New approaches for the synthesis of erythrinan alkaloids†

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Received 6th January 2009, Accepted 23rd February 2009
First published as an Advance Article on the web 24th March 2009
DOI: 10.1039/b900189a

A concise asymmetric total synthesis of (+)-erysotramidine is described, using chiral base desymmetrisation of a meso-imide, *N*-acyliminium addition, retro-Diels–Alder cycloaddition and radical cyclisation as the key steps. A related route, starting from a cyclobutene-fused imide, was explored, and established a novel construction of the *Erythrina* alkaloid skeleton using a key ring-opening/ring-closing metathesis step. Completion of this synthesis was thwarted by problems with the removal of an unwanted vinylic side-chain. Complementary enantiospecific routes to *Erythrina* systems were explored, starting from (*L*)-malic acid. Some unexpected observations were made concerning the diastereocontrol in malic acid-derived *N*-acyliminium ion cyclisations, where changing the protecting group of the alcohol function from acetate to OTIPS resulted in a dramatic change in diastereocontrol. Products from these reactions could be transformed into known intermediates for natural alkaloids, and into (+)-demethoxyerythratidinone itself, by means of radical cyclisations or intramolecular aldol reactions as the key steps.

Introduction

The *Erythrina* alkaloids constitute a large group of compounds isolated from the plants of the genus *Erthyrina*, which are widely distributed in tropical and sub-tropical areas.[1] These plants have been widely used in folk medicine, and are known to produce curare-like and hypnotic effects and to possess general CNS activity. More specific pharmacological effects associated with members of this alkaloid family include sedative, hypotensive and neuromuscular blocking activities.[2]

Structurally, the *Erythrina* alkaloids are characterised by their unique tetracyclic spiroamine framework (Fig. 1).

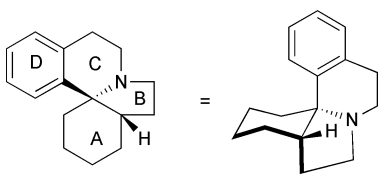

Fig. 1 *Erythrina* alkaloid skeleton.

According to the nature of the D-ring they are generally classified into aromatic types such as erysotramidine **1** and 3-demethoxyerythratidinone **2**, and non-aromatic types such as β-erythroidine **3** and cocculolidine **4**. According to the number and position of the olefinic bonds they also may be subdivided into dienoids with a conjugated diene unit such as erysotramidine **1** and β-erythroidine **3**, and alkenoids with only one double bond in the A-ring such as 3-demethoxyerythratidinone **2** and cocculolidine **4** (Fig. 2).[3]

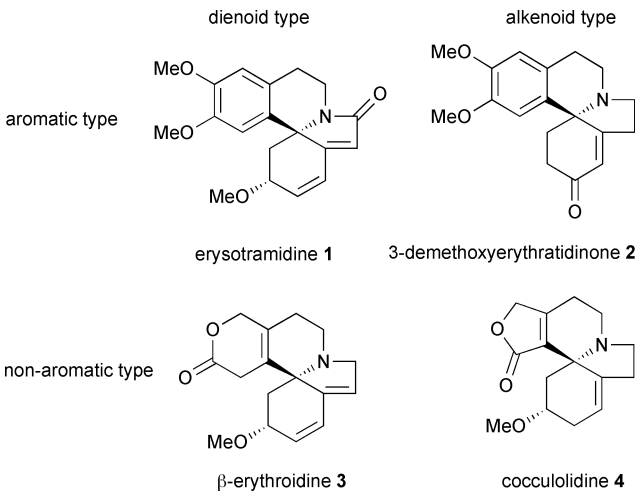

Fig. 2 Structural classifications of *Erythrina* alkaloids.

The *Erythrina* alkaloids have received considerable synthetic attention in recent decades owing to their intriguing biological activity and challenging characteristic polycondensed structures.[3] Many different approaches to the core spirocyclic system present in these alkaloids have been developed, and a number of syntheses of members of this family, in racemic form, have been completed. Recent examples include: synthesis of (±)-erythrocarine by Mori *et al.*,[4] using dienyne metathesis as the key step, synthesis of (±)-3-demethoxyerythratidinone by Padwa and Wang based on furan intramolecular Diels–Alder chemistry,[5] and the synthesis of (±)-erysotramidine by Tu *et al.* using an *N*-acyliminium ion cyclisation.[6]

By contrast, there are very few examples of *asymmetric* syntheses of erythrinan alkaloids, and only very recently have research

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† Electronic supplementary information (ESI) available: Experimental procedures and characterisation data. CCDC reference number 715824. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b900189a

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groups established enantioselective routes to compete with the original efforts of Tsuda *et al.*, in which *L*-DOPA derivatives were converted into targets, including **1** and **2**, by condensation or Diels–Alder strategies.[7] Notable efforts in this area include the synthesis of 3-demethoxyerythratidinone **2** by Allin *et al.*, using Meyer's chiral lactam approach,[8] a highly novel synthesis of *O*-methylerysodienone using axially chiral biphenyl intermediates by Matsumoto *et al.*,[9] and access to (+)-β-erythroidine **3** using a metathesis approach.[10]

Our own efforts in this area stemmed from our interest in accessing substituted polycyclic imides, amides, and derived substances from reactions of symmetrical imides with chiral lithium amide bases. In our previous work we established a new asymmetric synthesis of (+)-erysotramidine **1** using this type of chiral base approach, combined with a key *N*-acyliminium ion cyclisation,[11] and later we accessed (+)-3-demethoxyerythratidinone **2**, using a chiral pool approach in which we probed some unexpected diastereoselectivities in *N*-acyliminium ion cyclisations of malic acid derivatives.[12] Herein, we describe this work in full, including substantial unpublished chemistry in which we have attempted to further streamline our earlier syntheses, and developed rapid new access to the erythrinan system.

Chiral base synthesis of erythrinan systems

The retro-Diels–Alder approach

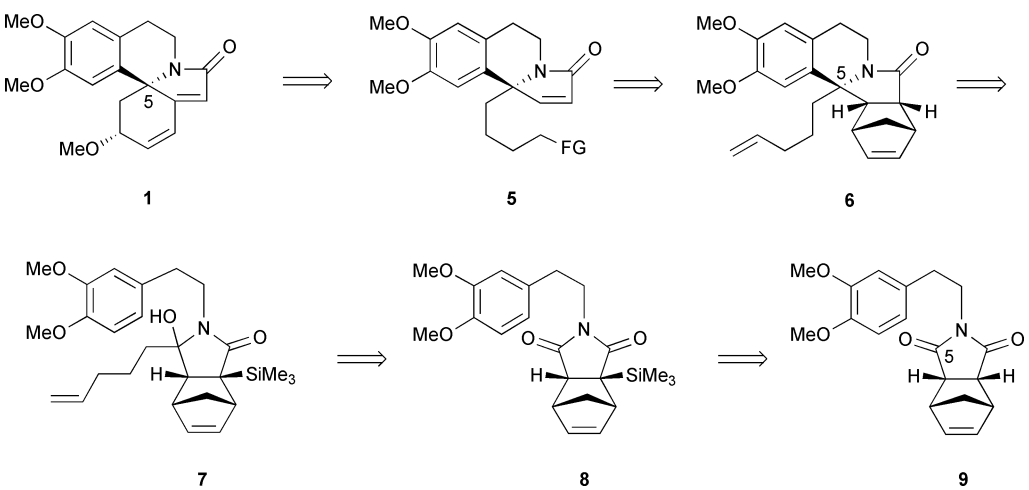
Our initial synthesis of the erythrinan system came about due to an ongoing interest in imide desymmetrisation using chiral bases, an approach that we had used to access other natural product motifs, including a proposed structure for an alkaloid called jamtine.[13] Our approach is outlined in retrosynthetic form in Scheme 1.

