of 2-azetidinone-tethered homopropargylic alcohols towards the synthesis of spiranic tetrahydrofuryl β-lactams in good yields.[54]

Halocyclisation of *cis*-3-(prop-2-ynyloxy/-enyloxy)-2-azetidinones to synthesise spiroazetidinones has been reported by Bari and co-workers.[55] This work has recently been extended further with 3-allyl-3-(phenyl/benzylthio)-2-azetidinones.[56] Only *cis*-3-allyl-3-benzylthio-2-azetidinones **101** underwent cyclisation upon reaction with bromine or iodine (Schemes 33 and 34), and both C7 α- and β-epimers of the spiro systems **103**–**106** were obtained. In



93 **92** **94**

Scheme 30.

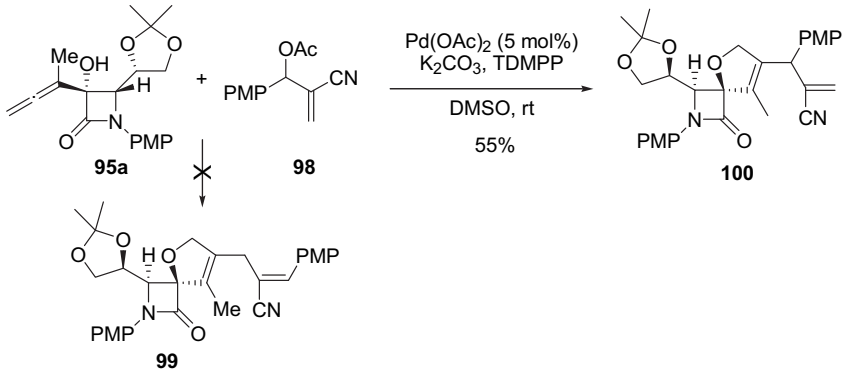


95 **96** **97**

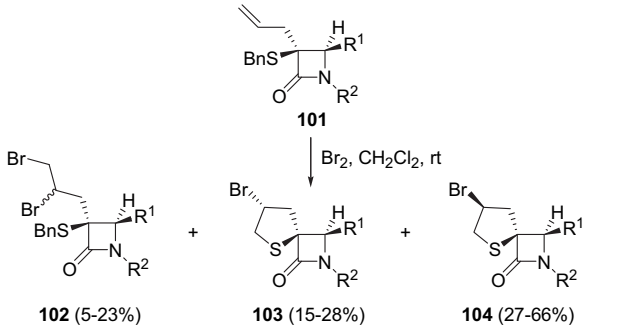
R = **a.** Me, **b.** Ph
Ar = **a.** Ph, **b.** 4-MeC_6H_4

(+)-**97a** R = Me, Ar = Ph (71%)
(+)-**97b** R = Me, Ar = 4-MeC_6H_4 (44%)
(+)-**97c** R = Ar = Ph (51%)
(+)-**97d** R = Ph, Ar = 4-MeC_6H_4 (50%)

Scheme 31.

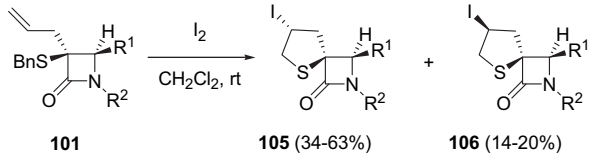


Scheme 32.



a. R^1 = Ph, R^2 = 4-$MeOC_6H_4$; **b.** R^1 = 4-$MeOC_6H_4$, R^2 = 4-$MeOC_6H_4$;
c. R^1 = 4-ClC_6H_4, R^2 = 4-MeC_6H_4; **d.** R^1 = R^2 = Ph; **e.** R^1 = Ph, R^2 = 4-ClC_6H_4

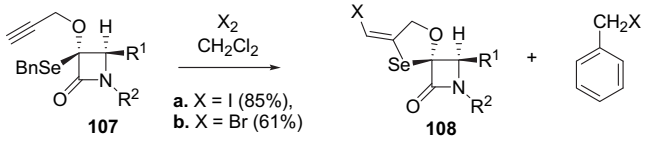
Scheme 33.



a. R^1 = Ph, R^2 = 4-$MeOC_6H_4$; **b.** R^1 = 4-$MeOC_6H_4$, R^2 = 4-MeC_6H_4;
c. R^1 = 4-ClC_6H_4, R^2 = 4-MeC_6H_4; **d.** R^1 = R^2 = Ph; **e.** R^1 = Ph, R^2 = 4-ClC_6H_4

Scheme 34.

the reaction with bromine, a side product **102** was obtained due to bromine addition across the carbon–carbon double bond. The reaction employing bromine favoured the formation of the β-epimer, whereas the reaction using iodine favoured the α-epimer. The preferential formation of the β-epimer indicated that bromocyclisation occurred by initial bromine addition across the double bond, and the complete mechanism involved coordination by halogen to form a π-complex followed by nucleophilic attack of the sulfur atom. The bromide retained a more stable pseudoequatorial position during the nucleophilic attack of sulfur on the carbon of the olefin/halogen complex. In the case of iodocyclisation, however, the sulfur atom was transformed into an electrophilic species first, which then interacted with the olefinic moiety followed by nucleophilic attack of a halide anion to form the five-membered ring. Halocyclisation of the 3-benzylselanyl-substituted 2-azetidinone **107** with bromine and with iodine occurred by a 5-*exo* ring-closure process affording 2-azetidinone **108** spiro-fused to a 1,3-oxaselenolane ring (Scheme 35).[57]



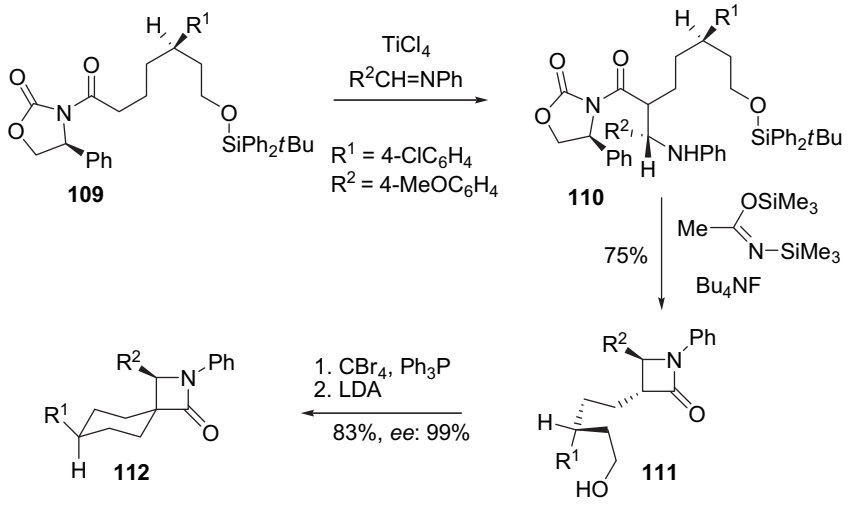
R^1 = Ph, R^2 = 4-MeC_6H_4

Scheme 35.

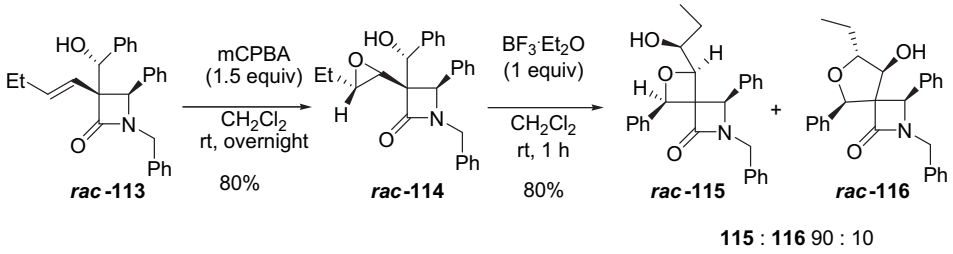
The ring closure of amine **110**, obtained by the addition of the enolates derived from substrate **109** across an imine, afforded 2-azetidinone **111**. The cyclisation of the C3 substituent in the latter 2-azetidinone **111** was performed via transformation of the hydroxyl group into the corresponding bromide followed by α-deprotonation with respect to the β-lactam carbonyl group utilising LDA and subsequent intramolecular nucleophilic substitution, leading to spiro-fused 2-azetidinone **112** with cholesterol absorption inhibition activity (Scheme 36).[58]

A good example of the application of monocyclic 2-azetidinones bearing an unsaturated side chain at C3 for the synthesis of spiro-fused 2-azetidinones has been reported by Tolomelli and coworkers.[59,60] The carbon–carbon double bond present in the butenyl group of 2-azetidinone **113** was transformed into epoxide **114** using *m*-CPBA, and treatment of the latter epoxide **114** with 1 equiv of $BF_3 \cdot Et_2O$ led to ring opening followed by cyclisation towards 2-azetidinones spiro-fused to an oxetane ring (**115**) and a tetrahydrofuran ring (**116**) in a 90:10 ratio (Scheme 37). The effect of the configuration at C4 was studied by carrying out the reactions of enantiomerically pure epoxide-substituted 2-azetidinones **117a** and **117b**. The former compound afforded a 2-azetidinone system **118a**, spiro-fused to an oxetane ring, as the major product and the 2-azetidinone **118b** as the minor product, whereas the latter compound (**117b**) afforded 2-azetidinone **119b**, spiro-fused to a tetrahydrofuran unit, as the major product and the 2-azetidinone **119a** as the minor product (Schemes 38 and 39).

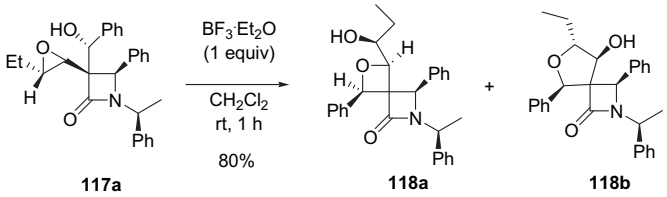
In related research, the carbon–carbon double bond of 3-methylidene-2-azetidinones has been subjected to epoxidation, cyclopropanation, Diels–Alder reaction and 1,3-cycloadditions, producing a variety of spiroazetidinones.[61,62] The study of the steric course indicated that reactions with the double bond occurred from the side opposite to the bulkier substituent at C4 of the starting 2-azetidinones. Epoxidation of the electron-poor, carbon–carbon double bond at C-3 of 2-azetidinones **120** occurred readily with a large variety of reagents, e.g., H_2O_2 in alkali, *t*-BuOOH, KClO, 3-chloroperbenzoic acid, or urea/H_2O_2 complex, forming spiroazetidinones **121** in 65–90% yields (Scheme 40).[61] The reactions of hydrazines with **120** led to the formation of adducts **122**,



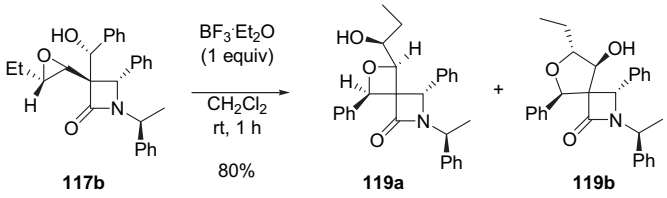
Scheme 36.



