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Enaminones: versatile intermediates for natural product synthesis*

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Abstract: Efforts in our laboratories to devise a general approach to the synthesis of alkaloids focus on the versatile reactivity of enaminones and related compounds containing the structural unit N–C=C–Z (Z = COR, CO_2R, CN, NO_2, SO_2Ar, etc.). This lecture presents an overview of our research with these useful building blocks. Themes to be elaborated include chemoselectivity and diastereoselectivity in reactions of enaminones, and the challenge of controlling absolute stereochemistry.

INTRODUCTION

The field of alkaloid synthesis teems with strategies that can be viewed as 'generalized' because they are easily adapted to provide access to a range of structurally diverse targets. The versatility and power of such unified general approaches was convincingly demonstrated about three decades ago in the influential work of Wenkert [1] and Stevens [2]. Since then, the number of broadly applicable strategies for alkaloid synthesis has burgeoned, and several have earned a secure place in the repertoire of organic chemists. Some useful, and often very potent, general approaches include variations on Diels–Alder and dipolar cycloadditions [3,4], iminium and acyliminium ion strategies in various manifestations [5], the use of tetrahydropyridinium and acylpyridinium intermediates [6], and methods involving chiral intermediates or auxiliaries such as α-cyanoamines, formamidines or oxazolidines [7].

To this impressive list of general strategies for alkaloid synthesis we have added another useful, if modest, approach. At the heart of our work are enaminones of various types whose ambident electrophilicity and nucleophilicity, not to mention their ability to participate in pericyclic and radical processes, open the doors to a sumptuous, and still relatively unexplored, chemistry. Strictly speaking, the term 'enaminone' should be reserved for a system such as that illustrated in Scheme 1 (top), i.e. a β-acylated enamine. From this perspective, the acyl group serves to modulate both the stability and the reactivity of the enamine unit, which is usually sensitive to hydrolysis and oxidation. However, one can also view enaminones as amides into which a vinyl fragment has been interpolated (Scheme 1, bottom). This alters both charge and orbital effects in the system, and profoundly changes its intrinsic reactivity. Regarding enaminones as vinylogous amides is also useful because it helps one to conceptualize analogous structures in which the interaction between nitrogen and a π-bonded, electron-withdrawing functional group is extended by vinylogy. The resulting 'push-pull' systems (vinylogous urethanes, cyanamides, ureas, nitramines and sulfonamides, amongst others; Fig. 1) will have substantially different properties depending

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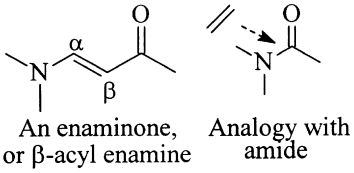


Scheme 1

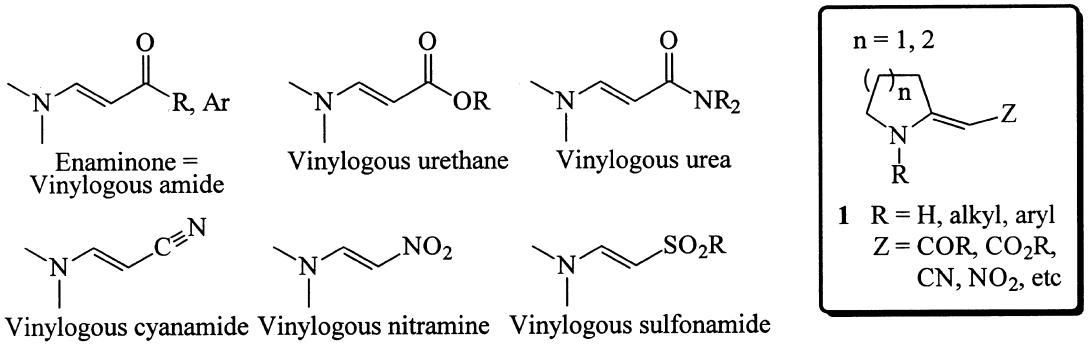


Fig. 1

on whether the β-substituent overwhelms or merely tempers the inherent reactivity of the enamine core. Exploring the changes that can be rung on these systems, and the resulting nuances in their synthetic applications, is an ongoing challenge for us. Aspects of the challenge will be described in this lecture, which gives an overview of our approach to the synthesis of alkaloids *via* enaminones and related compounds.