Access to the complete alkaloid framework, and ultimately natural products such as (+)–erysotramidine **1**, would be accomplished by a cyclisation of an α,β-unsaturated lactam **5**, in which a functional group (FG) in the side-chain appendage would facilitate a Michael-type cyclisation to form the required 6-membered ring. Based on some related work by Lete and co-workers,[14] we expected that the lactam **5** would be available by retro-Diels–Alder reaction of cyclopentadiene adduct **6**. As will be seen, the use of this framework serves as a device for controlling the stereochemistry of the crucial C-5 spirocyclic centre in **1**, which originates as one of the carbonyl functions of a starting imide. In initial work we chose a pentenyl side chain in lactam **6** to provide access to a functional group in **5** capable of subsequent annulation, whilst not interfering in earlier steps.

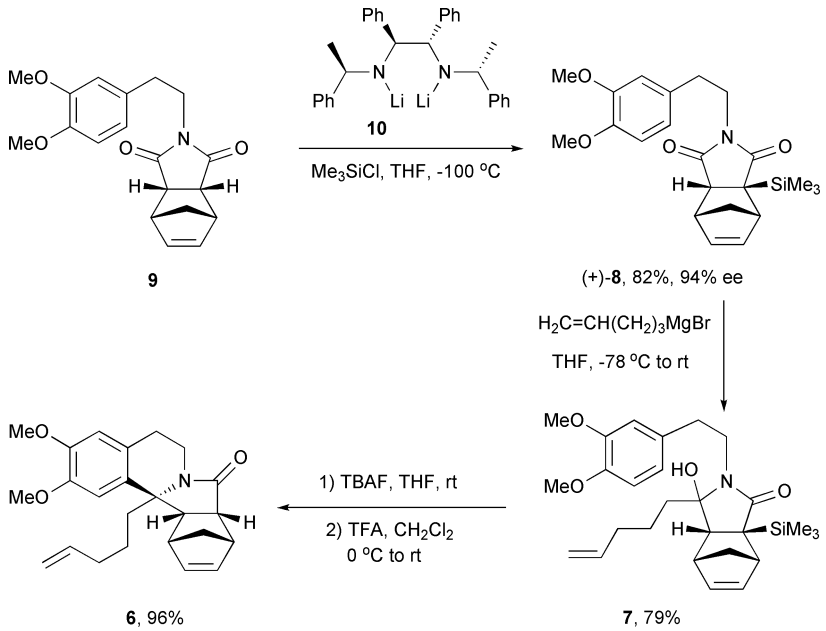
The crucial C-5 stereochemistry would be set up in an *N*-acyliminium ion cyclisation of hydroxylactam **7**, and control in this step was anticipated to arise by *exo*-attack of the electron-rich aromatic nucleus on the convex face of the reactive electrophile.[15] Asymmetric construction of **7** required differentiation of the two imide carbonyl functions of the readily available starting imide **9**, which would be achieved by temporary installation of a silicon substituent using a chiral base to give **8**. The first iteration of this idea proved successful, and access to the polycyclic lactam **6** is illustrated in Scheme 2.

Asymmetric silylation of imide **9** was most effective using the *bis*-lithium amide **10** (this transformation was effected in both enantiomeric series and also with racemic base), giving (+)-**8** in 94% ee.[16] Grignard additions to imide **8** proved to be completely regiocontrolled, C–C bond formation occurring only at the carbonyl function distal to the installed trimethylsilyl substituent. This appears to be a general result for such imides in reactions with organometallics and metal hydride reducing agents, and which we ascribe to steric inhibition of Lewis acid co-ordination.[17] Desilylation and acid-mediated *N*-acyliminium ion cyclisation then proved to be completely diastereoselective, provided that the latter reaction was conducted at 0 °C to room temperature. In our earliest attempts this reaction was carried out in CH_2Cl_2 at reflux, and small amounts of a minor diastereomer were formed that ultimately eroded the enantiomeric excess of later compounds to about 85% ee.[18]

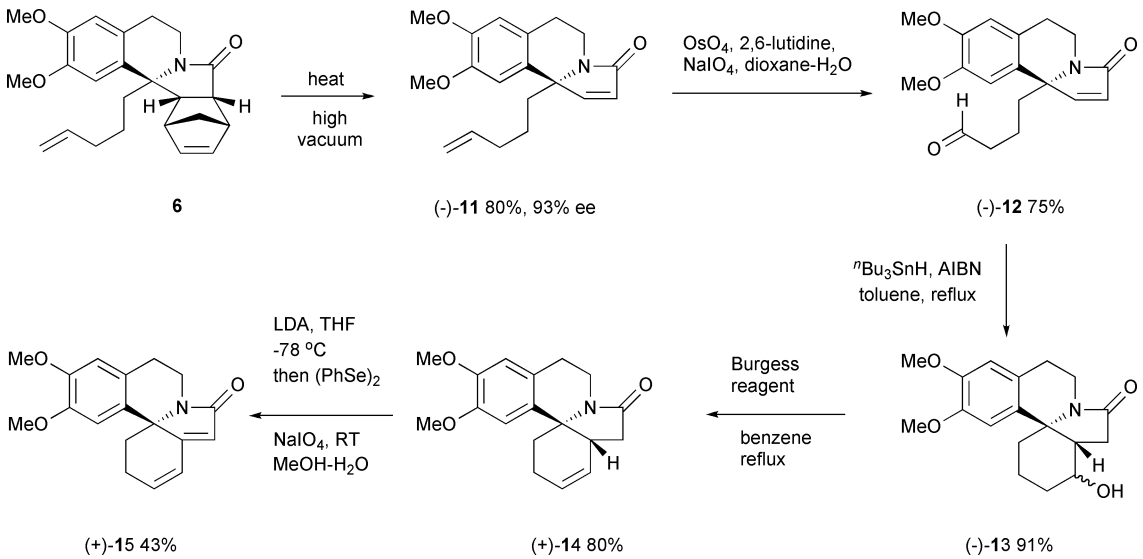
Further transformation of this series commenced with a retro-Diels–Alder reaction (Scheme 3), to give the lactam (–)-**11** in 93% ee, the absolute configuration of which had been established earlier,[18] and which was further secured by subsequent conversion into (+)-erysotramidine **1**. This transformation was carried out by the simple expedient of brief heating of **6**, placed in an



Scheme 1



Scheme 2



Scheme 3

outsized round-bottom flask under high vacuum, using a Bunsen burner.

