Synthesis via *N*-acyliminium cyclisations of *N*-heterocyclic ring systems related to alkaloids

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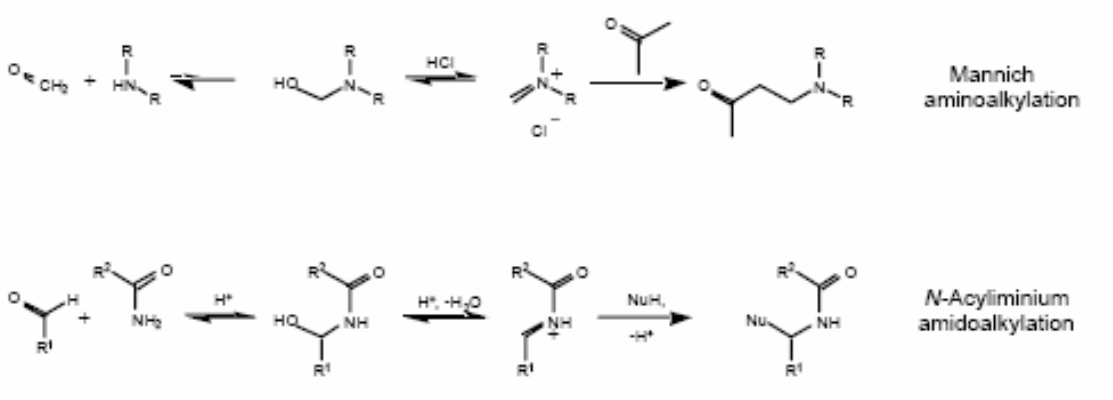
1. Introduction

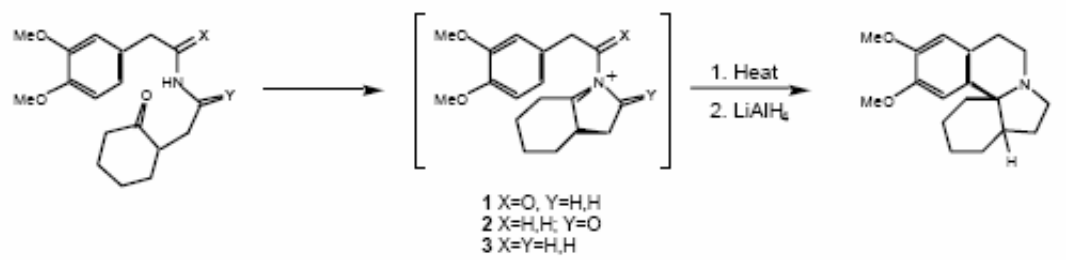
1.1 Iminium cyclisations versus acyliminium cyclisations

The development of cyclisations that proceed *via* *N*-acyliminium species (Scheme 1) is relatively recent, in contrast to cyclisations involving iminium cations, such as the venerable Mannich reaction,[1] the Bischler-Napieralski reaction[2] and the Pictet-Spengler reaction.[3] Both intermediates have been extensively employed in synthesis of alkaloidal and related systems, including some early uses of *N*-acyliminium ions in amidoalkylation reactions.[4]



Scheme 1

N-Acyliminium species were soon found to be reactive towards a wide variety of π-nucleophiles including alkenes, allenes, alkynes and aromatic and heteroaromatic systems.[5] The scope of this review is confined to *intramolecular* processes in which an *N*-acyliminium species is involved. An example is the synthesis of the erythrinane alkaloid skeleton (Scheme 2). The electrophilic reactivity of an iminium ion is greatly increased upon introducing a carbonyl group adjacent to the nitrogen atom, to give the corresponding *N*-acyliminium ion. The enhanced reactivity broadens the range of nucleophiles that can be used in carbon-carbon bond formation. For example, the erythrinane skeleton can be formed *via* either of the *N*acyliminium intermediates **1**[6] and **2**,[7] whereas cyclisation of the iminium ion **3** failed. Recent developments have shown the powerful stereocontrol available *via C*-nucleophilic additions to *N*-acyliminium species,[5-12] a key factor in their use for the synthesis of alkaloidal ring systems.



Scheme 2

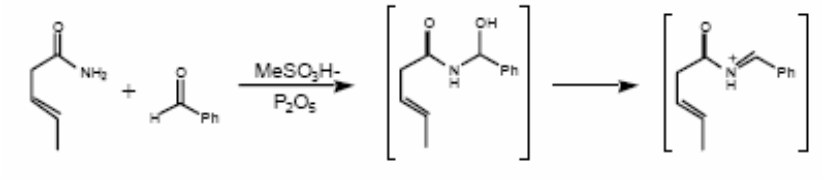
1.2 Generation of N-acyliminium ions

1.2.1 N-Acyliminium ions derived from α-oxygenated amides

Whereas iminium salts are frequently isolable, their *N*-acyliminium counterparts are far more reactive and seldom if ever isolated.[5,11,12] *N*-Acyliminium intermediates are usually generated *in situ*, often under acidic or Lewis acidic conditions; an example is the amidoalkylation reaction outlined in Scheme 1. Nucleophilic attack on the *N*-acyliminium intermediate is essentially

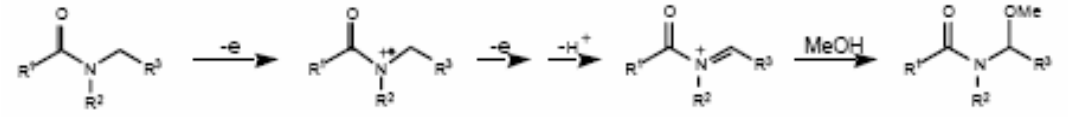
irreversible, affording the product. Such heterolysis of α-substituted amides is the most common route used in synthesis, the α-substituent often being an oxygen linkage that departs on protonation, although a variety of other substituents have been employed, including bisamides, α-chloroalkyl amides and α-thioalkyl amides.[5]

The α-oxygenated amide can be prepared by addition of an amide to an aldehyde or ketone under conditions of acid catalysis. An example is given in Scheme 3,[8] and the fate of the iminium species is discussed in sections 2.1 and 2.6.