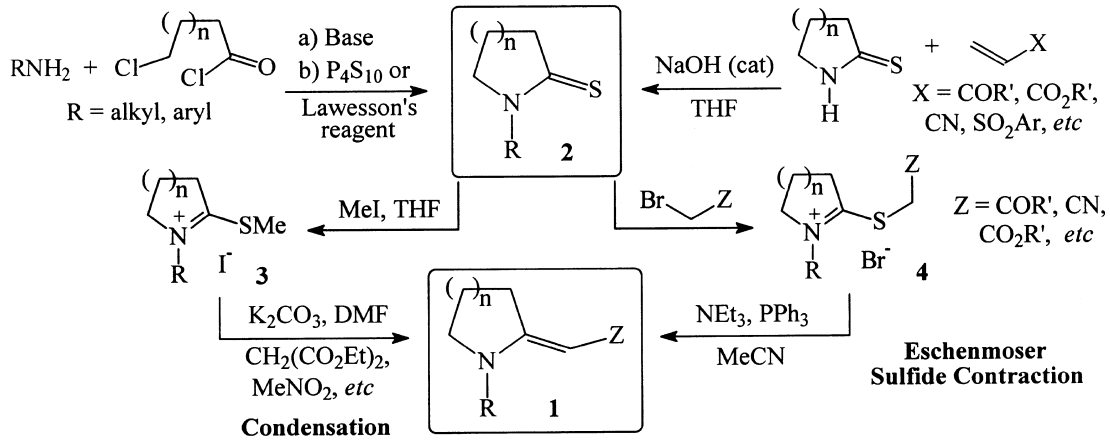
ACCESS TO ENAMINONES

Because the heteroatom in nitrogen-containing secondary metabolites is almost always found in a five- or six-membered ring, the β-substituted enamines used in our research are invariably derivatives of pyrrolidine or piperidine, and specifically ones with an exocyclic alkylidene substituent at C-2. Structure **1** (Fig. 1, inset), typical of the substrates with which we work, illustrates some of the easily varied features that are conducive to a general research protocol: tolerance to substituents (particularly on N), choice of ring size, and, of course, the all-important electron-withdrawing substituent Z on the enamine. The geometry of the C=C bond also matters; although **1** is shown as the *E* isomer, the hydrogen-bonded *Z* isomer tends to dominate when R = H.

Compounds **1** are accessible by many routes. We find it convenient to proceed *via* thiolactams **2**, which are themselves prepared either by thionating lactams made from primary amines and bifunctional reagents (e.g. 4-chlorobutyryl chloride or γ-butyrolactone), or by a useful conjugate addition of secondary thiolactams (pyrrolidine-2-thione or piperidine-2-thione derivatives) to acrylate esters, acrylonitrile and similar acceptors. Both routes accommodate a wide range of substituents on either reaction partner. More importantly, we introduce the alkylidene substituent at C-2 either by condensing a relatively acidic component (e.g. nitromethane, β-dicarbonyl compounds) with methylthioiminium salts **3** [8]; or by the Eschenmoser sulfide contraction, in which sulfur is extruded from the salts **4** that result when thiolactams **2** react with enolizable α-halocarbonyl compounds [9]. Some of the permutations are shown below (Scheme 2).

PATTERNS OF REACTIVITY IN ENAMINONES AND RELATED COMPOUNDS

Our preoccupation with enaminones and their relatives stems principally from their ability to function both as ambident nucleophiles and as ambident electrophiles, as shown Fig. 2 for the specific case of a vinylogous amide. Naturally, the expected 'enamine' nucleophilicity at N and C can be extended to the