The side chain of (–)-**11** was oxidised using a one-pot dihydroxylation–diol cleavage procedure to give aldehyde (–)-**12**.[19] Although we considered a number of possibilities for conversion of aldehyde **12** into a tetracyclic product, the first method tried worked extremely well. Thus, exposure of **12** to tributyltin hydride, under conditions described by Muller *et al.* for cyclisation of 5′-aldehyde nucleosides,[20] led efficiently to the desired hydroxy-lactam **13** as a mixture of diastereomers at the newly formed carbinol centre (*ca* 3:1 ratio). At this stage, as disclosed previously, full structure determination was possible for the major epimer of **13** by X-ray crystallography.[21] This type of radical *6-exo-trig* ring closure is comparatively rare compared to the *5-exo-trig* variants, and the very high yield in our successful example is probably due in part to the lack of a competing 1,5-hydrogen atom abstraction process. Further transformation of **13** was then possible by alcohol elimination, to give **14**, followed by selenium mediated dehydrogenation to give **15**, which was an intermediate in the synthesis of racemic erysotramidine, described by Padwa and Wang .[5] Diene **15** was then converted into (+)-erysotramidine following the Padwa protocol, which involves completely diastereocontrolled allylic hydroxylation, using SeO_2 (we recorded 21% yield, 79% based on recovered starting material), followed by alcohol methylation using Tsuda's method—KOH, MeI, Et_4NBr, THF (95%).[22]

Whilst our initial total synthesis was complete, we were aware of shortcomings in the chemical yields in later transformations, particularly the dehydrogenation step and the allylic oxidation. Believing that such functional group transformations were in

principal solvable issues, we focused on developing a second generation synthesis that would avoid the other shortcoming of the synthesis, namely the requirement for the retro-Diels–Alder process.

The metathesis approach

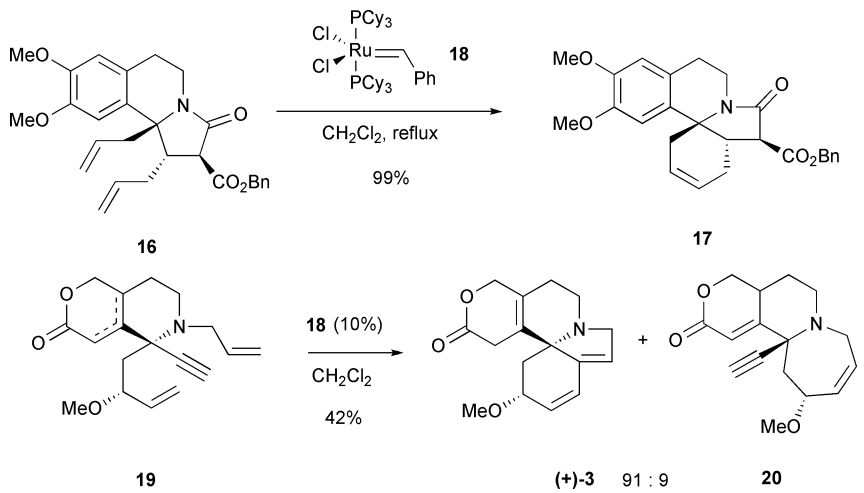
Whilst considering alternative variants of the imide desymmetrisation shown in Scheme 1, we were attracted to the idea of using metathesis for the key 6-membered ring-forming process. As mentioned above, the application of metathesis in the area of *Erythrina* alkaloid synthesis has been explored by other groups,[10,23] this work being largely contemporaneous with our own studies. Of particular relevance to our work was the ring-closure of diene **16** to give **17**, described by Lete and co-workers,[23] and the metathesis of **19** to give (+)-**3** and **20** in the aforementioned access to (+)-β-erythroidine,[10] both using Grubbs' first generation catalyst **18**, Scheme 4.

The efficient formation of **17** represents the key step in an efficient access to the *Erythrina* skeleton, but the route does not look easily amenable to asymmetric synthesis and no natural products have been accessed to date. The dienyne metathesis of **19** is clearly more challenging and the moderate chemical yield is off-set by the gain in molecular complexity. The problem here is the rather protracted access to **19** in enantio-pure form, which required in excess of 20 steps.

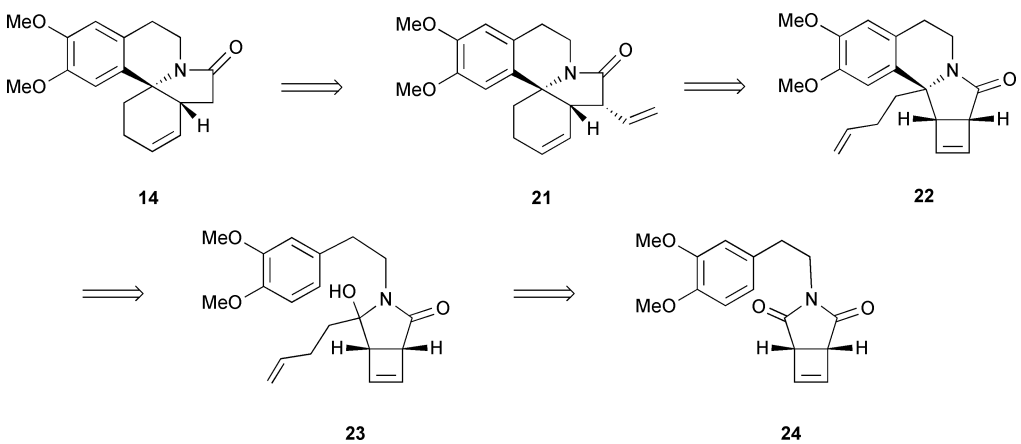
Bearing these aspects in mind, and wishing to further probe synthesis sequences that combined our asymmetric deprotonation protocol with a diastereoselective *N*-acyliminium cyclisation, we conceived the modified route to alkene **14** shown in Scheme 5.

According to this approach, desymmetrisation of a cyclobutene-fused imide **24** would be carried out in analogous fashion to that achieved previously with **9**, except that we now require addition of a butenyl (rather than pentenyl) side-chain, to give **23**. Cyclisation of hydroxylactam **23** to give **22** appeared reasonable, although the diastereocontrol available could not be guaranteed. Tetracyclic cyclobutene **22** would be primed for the key step, which involves ring-opening/ring-closing metathesis (RORCM) to give **21**, which has the complete erythrinan skeleton. Conversion of **21** into the previous intermediate **14** would then require removal of the unwanted vinyl side-chain, which we envisaged would be possible *via* oxidative cleavage.

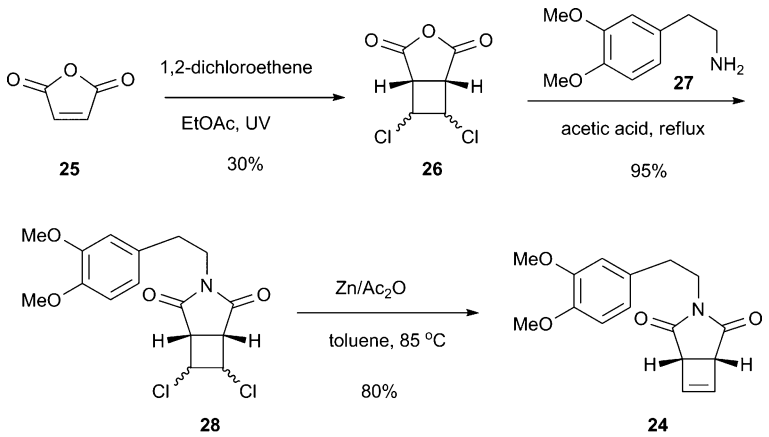
The required starting cyclobutene-imide **24** was synthesised *via* a three-step sequence in 22% overall yield from cheap and commercially available maleic anhydride **25** (Scheme 6).



