Pergamon

Tetrahedron 56 (2000) 6359–6383

TETRAHEDRON

Tetrahedron Report Number 537

The Synthesis of 1,(7)-Substituted Pyrrolizidin-3-ones

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Received 12 June 2000

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1. Introduction

Pyrrolizidine alkaloids are of widespread occurrence in plants. They are generally derivatives of hydroxylated pyrrolizidines (necine base moiety), which are often 1- and/or 7-(di)substituted by long highly branched chains (ester moiety).[1] Many of the alkaloids are hepatotoxic and some are carcinogenic.[1] Because of this potent biological activity and also because of the scope for stereochemical variation within a concise bicyclic framework, necine bases have emerged as attractive targets for the development of new synthetic methodology. One strategy, which has been extensively exploited, involves the assembly of the bicycle as a pyrrolizidin-3-one (hexahydropyrrolizin-3-one) unit **1**, which can be reduced to the necine base (e.g. with lithium aluminium hydride) at a late stage in the synthesis. Some typical examples of homochiral necine bases, which have been made in this way, are given in Fig. 1.

In this review the diverse syntheses of 1-monosubstituted-,

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PII: S0040-4020(00)00532-9

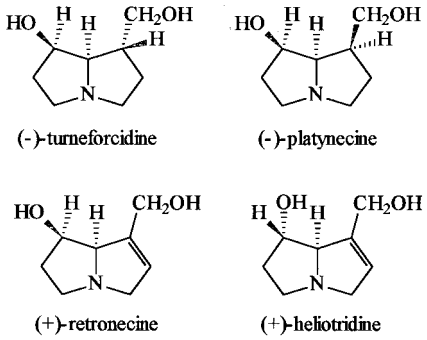
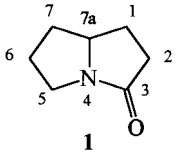


Figure 1. Some typical necine bases

7-monosubstituted- and 1,7-disubstituted pyrrolizidin-3-ones (including those of the parent compound **1**) are surveyed up to the end of 1998. This area has not been reviewed before. The pyrrolizidin-3-one nomenclature and numbering scheme is used consistently throughout, even in cases in which the strict priority order is not followed.



1

Although pyrrolizidin-3-ones are structurally based on a simple eight atom unit, there is considerable scope for application of different methods of ring synthesis due, at least in part, to the potential for stereochemical variation mentioned above. Thus there are 4 isomers (including enantiomers) of 1-substituted or 7-substituted pyrrolizidin-3-ones and 8 isomers of the 1,7-disubstituted derivatives. New techniques developed for stereocontrolled ring synthesis (discussed in detail below) include radical, anionic (e.g. vinyl anion), cationic (e.g. iminium ion) and carbenoid cyclisations, while pericyclic processes are exemplified by aza-Cope rearrangements and 1,3-dipolar cycloadditions. Many of these novel methods have been developed in the last 20 years. Indeed, nearly 90% of the papers cited in this review have been published since 1980, and nearly half since 1990; there is no sign of any abatement in this activity.

For ease of reference, the synthetic routes have been classified according to the number and the positions of the bonds formed in the final step of the sequence. This arrangement has been used by one of the authors in a previous review of the chemistry of unsaturated pyrrolizin-3-ones.[2]

Table 1. Product distribution, yields and diastereoisomeric excess of **5** after treatment of **2** with Bu_3SnH

R	X	R^1	**3**	**4**	de (**5**)
H	Cl	Ph	49	13	>90
H	Cl	Me	60	24	>90
H	SPh	Ph	67	25	>90
CO_2Et	Cl	Ph	77	–	100

2. Preparation of Pyrrolizidin-3-ones by Formation of One Bond

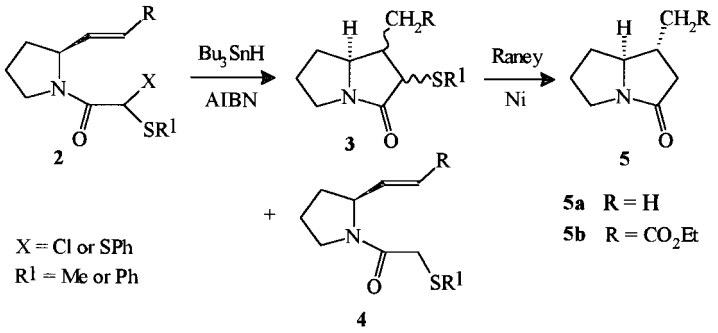
2.1. [1–2] Bond formation

This type of ring closure has been developed relatively recently and applied to the synthesis of 1-substituted pyrrolizidin-3-ones by both radical and ionic cyclizations. The cyclization precursors are often made from homochiral derivatives of proline, which sets the configuration at the C_{7a} centre.

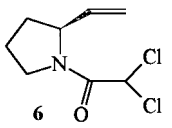
2.1.1. Radical cyclization. All the syntheses reported here used homochiral starting materials to produce optically active pyrrolizidin-3-ones.

Tributyltin hydride mediated. Ikeda and Ishibashi examined the tributyltin hydride (Bu_3SnH) mediated cyclization of *N*-allyl-α-chloro-α-thioacetamides and related compounds[3] and found that it proceeds regioselectively with high diastereoselectivity, as a result of minimising the steric repulsion between the substituent at C_1 and the C_7–C_{7a} bond in the transition state. The radical precursor **2**, prepared from (*S*)-prolinol, upon treatment with 1.1 equiv. of Bu_3SnH and a catalytic amount of azobisisobutyronitrile in boiling benzene, gave only the 5-*exo* product **3**, along with some reduction product **4** (Scheme 1 and Table 1). Desulfuration with Raney nickel provided the *trans*-pyrrolizidin-3-one **5** as the major product with good diastereoisomeric excess.[3c]

The related dichloroacetamide **6** gave **5a** (R=H) directly in 56% yield using 2.2 equiv of Bu_3SnH.[3c]



Scheme 1.



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Compound **5b** (R=CO_2Et) was converted into the aldehyde **7**, a precursor of (−)-trachelanthamidine (Scheme 2).[3c]

A similar radical cyclization of α-halogenoacetamides (e.g. **8**) has been reported, which involves an atom-transfer propagation using an excess of iodoethane as an iodine transfer agent (Scheme 3).[4] The stereoselective formation (de=94%) of optically active **9** has the advantage of allowing further functionalisation.

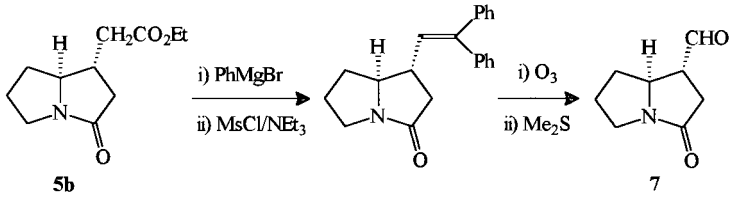
Metal-catalysed. Various metals (Pd, Ru, Cu, B) have been reported to act as catalysts for the atom transfer cyclization of 1-acyl-2-vinylpyrrolidines into *exo*-1-halogenomethylpyrrolizidin-3-ones. This method avoids the formation of reduction products and is more versatile than the tin hydride methodology for the elaboration of functionalities.

Mori initially cyclized the α-iodoamide **8** in the presence of a catalytic amount of $Pd(PPh_3)_4$ to give a mixture of three products, which were separated and treated individually (Scheme 4). The relative ratios of the cyclized products are dependent on experimental conditions.[5] More recently, the precursor **8** has been cyclized with triethylborane under mild conditions to afford only the iodopyrrolizidinone **9** with a small amount of its diastereoisomer (de >90%).[3g,3h]

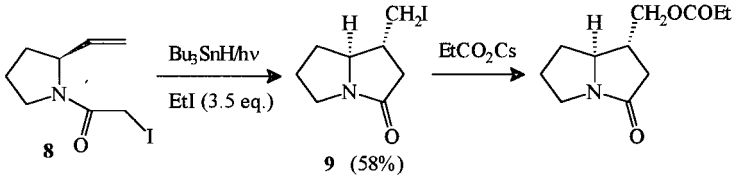
The ruthenium-catalysed chlorine-atom transfer cyclization of the precursors **2** has also been reported to proceed with high stereoselectivity (de=90%).[3a] The oxygen function was then introduced using cesium propanoate to give optically active **10** together with the cyclopropane **11** (Scheme 5).

Another radical cyclization involving an atom-transfer propagation has been reported, using a catalytic amount of copper(I) chloride (Scheme 6).[6] The particularly high stereoselectivity observed for this example may be a consequence of the added steric hindrance at C_2.

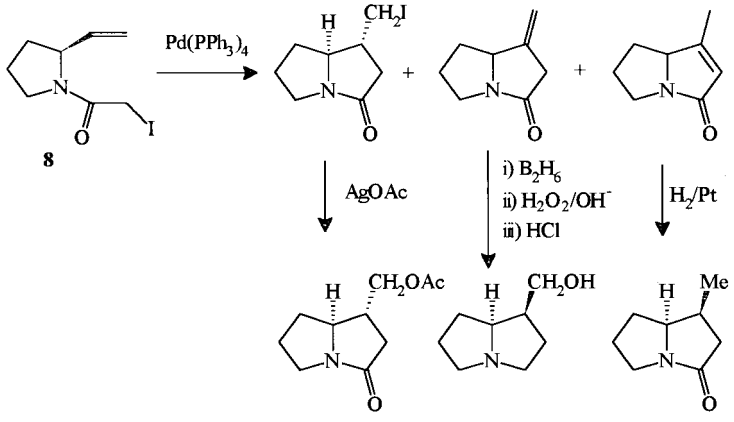
2.1.2. Ionic cyclization. Intramolecular Michael reaction of a suitably functionalised homochiral α-phenylsulfinyl acetamide gave **12** stereoselectively after reductive desulfuration (Scheme 7).[3b] Both enantiomers were produced, however, due to a partial epimerization at the 2-position of the pyrrolidine before cyclization.



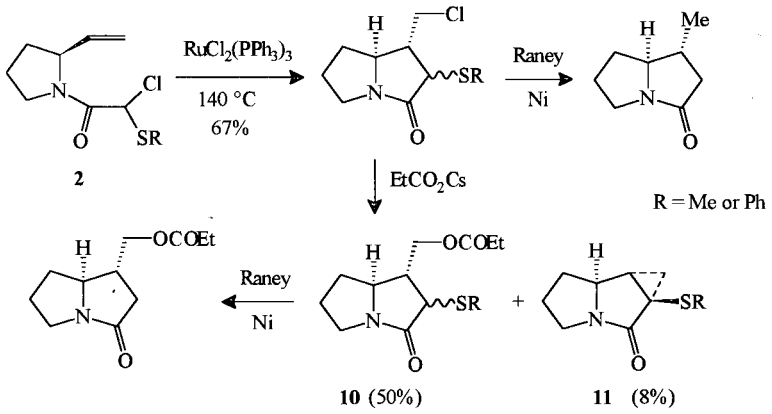
Scheme 2.



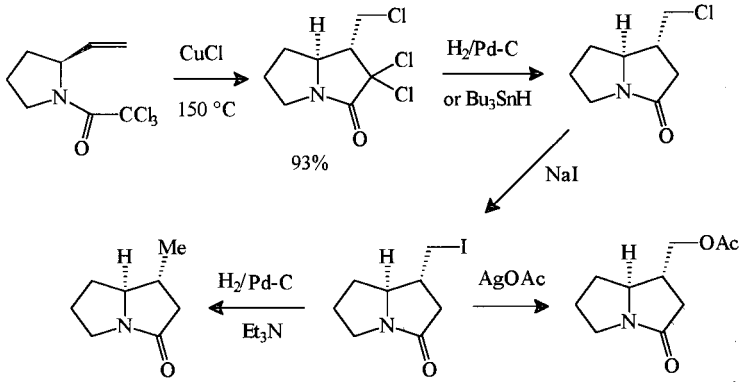
Scheme 3.