Scheme 2

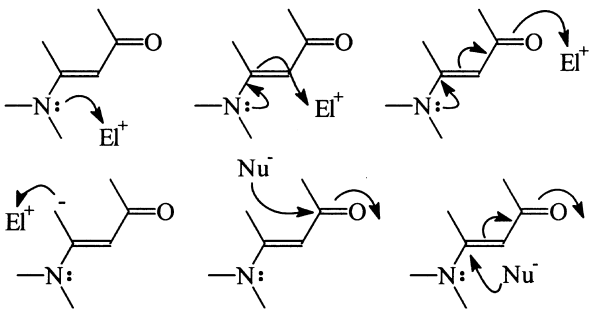
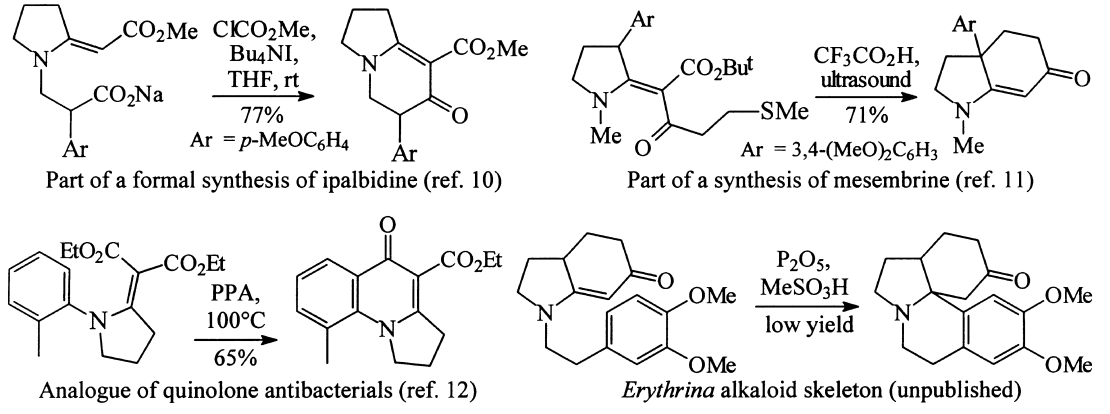


Fig. 2

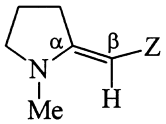
carbonyl group by conjugation (top row). In addition, deprotonation with strong bases (and, in some cases, acid-induced tautomerism) provides a further nucleophilic site β to N (second row, left). However, the systems also have 'enone' character, and may act as acceptors in both 1,2-and 1,4-additions (second row, centre and right). We regularly exploit the versatile reactivity of the N–C=C–Z unit by building it into systems containing additional nucleophilic or electrophilic sites that serve as complementary reaction partners. In this way the enaminone serves as a scaffold for annulation, and we can gain access to systems such as indolizidines, quinolizidines and perhydroindoles, all of which are common motifs in alkaloid structures. Some examples from our published and unpublished work are shown in Scheme 3.



Scheme 3

Whether enamine-like or enone-like reactivity will be dominant depends entirely on the substituent Z. NMR spectroscopy provides a rough-and-ready guide to *nucleophilic* behaviour, since increased electron density at the β-carbon is expected to be reflected in upfield shifts of the signals for this carbon and the attached vinyl proton. Chemical shifts for these sites are listed in the Table below for a series of model compounds **5** in which the only change is in substituent Z. Vinylogous cyanamide **5a** appears to be the system of choice when nucleophilic behaviour is desired, while vinylogous nitramine **5f** should be better as an acceptor. It must be stressed that the NMR spectroscopic data give only an approximate guide to reactivity. One cannot, for instance, gauge the electrophilicity of the α-C site from ^{13}C chemical shifts; for all the compounds shown, $\delta_{C\text{-}\alpha}$ lies in the narrow range 166 ± 4 p.p.m. Factors such as kinetic vs. thermodynamic effects also subvert simple predictions of reactivity; for example, equilibrium protonation of vinylogous urethane **5b** with dilute aqueous acid occurs on the enamine carbon, while oxygen is the preferred site of protonation for vinylogous amide **5e**. By contrast, vinylogous nitramine **5f** is not protonated by dilute acid.

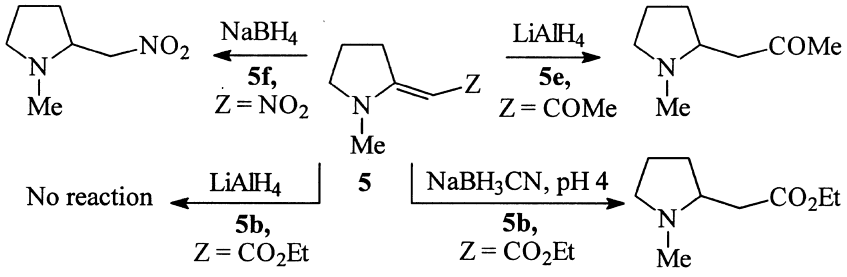
Table 1 Selected chemical shifts for 1-methyl-2-methylenepyrrolidenes **5**