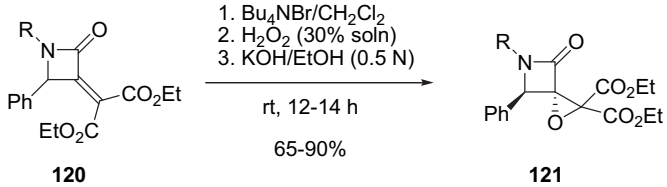
Scheme 37.



Scheme 38.



Scheme 39.



Scheme 40.

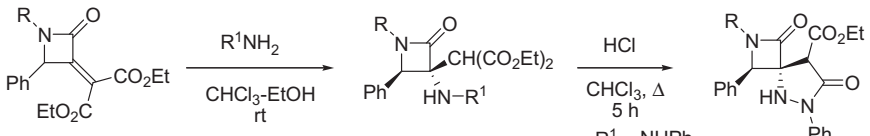
which cyclised upon acidic treatment forming spiroazetidinone **123** (Scheme 41).

2-Azetidinones **120** have also been subjected to cyclopropanation and Diels–Alder reaction.[61,62] Cyclopropanation of **120** in THF with the ylide derived from trimethylsulfoxonium iodide **124** in DMF formed 2-azetidinones **125**, spiro-fused to a cyclopropane ring (Scheme 42). In the Diels–Alder reaction of **120** with Danishefsky's diene **126**, a single product **127** was obtained in 95% yield. The Diels–Alder reaction with cyclopentadiene **128** yielded *endo* product **129** (Scheme 43) with cis-stereoselectivity suggesting that the reaction occurred at the side opposite to the bulkier substituent at C4.

Diazomethane reacted cleanly with α-methylidene-substituted 2-azetidinone **130** through *anti*-addition with respect to the CH_2OTBS group present at C4, forming diastereomeric 2-azetidinones **131a**,**b**, spiro-fused to a pyrazoline ring (Scheme 44).[63] Reactions of 3-silylated 2-azetidinones with α,β-unsaturated ketones are known to form propylidene 2-azetidinones, which undergo Diels–Alder reaction yielding the corresponding spiroazetidinones.[64]

2.4. Other methods

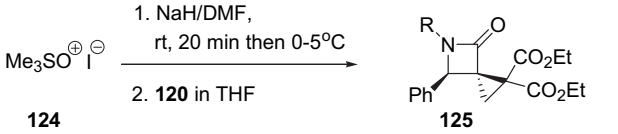
The synthesis of 1,4-disubstituted spiro(azetidine-3,1′-cyclopropanes) has been reported via a [3+2] dipolar cycloaddition of nitrones **132a**–**f** with bicyclopropylidene **133** in benzene at ambient or elevated temperature, forming the corresponding bis-spirocyclopropanated isoxazolidines **134a**–**f**. Treatment of the latter compounds with trifluoroacetic acid in acetonitrile furnished 3-spirocyclopropanated azetidin-2-ones **135a**–**f** (Scheme 45) with concomitant extrusion of ethylene, in excellent yields (Table 3).[65] A similar acid-catalysed fragmentative rearrangement of spirocyclopropanated cyclohexane-



120 R = PMP 122 123

122. R^1 = PhNH, NMe_2, 4-$HOOCC_6H_4NH$ (57%), MeOOCNH (41%), *t*-BuOOCNH (65%)

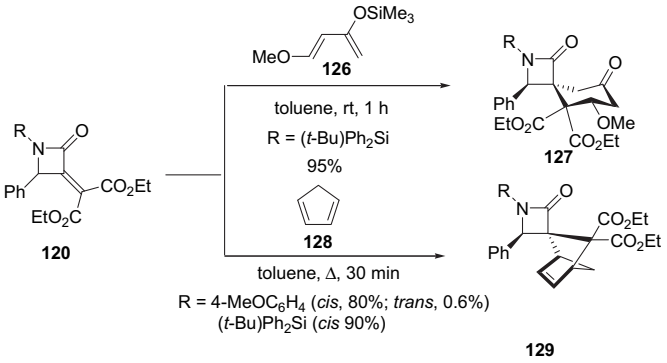
Scheme 41.



124 125

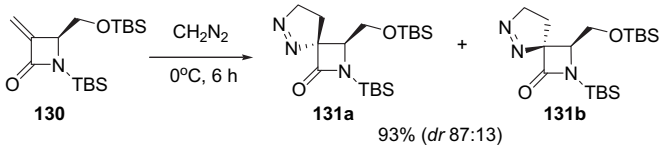
R = 4-$MeOC_6H_4$ (67%), (*t*-Bu)Ph_3Si (18%), 3,4-$(MeO)_2C_6H_3$ (48%)

Scheme 42.

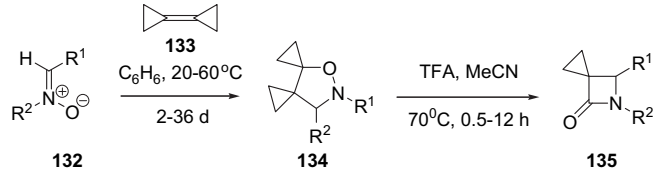


R = 4-$MeOC_6H_4$ (*cis*, 80%; *trans*, 0.6%)
(*t*-Bu)Ph_2Si (*cis* 90%)

Scheme 43.



Scheme 44.

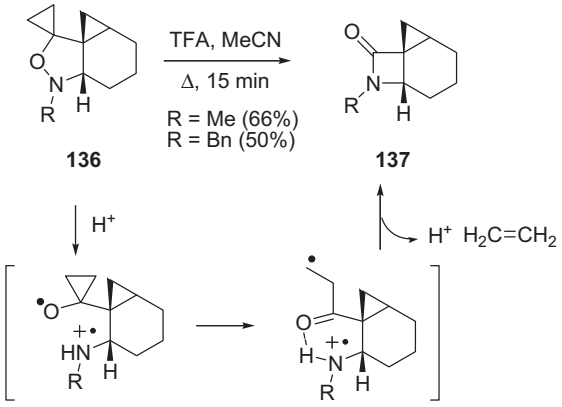


Scheme 45.

Table 3
Preparation of spirocyclopropanated isoxazolidines **134** and β-lactams **135**

132	R^1	R^2	134	Yield (%)	135	Yield (%)
a	CO_2Me	Bn	**a**	100	**a**	78
b	Ph	Bn	**b**	95	**b**	75
c	CN	Bn	**c**	94	**c**	75
d	CN	PMB	**d**	100	**d**	94
e	Ph	Me	**e**	93	**e**	96
f	2-Py	Me	**f**	71	**f**	96

fused isoxazolidines **136** afforded spirocyclopropanated 2-azetidinones **137**, fused to a cyclohexane ring (Scheme 46).[66] A mechanism was proposed involving cleavage of the protonated *N–O* bond of the isoxazolidine ring for its rearrangement to an azetidinone ring .[67] In an improved procedure, the one-pot, three-component reaction for the direct conversion of certain alkyl hydroxylamine hydrochlorides **139**, formaldehyde **138** or an alkyl glyoxalate and bicyclopropylidene **133** to furnish 3-spirocyclopropanated 2-azetidinones **140** has been carried out by microwave irradiation (Scheme 47).[68]



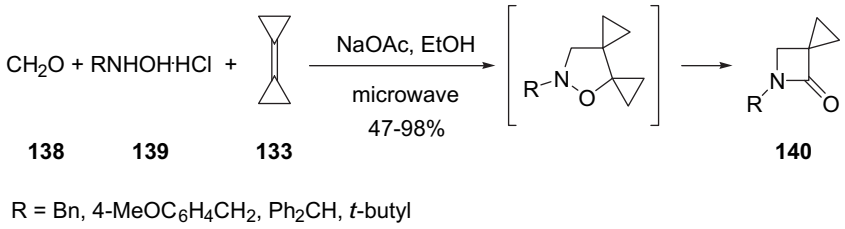
Scheme 46.

3. Reactions of spiro-fused β-lactams

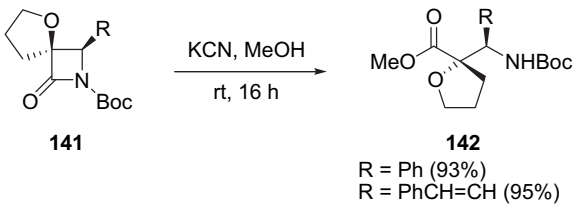
3.1. Ring-opening reactions

Ring-opening reactions of spiro-fused 2-azetidinones have been investigated utilising various hydrolytic, oxidative and reducing agents, and amino acid derivatives to get diverse types of ring-opening products. Although cleavage of the N1–C2 bond comprises the main ring-opening reaction of β-lactams, cleavage of other bonds is also known.

The cleavage of azetidin-2-ones **141**, spiro-fused to a tetrahydrofuran ring, by potassium cyanide in methanol at room temperature has been reported to yield β-amino esters **142** through methanolysis of the cyclic amide (Scheme 48).[69] A β-amino ester and a β-amino acid have also been formed by cleavage of a pyrrolidine spiro-fused 2-azetidinone ring by potassium cyanide in methanol and by sodium hydroxide in tetrahydrofuran, respectively.[28] In contrast, 4-oxoazetidine-2-carbaldehyde **143** undergoes a C4–N1 bond fission using 2-(trimethylsilyl)thiazole (TMST) yielding amide **144** (Scheme 49).[70] The azetidinones **37**, spiro-fused to an *N*-acyl/benzoyl thiazolidine ring, have been selectively hydrolysed by acid to form 2-substituted 1,3-thiazolidine-2-carboxylic acids **145** (Scheme 50).[24e] Similar cleavage of the 2-azetidinone ring has also been reported with hydrochloric acid in ethanol or with potassium hydroxide in ethanol.[71]



Scheme 47.



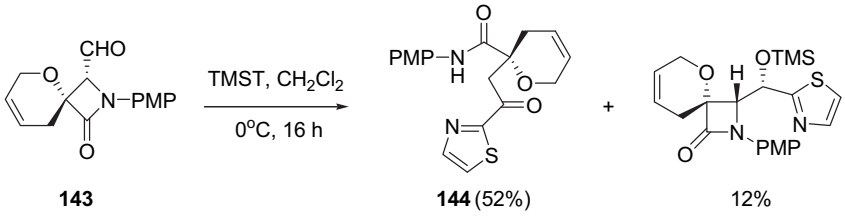
Scheme 48.

Hydrogenolysis of spiro β-lactams **146** bearing a formyl group has led to the rearranged bicyclic systems **147** via a C3–C4 β-lactam ring cleavage (Scheme 51).[26] The products were racemic because the process took place with racemisation at C3 of the initial 2-azetidinone ring. According to the proposed mechanism, after initial removal of the Cbz group of the pyrrolidine ring, a retro-Mannich type reaction resulted in ring opening of the 2-azetidinone ring. Hydrogenation of the cyclic imine and further nucleophilic addition of the secondary amine to the aldehyde group led to a bicyclic enamine, which underwent hydrogenation to afford the products **147**. Theoretical calculations were performed to study the ring-opening step.