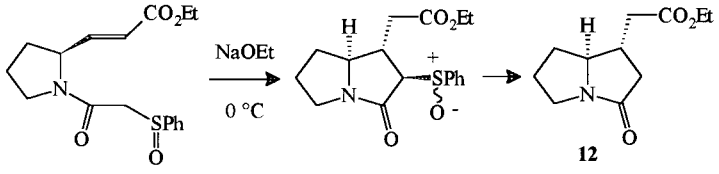
Scheme 4.



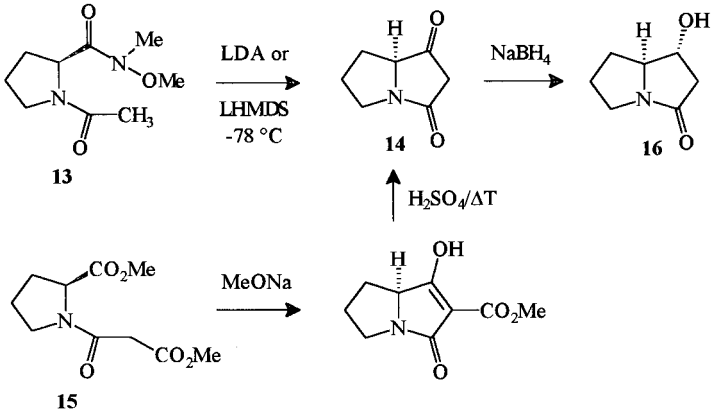
Scheme 5.



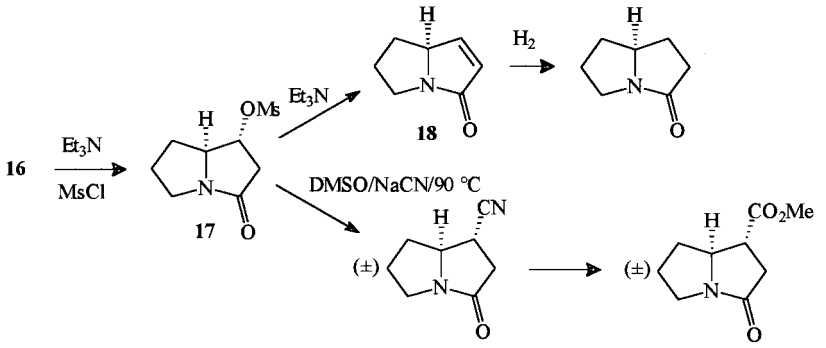
Scheme 6.



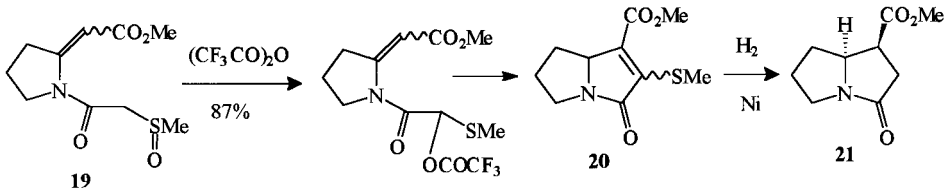
Scheme 7.



Scheme 8.



Scheme 9.



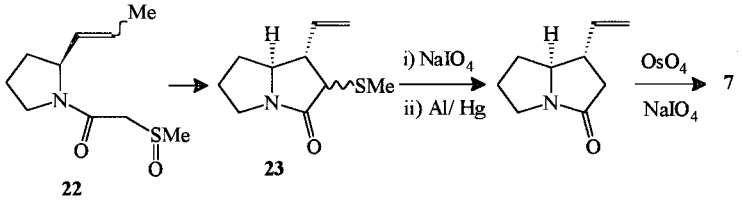
Scheme 10.

The homochiral dione **14** was formed either by base treatment of the acetamide derivative **13** or by Dieckmann cyclization of the *N*-malonyl intermediate **15** followed by hydrolysis and decarboxylation (Scheme 8).[7,8] Reduction with sodium borohydride gave **16** as the major diastereoisomer (de=90%), due to attack from the more crowded face. This unusual result could be a consequence of electrostatic repulsion between the hydride and the nitrogen lone pair. Partial reversal of selectivity was observed when K-selectride was used.[8] Further treatments afforded pyrrolam A **18** (93.5% ee) and other pyrrolizidin-3-ones (Scheme 9).[7] In the reaction of the mesylate **17** with sodium cyanide, loss of chirality was observed.

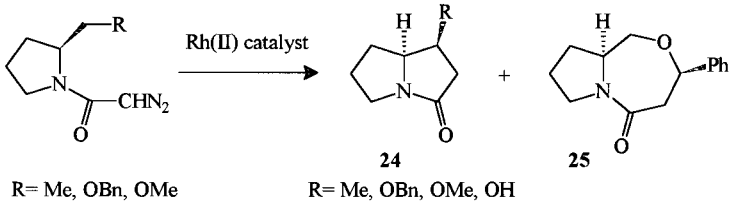
Ishibashi has shown that α-sulphinylacetamides such as **19** under Pummerer conditions (using trifluoroacetic anhydride) can act as initiators for olefin cyclization (Scheme 10). Hydrogenation of **20** over Raney nickel gave the racemic pyrrolizidinone **21** with high stereoselectivity.[3f]

Under the same conditions, **22** gave the pyrrolizidin-3-one **23** with the stereocentres at positions 1 and 7a uniquely defined. This product was transformed into the aldehyde **7** with a 75% optical purity (Scheme 11).[3e]

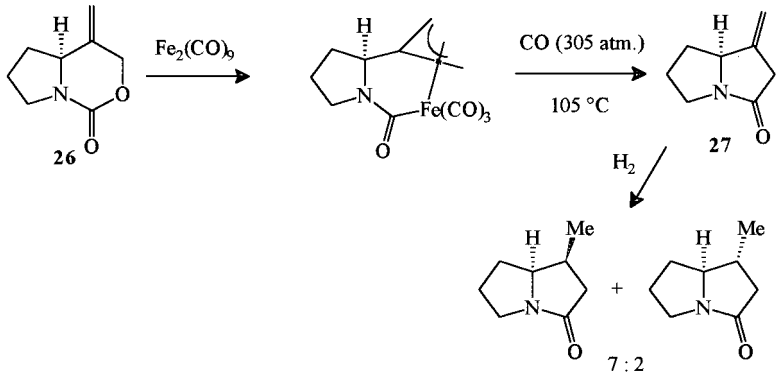
2.1.3. Carbene C–H insertion. Intramolecular C–H insertion reactions of metal carbenoids derived from chiral 2-substituted pyrrolidines were achieved in a very highly diastereoselective manner using dirhodium(II) imidazolidinone catalysts (Scheme 12).[9,10] Compound **24** (R=OBn, OMe) can then be easily converted into the hydroxy derivative (R=OH). The regioselectivity of the process is excellent except when R=OBn in which a C–H insertion also occurred into the benzylic position to give **25**.[9]



Scheme 11.



Scheme 12.



Scheme 13.

2.2. [2–3] Bond formation

Ley has reported the enantioselective synthesis of **27**, which could be converted into either precursors of (−)-heliotridane (as the major isomer formed by hydrogenation), or (−)-isoretronecanol (by treatment with diborane). The key steps in the cyclisation involve sequential formation of a π-allyltricarbonyliron lactam complex from the lactone **26** (derived from (*S*)-*N*-Boc-proline) followed by carbonylation (Scheme 13).[11]

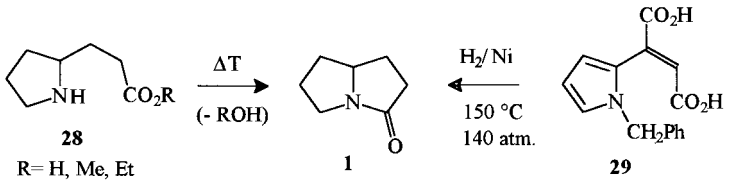
2.3. [3–4] Bond formation

Because the lactam bond is easily formed it is not surprising that the first pyrrolizidin-3-ones were prepared by intramolecular acylation of 2-substituted pyrrolidines. Simple heating of the unsubstituted pyrrolidylpropionic acid **28**, or its esters, afforded the parent compound **1** (Scheme 14).[12–16] The ethyl ester has even been reported to cyclize at room temperature over 1–2 days.[17] Another early synthesis of **1** has been achieved in one step from the pyrrole derivative **29** by hydrogenation under high pressure and temperature conditions.[18]

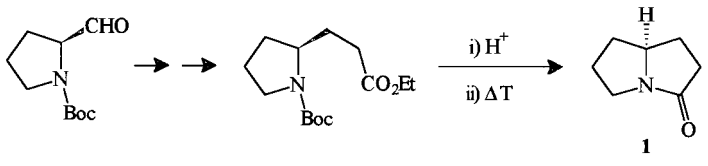
Formation of the [3–4] bond is effected commonly either by heating, treatment with a base or trimethyl aluminium, or by a combination of these methods. Enantioselective syntheses of pyrrolizidinones have been recently developed using homochiral pyrrolidine precursors. For example, the synthesis of (*S*)-pyrrolizidin-3-one **1** was carried out starting from *N*-Boc-prolinal (Scheme 15).[19,20] The (*R*)-enantiomer was formed by cyclization of the (*R*)-pyrrolidylpropionic acid **28**[21] and has also been obtained from hydrogenation of (*R*)-pyrrolam A **18**.[19]

2.3.1. Formation of 1-substituted pyrrolizidin-3-ones. The most important reactions under this heading involve the formation of racemic 1-alkoxycarbonylpyrrolizidin-3-one derivatives and the asymmetric synthesis of the 1-hydroxy compounds.