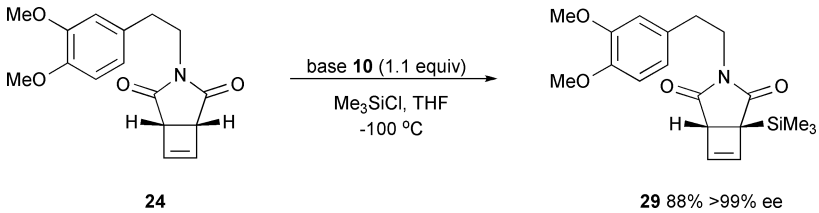
Scheme 4



Scheme 5



Scheme 6



Scheme 7

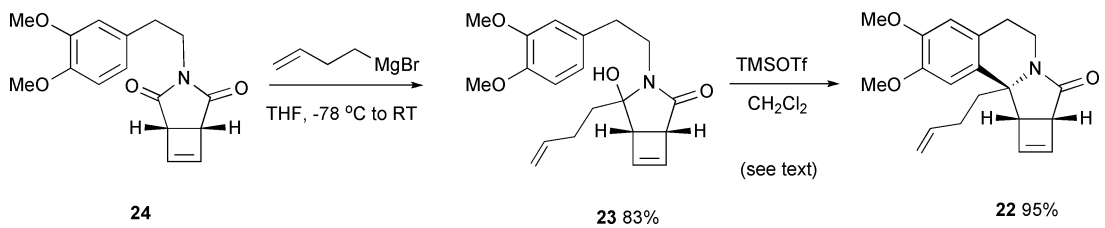
Irradiation of a dilute solution of maleic anhydride **25** and 1,2-dichloroethylene in degassed EtOAc in a pyrex photoreactor using light from a 400 W medium pressure Hg lamp led to a mixture of diastereomeric dichlorides **26** in 30% yield.[24] Condensation of anhydride **26** with amine **27** followed by dehalogenation using zinc/acetic anhydride delivered the cyclobutene product **24** successfully in multi-gram quantities. Although for preliminary studies we were content to use racemic compounds, we were interested to check that the chiral base mediated silylation of imide **24** could be conducted with high levels of selectivity.

To our satisfaction, application of the chiral base conditions used previously for imide **9** to the cyclobutene-fused imide **24** proved even more effective than before, the required product being isolated in high yield, and as a single enantiomer according to the limits of our HPLC assay, Scheme 7.

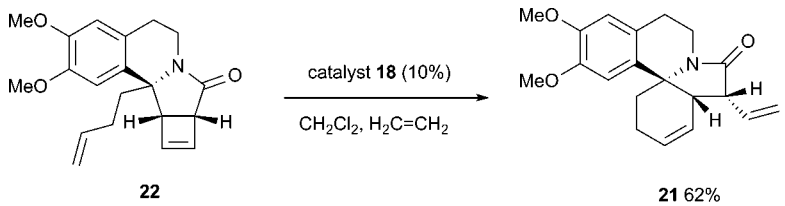
Having established that an asymmetric synthesis might be viable, we continued the route by Grignard addition to **24** to give racemic adduct **23**, followed by *N*-acyliminium cyclisation to give tetracyclic lactam **22** in racemic form, Scheme 8.

The cyclisation of **23** required significant fine-tuning in order to achieve high levels of diastereocontrol. Good selectivity could not be achieved using TFA, which we had employed previously; in fact use of this reagent in CH_2Cl_2 at reflux gave a 1:1 mixture of **22** and the C-5 epimer. Use of TIPSOTf gave promising results, with diastereoselectivities of up to 10:1 at low temperature (–78 °C), but also low conversions due to a sluggish reaction. TMSOTf provided excellent results provided that the reaction mixture was initially cooled to –78 °C and then warmed slowly to –4 °C. Under such conditions **22** was formed in 95% yield and with a diastereomer ratio of 20:1, favouring the isomer shown (the stereochemistry of this compound, arising from the expected *exo*-mode of attack was proven later).

With the acyliminium cyclisation product **22** in hand, we next sought to establish conditions for its conversion into **21** by ring-opening/ring-closing metathesis. The reaction was initially conducted using 4 mol% of Grubbs' first generation catalyst **18** but only a very small amount of the desired product **21** was formed (*ca.* 5%).[25] During their research on diastereoselective ring rearrangement metathesis, Blechert and co-workers had found that an ethylene atmosphere could prevent dimerisation and oligomerisation and could enhance the catalyst initiation rate.[26] Following their procedure the catalyst **18** (10 mol%) was added to



Scheme 8



22 **21** 62%

Scheme 9

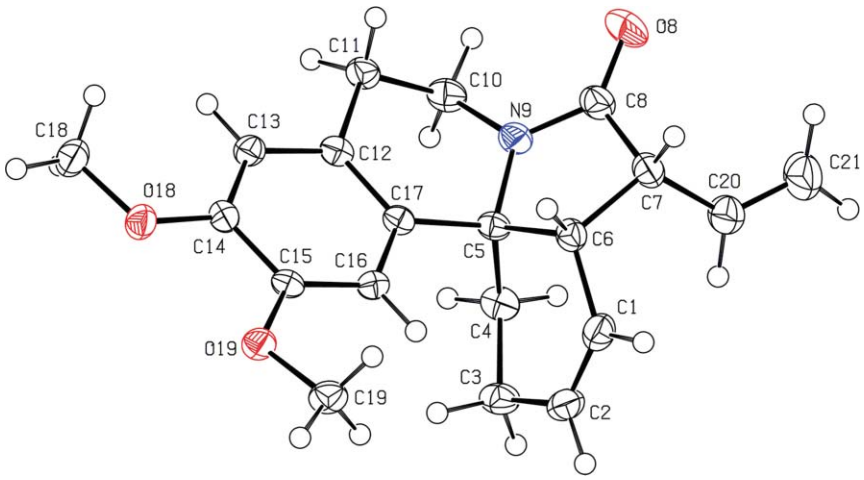


Fig. 3 X-ray crystal structure of metathesis product **21**. Displacement ellipsoids are drawn at the 50% probability level.

a degassed solution of cyclobutene **22** in CH_2Cl_2 which was then stirred under an ethylene atmosphere. Combined with an increase in the dilution of the reaction mixture, this protocol allowed us to achieve rearrangement of **22** into the erythrinan system **21** in 62% yield, Scheme 9.

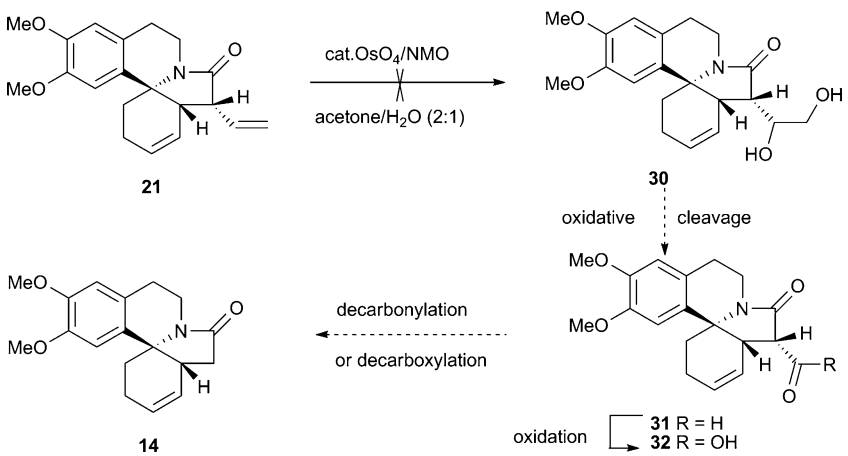
Although we also tested Grubbs' second generation catalyst,[27] and the Hoveyda–Grubbs catalyst,[28] these systems offered no advantage over catalyst **18**.