5

	Z	$\delta_{C\text{-}\beta}$ (ppm)	$\delta_{H\text{-}\beta}$ (ppm)
5a	CN	53.2	3.57
5b	CO_2Et	77.3	4.47
5c	$CONMe_2$	77.6	4.75
5d	SO_2Ph	86.4	4.83
5e	COMe	89.0	4.77
5f	NO_2 (ref. 8)	108.8	6.67

Changing Z also allows one to fine-tune the *electrophilic* reactivity of β-substituted enamine systems. Consider, for example, the reduction of the C=C bond in the model compounds **5** (Scheme 4). The vinylogous nitramine **5f** is a good enough acceptor to react with sodium borohydride at room temperature; the vinylogous amide **5e** is unaffected by sodium borohydride, but undergoes conjugate reduction with lithium aluminium hydride in ether at room temperature [13]—a clear manifestation of the 'enone' side of its constitution. However, even this vigorous reductant leaves vinylogous urethane **5b** untouched. Nevertheless, sodium cyanoborohydride, a very mild reductant, succeeds in bringing about the reduction of **5b** at pH 4, because protonation results in the intermediate formation of a readily reduced iminium ion.

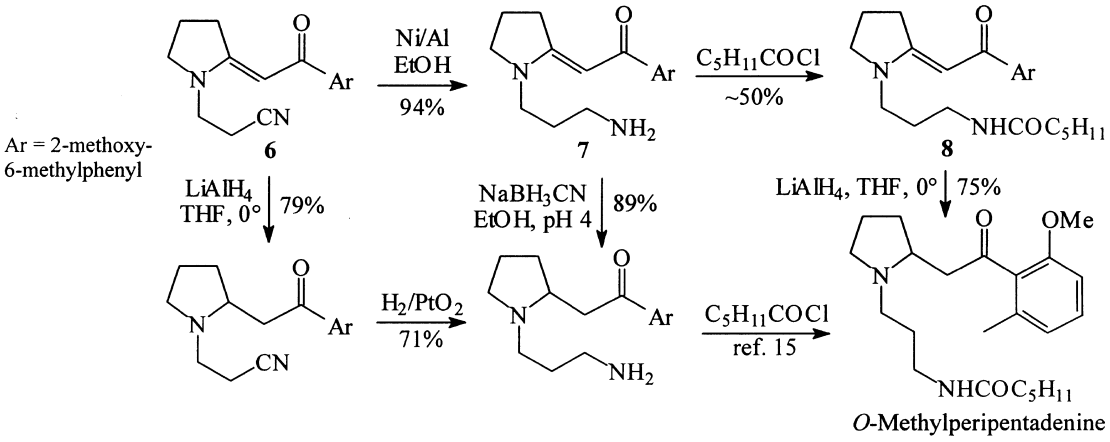


Scheme 4

CHEMOSELECTIVE TRANSFORMATIONS INVOLVING ENAMINONES

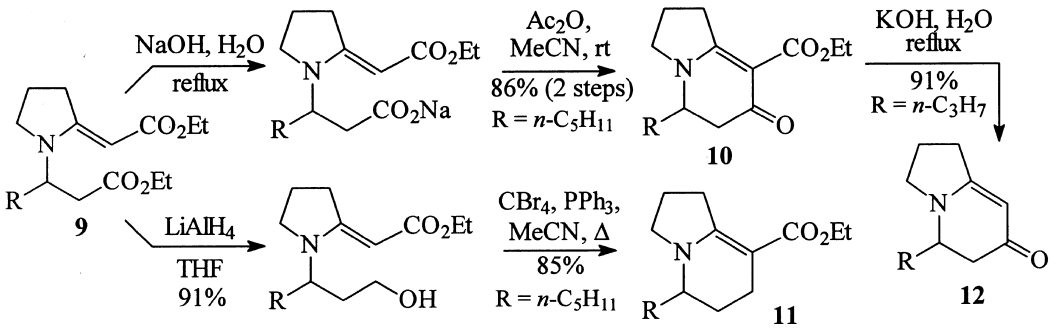
When compounds incorporating N–C=C–Z units also contain other functional groups, it is to be expected that chemoselective processes will add a further dimension to the synthetic utility of our versatile intermediates. Our synthesis of the simple pyrrolidine alkaloid peripentadenine [14] is a case in

point. A section of the synthesis illustrating several chemoselective transformations is shown in Scheme 5. Despite the variety of reducible functional groups in the vinylogous amides **6, 7** and **8**, careful choice of reagents permitted us to explore alternative synthetic 'loops' in the sequence, and thus optimize the timing of events. The final demethylation of *O*-methylperipentadenine to give the target alkaloid was accomplished in 92% yield with boron tribromide.