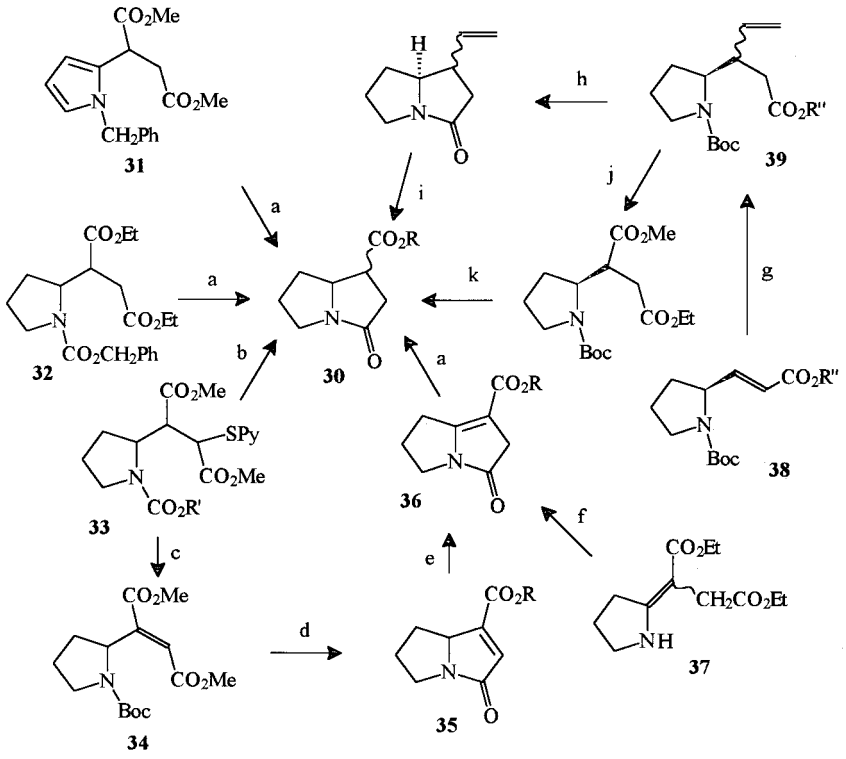
1-Alkoxycarbonylpyrrolizidin-3-ones **30** (R=Me, Et) have been synthesised generally from racemic *N*-protected 2-pyrrolidylbutanedioate esters (Scheme 16); initial deprotection, either by acidic hydrolysis or by hydrogenolysis, is followed by smooth cyclization to give **30** as a mixture of two pairs of diastereoisomers, often with poor selectivity. For example, **32**[22,23] and the thiopyridyl **33**[24] (R′=CH_2Ph, Py=2-pyridyl) afforded diastereomeric mixtures in ratios of 1.6:1 and 2.5:1, respectively, upon hydrogenation over Raney nickel and heating. Alternatively **33** (R′=*t*-butyl) gave the butenedioate ester **34** by oxidative elimination, which cyclized to **35**.[24] Double bond migration afforded the 1,7a-dehydropyrrolizidin-3-one **36**, which has also been synthesised from the diester **37**.[25] Hydrogenation of **36** proceeded selectively to yield solely the isomer of **30** in which the ester group is *trans* to the hydrogen atom at position 7a. The pyrrole precursor **31** was reported to



Scheme 14.



Scheme 15.



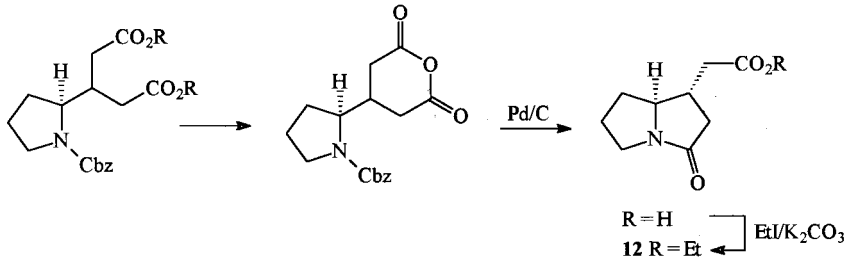
Scheme 16. (a) H_2; (b) Raney Ni/ΔT; (c) MCPBA; (d) CF_3CO_2H then NH_4OH; (e) SiO_2; (f) KH, 0°C; (g) DIBAL-BF_3·OEt_2, then $MeC(OEt)_3/H^+/\Delta T$, or $(CH_2CH)_2CuLi$/TMSCl; (h) H^+, then Pyr/DMPA; (i) [O], then CH_2N_2; (j) $RuCl_3$-$NaIO_4$, then CH_2N_2; (k) TFA then $AlMe_3$.

ring-close upon hydrogenation, after *N*-debenzylation and dearomatisation.[18] Two chiral syntheses starting from the optically active propenoate ester **38** (R″=Et) have been carried out. Either *ortho*-ester Claisen rearrangement of the allylic alcohol derivative (obtained by diborane reduction of **38**),[26] or cuprate conjugate addition[27] gave the vinyl derivative **39** (R″=Me or Et) as a diastereoisomeric mixture, in the respective ratios 2.6:1 and 6:1. Cyclization and oxidation can then be performed irrespective of order to yield **30**; the two enantiomerically pure diastereoisomers were separated by chromatography. The cuprate method was also applied to the synthesis of homochiral forms of 1-methylpyrrolizidin-3-one.[27]

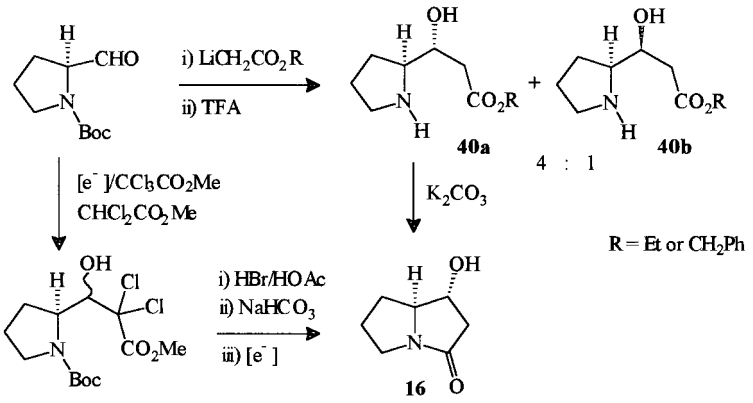
A very highly stereoselective lactamization of an anhydride derivative (de=97%) has been reported yielding the pyrrolizidinone **12** after esterification (Scheme 17). The stereoselectivity observed from the anhydride precursor is much higher than from the corresponding diester, due to a sterically more favourable transition state.[28]

Asymmetric syntheses of the hydroxy derivative **16** begin from Boc-(*S*)-prolinal. Hanson found that aldol condensation with lithioalkyl acetates occurred with moderate diastereofacial selectivity to give, after *N*-deprotection, a 4:1 ratio of the adducts **40**; recrystallisation gave pure chiral material and **40a** was then cyclized to the homochiral compound **16** (Scheme 18).[29] Alternatively the pure pyrrolizidinone can be obtained by recrystallisation at the later stage.[30,31] The hydroxy compound **16** can also be obtained by attack of electrochemically generated methyl dichloroacetate anions which proceeds in a highly selective *anti*-manner (de >99%) for the cyclization step.[32]

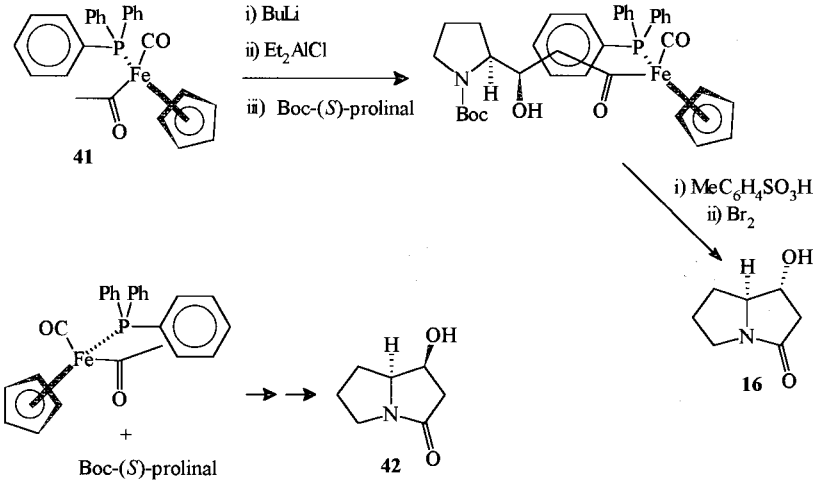
The aldol condensation using chiral acetate enolates derived from the iron complex **41** with protected (*S*)-prolinal provides excellent stereocontrol. *N*-cleavage and oxidative decomplexation gave enantiomerically pure **16**. Similarly homochiral **42** can be prepared from the other enantiomer of the iron complex (Scheme 19).[33] The observed



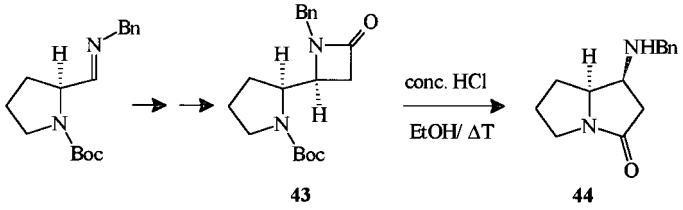
Scheme 17.



Scheme 18.



Scheme 19.



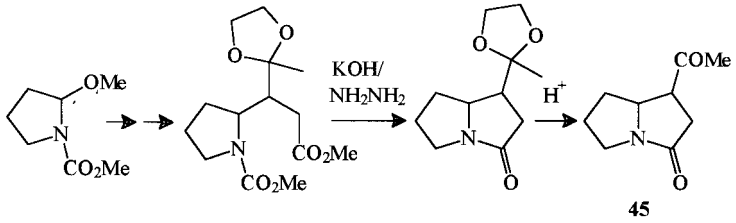
Scheme 20.

stereoselectivity can be rationalised by the concept of double asymmetric induction.

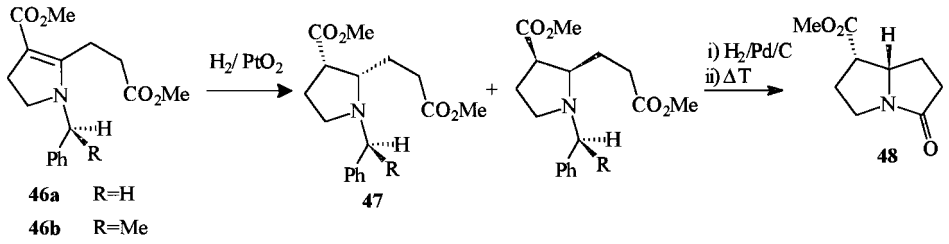
Initial work towards the synthesis of aminopyrrolizidinones has recently been reported; intramolecular rearrangement of the β-lactam precursor **43** under acidic conditions yielded optically active **44** (Scheme 20).[34]

Racemic 1-acetylpyrrolizidin-3-one **45** has been obtained from anodically generated 2-methoxy-1-methoxycarbonyl-pyrrolidine (Scheme 21).[22] The relative stereochemistry was not reported.

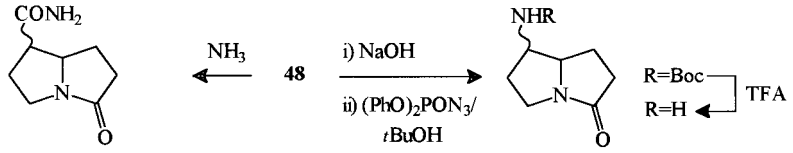
2.3.2. Formation of 7-substituted pyrrolizidin-3-ones. This method is limited by the requirement of having a



Scheme 21.



Scheme 22.



Scheme 23.

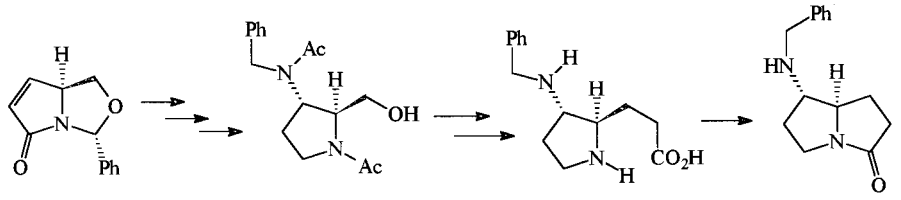
2,3-disubstituted pyrrolidine as starting material; such compounds are generally not readily accessible.