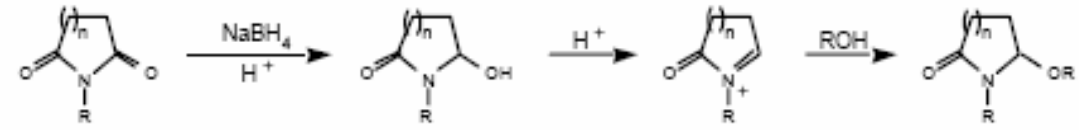
Scheme 3

The oxidation of amides or carbamates, usually performed electrochemically, is an effective and fairly general route to acyliminium ion precursors. Two single-electron transfer steps are involved (Scheme 4).[13]



Scheme 4

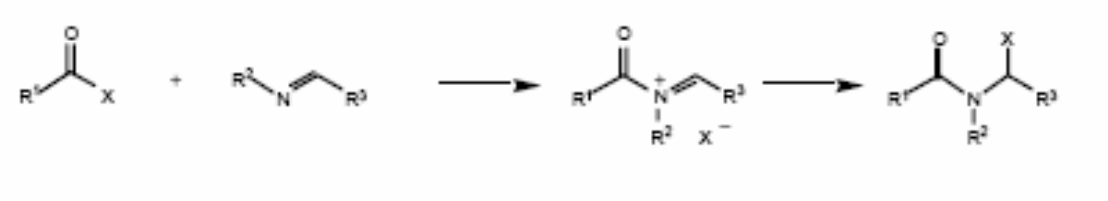
Reduction of cyclic imides in the presence of an alcohol affords the corresponding hydroxy lactam and /or the alkoxy lactam, useful precursors of cyclic *N*-acyliminium species (Scheme 5).[14] In the presence of other functionality, such reductions of imides are often highly regioselective.[15] Tertiary hydroxy lactams, produced by the reaction of cyclic imides with Grignard reagents, are also a source of *N*-acyliminium ions.[16]



Scheme 5

1.2.2 N-Acyliminium ions by N-acylation of imines

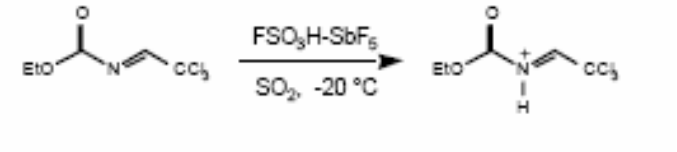
Imines, readily prepared by the condensation of an aldehyde or ketone with a primary amine, undergo acylation with an acid chloride or acid anhydride (Scheme 6). The adduct can act as the acyliminium species.[17]



Scheme 6

1.2.3 N-Acyliminium ions by N-protonation of N-acylimines

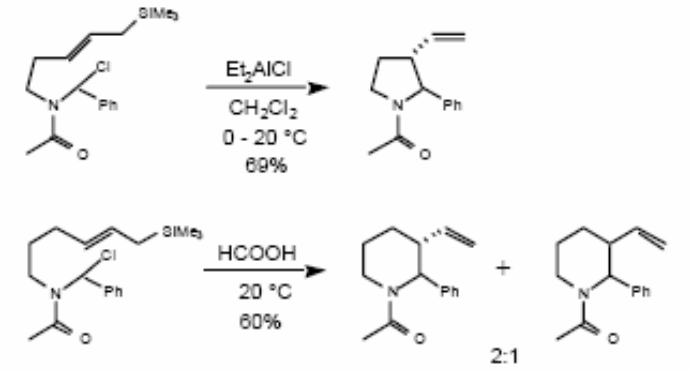
The protonation of *N*-acylimines is, in principle, a route to acyliminium species. However, it is not a general synthetic method because of the limitations in preparing *N*acylimines, and the forcing conditions required for their deprotonation. *N*-Acylimines readily tautomerise to the corresponding enamides, unless there are no α-hydrogen atoms, as in Scheme 7.[18]



Scheme 7

2 Construction of ring systems using N-acyliminium cyclisations

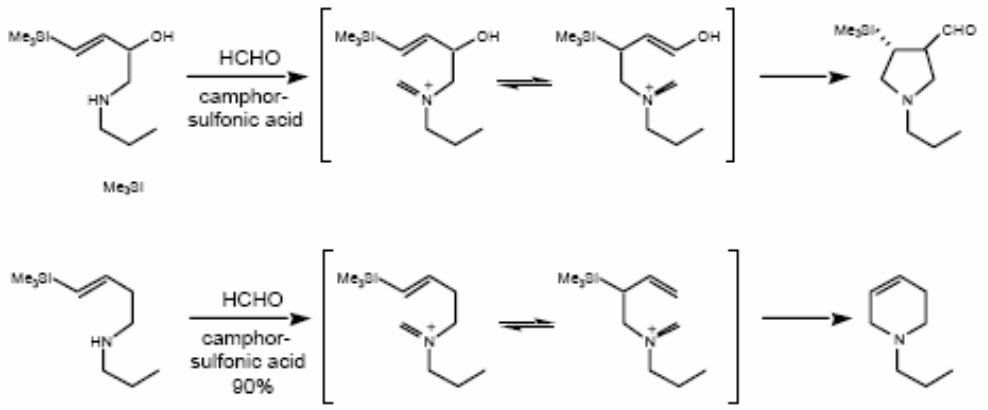
2.1 Pyrrolidines, piperidines and related rings