The stereochemical assignment of tetracyclic system **21** was established by x-ray crystallographic analysis, which confirmed the outcome of the previous key *N*-acyliminium ion cyclisation, Fig. 3.†

At this stage, the selective oxidative removal of the vinylic side-chain present in lactam **21** was our next task, which turned out to be remarkably difficult, and which unearthed some interesting chemistry.

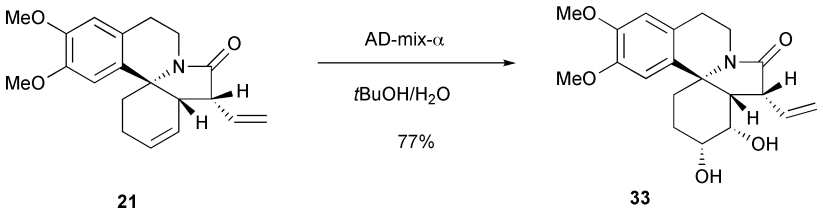
We envisioned that if the terminal alkene of **21** could be dihydroxylated selectively to give diol **30**, then subsequent oxidative cleavage and decarbonylation of the corresponding aldehyde **31** would give the known intermediate **14** which is a precursor of erysotramidine. The aldehyde **31** might alternatively be oxidised to give acid **32**, which would lead to **14** by decarboxylation (Scheme 10).

Unfortunately, dihydroxylation reactions of diene **21** were poorly regiocontrolled under standard conditions with both alkenes reacting, and furnishing mixtures of products. After some experimentation with the Sharpless asymmetric hydroxylation conditions,[29] we were able to obtain one product quite selectively,

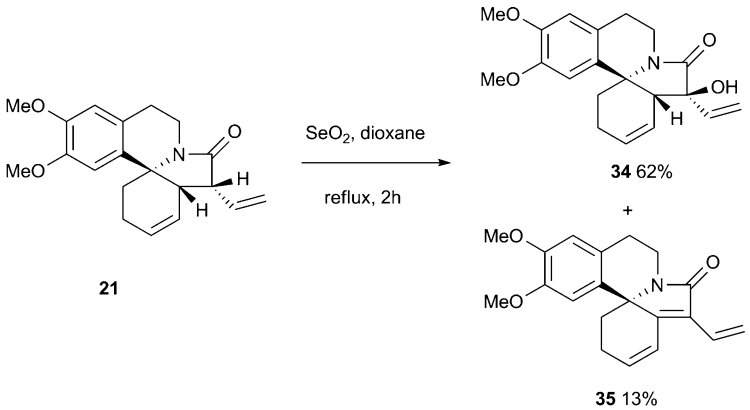


21 **30** **14**

Scheme 10



Scheme 11



Scheme 12

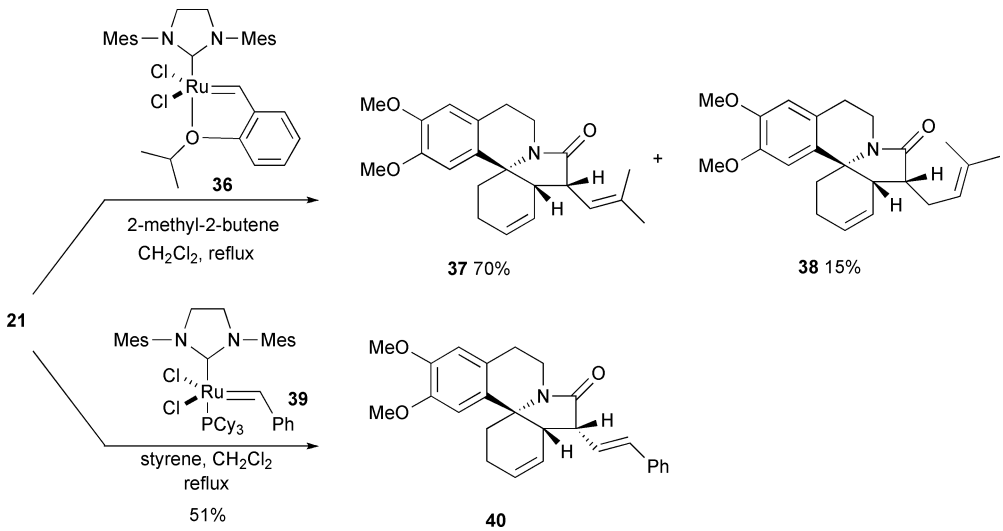
but this proved to be diol **33**, resulting from reaction at the internal alkene, Scheme 11.

Alternative oxidation conditions were explored in our search for useful regioselectivity. Thus treatment of substrate **21** with SeO_2 in dioxane under reflux resulted in formation of the tertiary alcohol **34** along with a small amount of dehydration product **35** (Scheme 12).

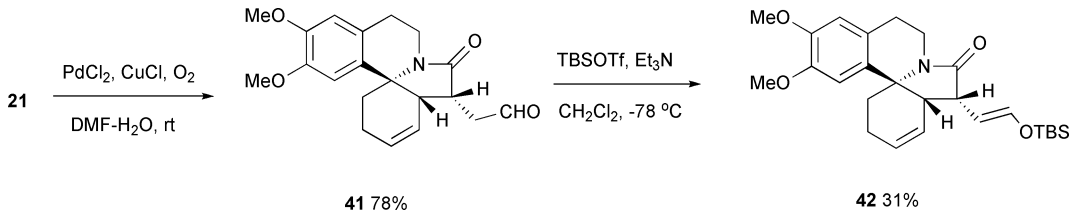
The transformations shown in Schemes 11 and 12 were not helpful to us, and at this stage it seemed quite difficult to selectively cleave the less electron rich terminal alkene directly. Instead we envisioned modifying the reactivity of the terminal alkene (and therefore changing the overall regioselectivity of subsequent reactions) by cross metathesis to give a more reactive, electron-rich alkene.

Treatment of diene **21** with Grubbs' catalyst **18** and vinyl acetate or vinyl trimethylsilane gave none of the desired cross metathesis product. However, a mixture of the desired product **37** and another one-carbon homologated by-product **38** were obtained in a combined 85% yield when substrate **21** was reacted with Hoveyda–Grubbs catalyst **36** and 2-methyl-2-butene (Scheme 13).[30]

Alternatively, the *trans* phenyl substituted alkene **40** was obtained in 51% yield when substrate **21** was treated with styrene and Grubbs' second generation catalyst **39**. We expected that either **37** or **40** might be available directly from cyclobutene **22** if required.



Scheme 13



41 78% **42** 31%

Scheme 14

With the new diene substrates **37** and **40** available we again examined dihydroxylation reactions. However under standard dihydroxylation conditions (cat.OsO_4/NMO/acetone–H_2O) both of these dienes gave only complex, polar mixtures of products. Treatment of compound **40** with O_3 at low temperature for several minutes, followed by work-up with Me_2S at room temperature led only to extensive degradation of the substrate.