The 7-ester derivative **48** was synthesised from the dihydropyrrole **46a**, initially as a racemate, by *cis*-hydrogenation of the double bond followed by debenzylation and ring closure (Scheme 22).[35] When a chiral auxiliary was used (e.g. **46b**) hydrogenation occurred with high diastereoselectivity (de=90%) to afford **47** as the major isomer; this is a consequence of steric hindrance due to the phenyl ring which is present in a single conformation on one of the faces of the dihydropyrrole **46b**.[35a,c] The mixture subsequently cyclized to give **48** contaminated by a small amount of its enantiomer. The racemate of **48** was used as a precursor of amido and amino derivatives (Scheme 23).[36]

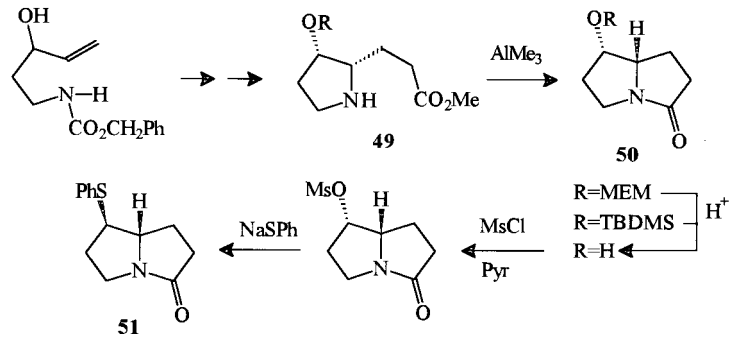
A homochiral 3-aminoprolinol has been prepared via the highly stereoselective 1,4-addition of benzylamine to an α,β-unsaturated lactam precursor (Scheme 24). Cyclisation of the propanoic acid derivative under basic conditions afforded *exo*-7-benzylaminopyrrolizidin-3-one as the only product (ee>95%).[37]

The chiral building blocks **49** (R=MEM, TBDMS), synthesised from Katsuki–Sharpless oxidation products of *N*-protected 3-hydroxypent-4-enylamines, cyclised smoothly to yield homochiral oxygenated pyrrolizidinones **50** (Scheme 25). The hydroxy derivative (R=H) was converted with inversion of configuration to the sulfide **51** via the mesylate.[38]

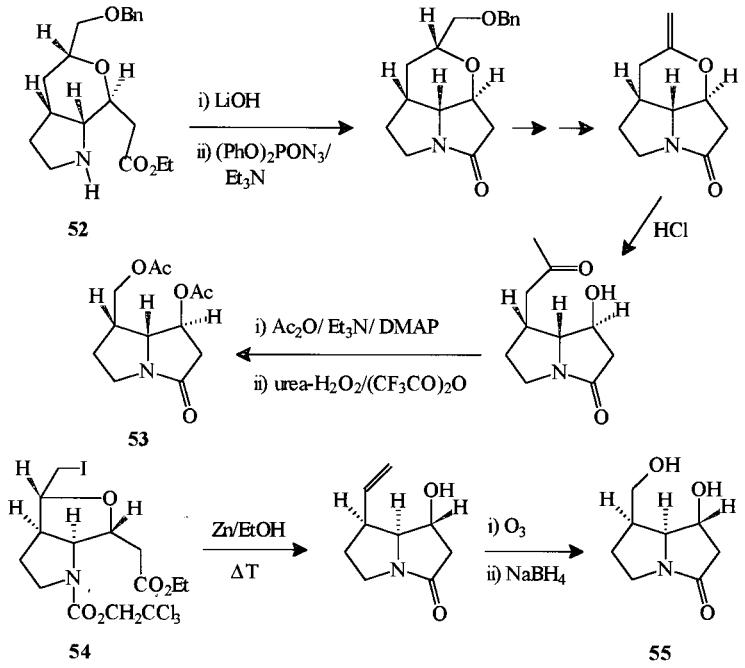
2.3.3. Formation of 1,7-disubstituted pyrrolizidin-3-ones. The stereocontrolled asymmetric synthesis of 1,7-disubstituted pyrrolizidinones, precursors of dihydroxy necine bases, from homochiral pyrrolidine derivatives, has been reported.[39] Cyclization of the enantiomerically pure



Scheme 24.



Scheme 25.



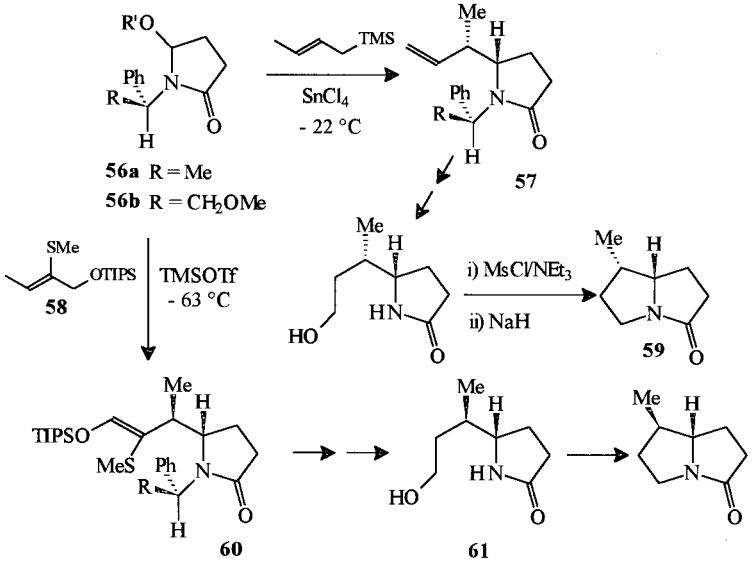
Scheme 26.

compounds **52** and **54** gave, after ring closure and functional group interconversion, the homochiral products **53** and **55**, respectively (Scheme 26).

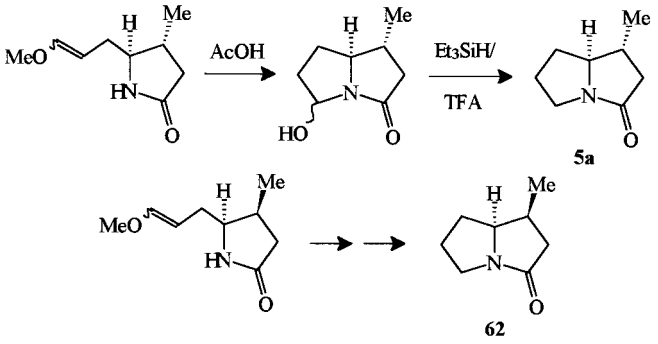
2.4. [4–5] Bond formation

Acyliminium ions bearing a chiral *N*-benzyl substituent react in a highly stereoselective manner with allylsilanes or allyl silyl ether derivatives, in particular where the hydrocarbon chain has a *trans* configuration.[40,41] The stereochemical course of the reaction from these two types of allyl precursors differs, allowing after further manipulation the synthesis of either (7*R*,7a*S*)- or (7*S*,7a*S*)-7-methylpyrrolizidin-3-one (Scheme 27). For example, compound **56a** yielded the major diastereoisomer **57** (along with three others) which could be transformed into the optically active pyrrolizidinone **59** (ee=68%) and its diastereoisomer in an 8:1 ratio.[40] Alternatively, addition of the thio-derivative **58** gave mainly **60**, which then yielded the pyrrolizidinone precursor **61** (de=92%, ee=72%).[41] Diastereofacial selectivity is also dependent on the chiral auxiliary; the reaction of **58** with **56b** gave the *anti*-adduct **60** as with **56a**, but the face differentiation is reversed leading to the enantiomer of **61** with high selectivity (de=92%, ee=98%). This is probably the result of a dipole interaction between the cationic iminium moiety and the methoxy group.

The synthesis of the enantiomerically pure methyl derivatives **5a** and **62** was achieved by treatment of chiral enol



Scheme 27.



Scheme 28.

ethers with acetic acid, followed by formal reduction of the hydroxy group (Scheme 28).[42]

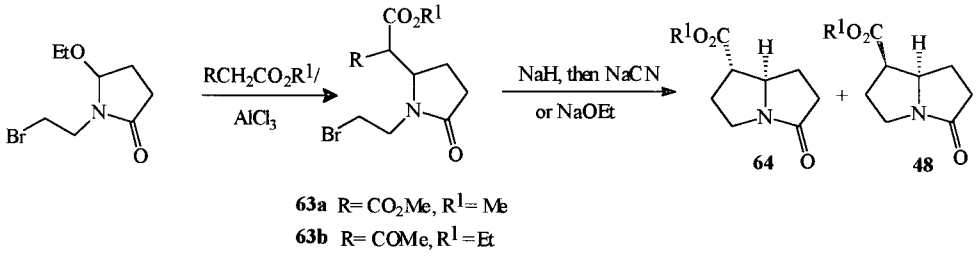
2.5. [6–7] Bond formation

In this section, several 7-substituted pyrrolizidinones were synthesised either by nucleophilic substitution or radical cyclization of 5-substituted 1-halogenoethylpyrrolidin-2-ones.

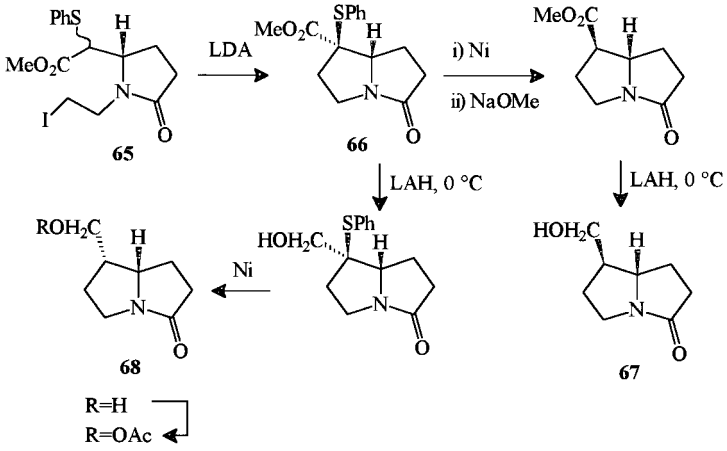
The ionic cyclization involves precursors such as **63** that can be prepared by amidoalkylation of cyclic acyl iminium ions (Scheme 29). The compounds **63** can then ring close in the presence of base, followed by further manipulation to give a mixture of racemic diastereoisomers **64** and **48** in the ratios of 4:1 and 1:1 from **63a** and **63b**, respectively.[43]

Cyclization of a 60:40 mixture of diastereoisomers **65**, obtained by amidoalkylation using tin(II) enolates, afforded **66** which was shown to be the sole product by ^{1}H NMR spectroscopy.[44] This selectivity could be a consequence of repulsive steric interactions between the thiophenyl group and the pyrrolidinone in the transition state leading to the alternative isomer. Desulfuration followed by treatment with sodium methoxide afforded the thermodynamically more stable ester which was reduced to the homochiral hydroxymethyl derivative **67** (Scheme 30). Alternatively reduction and desulfuration of **66** gave the other diastereoisomer **68** (R=H) as the major compound together with **67** in a 71:29 ratio.

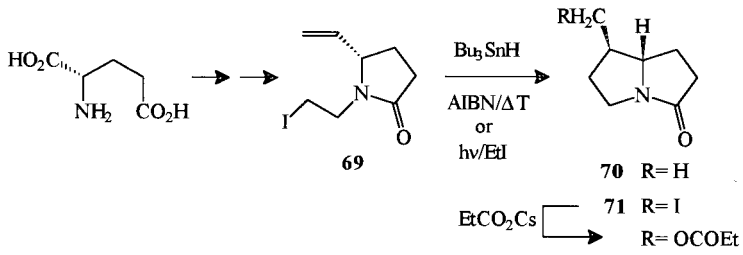
The radical method for [6–7] bond formation involves tributyltin hydride mediated cyclization of the pyrrolidinone **69**, derived from L-glutamic acid, to afford the homochiral pyrrolizidinones **70** (AIBN/ΔT) or **71** (hν/EtI) in a highly stereoselective manner (de=97%) (Scheme 31).[45]



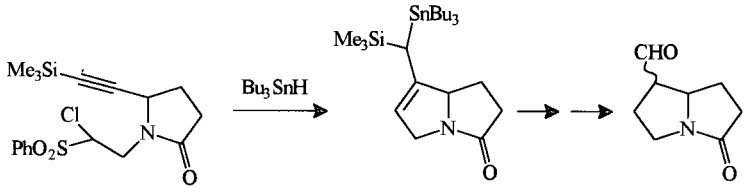
Scheme 29.