Scheme 5

Scheme 6 shows aspects of chemoselectivity in the reaction of vinylogous urethanes, which turn out to be remarkably robust under conditions that normally affect esters. The specific examples cited (R = *n*-pentyl, *n*-propyl) are taken from our syntheses of two alkaloids found in the skins of dendrobatid frogs [16–18], but the principles are general. It is the saturated ester of substrate **9** that is hydrolysed (upper row) or reduced (lower row); the vinylogous urethane emerges unscathed. This useful discrimination between the two esters permits activation of the transformed group for acylative and alkylative cyclizations to give products **10** and **11**, respectively. Ironically, since **10** is also a β-keto ester, it becomes quite easy to hydrolyse and decarboxylate the vinylogous urethane to give **12**. The functionalized bicyclic systems that result from cyclizations similar to those illustrated are suitable for elaboration to a wide variety of alkaloids. Moreover, the cyclized products are still 'enaminones'; they retain the structural features required for our general approach to alkaloid synthesis, and one can envisage further exploitation of the embedded functionality.

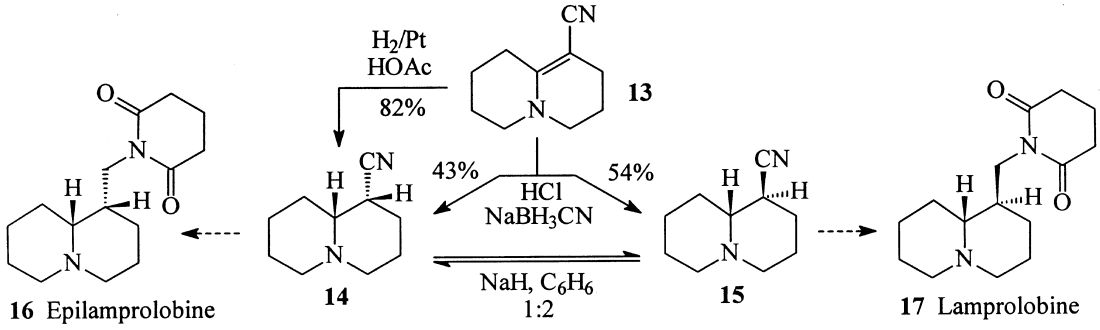


Scheme 6

DIASTEREOSELECTIVITY

Our general approach to alkaloid synthesis would have limited value if it failed to address the crucial topic of stereochemistry. Fortunately, opportunities abound for investigating the control of both relative and absolute stereochemistry. Scheme 7 shows a simple example of diastereoselection. Reduction of the

C=C bond of the bicyclic vinylogous cyanamide **13**, prepared by a similar reaction sequence to that shown in Scheme 6, can yield two diastereoisomeric cyanoquinolizidines, **14** and **15**. When **13** was hydrogenated over a platinum oxide catalyst in acetic acid, the *cis*-hydrogenated product **14** was obtained in 82% yield, accompanied by only 6% of isomer **15**. By contrast, reduction with sodium cyanoborohydride at pH 4 gave a nearly equal mixture of products (43% and 54%, respectively). The proportion of **15** could be increased to about 2:1 by equilibration of the isomer mixture with sodium hydride in boiling benzene. The separated isomers were readily converted into the alkaloids (±)-epilamprolobine **16** and (±)-lamprolobine **17** by straightforward transformations [19]. A point of interest is that the C≡N functional group not only regulates the reactivity of the pivotal 'enaminone', but itself becomes incorporated into the target alkaloids. (An example of diastereoselection relative to a third stereogenic centre will be shown in Scheme 9.)