Scheme 8

Intramolecular amidoalkylation of certain *(Z)*-allylsilanes proceeds more stereoselectively to give the pyrrolidines than to give the piperidines (Scheme 8).[19,20] Pyrrolidines can be obtained *via* *N*-acyliminium cyclisations of vinylsilanes involving a cationic azonia-Cope rearrangement followed by a Mannich cyclisation of the resulting allylsilyl iminium ion (Scheme 9).[21] The cyclisation of certain vinylsilanes has been shown to afford 1,2,5,6-tetrahydropyridines indirectly, *via* an azonia-Cope rearrangement followed by cyclisation of the resulting allylsilane (Scheme 9).[21] Both *(E)*-and *(Z)*-vinylsilanes give this ring-closure. Related cyclisations

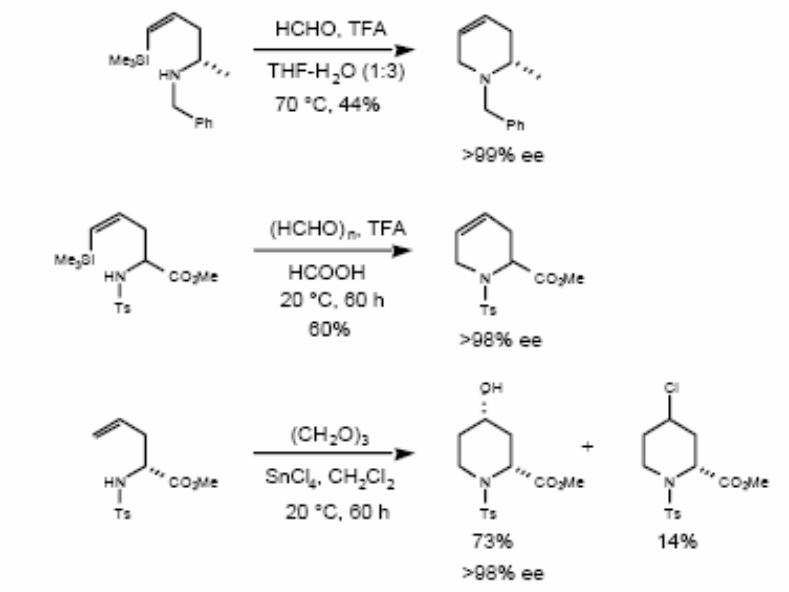
proceeding *via* azonia-Cope rearrangements have provided access to pyrrolizidine and indolizidine derivatives.[22]



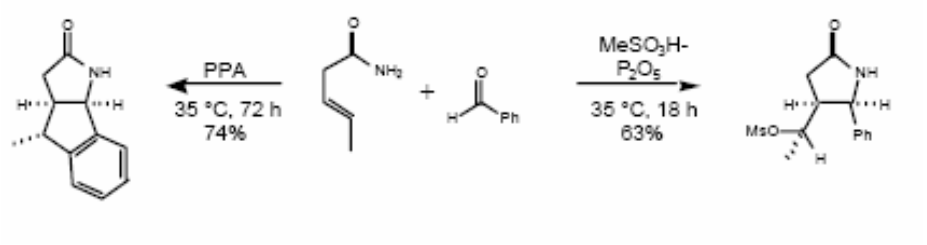
Scheme 9

Despite an earlier report, vinylsilanes have been shown to afford 1,2,5,6-tetrahydropyridines with negligible loss of ee under optimal conditions.[23] Hiemstra[24] reasoned that an α-ester group would suppress the azonia-Cope equilibrium (that leads to racemisation of the chiral centre) because the strong electron-withdrawing effect of the ester would provide a large electronic difference between the two possible cations. Indeed, the absolute configuration at the α-centre was retained in examples with α-ester susbtituents (Scheme 10).[24]

Stereoselective formation of piperidinones is possible that depends upon the nature of the acidic medium (Scheme 11).



Scheme 10

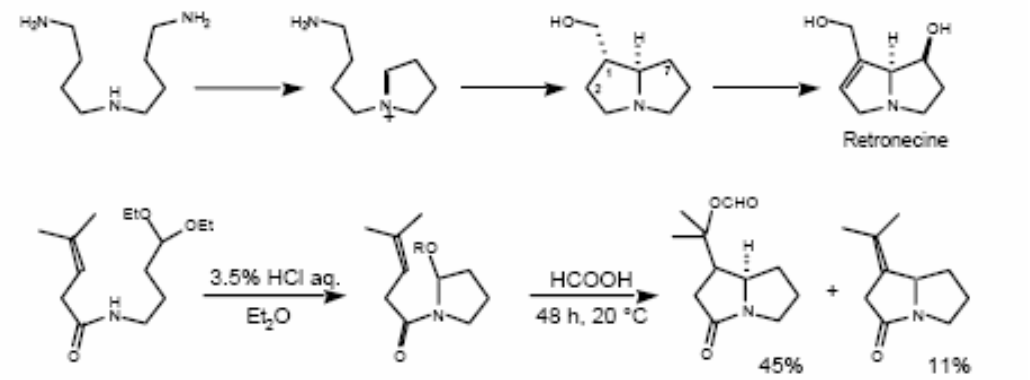


Scheme 11

2.2 Pyrrolizidines

The possibility of the *direct* formation of a five-membered ring *via* an acyliminium species has seldom been realized.[25,26] The natural abundance and medicinal significance of pyrrolidine and pyrrolizidine rings[27] makes their construction under biomimetic conditions a significant challenge. The pyrrolizidine alkaloids form a class of compounds of central pharmacological interest, *e.g.* australine, a potent inhibitor of amyloglucosidase.[27] While an azonia-Cope rearrangement provides an *indirect* route to the pyrrolizidine ring,[28] it places a substituent at C-2, which is normally inappropriate to the synthesis of a pyrrolizidine alkaloid.