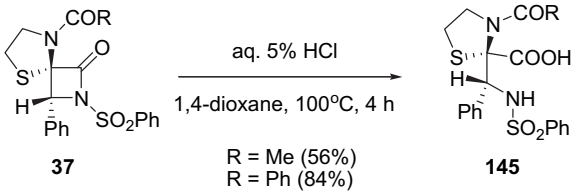
Hydrogenolysis of 2-azetidinones **37**/**38** spiro-fused to a 1,3-thiazolidine ring in ethyl acetate using Raney nickel as a catalyst has been reported to result in cleavage of both rings, forming an acyclic *N*-phenylsulfonamide **148** and an imidazole **149** (Scheme 52). This reaction did not occur when 10% Pd/C was used as a catalyst in various solvents, such as ethanol, acetic acid and ethyl acetate.[71]

Treatment of 2-azetidinones **135**, spiro-fused to a cyclopropane unit, with *tert*-butyl glycinate or with *tert*-butyl (*S*)-phenylalaninate **150** in DMF led to ring opening of the 2-azetidinone moiety to give β-peptides **151a**–**c** in good yields (Scheme 53).[65] A spiroazetidinone from the same series with a methyl carboxylate group at C4, however, failed to undergo ring opening, even upon prolonged heating, and afforded a new spiroazetidinone by transformation of the ester group.[62]

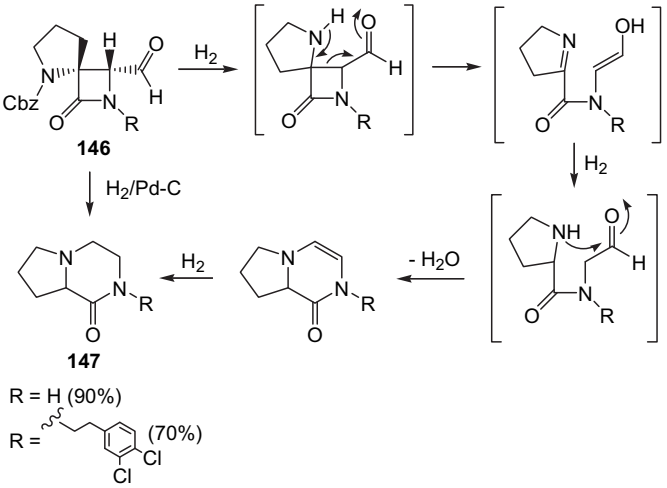
An acid-catalysed fragmentative rearrangement of oxazolidines **152** has been described to result in the formation of spirocyclopropanated 2-azetidinones **153**, fused to a cyclopentane ring, which underwent N1–C2 ring opening to furnish *N*-acylated β-amino acids **154** (Scheme 54).[66]



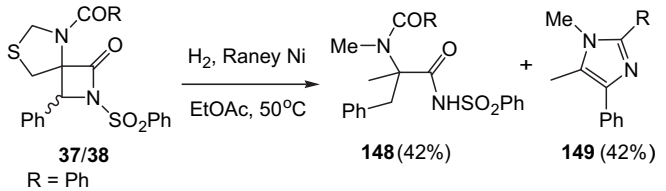
Scheme 49.



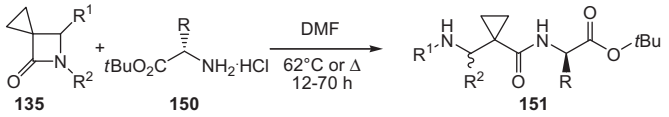
Scheme 50.



Scheme 51.

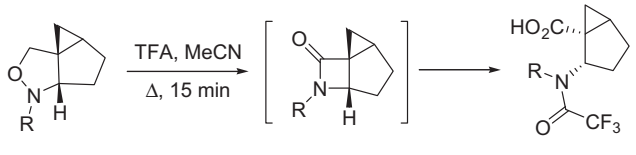


Scheme 52.



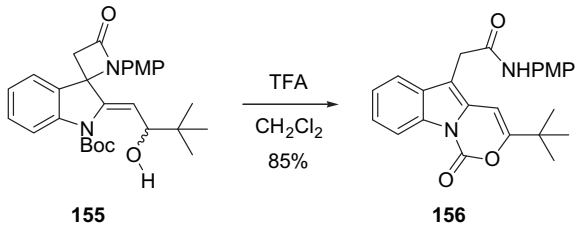
151: a. R^2 = COPh, R^1 = Ph; R = H (61%)
b. R^2 = CO_2tBu, R^1 = CN; R = H (84%)
c. R^2 = CO_2tBu, R^1 = CN; R = Bn (81%)

Scheme 53.



Scheme 54.

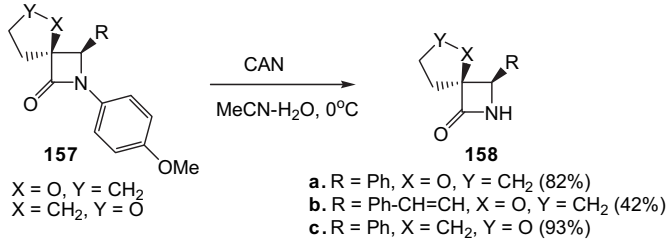
Treatment of 2-azetidinone **155** with trifluoroacetic acid in a study directed towards the synthesis of naturally occurring chartellines led to N1–C4 fission of the 2-azetidinone ring, together with cyclisation of the substituent on the indoline ring to oxazinone **156** (Scheme 55).[72]



Scheme 55.

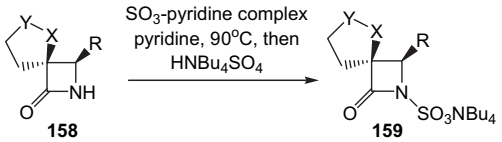
3.2. Reactivity of substituents attached to the ring nitrogen atom

The removal of 4-methoxyphenyl, benzyl and bis(4-methoxyphenyl)methyl groups from the nitrogen atom of 2-azetidinone rings has been reported by means of various reagents. A commonly used reagent in this respect is cerium(IV) ammonium nitrate, e.g., for the removal of the 4-methoxyphenyl group from 2-azetidinones **157** to afford **158a–c** (Scheme 56).[23,27,72a] The *N*-unsubstituted spiro-fused 2-azetidinones thus obtained are useful for transformation into other spiro-fused 2-azetidinones through N-functionalisation, e.g., N-sulfonylation of azetidin-2-ones **158** has been achieved using a sulfur trioxide/pyridine complex, forming sulfamate tetrabutylammonium salts **159a–c** (Scheme 57).[23] Similar reactions have been performed on 2-azetidinones spiro-fused to pyrrolidine.[28] Another example of 2-azetidinone (**160**) nitrogen



a. R = Ph, X = O, Y = CH_2 (82%)
b. R = Ph-CH=CH, X = O, Y = CH_2 (42%)
c. R = Ph, X = CH_2, Y = O (93%)

Scheme 56.



a. R = Ph, X = O, Y = CH_2 (76%)
b. R = PhCH=CH, X = O, Y = CH_2 (82%)
c. R = Ph, X = CH_2, Y = O (85%)

Scheme 57.

deprotection followed by reaction of the corresponding product **161** with phenylacetaldehyde **162** affording the spiroazetidinone **163** is shown in Scheme 58.[72a]

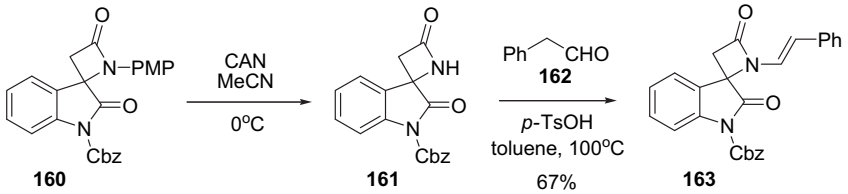
N-Benzyl-2-azetidinones **135**, spiro-fused to a cyclopropane unit, have been reacted with different oxidizing agents, such as Cr (VI) oxide, potassium permanganate and CAN. With the former two reagents, oxidation took place at the benzylic carbon atom leading to the formation of *N*-benzoyl-substituted spiroazetidinones **164a–c** (Scheme 59) (Table 4).[65] The reaction with CAN led to the formation of a mixture of *N*-benzoyl spiroazetidinone **164c** (39%) and the corresponding *N*-unsubstituted spiroazetidinone (38%).

An *N*–H spiroazetidinone **165** was transformed into the *N*-Boc-protected derivative **166** using a standard protocol (Scheme 60).[65]

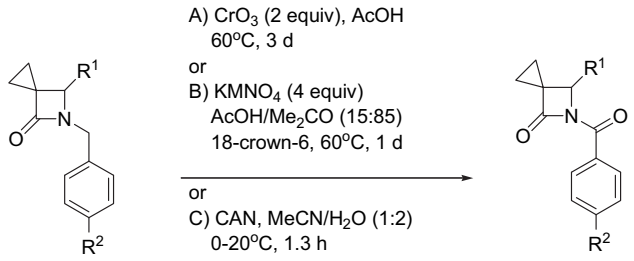
Weinreb and co-workers have described the Cu(I)-catalysed coupling of spiro-fused 2-azetidinone **167** with (*E*)-chloroiodovinylimidazole **168** to furnish the corresponding β-chloroenamide **169** (Scheme 61) en route to chartelline.[73]

3.3. Reactivity of substituents attached to the ring carbon atoms

The reduction of 2,6-diazaspiro[3.3]heptan-1-one **74** has been investigated with monochloroalane (formed in situ from $LiAlH_4$ and $AlCl_3$) and with borane under different reaction conditions. No reduction occurred using 1 equiv of the former reagent in tetrahydrofuran at 40 °C, whereas reversible complexation to borane was observed with the latter reagent. With 5 equiv of monochloroalane, the reductive removal of the carbonyl group was achieved, forming 2,6-diazaspiro[3.3]heptane **170** in 78% yield (Scheme 62).[41] Treatment of 2,6-diazaspiro[3.3]heptan-1-one **74** under transfer hydrogenation conditions resulted in the removal of the benzyl group



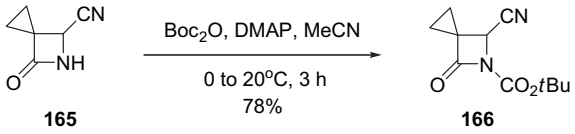
Scheme 58.



Scheme 59.