Scheme 30.



Scheme 31.



Scheme 32.

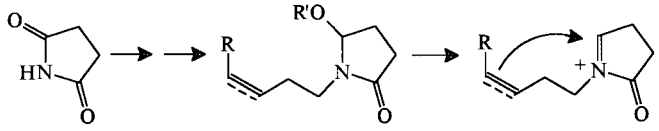
Compound **71** was formed in the presence of iodoethane under the conditions previously reported (Scheme 3).[4] The radical cyclisation process could be extended by the use of trimethylsilylacetylene precursors (Scheme 32).[45,46] The 6,7-dehydropyrrolizidin-3-one thus obtained could be further converted to 7-formylpyrrolizidin-3-one as a diastereoisomeric mixture.[46]

2.6. [7–7a] Bond formation

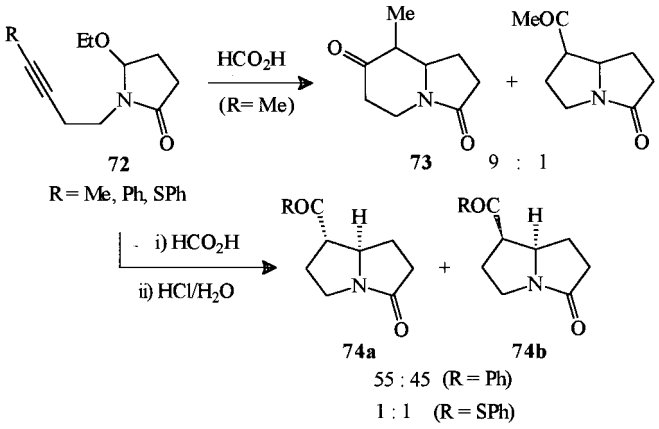
Most of the pyrrolizidin-3-one syntheses reported in this section involve cyclization of either acyl iminium ions or α-acylamino radicals. These can both be generated from precursors derived from readily available *N*-substituted succinimides, which makes this route attractive. Numerous 7-substituted and a few 1,7-disubstituted pyrrolizidin-3-ones have been synthesised by this route.

2.6.1. Acyl iminium ion cyclization. Acyl iminium cations are easily generated from hydroxy or alkoxylactams, either under acidic conditions, or in neutral conditions via their mesylate derivatives (Scheme 33). They are then trapped by internal π-nucleophiles—suitably functionalised acetylenes or olefins—to give either pyrrolizidinones or indolizidinones, depending on the substitution pattern.[47]

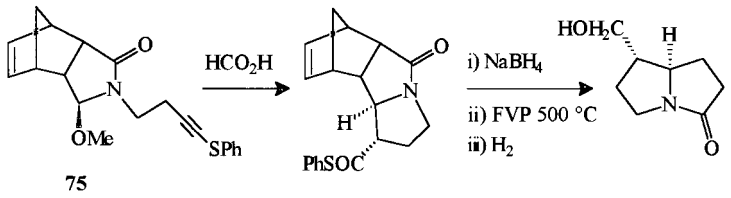
For example, Speckamp found that the methylacetylene derivative **72** (R=Me) gave mainly the 6-*endo* product **73** (Scheme 34).[47c,e] In contrast, the phenylacetylenes **72** (R=Ph) and phenylthioacetylene **72** (R=SPh) gave the 5-*exo* products **74** with complete regioselectivity.[47d] In



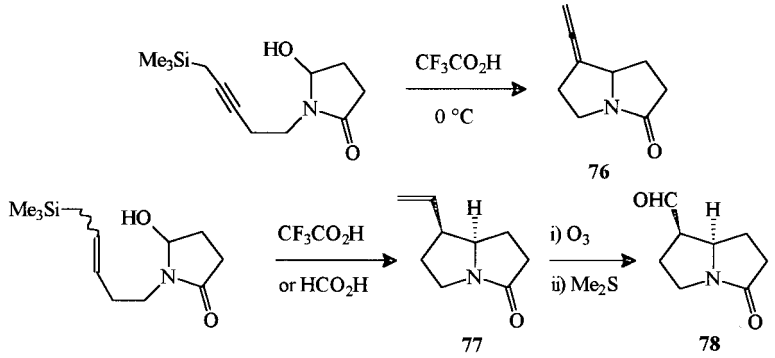
Scheme 33.



Scheme 34.



Scheme 35.



Scheme 36.

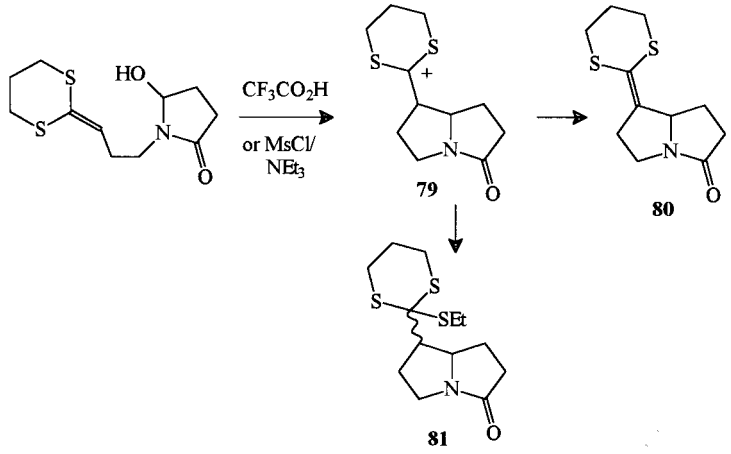
this case, the stereochemical outcome was particularly poor, although isomerisation into the thermodynamically more stable isomer **74a** was possible by treatment with base.

Koizumi has reported a long enantioselective synthesis of (+)-laburnine using the chiral phenylthiolactam **75** (prepared in ten steps from maleimide and 10-mercaptoisoborneol).[48] Cyclization with formic acid proceeds with high diastereoselectivity from the less hindered face. Reduction of the thioester adduct followed by retro Diels–Alder reaction under flash vacuum pyrolysis (FVP) conditions and hydrogenation gave the pure (7*S*,7a*R*)-7-hydroxymethylpyrrolizidin-3-one precursor of (+)-laburnine (Scheme 35).

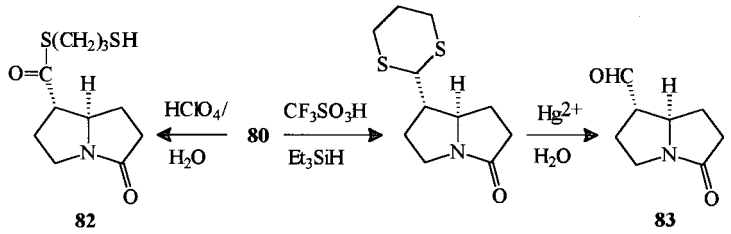
Intramolecular cyclizations with either propargyl- or allylsilanes occur with complete regiocontrol, due to the β-effect of silicon, to give respectively the allene **76** and the vinylpyrrolizidinones **77** as the only isomers (Scheme 36).[47a,b] Ozonolysis of **77** can then afford the racemic aldehyde **78**. In this case, the stereochemical course of the cyclization, which leads to the formation of the less thermodynamically stable diastereoisomer, could be controlled by the more stable chair-like transition state.

Chamberlin reported that the regioselective acyl iminium cyclization of ketene dithioacetals can be induced either by treatment with trifluoroacetic acid or mesyl chloride/triethylamine to give compound **80** (Scheme 37).[49] The cationic intermediate **79** has been trapped by ethanethiol to give **81** as a 3:1 mixture of diastereoisomers. Further functionalisation of **80** gave rise to the thermodynamically more stable *trans*-pyrrolizidin-3-ones **82** and **83** as single products (Scheme 38).[49b] 6,7-Dehydropyrrolizidin-3-ones have also been formed by double bond migration of **80**.

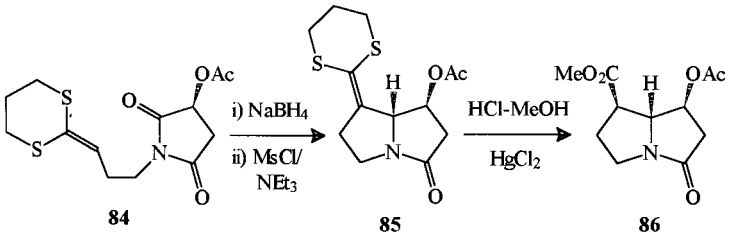
This methodology has been extended to the enantioselective synthesis of the 1,7-disubstituted pyrrolizidinone **86** from the chiral precursor **84** (Scheme 39). The initial reduction of the imide moiety was found to be regioselective and the



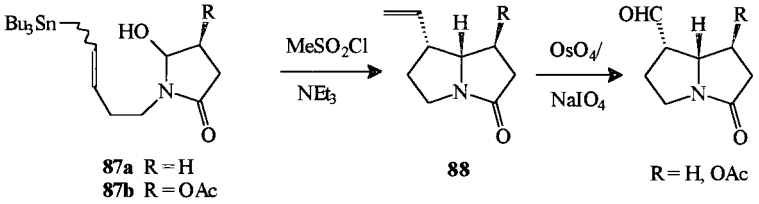
Scheme 37.



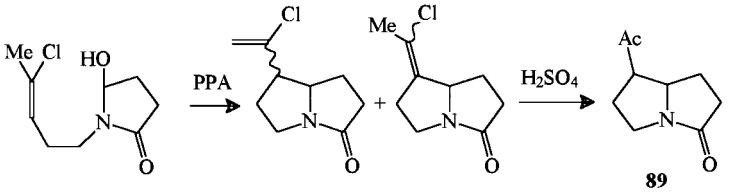
Scheme 38.



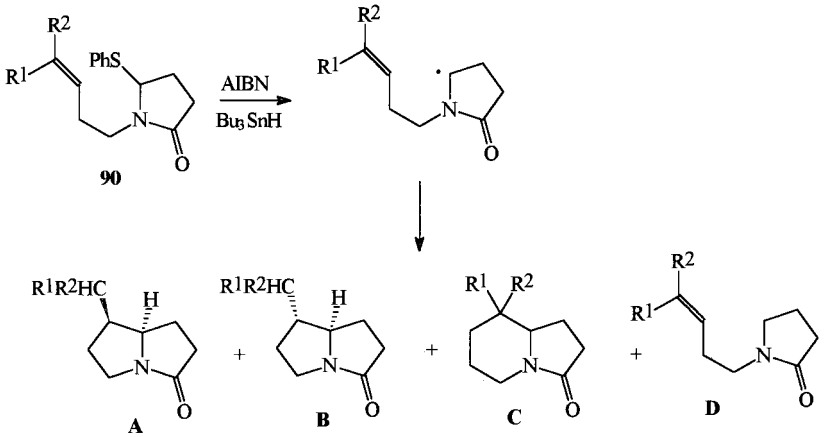
Scheme 39.



Scheme 40.

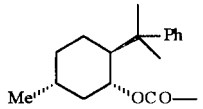


Scheme 41.



Scheme 42.