An iminium intermediate is implicated in the biosynthetic pathway to the pyrrolizidine alkaloids such as retronecine (Scheme 12).[29] In attempt to contrive a cationic cyclization related to this biosynthesis, a one-pot synthesis of the pyrrolizidine ring from an acyclic precursor, was achieved.[10] It proceeded directly (*i.e.* without skeletal rearrangement) and with the biomimetic formalism of Scheme 12. Using 97% HCOOH (25 °C, 6 h) the acetal gave the pyrrolizidine ester (49%) directly, together with the exocyclic alkene (12%).

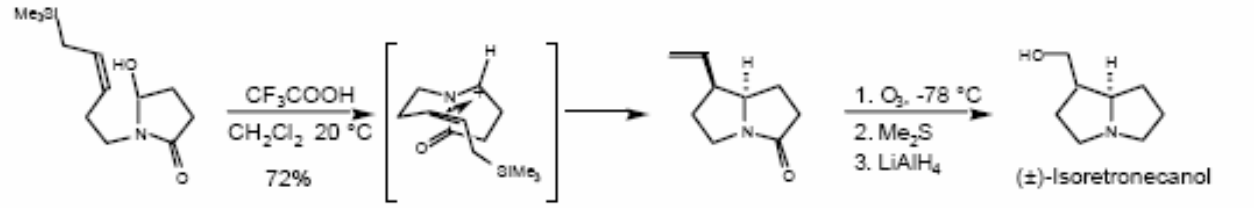


Scheme 12

Alternatively, treatment of the acetal with 3.5% hydrochloric acid in diethyl ether afforded a 1:1 mixture of the monocyclic intermediate (R = H and OEt); this mixture was cyclized with 97% HCOOH (25 °C, 48 h) to give the pyrrolizidine ring (45%), and the exocyclic alkene (11%).[10] The pattern of reactivity is ascribed to an acyliminium species, analogous to the biosynthetic iminium intermediate that leads to retronecine. The relative configuration of the

bicyclic formate ester was confirmed by X-ray crystallography on a single crystal. MM2 calculations indicate that this ester is *less* thermodynamically stable (nonbonding interactions with the 1β-substituent) by some 4 kcal mol[1] than its *exo*-epimer. Nonbonding interactions developing between the pyrrolidinium ring and the methyl group nearer to it would disfavour formation of the 1-*exo*-epimer. This study shows that placement of a carbonyl group in the chain of the *second* ring to be formed is consistent with both sequential cyclization and isolation of a single diastereoisomeric pyrrolizidine, also the kinetic product. Such direct cyclizations could provide succinct routes to the synthesis of a variety of pyrrolizidine alkaloids.

The regiochemistry of an *N*-acyliminium ion cyclisation can be influenced by altering the electronic bias of the π-nucleophile. Thus, silicon-directed *N*-acyliminium ion cyclisations can provide efficient routes to pyrrolizidines.[30] The relative configuration arises from a chair transition state (albeit with an axial trimethylsilylmethyl group) as opposed to the higher energy boat transition state. In this way (±)-isoretronecanol was synthesised (Scheme 13).[30]

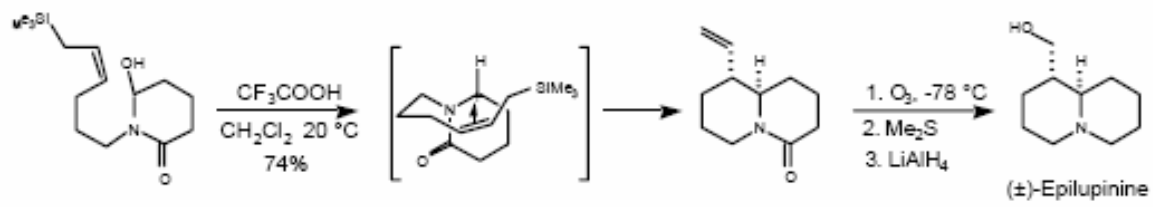


Scheme 13

Related allylstannane cyclisations also gave very high diastereoselection and were performed under conditions that avoid the generation of acid, which decomposes the allylstannane group; an asymmetric synthesis was achieved.[31]

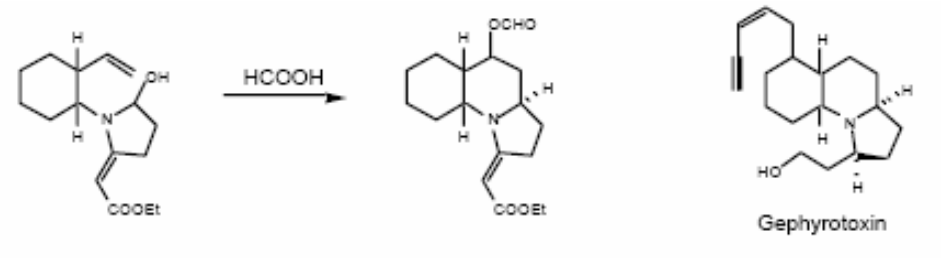
2.3 Indolizidines

Silicon-directed *N*-acyliminium ion cyclisations provided an efficient route to epilupinine (Scheme 14). The relative configuration arises from a chair transition state in which the allylsilane adopts an equatorial position, thus leading *via* a cationic complex to the desired diastereoisomer.[30] In a formal total synthesis of (±)-epilupinine, a furan used as the π-nucleophile afforded not the expected fused furan, but the product of its formal hydrolysis, considered to arise by cyclisation to the expected oxonium ion, followed by a [1,5] shift of hydrogen.[32]