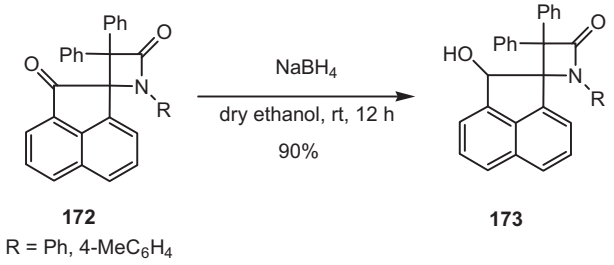
Table 4
Synthesis of spiro β-lactams **164** from **135**

135	R^1	R^2	Reagent	164	Yield (%)
a	CO_2Me	H	A	**a**	44
b	Ph	H	B	**b**	28
d	CN	4-MeO	C	**c**	39



Scheme 60.

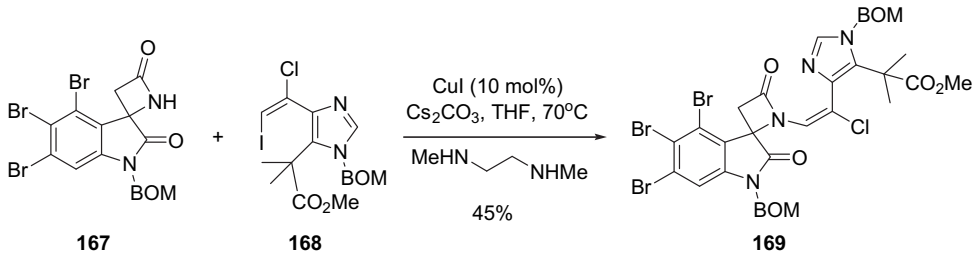
literature, e.g., treatment of spiro-2-azetidinone **172** with sodium borohydride led to reduction of the ketone to alcohol forming **173** (Scheme 64).[11] Treatment of spiro-fused 2-azetidinones **174** with sodium hydroxide in ethanol resulted in cleavage of the *N*-diarylacyl group of the indolinone ring, leading to 2-azetidinones **175**, spiro-fused to *N*-unsubstituted indolinone, in quantitative yields (Scheme 65).[74]



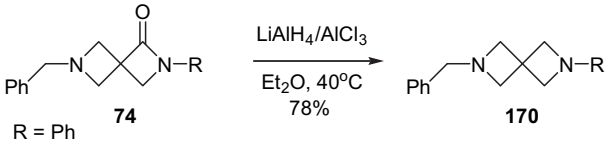
Scheme 64.

The dioxalane ring present at the C4 side chain of the pyrrolidine-fused spiroazetidinones **45** and **176** has been reported to undergo ring opening upon treatment with *p*-TsOH to form new spiro-fused 2-azetidinones **177**. Oxidation of the 1,2-diol group in the latter compounds upon treatment with sodium iodate afforded spiro-fused 2-oxoazetidine-4-carbaldehydes **178** (Scheme 66).[26,27]

The racemate of 2-azetidinone **179**, spiro-fused to *N*-Boc pyrrolidine, has been resolved via reductive deprotection of the pyr-

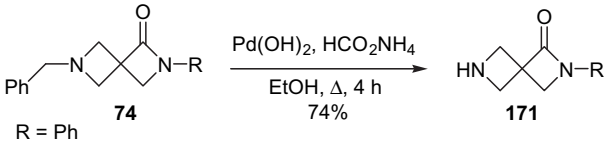


Scheme 61.



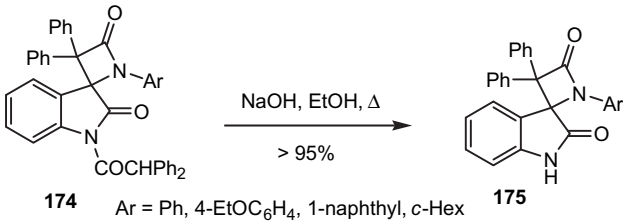
Scheme 62.

present at the azetidine nitrogen atom, affording a new 2-azetidinone **171** spiro-fused to a *N*-unsubstituted azetidine ring (Scheme 63).



Scheme 63.

The 2-azetidinones, obtained from the reaction of diphenylketene with imines, are known to be fairly stable compounds. Reactions of such β-lactams with various reagents in which the 2-azetidinone ring is retained at the cost of transformation of other functional group(s) in the molecule have been reported in the

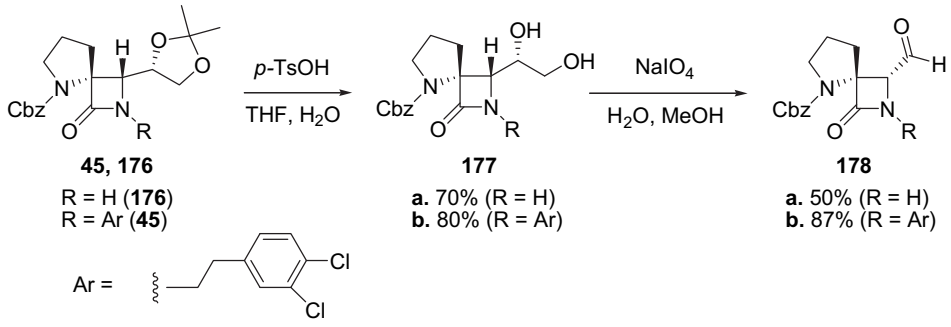


Scheme 65.

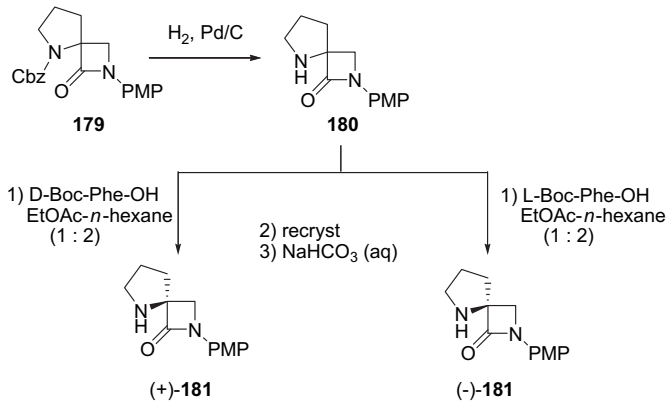
rolidine nitrogen to afford enantiomerically pure spiroazetidinones **181** via the 2-azetidinone **180** (Scheme 67).[28]

Treatment of *N*-benzoyl spiroazetidinone **164a** bearing an alkoxycarbonyl group at C4 with *tert*-butyl glycinate has been reported to afford a new spiroazetidinone **182** through an ester-to-amide functional-group transformation (Scheme 68).[65]

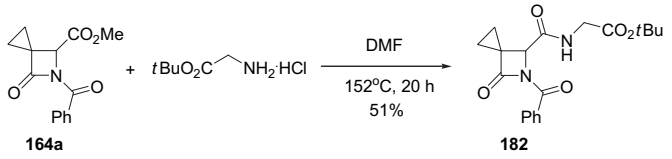
The 1,3-thiazolidine ring spiro-fused to 2-azetidinones **183** and **184** has been described to undergo oxidative cleavage upon treatment with molecular iodine as an oxidant in the presence of wet alumina to afford the corresponding azetidin-2,3-diones **185a**–**e** in fair-to-good yields (Scheme 69).[75] The products were not very stable, and hence their enantiomeric excesses could be determined only by ^{1}H NMR spectroscopy—using (+)-Eu(hfc)$_3$ as a chiral shift



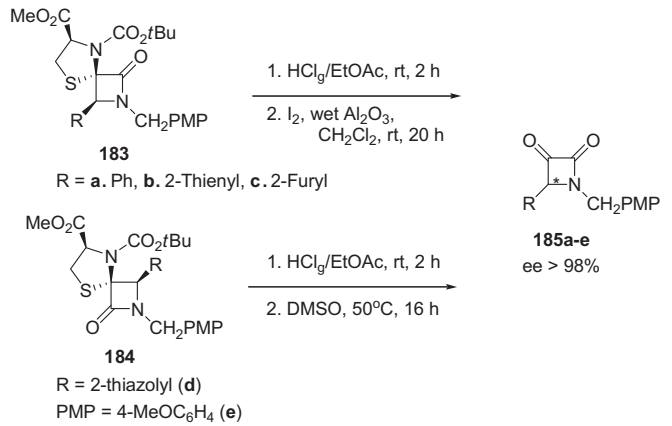
Scheme 66.



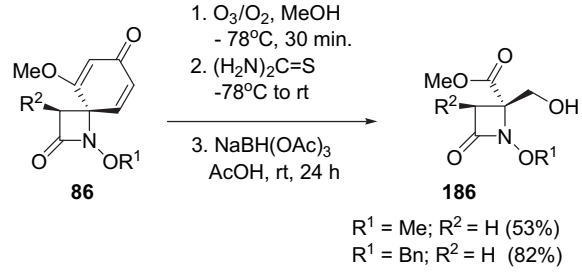
Scheme 67.



Scheme 68.

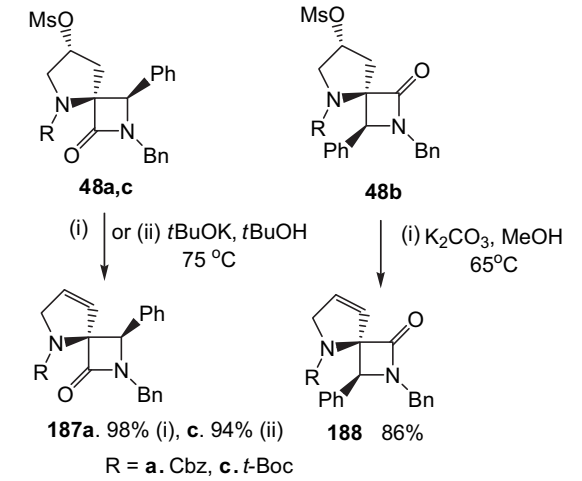


Scheme 69.



Scheme 70.