Table 2. Treatment of **90** with Bu_3SnH; product distribution and yields

R^1	R^2	A (%)	B (%)	C (%)	D (%)
H	H	45	4	23	12
Me	H	42	5	22	13
H	Me	45	7	4	25
Me	Me	60	15	–	12
H	CH(Me)OAc	77	9	4	5
H	CH_2OAc	39	9	11	5
H	CO_2^tBu	73	8	–	–
H	CN	76	8	–	–
H		76	8	–	–
$SiMe_3$	SPh	58	13	–	3

subsequent cyclization exhibited high diastereoselectivity (de=97%), because the acetoxy group blocks the upper face. The key compound **85** was obtained in only four steps from (*S*)-malic acid.[49a,c] Treatment of this intermediate with mercuric chloride in acidic alcohol gave **86**, a precursor of (+)-hastanecine. Compound **85** was also converted to six other saturated and unsaturated pyrrolizidine diols, in eight steps or fewer.[49a]

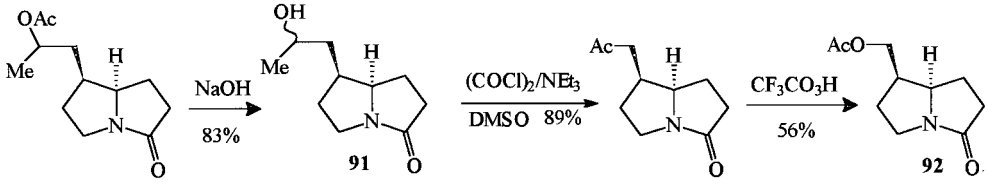
Intramolecular cyclization of the allylstannane derivatives **87** selectively afforded the 7-vinylpyrrolizidin-3-ones **88** (R=H, OAc), which were further oxidised to the corresponding aldehydes (Scheme 40).[50] Although the cyclization can be accomplished via a free radical process, the cationic pathway proved to be superior, giving a particularly high diastereoselectivity (de≥98%). The stereochemistry is probably controlled by the same features as in a previous example (Scheme 36). As with Chamberlin's work (Scheme 39), an enantioselective synthesis was made possible using the chiral precursor **87b** (R=OAc).[50a]

Chloroalkenes react with acyl iminium ions to give a mixture of two geometric isomers that yield the acetyl derivative **89** on treatment with concentrated sulfuric acid.[51] The stereochemistry was not determined (Scheme 41).

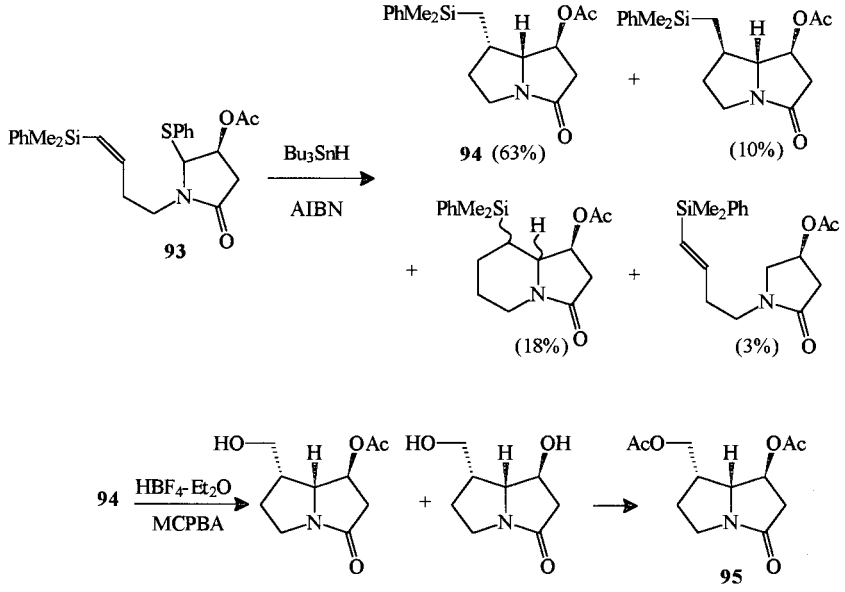
2.6.2. α-Acylamino radical cyclization. Most of the work reported in this section is due to Hart and his coworkers who extensively studied α-acylamino radical cyclizations.[52] The radicals are generated by treatment of *N*-substituted-5-phenylthiopyrrolidin-2-ones with tributyltin hydride in the presence of an initiator such as AIBN.

Ethylene derivatives. Radical cyclizations of the ethylene derivatives **90** yield a mixture of the pyrrolizidinones **A** and **B**, indolizidinones **C** and reduction products **D** (Scheme 42 and Table 2).[52a,c,d,f] It is worth noting that the amount of **D** could be reduced or even eliminated by carrying out the reaction at higher dilution.[52c]

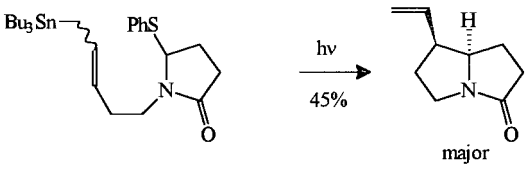
The first notable feature of this reaction is its regiochemical course; in all cases, the pyrrolizidinone formation (5-*exo* product) is favoured over that of the indolizidinone (6-*endo* product). This is thought to be due to steric effects,



Scheme 43.



Scheme 44.



Scheme 45.

which decrease the rate of the *endo* cyclization. A second feature is the relative consistency of the diastereoisomer ratios **A** to **B** observed (4:1≤**A**: **B**≤11:1). This suggests that the stereochemical course of the *exo* cyclization process depends on geometrical rather than electronic factors, although the reasons for this selectivity are poorly understood.

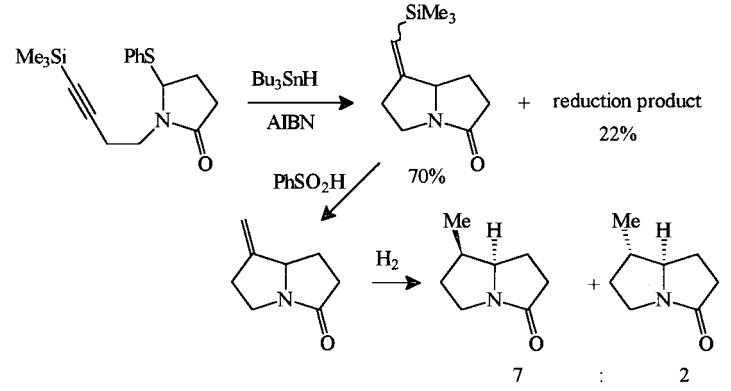
From a synthetic point of view, the diastereomeric mixture of sulphides **A** and **B** (R^1=$SiMe_3$, R^2=SPh) was transformed into the corresponding aldehydes **78** and **83** in moderate yield (30%).[52c] More successfully, hydrolysis of the isolated pyrrolizidinone **A** [R^1=H, R^2=CH(Me)OAc] gave the alcohol analogues **91** which were oxidised in two steps to the acetate **92** via the ketone intermediate (Scheme 43).

An enantioselective synthesis of (−)-dihydroxyheliotridane has been carried out from the chiral precursor **93**, derived from (*S*)-3-acetoxysuccinimide (Scheme 44).[52a] After separation by column chromatography, the major cyclization product **94** was oxidised to give two products which were converted to the diacetate **95**, a precursor of (−)-dihydroxyheliotridane.

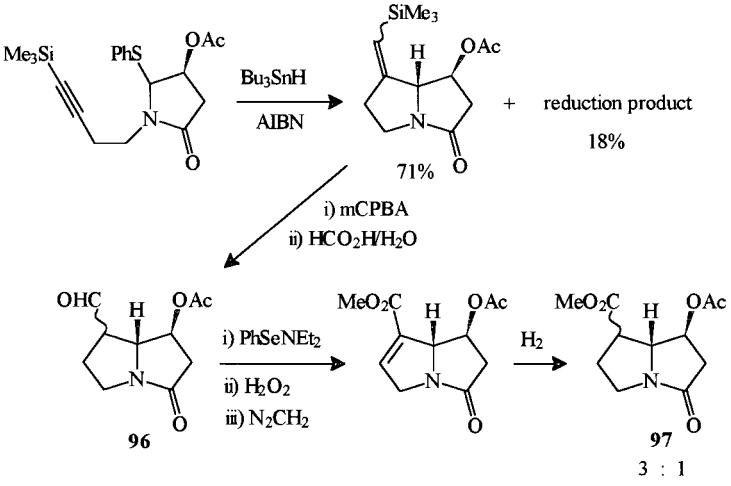
Keck has shown that allylstannane derivatives gave, under radical conditions, pyrrolizidinones with good stereoselectivity (ratio 11:1) (Scheme 45).[50] Ionic cyclization, however, proved to be more efficient in that particular case (see Section 2.6.1).

Acetylene derivatives. Radical cyclization of acetylenes gives a mixture of pyrrolizidinones, indolizidinones and reduction products, the relative ratios of which are greatly dependent on the terminal alkyne substituent.[52b,e] When this is a trimethylsilyl group, synthetically useful yields of pyrrolizidinones were produced as exemplified in Scheme 46.[52e]

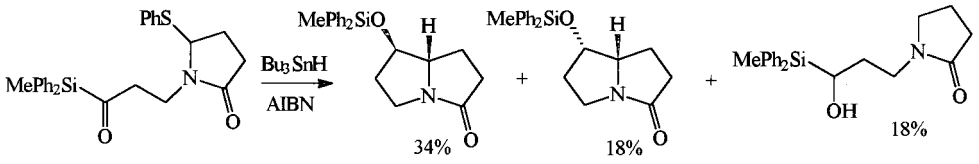
A more elaborate enantioselective synthesis of the disubstituted pyrrolizidinones **96** and **97** was achieved by functionalisation of the initial cyclized adduct (Scheme 47).[52b] Further elaboration of the unsaturation obtained at



Scheme 46.



Scheme 47.



Scheme 48.

the cyclization stage, however, did not allow a good stereoselectivity to be attained at the 7-position.

Acylsilane derivatives. Intramolecular cyclisation of α-acylamino radicals with an acylsilane functionality gave 7-silyloxypyrrolizidin-3-ones with low diastereoselectivity, along with some reduction product (Scheme 48).[53]

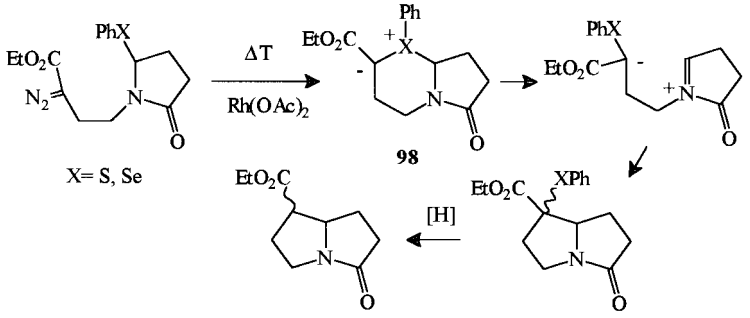
2.6.3. Others. The synthesis of pyrrolizidinones by intramolecular carbenoid displacement of diazo-selenide and diazo-sulphide derivatives has been reported.[54] The mechanism involves the ylide intermediate **98** (Scheme 49). A 1:1 mixture of diastereoisomers was obtained after reduction of the cyclization products.

The vinyl anion formally generated from the iodo derivative **99** cyclized to give the polar hydroxy compound **100** which, upon treatment with *p*-toluenesulfonic acid, afforded 1,2-dihydropyrrolizin-3-one.[55] Hydrogenation then yielded the unsaturated perhydro structure **1** (Scheme 50).