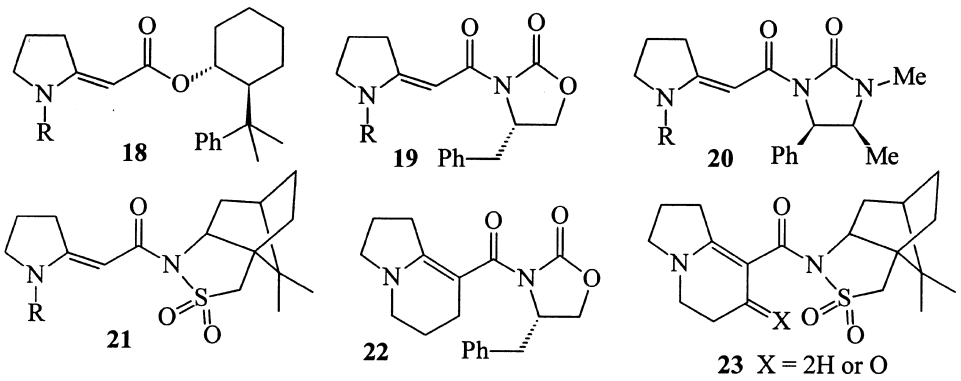


Scheme 7

ENANTIOSELECTIVITY

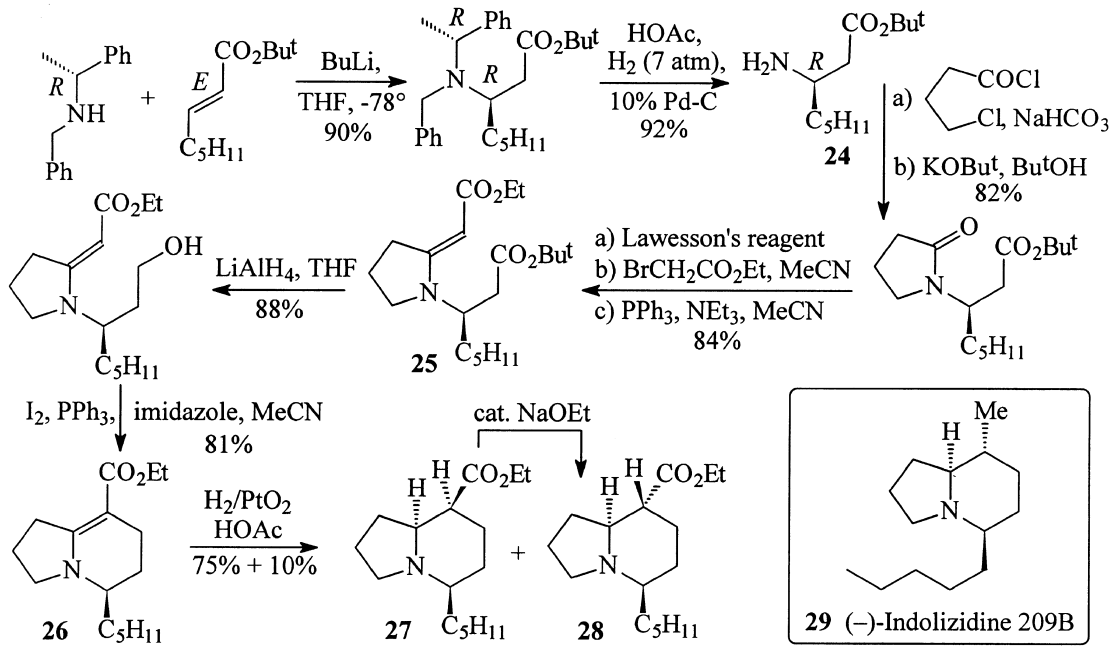
In the above example there is, of course, no control over the absolute stereochemistry of the products, since both faces of the C=C bond are intrinsically equally susceptible to attack by the reductant. However, logical ways to surmount the hurdle of absolute stereocontrol are readily envisaged. An obvious approach is to use chiral reducing agents (e.g. chiral boranes) to achieve the desired enantioselective reduction, but this has been rather unsuccessful for us. A different strategy involves the incorporation of chiral auxiliaries into substituent Z in the fundamental N–C=C–Z unit, the expectation being that the asymmetric units will 'block' one face of the C=C bond and thus impart a diastereofacial bias to its reactions. We have tested this idea with chiral vinylogous urethanes **18** and three sets of vinylogous ureas **19–21** containing familiar chiral auxiliaries such as oxazolidinone, imidazolinone and camphorsultam [R = Me, $(CH_2)_3OAc$, $(CH_2)_2CO_2Et$]. Here, too, our results have been unpromising, part of the problem being the lability of the auxiliary in **19–21** towards reducing agents. Attempts to use metal ions to lock the carbonyl groups into a specific chelation-controlled orientation and thereby impart a measure of rigidity to the systems have also been unsatisfactory. The more rigid bicyclic systems **22** and **23** have, however, given encouraging results. Nevertheless, the ideal auxiliary remains elusive; we do not yet have a mutually compatible combination of reactants and reagents (Scheme 8).