The removal of the mesyloxy group from the pyrrolidine ring of spiroazetidinones **48** through elimination in a basic medium has been deployed to create a carbon–carbon double bond, resulting in a pyrroline ring system (Scheme 71).[30] Thus, treatment of *N*-Cbz-protected compounds **48a** and **48b** with potassium carbonate led to the formation of enantiomeric products **187a** and **188**, respectively. However, the corresponding *N*-Boc-protected pyrrolidine **48c** did not afford the desired pyrroline, even upon prolonged heating with potassium carbonate in methanol. Treatment of this *N*-Boc-protected compound with potassium *tert*-butoxide in *tert*-butanol, however, led to elimination of the mesyloxy group, forming the desired 2-azetidinone bearing a pyrroline ring. A similar removal of a mesyloxy group and conversion of a pyrrolidine into a pyrroline ring in the presence of potassium carbonate has been reported by Khasanov and co-workers as well.[29]



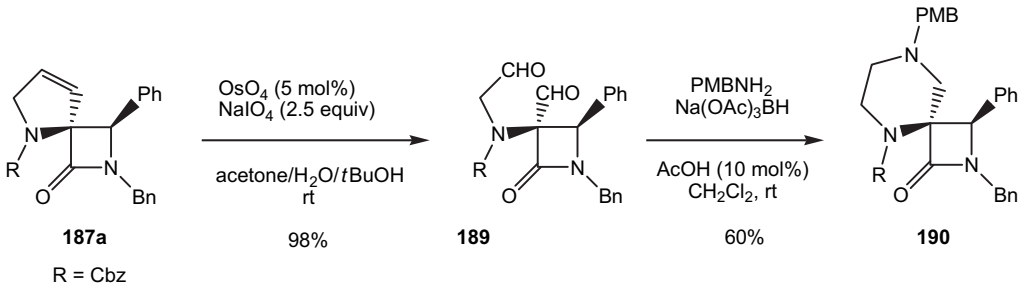
Scheme 71.

reagent—and not by HPLC. In another report, the cleavage of the cyclohexadienone ring spiro-fused to 2-azetidinones **86** has been realised through a series of reactions starting with ozonolysis, forming methyl *N*-alkoxy 4-hydroxymethyl-2-oxoazetidine-4-carboxylates **186** (Scheme 70).[48]

Classical carbon–carbon double-bond transformations have been explored to synthesise various spiro-fused 2-azetidinones starting from spiroazetidinone **187a**.[30] Reactions with a nitrone, with ethyl diazoacetate in the presence of copper triflate, and with *m*-chloroperbenzoic acid led to [2+3] cycloaddition, cyclopropanation, and epoxidation forming new classes of spiro-fused 2-azetidinones. Oxidative cleavage of alkene **187a** with osmium tetroxide in the presence of sodium periodate led to pyrroline ring opening forming the monocyclic 2-azetidinone **189** containing two carbaldehyde groups. Reductive amination of this 2-azetidinone with $Na(AcO)_3BH$ in the presence of 4-methoxybenzylamine led to the synthesis of 2-azetidinone **190**, spiro-fused to a piperazine ring (Scheme 72).[30]

metathesis and cross metathesis (ROM–CM) upon treatment with Grubbs' ruthenium catalyst, forming new 2-azetidinones **194** spiro-fused to a tetrahydrofuran system (Scheme 74).[76] By using β-lactams bearing different substituents at the C3 position of the 2-azetidinone ring, condensed bicyclic 2-azetidinones spiro-fused to another ring have been synthesised. The different C3 substituents were introduced by converting the 3-acetoxy derivative into the corresponding alcohol **195** (Scheme 75) and reacting the latter with allyl bromide, acryloyl chloride and 3-butenoic acid to afford the 2-azetidinones **196**, **197** and **198**, respectively (Scheme 76).[76]

Thermolysis of spiro-fused 2-azetidinone-oxadiazolines in the presence of alkenes has been reported to give 2-azetidinones, spiro-fused to cyclopropanes.[77] The formation of these products was



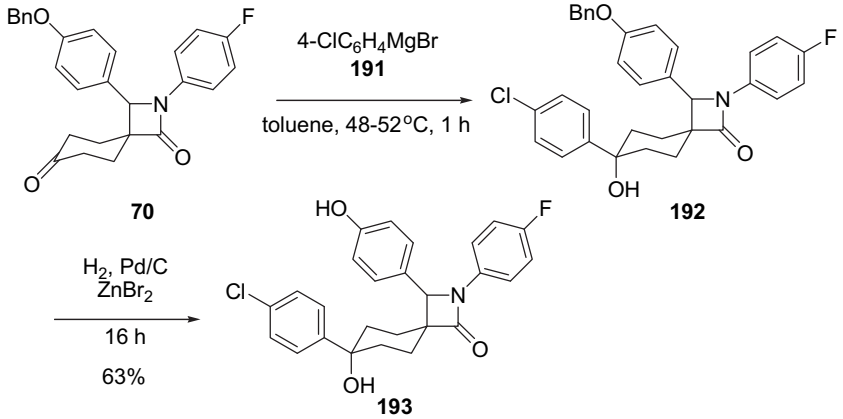
187a R = Cbz — 98% — **189** — 60% — **190**

Scheme 72.

Treatment of 2-azetidinone **70**, spiro-fused to a cyclohexanone ring, with the Grignard reagent **191** led to conversion into cyclohexanol **192**. Reductive removal of the benzyl group in the latter compound **192** afforded the cholesterol absorption inhibitor **193** (Scheme 73).[40]

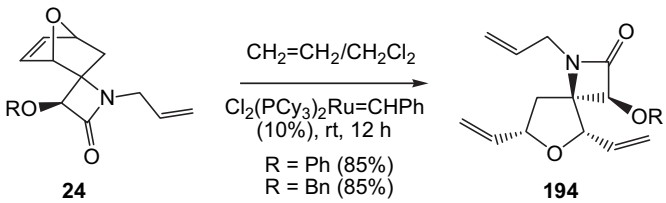
The spiro-fused 2-azetidinones **24**, formed through Staudinger reaction of the imine derived from 7-oxanorbornenone with 2-alkoxyacetyl chlorides, underwent a sequence of ring-opening

explained through a sequence of reactions beginning with a 1,3-dipolar cycloreversion of an oxadiazoline to form a carbonyl ylide. The latter fragmented to acetone and a 2-azetidinone-4-ylidene, which added to the alkene to afford spiro-fused 2-azetidinones. Thermolysis of 2-oxospiro(azetidine-4,2′-oxadiazoline) derivatives **199** in the presence of aryl isocyanates **201** afforded both *N*- and *O*-lactam substituted spiro(azetidin-2-one-4,3′-indol-2′-one) derivatives **202** and **204** (Scheme 77).[78] The reaction occurred through



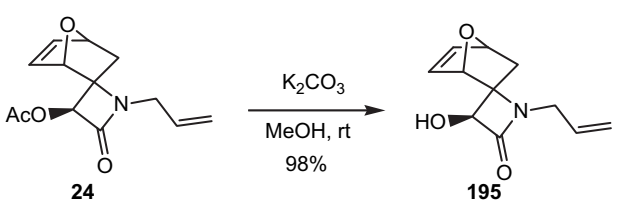
70 — **192** — **193**

Scheme 73.



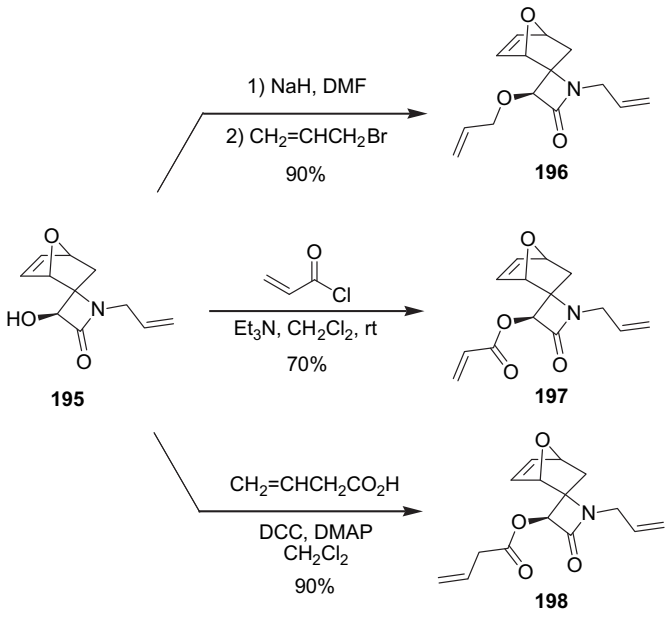
24 — **194**

Scheme 74.



24 — **195**

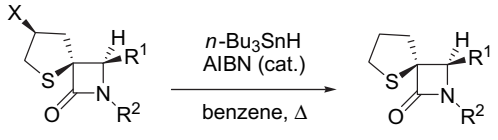
Scheme 75.



Scheme 76.

reaction afforded moderate-to-good overall yields (65–86%) of **202** (*N*-substituted) and **204** (*O*-substituted) adducts with the ratio of the latter over the former from 1:1 to 2:1. When the reaction was carried out with an equimolar amount of the substrate, spiroazetidinone **203** was also obtained as a product. The formation of this side product was eliminated by carrying out the reaction taking 2 mol of carbene precursors and 1 mol of isocyanates.

Dehalogenation studies have been carried out on 2-azetidinones, spiro-fused to 3′-bromo- and 3′-iodo-tetrahydrothiophene. Treatment of these compounds **104** or **106** with *n*-tributyltin hydride (1.2 equiv) in the presence of a catalytic amount of AIBN in benzene under reflux led to removal of the halogen, affording spiroazetidinones **205** in good yields (Scheme 78).[56]



104 or **106**

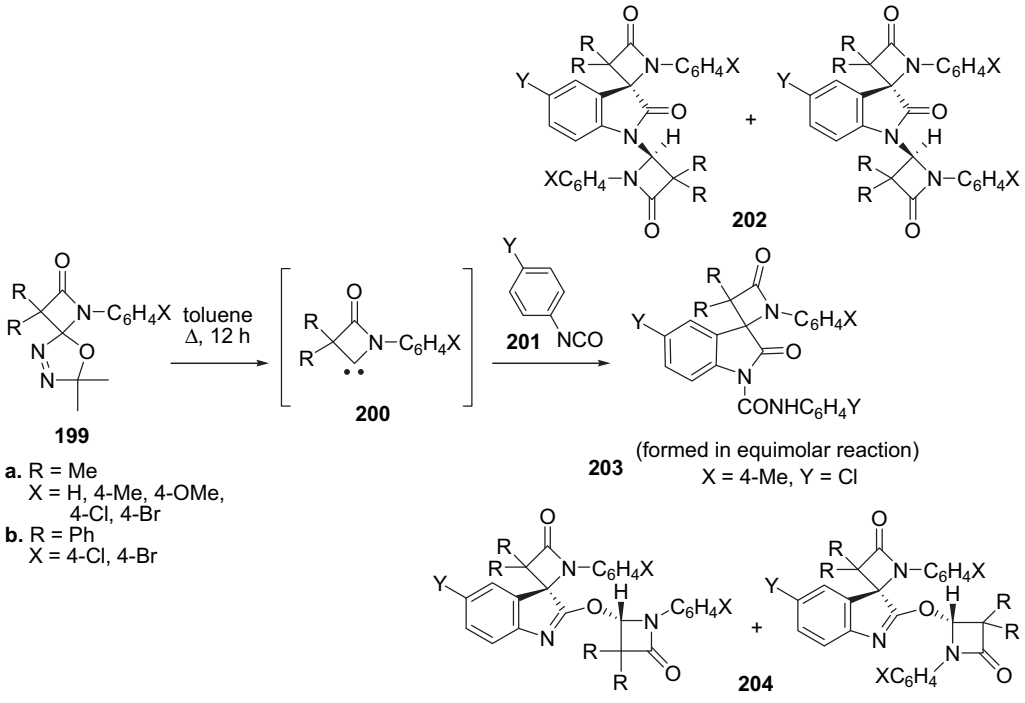
X = Br, I

205

a. R^1 = Ph, R^2 = 4-MeOC_6H_4 (75%)

b. R^1 = R^2 = Ph (70%)

Scheme 78.