After considering alternative reactions that might prove selective for a terminal alkene over an internal cyclohexene we selected the Wacker oxidation reaction as a candidate for exploration, since this would be expected to convert the mono-substituted alkene into a methylketone, which might then prove amenable to cleavage *via* oxidative conditions (or perhaps a retro-acylation).[31] To our surprise, the reaction of diene **21** under standard Wacker oxidation conditions ($PdCl_2$–CuCl–O_2) gave aldehyde **41** in good yield, Scheme 14.

This type of anomalous regiochemistry has been observed previously in the Wacker reactions of α-vinyl-β-lactams, and it was postulated that palladium coordination to the Lewis basic lactam function was responsible.[32] This transformation was at least selective for the terminal alkene, and provided us with one final opportunity to cleave this appendage by enol silane formation, followed by oxidation. Although we formed the sensitive enol silane **42** in modest yield, we were unable to effect subsequent cleavage using standard dihydroxylation conditions.

In a final effort to achieve our goal of cleaving the unwanted vinyl group in **21** we resorted to an alkene protection strategy. Treating the substrate **21** with pyridinium tribromide resulted in the formation of dibromide **43** in moderate yield (Scheme 15).

Reaction of this dibromide with O_3 at −78 °C and then with zinc/acetic acid at 40 °C to decompose the ozonide, gave the primary alcohol **44** in excellent yield, rather than the expected aldehyde. Preliminary attempts to remove the remaining hydroxymethyl group by a retro-aldol process, by heating under basic conditions, proved ineffective.

At this stage our patience and materials were exhausted. Although ultimately it may be possible to employ one or more of the intermediates prepared here in a natural product synthesis, it had become clear that the problems involved in removal of the vinyl side-chain in diene **21** made the route too long to pursue further.

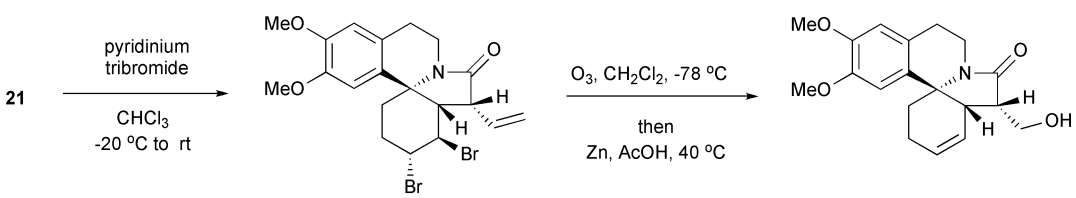
Review and outlook for the imide desymmetrisation strategy to erythrinans

Inevitably, our perspective on this total synthesis project changed and developed whilst the work progressed, and it is appropriate to both assess the work carried out and to sketch out some opportunities that have been identified for further study.

Our initial synthesis of (+)–erysotramidine proceeded in 12 chemical steps from the readily available imide **9** and employed chiral base-mediated imide silylation as a way of distinguishing the two imide C=O functions in an addition reaction employing a Grignard addition. It is clear that a process involving *direct* asymmetric organometallic addition to the imide **9** would be superior to our three-step approach, which involves silylation, addition and then de-silylation. However, to our knowledge no established methodology exists for this type of asymmetric addition, and our preliminary efforts to identify useful leads in this area, for example using Grignard reagents in the presence of sparteine, were not successful.[33]

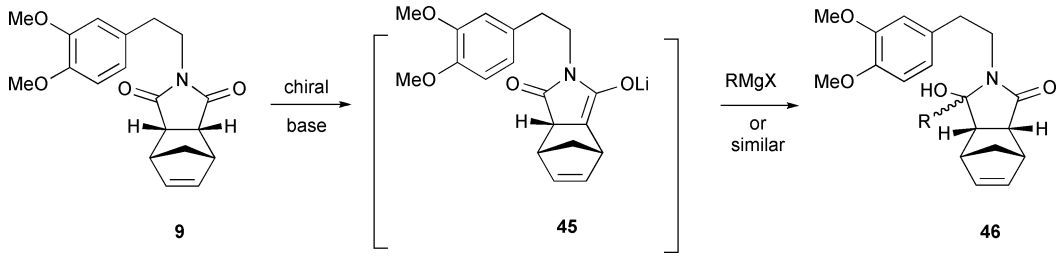
As an interim measure it appeared to us that we might be able to streamline the chiral base three-step desymmetrisation if, instead of silylating the enolate, we could add organometallic reagents directly to the lithium enolate itself, Scheme 16.

The lithium enolate in intermediate **45** would act as a protecting group for one of the two imide C=O functions, enabling selective addition at the other position. Unfortunately, it proved impossible to realize this concept using imides. At the low temperatures employed for the chiral base reactions the addition of Grignard reagents to enolates like **45** did not proceed, whereas organolithiums simply converted **45** into the well-known *bis*-enolates. At higher temperatures (above −60 °C) we identified a tendency for racemisation of the intermediate imide mono-enolates, which undermined the process proposed in Scheme 16. Subsequently, we *were* able to realize the principle of using chiral



43 45% **44** 97%

Scheme 15



Scheme 16

base generated enolates as electrophiles in this type of process but with rather different types of substrate, namely 2,2-disubstituted 1,3-diketones.[34]

The success of the metathesis process shown in Scheme 9 was tempered by the severe problems in removing the unwanted vinylic side-chain appendage. Also, although the metathesis route avoided the clumsy retro-Diels–Alder process, the requirement for an unusual cyclobutene-fused imide added synthetic steps. From commercial starting materials the metathesis route actually worked out longer than the retro-Diels–Alder route.

At present it appears to us that an optimal asymmetric synthesis of the erythrinan system has yet to emerge. The types of metathesis ring closure shown in Schemes 4 and 9 appear attractive if concise asymmetric access to correctly substituted metathesis precursors can be achieved.

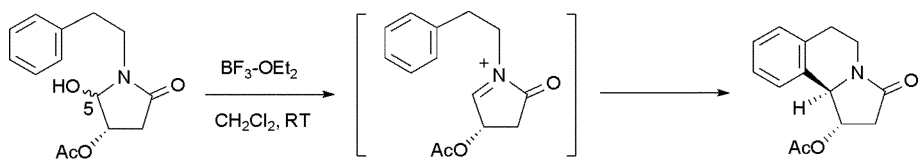
Chiral pool synthesis of erythrinan systems using (*L*)-malic acid

During the course of our studies on the chiral base route to *N*-acyliminium precursors for assembling the erythrinan system, it became clear that complementary access to such intermediates should be possible starting from (*L*)-malic acid. Lee and co-workers had observed that the cyclisation of hydroxylactam **47** gave the tricyclic pyrrolidinoisoquinoline product **49** as a single diastereoisomer, Scheme 17.[35]