Scheme 14

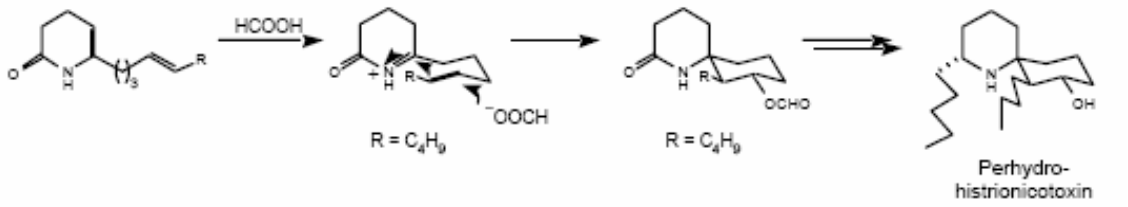
In the context of synthesising derivatives of gephyrotoxin, an alkaloid from the neotropical frog *Dendrobates histrionicus*, intramolecular *N*-acyliminium cyclisations using a vinyl group as the nucleophile afforded the tricyclic ring system with the desired relative configuration (Scheme 15).[33]



Scheme 15

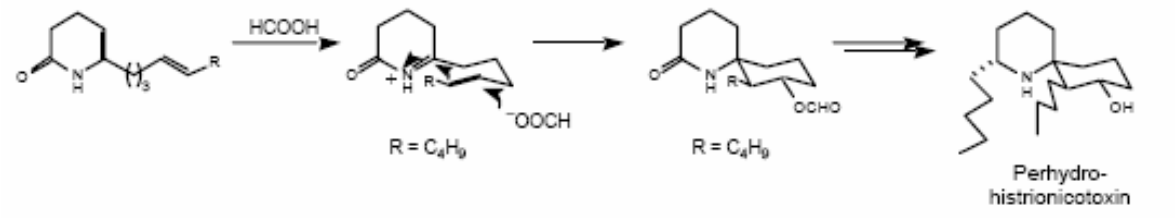
2.4 Spirocyclic systems

Cyclisation of a 9:1 mixture of endocyclic: exocyclic enamides in anhydrous formic acid proceeded *via* a presumed chair-like transition state with the acyliminium moiety adopting a pseudo-equatorial position (Scheme 16), permitting an antiperiplanar addition to give a spirocyclic amide that led to a formal total synthesis of perhydrohistrionicotoxin.[34] Both perhydrohistrionicotoxin and histrionicotoxin block post-synaptic membrane depolarisation but do not interfere with acetylcholine binding.[16,34]



Scheme 16

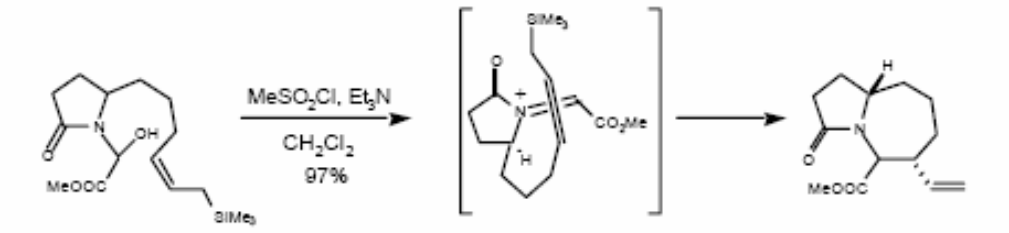
Tanis has used a furan ring as the π-nucleophile terminator in *N*-acyliminium cyclisations. In a formal total synthesis of perhydrohistrionicotoxin, a two-phase mixture of formic acid in cyclohexane (Scheme 17) was used to form the key spirocyclic furan which was then oxidatively cleaved and hydrogenated to give the spirocyclic amide that was subsequently converted into a known precursor of the alkaloid.[32]



Scheme 17

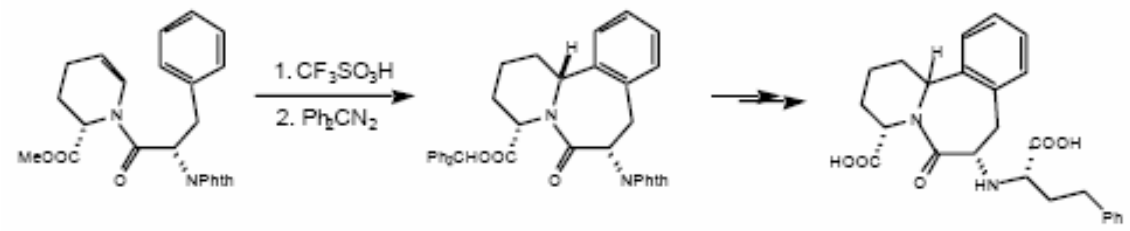
2.5 Ring systems containing a seven-membered or eight-membered ring

A highly stereoselective cyclisation leading to a seven-membered ring is known, and proceeds in excellent yield (Scheme 18).[35]



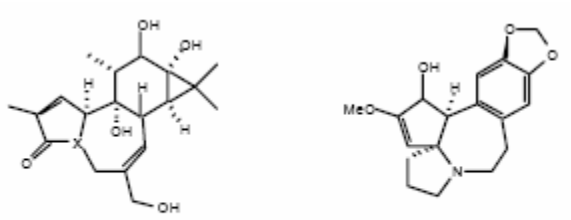
Scheme 18

An extremely potent inhibitor of angiotensin-converting enzyme was synthesised using an *N*-acyliminium cyclisation generated from an *N*-acyl enamine to construct the fused tricyclic system (Scheme 19).[36]