a. R = Me
X = H, 4-Me, 4-OMe, 4-Cl, 4-Br

b. R = Ph
X = 4-Cl, 4-Br

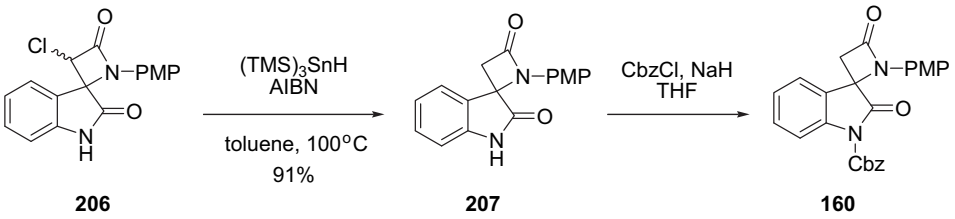
202 and **204**

if R = Me:
X = H, Y = Me; X = H, Y = Cl; X = 4-Me, Y = Me; X = 4-Me, Y = Cl; X = 4-MeO, Y = H; X = 4-MeO, Y = Me; X = 4-MeO, Y = Cl; X = 4-Cl, Y = Me; X = 4-Br, Y = Me
if R = Ph:
X = 4-Cl, Y = Cl; X = 4-Br, Y = Cl

Scheme 77.

the addition of an intermediate cyclic acylaminocarbene **200**, generated in situ by thermal decomposition of the oxadiazoline ring in the substrates **199**, to isocyanates **201**. The nature of the substituents on the phenyl group in both the carbenes and the isocyanates had a negligible effect on the outcome of these reactions. In all cases, the

Treatment of spiroazetidinone **206**, synthesised applying Staudinger reaction conditions, with tris(trimethylsilyl)tin hydride resulted in dechlorination at C3, forming spiroazetidinone **207** (Scheme 79). The indolinone NH group in the latter compound was Cbz protected using a standard protocol furnishing **160**.[72]



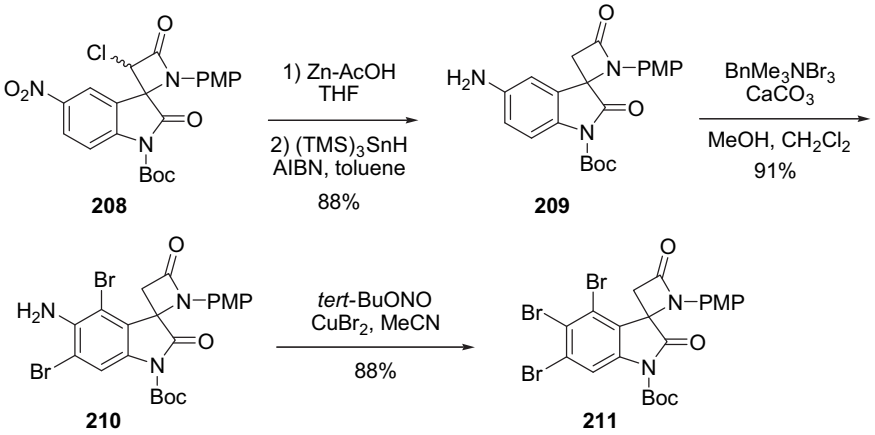
Scheme 79.

2-Azetidinone **211**, spiro-fused to tribrominated indolinone, required in a synthetic approach to chartelline, was obtained by a sequence of reactions involving reductive removal of the chloro atom and reduction of the nitro group to an amino group, aromatic dibromination and replacement of the aromatic amino group by a bromo atom in spiroazetidinones **208**, **209** and **210**, respectively (Scheme 80).[72]

by the reaction of the aldehyde group with the activated carbon–carbon double bond, giving rise to compound **217** (Scheme 82).[72]

4. Bioactive spiro-fused β-lactams

The antibacterial[79] and antiviral[80] activities of spiroazetidinones have already been reported in 1978 and 1990, respectively. Spi-

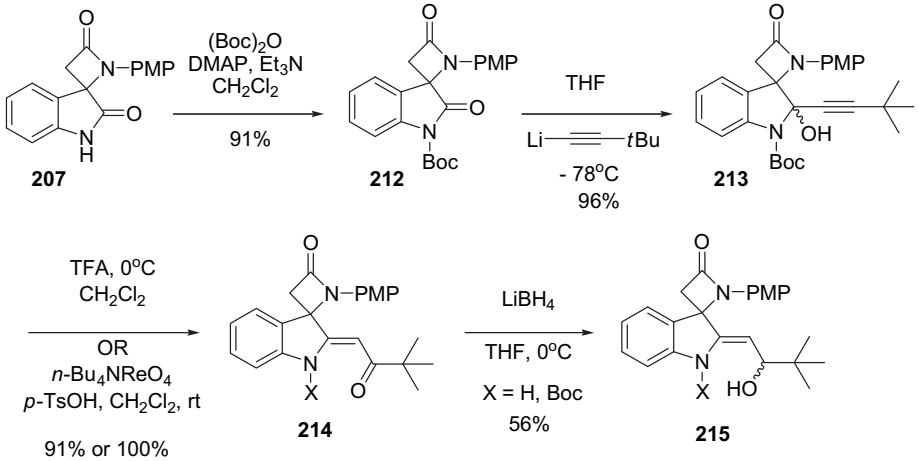


Scheme 80.

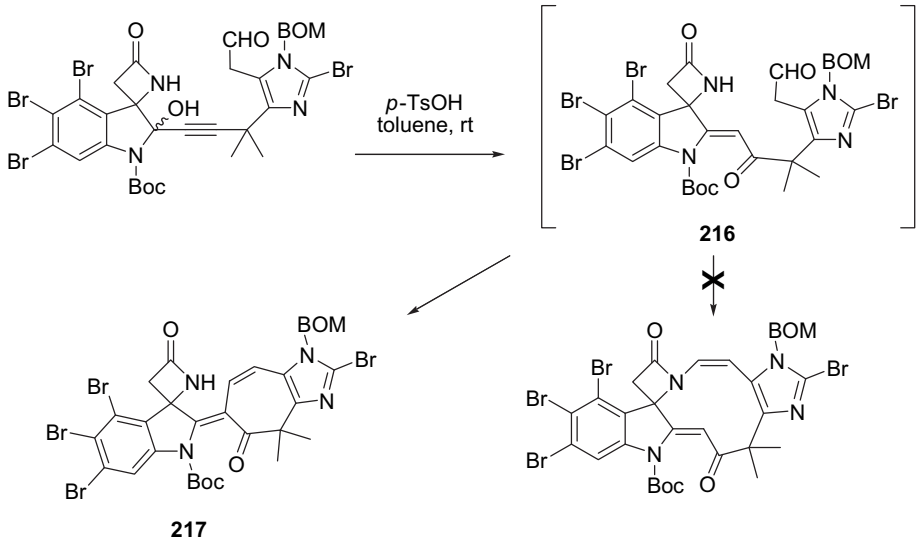
Selective addition of lithium *tert*-butylacetylide across the γ-lactam carbonyl moiety in spiroazetidinone **212** has been shown to result in the formation of a new spiro-fused 2-azetidinone **213**. A further transformation of this azetidinone to azetidinone **215** via reduction of azetidinone **214** is shown in Scheme 81.[72] A strategy to construct the 10-membered ring of the naturally occurring chartelline by intramolecular condensation of the β-lactam nitrogen atom with carboxaldehyde in **216** failed, due to the formation of a seven-membered ring

roazetidinone **218** (Fig. 4) has been found to be an inhibitor of both poliovirus and human rhinovirus 3C-proteinases. Spiroazetidinones have also been reported to act as cholesterol absorption inhibitors (CAIs), with spiroazetidinones SCH 54016 **219** and SCH 58053 **220** (Fig. 4) showing an excellent cholesterol absorption inhibitory activity.[81]

2-Azetidinones, spiro-fused to oxetane and tetrahydrofuran (Fig. 5), have been evaluated as acetyl-CoA cholesterol acyltransferase



Scheme 81.



Scheme 82.

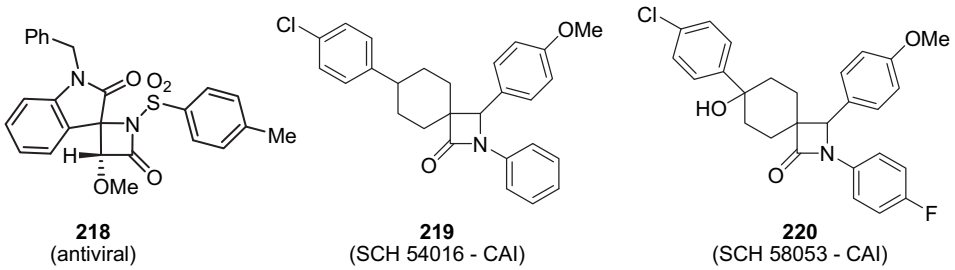


Fig. 4. Bioactive spiro-fused β-lactams **218**–**220**.

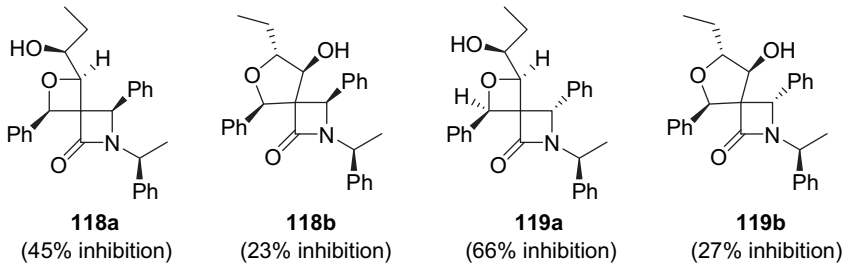


Fig. 5. Spiro-fused β-lactam ACAT inhibitors **118** and **119**.

(ACAT) inhibitors,[59] showing modest activity (23–66% inhibition). Interestingly, oxetane-fused azetidinones (**118a** and **119a**) showed higher activity in comparison to tetrahydrofuran-fused azetidinones (**118b** and **119b**).

N-Methylthio-2-azetidinone **221** (Fig. 6) spiro-fused to tetrahydrofuran exhibits antibacterial activity against Bacilli.[82] This β-lactam was screened according to the Kirby–Bauer method of well diffusion on agar plates.

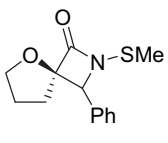


Fig. 6. Antibacterial spiro-fused β-lactam **221**.