A different, and more productive, approach to handling absolute stereochemistry has been to incorporate homochiral building blocks into our reactants. β-Amino acids and esters, which can be prepared enantioselectively by numerous methods [20], are natural candidates for our work. Our synthesis of the amphibian alkaloid (–)-indolizidine 209B [17] uses the (*R*)-(–)-amino-ester **24**, prepared as shown in Scheme 9 by means of a reasonably general method devised by Davies & Ichihara [21]. This valuable route involves conjugate addition of lithium *N*-benzyl-*N*-[(1*R*)-1-phenylethyl]amide (or its enantiomer) to *t*-butyl (*E*)-alk-2-enoates to give the desired adducts in excellent chemical yields, reproducibly high diastereoselectivities (>95% d.e.), and with a predictable stereochemical outcome [22]. Hydrogenolysis of both benzyl groups (7 atm. H_2, 10% Pd-C, acetic acid) then yields enantiomerically pure β-amino esters. In our example, incorporating amino-ester **24** into the optically active vinylogous urethane **25** used chemistry similar to that illustrated in Scheme 2, while the transformation of **25** into the (+)-bicyclic



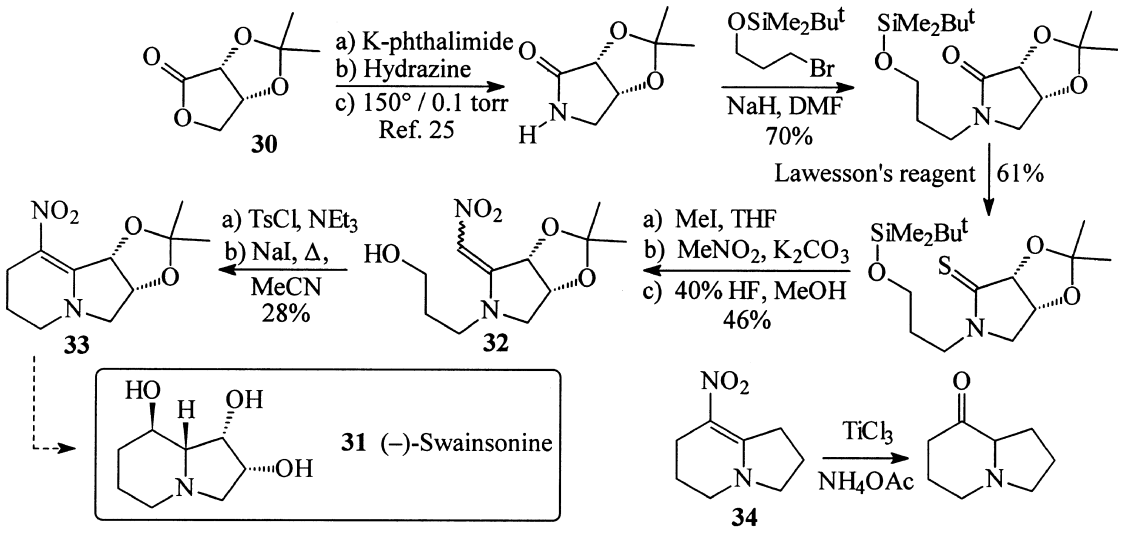
Scheme 8

vinylogous urethane **26**—another example of the nucleophilicity of enaminones in action—employed principles akin to those shown in Scheme 6. At this point we were able to adapt the diastereoselective transformation shown in Scheme 7. Reducing the C=C bond of (+)-**26** introduces two new stereogenic centres whose configurations have to be controlled not only in relation to each other, but also in relation to the more remote (*R*) stereogenic centre already present at C-5. We found that *cis*-catalytic hydrogenation took place on the face of the double bond further away from the pentyl substituent—effectively, the less hindered face. Product **27** was readily equilibrated with base to give diastereoisomer **28** in which all substituents on the six-membered ring are equatorial. The synthesis of (–)-indolizidine 209B **29** was completed by defunctionalization of the ester (Scheme 9).