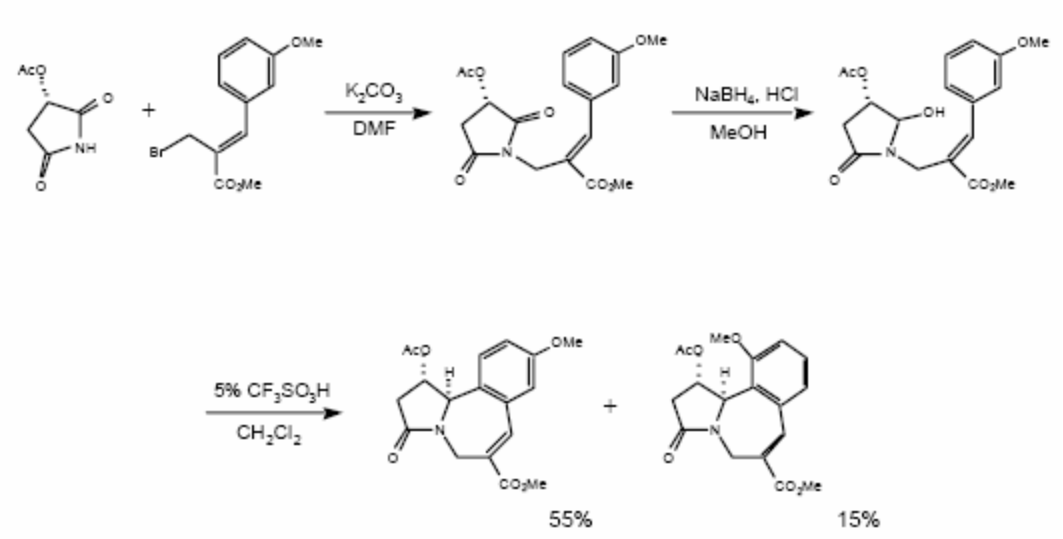


Scheme 19

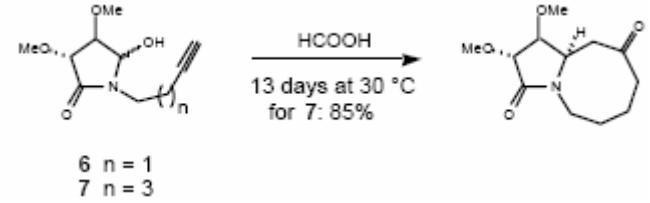
Certain hydroxylated compounds containing a central seven-membered ring possess either tumour-promoting activity (as for phorbol which is used as a probe for cancer elucidation) or anti-cancer properties (as does cephalotaxine). The latter illustrates the desirability of a central seven-membered nitrogenous ring. Accordingly, an enantioselective synthesis of an aromatic 5-7-6 fused system related to phorbol was undertaken (Scheme 20), and was achieved *via* an *N*-acyliminium cyclisation, the aromatic nucleophile being directed by the steric bulk of an acetate group to the opposite face of the iminium secies.[10]



Phorbol (**4**) X = C(β-OH) Cephalotaxine (**5**)



Scheme 20

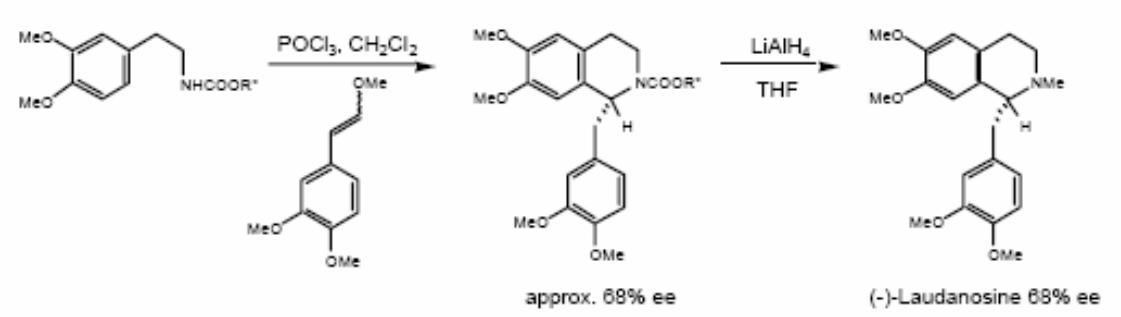


Scheme 21

In related cyclisations, carbinol lactam **6** leads to a 1:1 mixture of diastereoisomeric indolizidine derivatives, whereas the two-carbon homologue **7** affords an excellent yield of a single diastereoisomer (Scheme 21).[37]

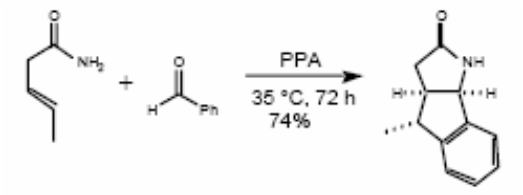
2.6 Polycyclic and bridged systems

N-Acyliminium ion cyclisations can be subject to the influence of a chiral auxiliary on the nitrogen atom. Generally the diastereoisomeric excesses that result have not been high, although intramolecular versions offer some promise. For example, (-)-laudanosine was synthesised in 68% ee by using (-)-8-phenylmenthyl as the chiral auxiliary. Unfortunately the diastereoisomers that resulted could not be separated, and so the mixture was reduced to give the tetrahydroisoquinoline (Scheme 22).[38]