5. Concluding remarks

Spiro-fused 2-azetidinones have drawn considerable interest in recent years, due to a number of biological activities associated with this class of compounds. Within the various approaches to the construction of the spiro framework, the Staudinger ketene–imine cycloaddition occupies a central place. Various cyclic ketenes, some derived from natural compounds, such as L-proline, have been reacted with imines to afford spiro-fused 2-azetidinones, often in a stereoselective manner. The cyclisation of β-amino acids and β-functionalised amides under thermal and photochemical conditions has led to the synthesis of some novel spiro-fused 2-azetidinones. The cyclisation reactions of substituents present at monocyclic 2-azetidinones, e.g., halocyclisation of an allylic group, are newer approaches to create a spiro-carbon centre, as well as the cycloaddition reactions of the exocyclic carbon–carbon double bond of methylidene-2-azetidinones. Transformations of functionalities present at

spiro-fused 2-azetidinones have further led to the discovery of many novel spiro-fused 2-azetidinones. Ring-opening reactions have contributed to the discovery of biologically important classes of compounds, such as β-amino acids, β-amino esters and amides. The structures of some spiro-fused 2-azetidinones have been established by X-ray crystallography. The synthetic endeavours to chartellines have contributed to the discovery of many novel spiro-fused 2-azetidinones and their chemistry before the final synthesis of chartelline C was accomplished in 2006. Hopefully, the synthesis and chemistry of spiro-2-azetidinones will continue to attract researchers in the near future and more interesting results will be forthcoming.

Acknowledgements

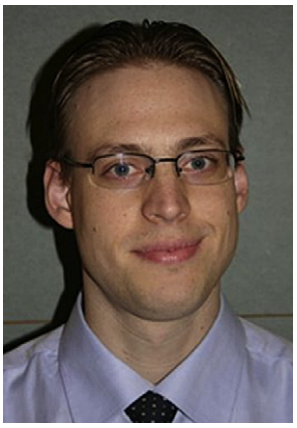
The authors are indebted to the Chemistry Department at the University of Botswana, to the 'Fund for Scientific Research—Flanders' (FWO-Vlaanderen) and to Ghent University (GOA), for financial support.

References and notes

1. (a) *The Organic Chemistry of β-lactams*; George, G. I., Ravikumar, B. T., Eds.; VCH: New York, NY, 1993; p 295; (b) Manhas, M. S.; Bose, A. K. *Chemistry of Penicillin, Cephalosporin C and Analogs*; Mercel Dekker: New York, NY, 1969; (c) De Kimpe, N. In *Azetidines, Azetines and Azetes in Comprehensive Heterocyclic Chemistry-II*; Katritzky, A. R., Ramsden, C. A., Scriven, E., Taylor, R., Eds.; Pergamon: Oxford, 1995; Vol. 1B, p 507; (Padwa, A., Ed.).
2. Singh, G. S. *Mini-Rev. Med. Chem.* **2004**, *4*, 69.
3. Singh, G. S. *Mini-Rev. Med. Chem.* **2004**, *4*, 92.
4. (a) Singh, G. S.; D'hooghe, M.; De Kimpe, N. In *Azetidines, Azetines and Azetes in Comprehensive Heterocyclic Chemistry-III*; Katritzky, A. R., Ramsden, C. A., Scriven, E., Taylor, R., Eds.; Elsevier: UK, 2008; Vol. 2, p 1; (Stevens, C., Ed.); (b) Singh, G. S. *Tetrahedron* **2003**, *59*, 7631; (c) Deshmukh, A. R. A. S.; Bhawal, B. M.; Krishnaswami, D.; Govande, V. V.; Shinkre, B. A.; Jayanthi, A. *Curr. Med. Chem.* **2004**, *11*, 1889; (d) Alcaide, B.; Almendros, P. *Curr. Med. Chem.* **2004**, *11*, 1921; (e) Hwu, J. R.; Ethiraj, K. S.; Hakimelahi, G. H. *Mini-Rev. Med. Chem.* **2003**, *3*, 305; (f) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Rev.* **2007**, *107*, 4437; (g) Ojima, I. *Acc. Chem. Res.* **1995**, *28*, 383; (h) Ojima, I.; Delaloge, F. *Chem. Soc. Rev.* **1997**, *26*, 377; (i) Alcaide, B.; Aragoncillo, C.; Almendros, P. In *Cephalosporins in Comprehensive Heterocyclic Chemistry-III*; Katritzky, A. R., RamsdenC, A., Scriven, E., Taylor, R., Eds.; Elsevier: UK, 2008; Vol. 2, p 111; (Stevens, C., Ed.); (j) Marchand-Brynaert, J.; Brulé, C. In *Penicillins in Comprehensive Heterocyclic Chemistry-III*; Katritzky, A. R., Ramsden, C. A., Scriven, E., Taylor, R., Eds.; Elsevier: UK, 2008; Vol. 2, p 173; (Stevens, C., Ed.); (k) Fisher, J. F.; Meroueh, S. O.; Mobashery, S. *Chem. Rev.* **2005**, *105*, 395; (l) France, S.; Weatherwax, A.; Taggi, A. E.; Lectka, T. *Acc. Chem. Res.* **2004**, *37*, 592.
5. Baran, P. S.; Shenvi, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 14028.
6. (a) Xu, J. *Arkivoc* **2009**, *ix*, 21; (b) Jiao, L.; Liang, Y.; Xu, J. X. *J. Am. Chem. Soc.* **2006**, *128*, 6060.
7. Dandia, A.; Singh, R.; Sharma, P. *Heteroat. Chem.* **2003**, *14*, 468.
8. Bose, A. K.; Anjaneyulu, V.; Bhattacharya, S. K.; Manhas, M. S. *Tetrahedron* **1967**, *23*, 4769.
9. Fahr, E.; Doppert, K.; Konigsdorfer, K.; Scheckenbach, F. *Tetrahedron* **1968**, *24*, 1011.
10. Shridhar, D. R.; Ram, B.; Narayana, B. L.; Awasthi, A. K.; Reddy, G. J. *Synthesis* **1984**, 846.
11. Singh, S. B.; Mehrotra, K. N. *Can. J. Chem.* **1982**, *60*, 1901.
12. Singh, G. S.; Mehrotra, K. N. *Indian J. Chem., Sect. B* **1985**, *24*, 129.
13. (a) Singh, G. S.; Singh, T.; Lakhan, R. *Indian J. Chem., Sect. B* **1997**, *36*, 951; (b) Singh, G. S.; Mmolotsi, B. J. *J. Heterocycl. Chem.* **2006**, *43*, 1665; (c) Singh, G. S.; Luntha, P. *Eur. J. Med. Chem.* **2009**, *44*, 2265.
14. Jarrahpour, A.; Khalili, D. *Tetrahedron Lett.* **2007**, *48*, 7140.
15. Azizian, J.; Sarrafi, Y.; Mehrdad, M. *Indian J. Chem., Sect. B* **2000**, *39*, 304.
16. Nishikawa, T.; Kajii, S.; Isobe, M. *Synlett* **2004**, 2025.
17. Nishikawa, T.; Kajii, S.; Isobe, M. *Chem. Lett.* **2004**, *33*, 440.
18. Robertson, J.; Bell, S. J.; Krivokapic, A. *Org. Biomol. Chem.* **2005**, *3*, 4246.
19. Barba, V.; Hernandez, C.; Rojas-Lima, S.; Farfin, N.; Santillan, R. *Can. J. Chem.* **1999**, *77*, 2025.
20. Arjona, O.; Csáky, A. G.; Murcia, M. C.; Plumet, J. *Tetrahedron Lett.* **2002**, *43*, 6405.
21. (a) Elkanzi, N. A. A. *Phosphorus, Sulfur Silicon Relat. Elem.* **2008**, *183*, 2040; (b) Khalafallah, A. K.; Elkanzi, N. A. A.; Soleiman, H. A.; Younis, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **2006**, *181*, 2483; (c) Khalafallah, A. K.; Koraiem, A. I. M.; Abudooh, A. M.; Shindy, H. A.; Elmagid, N. A. *Asian J. Chem.* **1996**, *8*, 529.
22. Rojas-Lima, S.; Santillan-Sid, L.; Lopez-Ruiz, H.; Alvarez-Hernandez, A. *Heterocycles* **2007**, *71*, 531.
23. Alonso, E.; del Pozo, C.; Gonzalez, J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 571.
24. (a) Cremonesi, G.; Croce, P. D.; La Rosa, C. *Tetrahedron* **2004**, *60*, 93; (b) Croce, P. D.; Ferraccioli, R.; La Rosa, C. *Tetrahedron* **1995**, *51*, 9385; (c) Croce, P. D.; Ferraccioli, R.; La Rosa, C. *Tetrahedron* **1999**, *55*, 201; (d) Croce, P. D.; La Rosa, C. *Tetrahedron: Asymmetry* **1999**, *10*, 1193; (e) Cremonesi, G.; Croce, P. D.; La Rosa, C. *Helv. Chim. Acta* **2005**, *88*, 1580.
25. Croce, P. D.; Cremonesi, G.; Fontana, F.; Forni, A.; La Rosa, C. *Tetrahedron: Asymmetry* **2005**, *16*, 3371.
26. Macias, A.; Alonso, E.; Venturini, A.; Gonzalez, J. *J. Org. Chem.* **2004**, *69*, 7004.
27. Macias, A.; Alonso, E.; del Pozo, C.; Gonzalez, J. *Tetrahedron Lett.* **2004**, *45*, 4657.
28. Macias, A.; Ramallal, A. M.; Alonso, E.; del Pozo, C.; Gonzalez, J. *J. Org. Chem.* **2006**, *71*, 7721.
29. Khasanov, A. B.; Ramirez-Weinhouse, M. M.; Webb, T. R.; Thiruvazhi, M. *J. Org. Chem.* **2004**, *69*, 5766.
30. Cremonesi, G.; Croce, P. D.; Fontana, F.; La Rosa, C. *J. Org. Chem.* **2010**, *75*, 2010.
31. Alonso, E.; Lopez-Ortiz, F.; del Pozo, C.; Perlta, E.; Macias, A.; Gonzalez, J. *J. Org. Chem.* **2001**, *66*, 6333.
32. Trabocchi, A.; Lalli, C.; Guarna, F.; Guarna, A. *Eur. J. Org. Chem.* **2007**, 4594.
33. Chinchinalkar, P. M.; Puranik, V. G.; Deshmukh, A. R. A. S. *Tetrahedron* **2007**, *63*, 9179.
34. Jarrahpour, A.; Ebrahimi, E. *Molecules* **2010**, *15*, 515.
35. Tsuno, T.; Kondo, K.; Sugiyama, K. *J. Heterocycl. Chem.* **2006**, *43*, 21.
36. Zhou, A.; Cao, L.; Li, H.; Liu, Z.; Pittmann, C. U., Jr. *Synlett* **2006**, 201.
37. (a) Singh, G. S.; Siddiqui, N.; Pandeya, S. N. *Asian J. Chem.* **1993**, *4*, 788; (b) Singh, G. S.; Siddiqui, N.; Pandeya, S. N. *Boll. Chim. Farm.* **1994**, *133*, 76; (c) Agrawal, R.; Agrawal, C.; Singh, C.; Mishra, V. S. *Indian J. Chem.* **1989**, *28B*, 893; (d) Singh, G. S.; Singh, T.; Lakhan, R. *Indian J. Chem.* **1997**, *36B*, 951.
38. Ikeda, M.; Uchino, T.; Yamano, M.; Watanabe, Y.; Ishibashi, H.; Kido, M. *Chem. Pharm. Bull.* **1986**, *34*, 4997.
39. Chowdary, N. S.; Suri, J. T.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 2507.
40. Wu, G.; Tormas, W. *J. Org. Chem.* **1997**, *62*, 6412.
41. Stocks, M. J.; Hamza, D.; Pairaudeau, G.; Stonehouse, J. P.; Thorn, P. V. *Synlett* **2007**, 2587.
42. Arnott, G.; Clayden, J.; Hamilton, S. D. *Org. Lett.* **2006**, *8*, 5325.
43. Clayden, J.; Hamilton, S. D.; Mohammed, R. T. *Org. Lett.* **2006**, *8*, 3673.
44. Ishibashi, H.; Higuchi, M.; Ohba, M.; Ikeda, M. *Tetrahedron Lett.* **1998**, *39*, 75.
45. Liang, J. X.; Chen, J. B.; Du, F. X.; Zeng, X. H.; Li, L.; Zhang, H. B. *Org. Lett.* **2009**, *11*, 2820.
46. Bittermann, H.; Boeckler, F.; Einsiedel, J.; Gmeiner, P. *Chem.—Eur. J.* **2006**, *12*, 6315.
47. Bittermann, H.; Gmeiner, P. *J. Org. Chem.* **2006**, *71*, 97.
48. Wardrop, D. J.; Burge, M. S. *J. Org. Chem.* **2005**, *70*, 10271.
49. Baran, P. S.; Shenvi, R. A.; Mitsos, C. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3714.
50. Carle, J. S.; Christophersen, C. *J. Org. Chem.* **1980**, *45*, 1586; Carle, J. S.; Christophersen, C. *J. Am. Chem. Soc.* **1979**, *101*, 492; Carle, J. S.; Christophersen, C. *J. Am. Chem. Soc.* **1980**, *102*, 5107; Christophersen, C. *Acta Chem. Scand.* **1985**, *B39*, 517.
51. Bose, A. K.; Garrat, G.; Pelosi, J. J. *J. Org. Chem.* **1963**, *28*, 730.
52. Alcaide, B.; Almendros, P.; Campo, T. M.; Rodriguez-Acebes, R. *Tetrahedron Lett.* **2004**, *45*, 6429.
53. Alcaide, B.; Almendros, P.; del Campo, T. M.; Quiros, M. T. *Chem.—Eur. J.* **2009**, *15*, 3344.
54. Alcaide, B.; Almendros, P.; Martínez del Campo, T.; Carrascosa, R. *Eur. J. Org. Chem.* **2010**, 4912.
55. Bhalla, A.; Venugopalan, P.; Bari, S. S. *Eur. J. Org. Chem.* **2006**, 4943.
56. Arora, R.; Venugopalan, P.; Bari, S. S. *J. Chem. Sci.* **2010**, *122*, 1.
57. Bhalla, A.; Venugopalan, P.; Bhasin, K. K.; Bari, S. S. *Tetrahedron* **2007**, *63*, 3195.
58. Chen, L. Y.; Zaks, A.; Chakalmanni, S.; Dugar, S. *J. Org. Chem.* **1996**, *61*, 8341.
59. Benfatti, F.; Cardillo, G.; Gentilucci, L.; Tolomelli, A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1946.
60. Benfatti, F.; Cardillo, G.; Gentilucci, L.; Tolomelli, A. *Eur. J. Org. Chem.* **2007**, 3199.
61. Gurtler, S.; Johner, M.; Ruf, S.; Otto, H. H. *Helv. Chim. Acta* **1993**, *76*, 2958.
62. Strauss, A.; Otto, H. H. *Helv. Chim. Acta* **1997**, *80*, 1823.
63. Anklam, S.; Liebscher, J. *Tetrahedron* **1998**, *54*, 6369.
64. Ruff, S.; Otto, H. H. *Helv. Chim. Acta* **1995**, *78*, 629.
65. Zanobini, A.; Gensini, M.; Magull, J.; Vidovic, D.; Kozhushkov, S. I.; Brandi, A.; de Meijere, A. *Eur. J. Org. Chem.* **2004**, 4158.
66. Marradi, M.; Brandi, A.; Magull, J.; Schill, H.; de Meijere, A. *Eur. J. Org. Chem.* **2006**, 5485.
67. (a) Cordero, F. M.; Pisaneschi, F.; Salvati, M.; Paschetta, V.; Ollivier, J.; Salaun, J.; Brandi, A. *J. Org. Chem.* **2003**, *68*, 3271; (b) Cordero, F. M.; Salvati, M.; Pisaneschi, F.; Brandi, A. *Eur. J. Org. Chem.* **2004**, 2271; (c) Cordero, F. M.; Pisaneschi, F.; Goti, A.; Ollivier, J.; Salaun, J. *J. Am. Chem. Soc.* **2000**, *122*, 8075.
68. Zanobini, A.; Brandi, A.; de Meijere, A. *Eur. J. Org. Chem.* **2006**, 1251.
69. Alonso, E.; Pozo, C. D.; Gonzalez, J. *Synlett* **2002**, 69.
70. Alcaide, B.; Almendros, P.; Redondo, M. C. *Eur. J. Org. Chem.* **2007**, 3707.
71. Croce, P. D.; La Rosa, C. *Heterocycles* **2000**, *53*, 2653.
72. (a) Sun, C.; Lin, X.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 3159; (b) Nair, V.; Deepthi, A. *Chem. Rev.* **2007**, *107*, 1862; (c) Sridharan, V.; Menendez, J. C. *Chem. Rev.* **2010**, *110*, 3805.
73. Sun, C.; Camp, J. E.; Weinreb, S. M. *Org. Lett.* **2006**, *8*, 1779.
74. Singh, G. S. *J. Heterocycl. Chem.* **2000**, *37*, 1355.
75. Cremonesi, G.; Croce, P. D.; Fontana, F.; La Rosa, C. *Tetrahedron: Asymmetry* **2008**, *19*, 554.
76. Csaky, A. G.; Medel, R.; Murcia, M. C.; Plumet, J. *Helv. Chim. Acta* **2005**, *88*, 1387.
77. Zoghbi, M.; Horne, S. E.; Warkentin, J. *J. Org. Chem.* **1994**, *59*, 4090.
78. Cheng, Y.; Wang, B.; Cheng, L.-Q. *J. Org. Chem.* **2006**, *71*, 4418.
79. Sheehan, J. C.; Chacko, E.; Lo, Y. S.; Ponzi, D. R.; Sato, E. *J. Org. Chem.* **1978**, *43*, 4856.
80. Skiles, J. W.; McNeil, D. *Tetrahedron Lett.* **1990**, *31*, 7277.
81. Dugar, S.; Clader, J.; Chan, T. M.; Davis, H. *J. Med. Chem.* **1995**, *38*, 4875.
82. Turos, E.; Long, T. E.; Heldreth, B.; Leslie, J. M.; Reddy, G. S. K.; Wang, Y.; Coates, C.; Konaklieva, M.; Dickey, S.; Lim, D. V.; Alonso, E.; Gonzalez, J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2084.