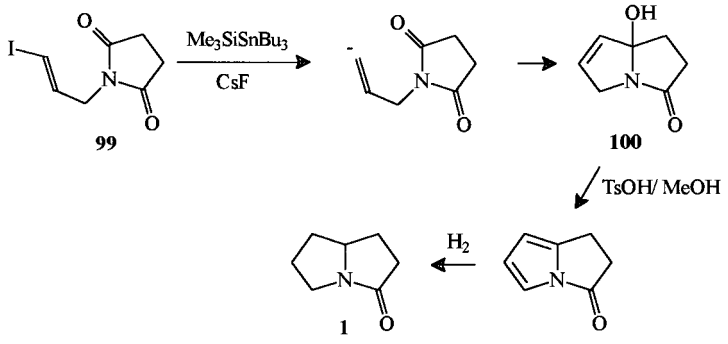
2.7. [7a–1] Bond formation

Cyclization of the acyl iminium ion derived from the anodically prepared pyrrolidine **101** has been reported (Scheme 51).[56] Demethoxycarbonylation under thermodynamic control gave a 4:1 ratio of diastereoisomers **30**.

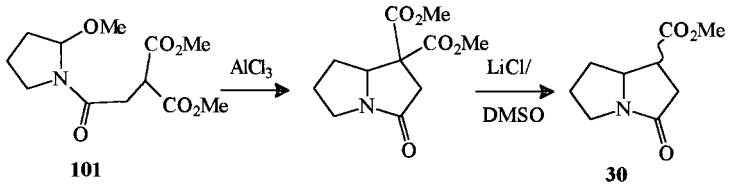
Ring closure can also be attained by intramolecular photoreduction of the α-ketoester **102** which can enolize



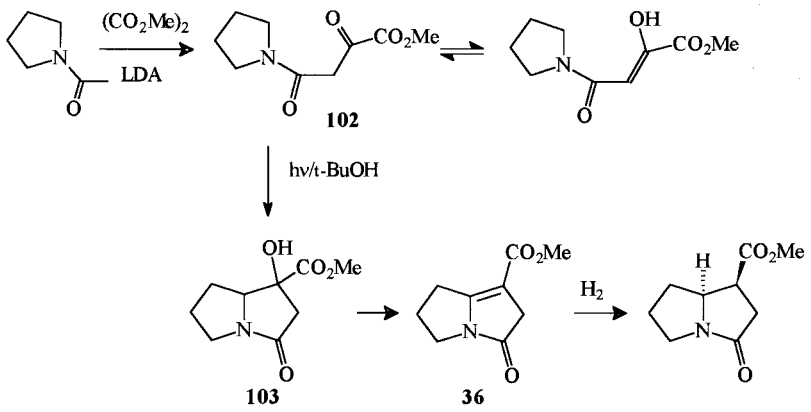
Scheme 49.



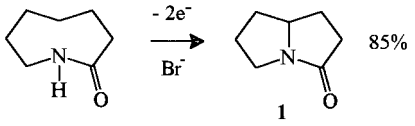
Scheme 50.



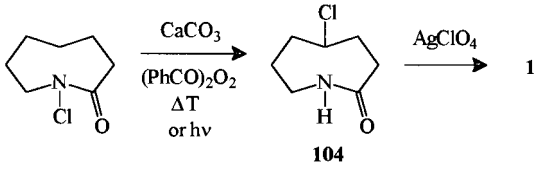
Scheme 51.



Scheme 52.



Scheme 53.



Scheme 54.

in solution (Scheme 52).[57] Irradiation in *t*-butyl alcohol destabilized the enol form and consequently afforded **103**, which can be dehydrated to **36** and hydrogenated stereoselectively to give, as reported elsewhere,[24,25] the *cis*-hexahydro derivative.

2.8. [7a–4] Bond formation

Elofson et al. made the parent pyrrolizidinone **1** by anodic oxidation conducted in the presence of halide ions (Scheme 53).[58]

It has been reported that the photochemical or peroxide initiated conversion of *N*-chloroazacyclooctan-2-one gave the transannular product **104** in 75% yield, which then easily cyclised to **1** (Scheme 54).[14]

3. Preparation of Pyrrolizidin-3-ones by Formation of Two Bonds

3.1. [1–2;3–4] Bond formation

The dioxopyrrolizidine system **105** was prepared by condensation of ethyl 2-pyrrolidylacetate and diethyl oxalate.[59] It was then reduced, dehydrated and hydrogenated in a *cis* manner to give *cis*-1-ethoxycarbonylpyrrolizidin-3-one, apparently with high stereoselectivity (Scheme 55).

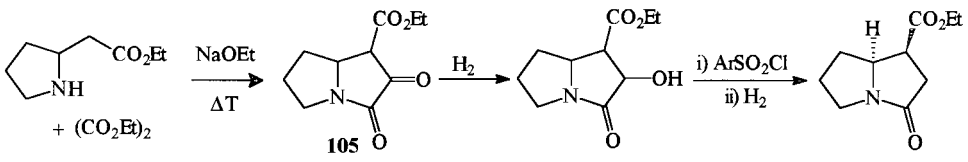
3.2. [3–4;4–5] Bond formation

Tandem [4+2]/[3+2] cycloadditions of nitroalkenes allow the simultaneous creation of stereocentres at the positions 1, 2, 7 and 7a of pyrrolizidin-3-ones via the formation of a nitrosoacetal intermediate.[60] For example, cycloaddition of 2-benzoyloxynitroethylene with a chiral vinyl ether (G^*=1*S*,2*R*-2-phenylcyclohexyl) gave with high selectivity the nitronate **106**, which was reacted with dimethyl maleate to afford the key compound **107** as a single diastereoisomer (Scheme 56). Hydrogenolysis under optimised conditions is thought to generate **108** that, after ring closure, yielded the pyrrolizidinone **109** in 68% yield and 97.7% enantiomeric purity. Removal of the 2-hydroxy group by a free radical method then provided the precursor of (−)-hastanecine.

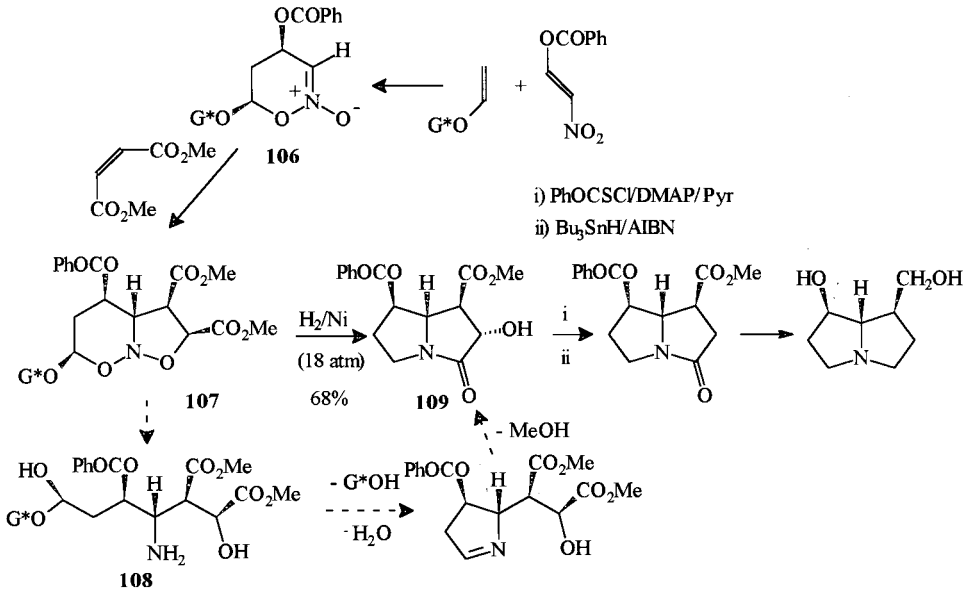
A similar methodology was applied to the synthesis of (−)-detoxinine **110**, obtained by the hydrolysis of homochiral 1,7-dihydroxypyrrolizidin-3-one (Scheme 57).[60b]

3.3. [3–4;7a–1] Bond formation

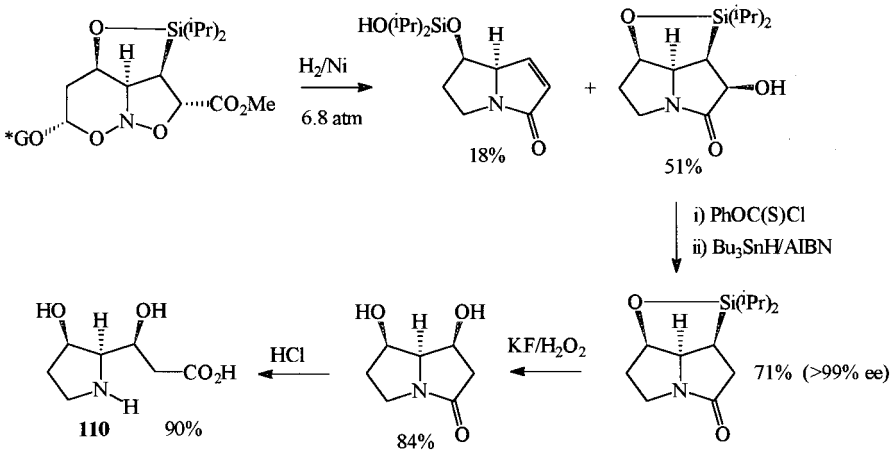
α-Aminoalkyl radicals, generated by irradiation of pyrrolidines in the presence of anthraquinone or benzophenone, undergo regiospecific additions with α,β-unsaturated



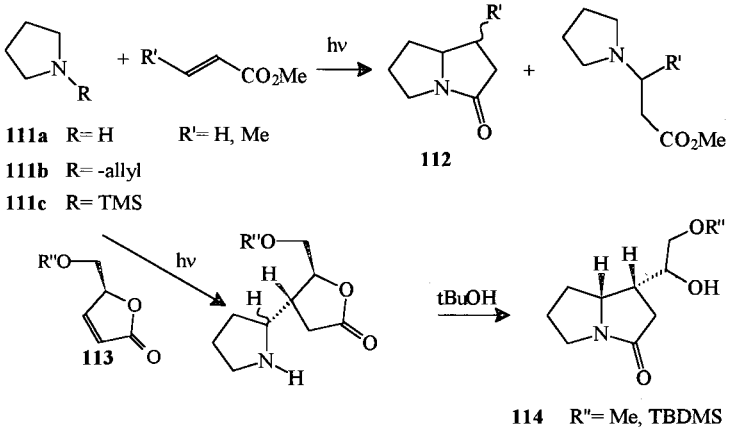
Scheme 55.



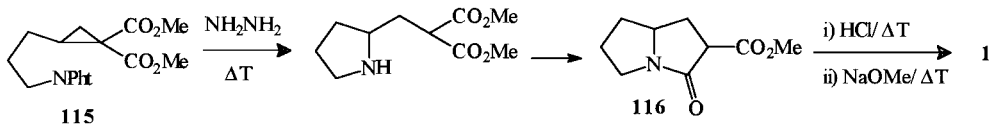
Scheme 56.