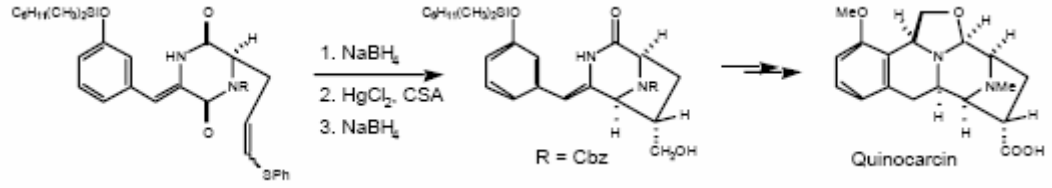
Scheme 22

N-Acyliminium intermediates can be involved in tandem cyclisations to give polycyclic systems with stereocontrol (Scheme 23).[8] The first ring closure provides a *cis*-disubstituted pyrrolidinone whose vinylic substituent is protonated to give a cation that undergoes intramolecular Friedel-Crafts type cyclialkylation of the phenyl substituent to give the tricyclic system as the sole diastereoisomer isolated.[8]



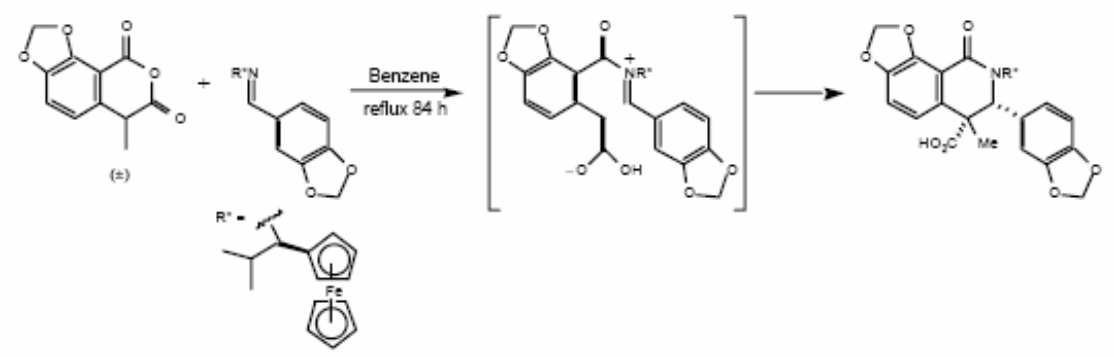
Scheme 23

A total synthesis of racemic quinocarcin, an antitumour antibiotic, proceeded *via* reduction of an acylated amide to the carbinol followed by an *N*-acyliminium ion-mediated cyclisation and subsequent reduction of the resultant aldehyde to give the corresponding alcohol (Scheme 24).[39]



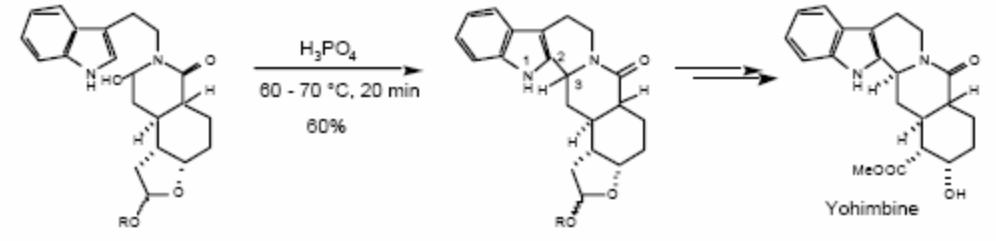
Scheme 24

An auxiliary-controlled *N*-acyliminium ion cyclisation has been described that affords predominantly a single diastereoisomer (Scheme 25). The bulky chiral auxiliary leads to a sluggish reaction, but the auxiliary can be cleaved with trifluoroacetic acid.[40]



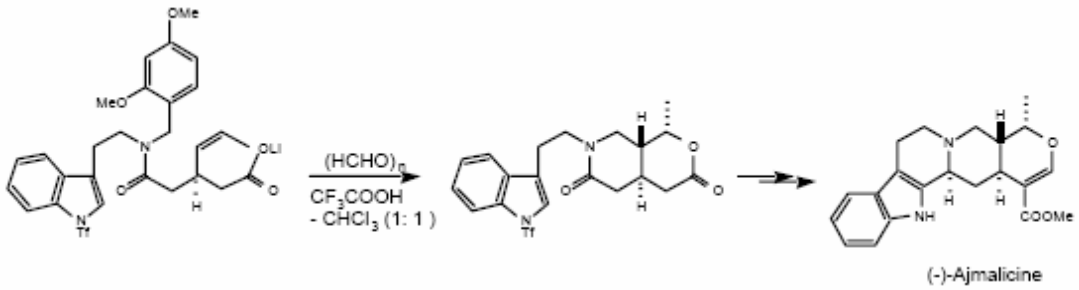
Scheme 25

A formal total synthesis of the aphrodisiac alkaloid yohimbine[41] involved cyclisation of a periodate cleavage product of a 1,2-diol, very probably the hydroxylactam in Scheme 26, to give the hexacyclic amide of the pseudoyohimbine stereochemistry (*i.e.* β-H at C-3). This was transformed into pseudoyohimbine, which had previously been epimerised to yohimbine.



Scheme 26

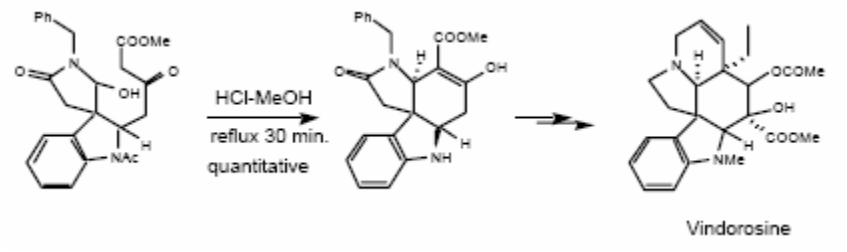
Ajmalicine is an alkaloid isolated from the roots of *Catharanthus roseus* and is widely used to treat cardiovascular disease. A total synthesis of (-)-ajmalicine involved as a key step a carboxylate-terminated *N*-acyliminium cyclisation, which assembled the DE ring system in one step (Scheme 27).[42] The acid first cleaves the benzylic group, prior to formation of the acyliminium species.