Scheme 9

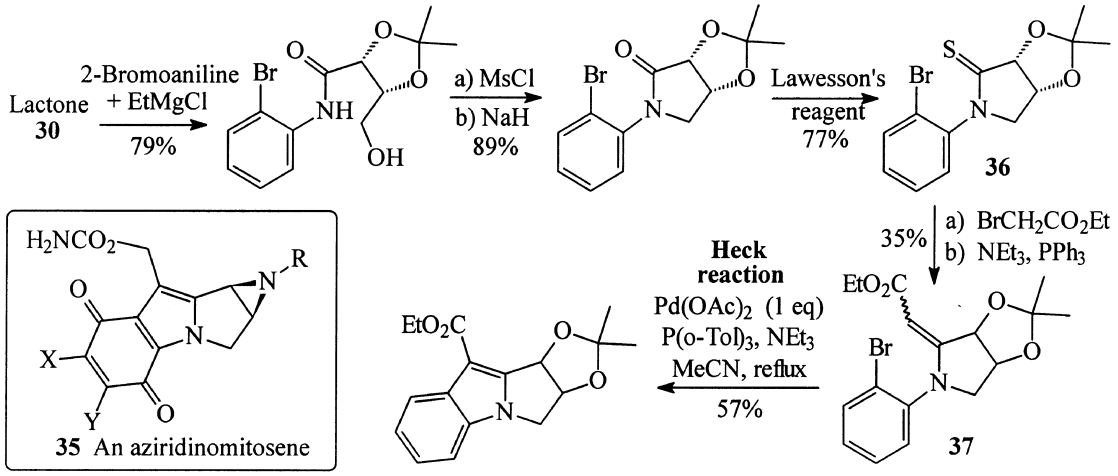
Two final examples, taken from work in progress, show how we can tap into the 'chiral pool' for our homochiral building blocks. Lactone **30** is readily available in quantity by peroxide-induced degradation of D-isoascorbic acid [23]. Aminolysis of the ring and recyclization gives 2,3-dioxygenated pyrrolidinones that lend themselves to the synthesis of some important natural product targets. Scheme 10 shows our progress towards the noteworthy indolizidinetriol (–)-swainsonine **31** [24], a



Scheme 10

powerful inhibitor of mannosidases, and of great interest as an immunomodulator and anti-cancer agent. The 'enaminone' at the heart of the synthesis is, in fact, a vinylogous nitramine, **32**. However, as we have come to expect, its nucleophilicity is poor, and we have struggled to cyclize it to the indolizidine **33**. Completion of the synthesis will require Nef reaction and stereoselective reduction of the resulting ketone as nontrivial steps. So far we have found that the Nef reaction works on the model system **34** with titanium(III) chloride in ammonium acetate buffer.

Aziridinomitosenes of general type **35** are biological intermediates in the bioreductive activation of mitomycins, which are clinically important anti-tumour agents isolated from *Streptomyces* species [26]. Our current progress towards such compounds is outlined in Scheme 11. With lactone **30** as the homochiral starting material, we have so far produced the optically pure pyrrolidine-2-thione **36** in a fairly efficient four-step synthesis that works well on a multigram scale. The transformations from **36** onwards have been probed only with racemic substrates, and we have yet to optimize the sulfide contraction that gives rise to the vinylogous urethane **37** (isolated, unusually, as a 1:1 mixture of geometrical isomers). The most significant finding in our model studies has been a novel participation of vinylogous urethane **37** in an intramolecular Heck reaction to form the pyrrolo[1,2-*a*]indole core of the target compounds. By showing that this is a general reaction of many *N*-(2-bromoaryl) enaminones



Scheme 11

related to our prototypical system **1** [27], we have added a new dimension to the reactivity of these versatile compounds.

SUMMARY

This overview has shown that we have a flexible and general strategy for the synthesis of a structurally diverse range of nitrogen-containing natural products and heterocycles. The approach is conceptually and experimentally simple, eschews exotic transformations, and uses affordable and familiar materials wherever possible. We hope that this lecture, a contribution to the 7th International Conference on Chemistry in Africa, will reassure colleagues from elsewhere on the continent that the pursuit of organic synthesis can be cost-effective and eminently achievable despite the obstacles posed by economic constraints and scientific isolation.

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