Biographical sketch

Girija S. Singh was born in Sasaram (Bihar), India. He received his B.Sc. and M.Sc. degrees from the U.P. College (then Gorakhpur University), Varanasi, India, in 1977 and 1979, respectively. He received his Ph.D. degree from the Banaras Hindu University (BHU), India, completing his doctoral thesis on the reactions of diazoalkanes and diazoketones with imines, amines and hydrazones in October, 1984. During his research for the Ph.D. degree, he was recipient of the junior- and senior-research fellowships of the CSIR, New Delhi. Since then he has occupied teaching and research positions in various universities, such as Banaras Hindu University, India (PDF, Research Associate, Pool-Officer, Reader), Osaka University, Japan (PDF), University of Zambia (Lecturer) and University of Botswana (Lecturer, Senior Lecturer, Associate Professor). He has authored 65 publications in books and in peer-reviewed journals. His research interests include the study of synthesis and reactivity of biologically important heterocycles, reactions of carbenoids, metal-catalyzed oxidations and organic chemistry education.



Matthias D'hooghe was born in Kortrijk, Belgium, in 1978. He received his Master's diploma in Bioscience Engineering—Chemistry from Ghent University (Belgium) in 2001. Subsequently, he enrolled in a Ph.D. program at Ghent University with Prof. N. De Kimpe as a promoter, studying the synthesis and reactivity of 2-(bromomethyl)aziridines. He obtained his Ph.D. degree in 2006 and was elected as a laureate of the DSM Science & Technology Awards 2007 for outstanding Ph.D. research. In April 2007, he became Assistant Professor in the group of Prof. N. De Kimpe. In June–July 2009, he performed a short postdoctoral stay at Eindhoven University of Technology (The Netherlands) in the field of homogeneous catalysis under the supervision of Prof. D. Vogt. In October 2010, he was promoted to Associate Professor (Professor in the rank of Lecturer) at the Department of Sustainable Organic Chemistry and Technology, Faculty of Bioscience Engineering, Ghent University. His main research interests include the chemistry of small-ring azaheterocycles, with a special focus on aziridines, azetidines and β-lactams. He is the author of 65 publications in international peer-reviewed journals.

Norbert De Kimpe obtained the diploma of chemical agricultural engineer in 1971, the Ph.D. degree in 1975, and the habilitation degree in 1985, all from Ghent University, Ghent (Belgium). He performed postdoctoral research work at the University of Massachusetts, Harbor Campus, at Boston (USA) (1979) and at the Centre National de Recherche Scientifique (CNRS) in Thiais, Paris (France) (1983), where he worked on unstable nitrogen-substituted sulfenyl derivatives and electron-deficient carbenium ions, respectively. He made his scientific career at the Belgian National Fund for Scientific Research, where he went through all stages up to the position of Research Director. During this career, he was affiliated with the Department of Organic Chemistry, Faculty of Bioscience Engineering at Ghent University, where he took up teaching positions since 1987. He is now full professor in organic chemistry at the latter institution. He was a guest professor at the Centre Universitaire de Recherche sur la Pharmacopée et la Médecine Traditionelle in Butare (Rwanda, Central Africa), and at the Universities of Perpignan (France), Helsinki (Finland), Leuven (Belgium), Siena (Italy), Barcelona (Spain), Sofia (Bulgaria), Buenos Aires (Argentina), and Pretoria (South Africa). He was awarded the degree of Doctor honoris causa from the Russian Academy of Sciences in Novosibirsk (Russia) in 1998 and from the University of Szeged (Szeged, Hungary) in 2007. He obtained the Medal of Honour of Sofia University (Bulgaria) in 2006 and was awarded the A.N. Kost medal of the Mendeleev Russian Chemical Society in 2010. He is Member of the Royal Flemish Academy of Belgium, Section Natural Sciences and the Academia Scientiarum et Artium Europea (European Academy of Sciences and Arts), Salzburg (Austria). He is Fellow of the Royal Society of Chemistry (UK) and IUPAC Fellow. He is the author of 550 articles in international peer-reviewed journals. His research interests include (1) the synthesis of heterocyclic compounds, with focus on agrochemicals, pharmaceuticals, and natural products, (2) flavour chemistry, and (3) the bioassay-guided isolation of bioactive natural products from medicinal plants.