Scheme 27

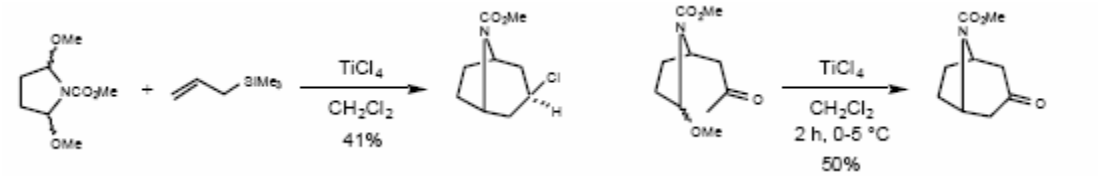
Reduction of an imide with acidic borohydride is often regioselective, as was the case in a formal total synthesis of vindorosine (Scheme 28).[43] The carbinol lactam served as the direct

precursor of the *N*-acyliminium ion which underwent intramolecular cyclisation with an acetoacetate side-chain as the nucleophile.



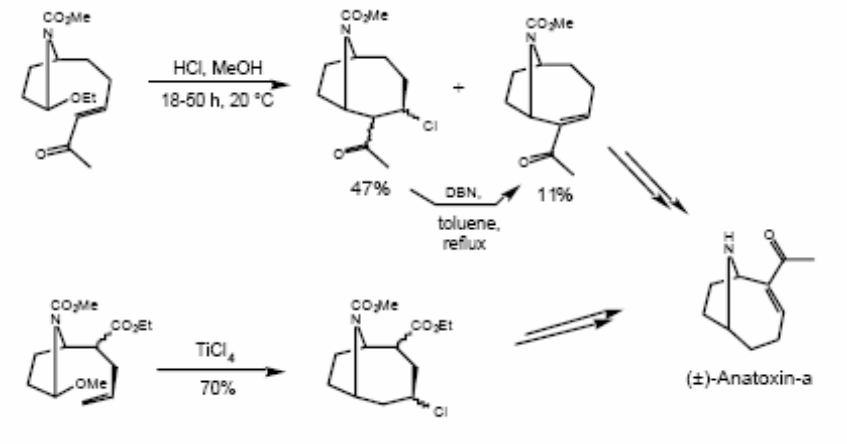
Scheme 28

Tropane-like systems can be prepared by Lewis acid-induced cyclisation of alkene[44] or enolic[45] π-nucleophiles (Scheme 29).



Scheme 29

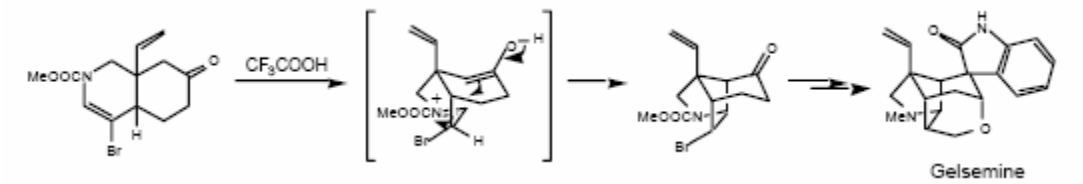
8-Azabicyclo[3.2.1] systems can also be prepared by similar cyclisations, either using mineral acid[46] or $TiCl_4$ (Scheme 30). In the latter sequence,[47] the α-methoxy precursor was prepared by anodic oxidation of the amide; $TiCl_4$ cyclisation afforded the bicyclo system which was converted into the potent neuromuscular toxin anatoxin a. This alkaloid was also prepared *via* cyclisation of an unfunctionalised alkene (Scheme 30), the overall yield of the unsaturated ketone being 60%. Subsequent deprotection gave anatoxin a.[46]



Scheme 30

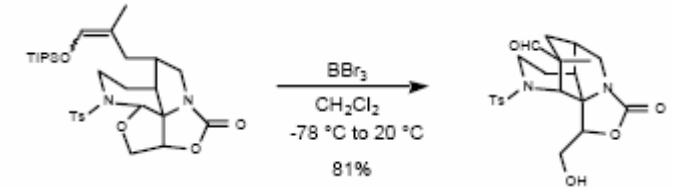
A total synthesis of gelsemine, the major alkaloidal component of yellow jasmine, proceeded

via a Mannich cyclisation involving a boat conformation of the enolic π-system.[48] The sole diastereoisomer derived from protonation to give the bromo epimer that is the more thermodynamically stable (*i.e.* exocyclic bromine atom). A Heck reaction was used to introduce the spiro-oxindole, and subsequent base-induced equilibration led to an extremely elegant assembly of the full skeleton, and then in only three further steps to racemic gelsemine.



Scheme 31

The marine alkaloids the sarains A-C possess antitumour activity and contain a diazatricyclic core that has been constructed using the first example of an intramolecular *N*tosyliminium cyclisation, in which the nucleophile was a silyl enol ether.[49] A 3:1 mixture of diastereoisomers at the carbon atom bearing the aldehyde group resulted, the major epimer being shown in Scheme 32. The cyclisation could not be achieved using $SnCl_4$, $Et_2O.BF_3$ or Me_3Al.



Scheme 32

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