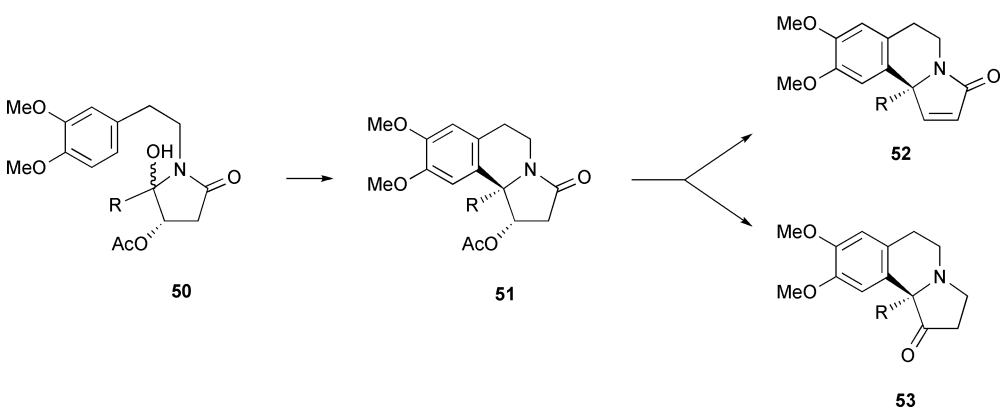
The stereochemical outcome results from neighbouring group participation by the acetoxy group, which is known to control this type of overall *anti*-addition.[36]

Adopting this synthesis to our needs, we proposed that effective access to natural product targets might be gained by ring closure of hydroxylactam intermediate **50**, which we expected would give lactam **51** as the major (or sole) diastereoisomer, Scheme 18.

We could then envisage elimination of acetic acid from **51** to give unsaturated lactam **52**, which is a generic structure that includes our previously established intermediate **11** for (+)-erysotramidine synthesis (R = pentenyl). As will be seen, rather than converge with the previous synthesis, we chose an alternative R group in **51**, which then enabled modified access to a known erysotramidine intermediate. Alternatively, it appeared possible that functional group manipulation could lead to an aminoketone of general



Scheme 17



Scheme 18

structure **53**, which could then be usefully advanced *via* known aldol chemistry, provided an appropriate ketone appendage were installed in the R group.

Our exploration of these ideas led to some unexpected observations concerning the cyclisations of *N*-acyliminium ions derived from malic acid, and enabled us to establish two distinct synthetic routes to 3-demethoxyerythratidinone (**2**).

Observation of unexpected selectivity in an *N*-acyliminium ion cyclisation

In order to probe these ideas we explored Grignard addition reactions to the imide **54**, which was readily prepared from (*L*)-malic acid by standard procedures, Scheme 19.

Addition of but-3-enylmagnesium bromide **55** to imide **54** gave hydroxylactam **56** as a mixture of inseparable diastereomers (about 3:1) in a completely regiocontrolled fashion. Selective addition to the carbonyl group proximal to the acetoxy function was expected, based on a closely related Grignard addition described previously, in which the ring acetate was retained.[37] In our case we employed an excess of Grignard reagent (5 equiv.) to maximize chemical yields, which also deacylated the secondary alcohol. The high regioselectivity of Grignard reagent addition to the α-oxygenated C=O function has been attributed to both the oxygen inductive effect and to complex induced proximity effects (CIPE).[38]

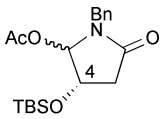
Reaction of **56** with acetic anhydride re-installed the secondary acetate without affecting the tertiary hydroxyl function, and subsequent treatment with TIPSOTf then gave the tricyclic lactam **57** in good yield but with a surprisingly low diastereomer ratio of 3:1 (major isomer shown), compared to the precedent illustrated in Scheme 17. Acetoxy-lactam **57** was then converted into the unsaturated counterpart **58** (the butenyl homologue of **11**) by treatment with NaH, and the modest enantiomeric excess of this product (47% ee) mirrored the low diastereomer ratio of the precursor **57**.

Following unsuccessful attempts to enhance the selectivity of the key cyclisation by altering the reaction conditions or Lewis acids employed, we decided to change the ring OAc substituent for a bulky OTIPS group, Scheme 20.

Silylation of **56**, followed by Lewis-acid treatment of hydroxylactam **59**, as described by Lee (Scheme 17) but initially at low temperature, then furnished lactams **60** and **61** in good yield and over 9:1 selectivity. Surprisingly, the major product of this reaction was the *syn*-adduct **60**, in which aromatic attack on the *N*-acyliminium intermediate had occurred from *the same side of the lactam ring as the OTIPS substituent*. The stereochemical assignment of the lactam **60** followed an X-ray structure determination, as described previously.[12]

Lactams **60** and **61**, were easily separated by chromatography, and deprotection of **60**, acetylation of the so-formed alcohol and elimination of acetic acid as before, gave enantiomerically pure (+)-**58**.

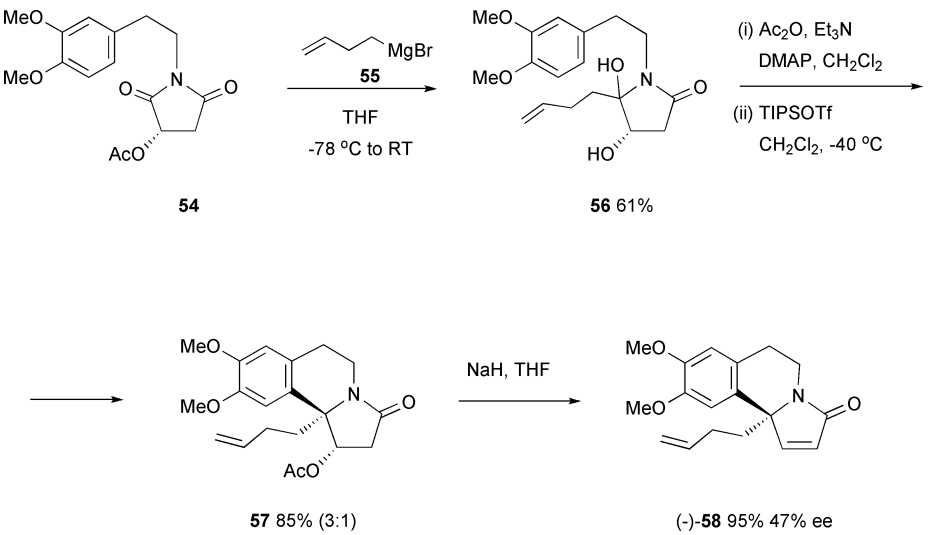
This type of *syn* selectivity has been reported previously for *inter*molecular reactions of acetoxylactam **62** in both the N–H and N–Bn series. Reactions with allyl, propargyl and allenylsilanes, and stannanes, under Lewis acid catalysis, gave product ratios ranging from 3.8:1 to >100:1.[39]



62

This *cis*-selectivity was attributed to a stereoelectronic effect (Cieplak effect) involving a preferred *syn* alignment of the (relatively electron-rich) C–H at C-4 bond and the emerging σ* orbital at the reacting centre. This effect appears rather dependent upon the nitrogen substituent, the nucleophile and the reaction conditions, and the few selectivities reported to date are mainly modest.[40,41] This effect appears not to have been observed before in additions of aromatics to *N*-acyliminium ions, and we were interested to test the stereoelectronic explanation by testing an additional lactam series.

We selected for further study the parent system analogous to that shown in Scheme 17, in which the C-5 substituent is hydrogen, Scheme 21.