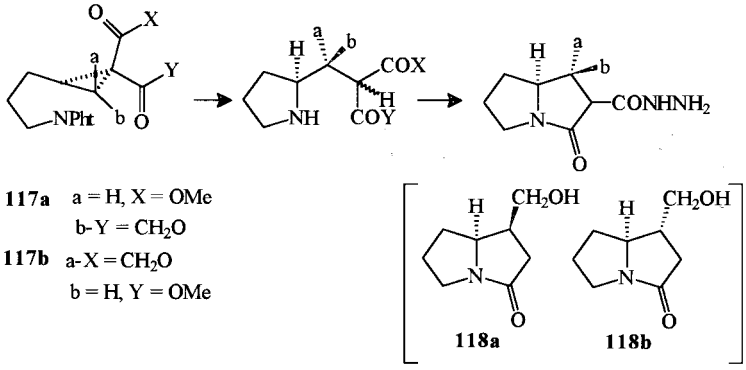
Scheme 57.



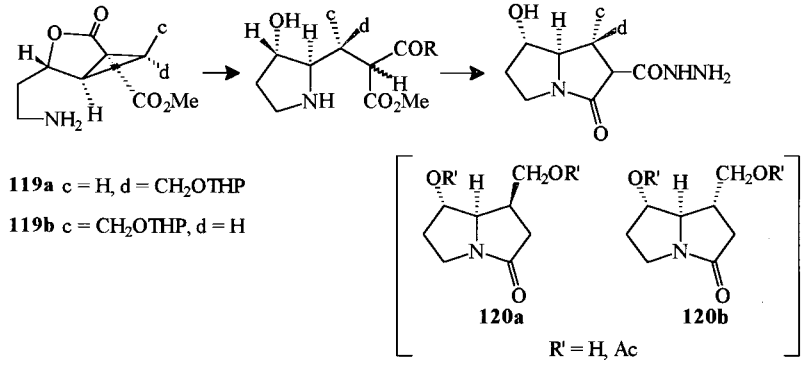
Scheme 58.



Scheme 59.



Scheme 60.

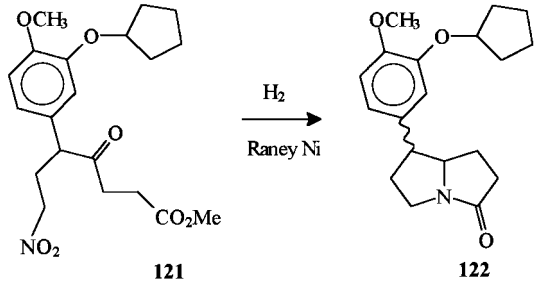


Scheme 61.

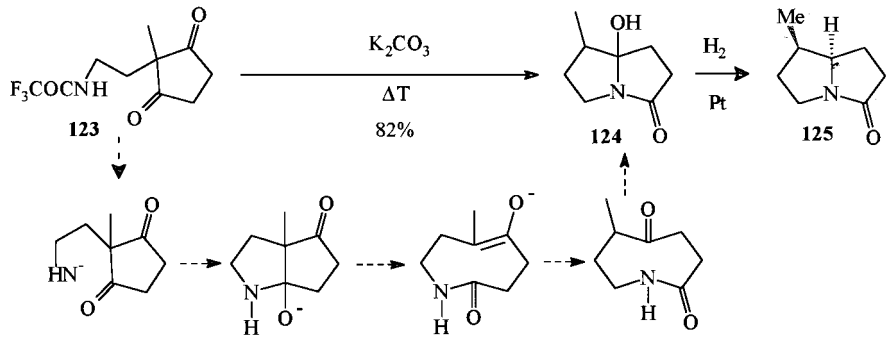
esters.[61,62] Subsequent cyclization of the initial adduct yields the pyrrolizidinone ring system. In the case of unsubstituted pyrrolidine (**111a**) the nucleophilic conjugate addition products predominated, although their formation could be reduced by lowering the temperature (Scheme 58).[61b] This problem could be overcome by using the *N*-substituted pyrrolidine **111b**, but yields of **112** remained poor (≤10%).[61a] Addition of **111c** to the butenolide **113** occurred with high stereoselectivity at the butenolide centre.[62] In situ conversion of the presumed photoadduct gave the optically active pyrrolizidinone **114** in 15% yield after purification by chromatography.

3.4. [3–4;7a–4] Bond formation

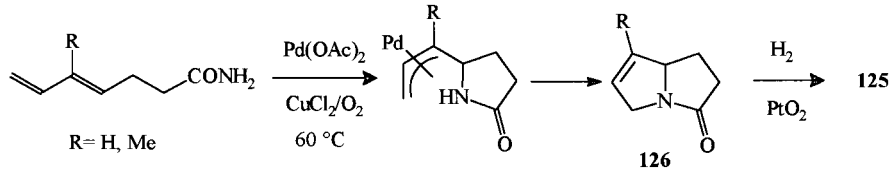
Intramolecular nucleophilic attack of activated cyclopropanes has been used to generate pyrrolizidinones.[63] For example, heating of the phthalimido precursor **115** in the presence of base gave the 2-ester derivative **116** via a non-isolated pyrrolidine intermediate (Scheme 59).[63c] Hydrolysis and decarboxylation then afforded the parent compound **1**. This methodology was then applied to the synthesis of racemic 1-substituted and 1,7-disubstituted pyrrolizidin-3-ones with high selectivity. In all cases, the amines, released upon treatment of phthalimido precursors with excess hydrazine, caused ring opening of the activated cyclopropane moiety with inversion of configuration. After removal of the 2-substituent, this sequence provided the hydroxymethyl compounds **118a** and **118b**, respectively, from **117a** and **117b** (Scheme 60).[63b] Extension to the disubstituted



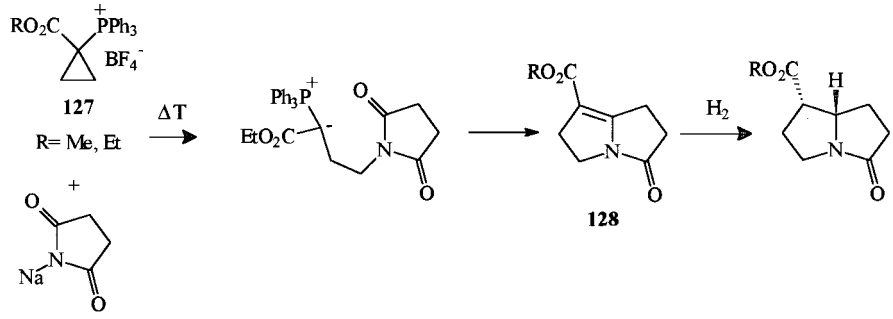
Scheme 62.



Scheme 63.



Scheme 64.

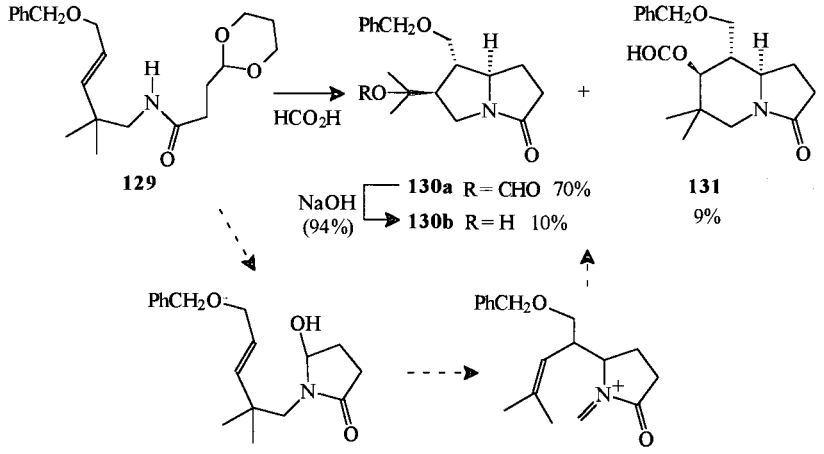


Scheme 65.

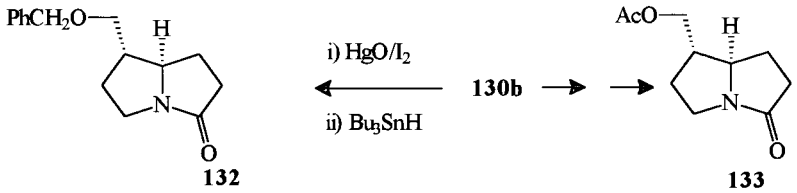
series provided the dihydroxy derivatives **120a** and **120b** (R′=H) and their diacetates (R′=Ac), respectively, from **119a** and **119b** (Scheme 61).[63a]

The tandem cyclization of the amine derived from the nitro compound **121** has been reported to give the two diastereoisomers of **122** as a 2:1 mixture (Scheme 62).[64]

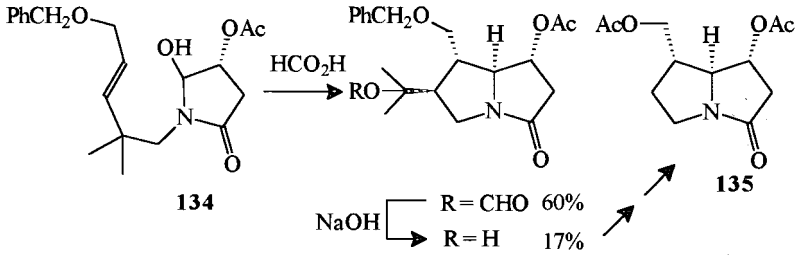
A base-catalysed one pot reaction described as a 'criss-cross annulation' provided the pyrrolizidinone **124**, in



Scheme 66.



Scheme 67.



Scheme 68.

one step from the cyclopentanedione derivative **123**, by the mechanism shown in Scheme 63.[65] Stereoselective hydrogenation of **124** afforded 7-methylpyrrolizidin-3-one **125**.

3.5. [4–5;7a–4] Bond formation

The two rings of the pyrrolizidinone system can be made in one step by 1,4-intramolecular addition of an amide onto a diene via a π-allyl intermediate (Scheme 64).[66] These reactions were carried out in the presence of a palladium(II) catalyst with copper(II) as a reoxidising agent. Hydrogenation of the resulting dehydropyrrolizidinone **126** (R=Me) afforded **125** as a single diastereoisomer.

3.6. [4–5;7a–7] Bond formation

Intermolecular nucleophilic ring opening of the cyclopropanes **127** by sodium succinimide, followed by intramolecular Wittig reaction, generated the dehydropyrrolizidinones **128** (R=Me, Et) (Scheme 65).[67,68] These were then hydrogenated selectively to the *cis*-perhydro compound.

4. Preparation of Pyrrolizidin-3-ones by Formation of Three Bonds

Hart synthesized a few pyrrolizidin-3-ones by using the aza-Cope rearrangement of acyliminium ions, followed by stereoselective cyclization.[69] For example, compound **129** in formic acid gave a mixture of the pyrrolizidinones **130a** (70%) and **130b** (10%) and the indolizidinone **131** (9%) by the mechanism shown (Scheme 66). The formation of the alcohol derivative **130b** could be completed by saponification of **130a**. Degradation of the hydroxypropyl group then provided the racemic 7-substituted pyrrolizidinones **132** and **133** (Scheme 67).[69c]

The method was applied to the enantioselective synthesis of the 1,7-disubstituted derivative **135**, by cyclization of **134** derived from (*R*)-acetoxysuccinic anhydride (Scheme 68).[69a,b]

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Biographical sketch

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Hamish McNab studied at the University of St. Andrews, Scotland, from 1967–1974, graduating with a BSc (1971) and obtaining a PhD (1974), in the field of nitrogen heterocyclic chemistry under the supervision of Douglas Lloyd. He then carried out postdoctoral work on flash vacuum pyrolysis with Bill Crow at the Australian National University, Canberra (1975-1976). He has been at The University of Edinburgh since 1977, where he is now a Reader in Chemistry. His current work is concerned with the discovery of new pyrolytic processes and their application in heterocyclic chemistry. He has published over 180 papers.