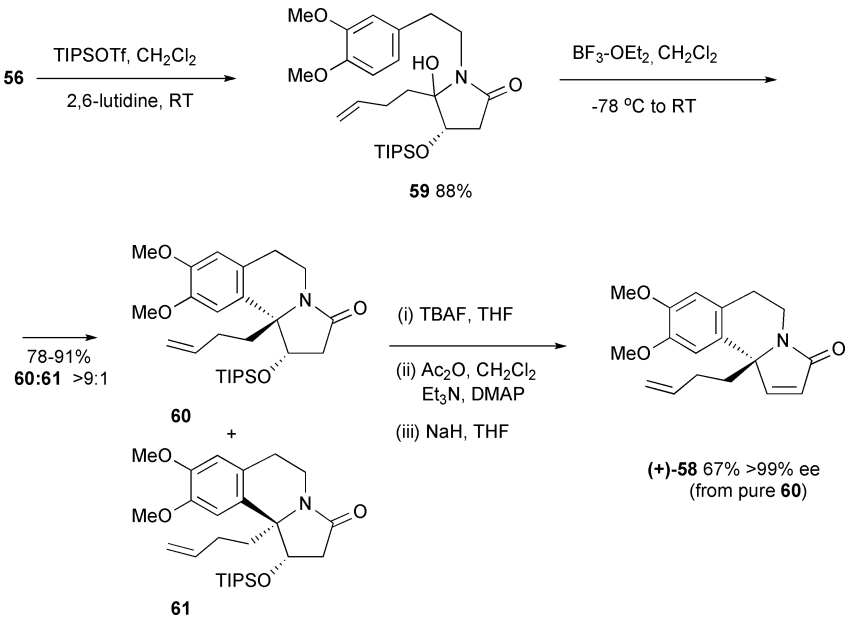
54

56 61%

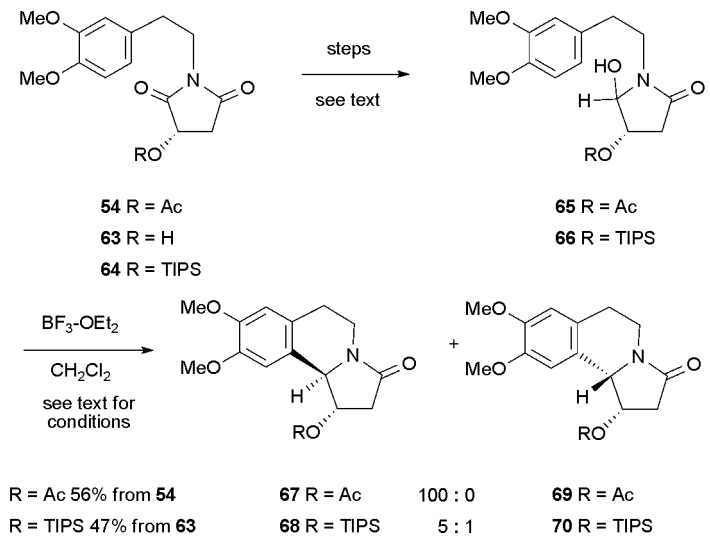
57 85% (3:1)

(-)-**58** 95% 47% ee

Scheme 19



Scheme 20



Scheme 21

Initially, for comparison with the result in Scheme 17 we converted **54** into **65** by reduction with $NaBH_4$ in CH_2Cl_2–MeOH, and then carried out the cyclisation using BF_3-OEt_2 in CH_2Cl_2 between 0 °C and room temperature. As expected, only a single diastereomeric lactam product (**67**), resulting from the expected *anti*-attack, was obtained.

In order to test for the '*syn*-effect', we then prepared OTIPS derivative **66**, by routine transformations from **54**, and then effected cyclisation using BF_3-OEt_2 in CH_2Cl_2 at the lowest viable temperature, –40 °C to RT, so as to mimic the conditions in Scheme 20, and maximise selectivity. The cyclisation gave two diastereomeric tricyclic products **68** and **70** in a 5:1 ratio, which is the same sense of selectivity as the acetate series. This result seems to suggest a steric argument for the *syn*-selectivity leading to the butenyl derivative **60**, since the effect does not seem to operate for the parent system where the C-5 substituent is simply a proton.

At present we consider the most likely explanation for the selective formation of **60** is based on a conformational relay effect as illustrated in Fig. 4.

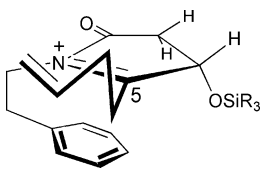


Fig. 4

Examination of molecular models suggests that in the intermediate *N*-acyliminium ion the bulky TIPS group (R = ^{i}Pr) pushes the butenyl group to the opposite (top) face of the lactam ring, which results in attack of the aromatic group from the same side

as the OTIPS substituent. In the simpler system, where the C-5 substituent is a proton, the relay effect is lost and the reaction displays modest *anti*-selectivity.

Access to known *Erythrina* intermediates using Clive's radical cyclisation protocol

With ready access to unsaturated lactam **58**, we considered various options to complete the construction of the erythrinan skeleton. One possibility was to effect Michael addition of a vinyl group to **58**, followed by ring closing metathesis which, starting with (+)-**58** would then lead to (–)-**14** (depending upon the stereochemistry of **71**), Scheme 22.

This idea was soon abandoned since we found the starting lactam to be resolutely unreactive to a range of vinyl cuprate reagents, and also to rhodium catalysed reaction with potassium vinyltrifluoroborate. We were also aware that, in the aforementioned access to lactam **16**, Lete and co-workers had found very similar problems and had resorted to incorporation of a further carboxymethyl group to activate the Michael addition process.[42]

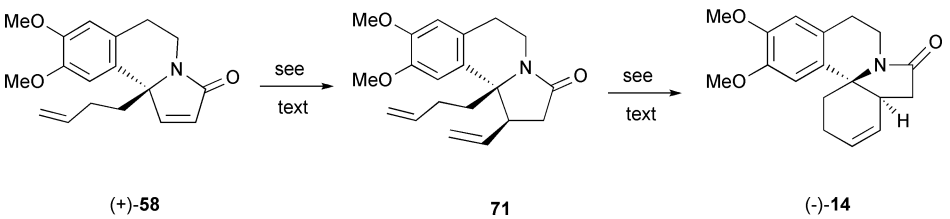
Instead we returned to the use of radical chemistry, and adopted a method described by Clive and co-workers for the synthesis of functionalised ring-fused bicyclic compounds.[43] The method involves the radical cyclisation of a β-hydroxyselenide, which in our case was readily available by addition to the unsaturated side-chain appendage, Scheme 23.

Treatment of unsaturated lactam (+)-**58** with phenylselenyl chloride in aqueous acetonitrile afforded the hydroxylselenide **72** efficiently as a mixture of diastereoisomers in a ratio of 3:1.[44] No regioisomeric hydroxyselenide was isolated. For the radical cyclisations, solutions of triphenyltin hydride and AIBN in benzene were added to a refluxing solution of the hydroxyselenide **72** in the same solvent over 8–10 hours using a syringe pump. Reflux was continued for another 4 hours after the end of addition. The desired cyclised product **73** was then isolated in 85% yield and as a 1:1 mixture of diastereoisomers. Thus by a two-step procedure the unsaturated lactam (+)-**58** was successfully converted into the *Erythrina* alkaloid skeleton **73**, which is a known intermediate in Tu and co-worker's synthesis of (±)-erysotramidine.[6]

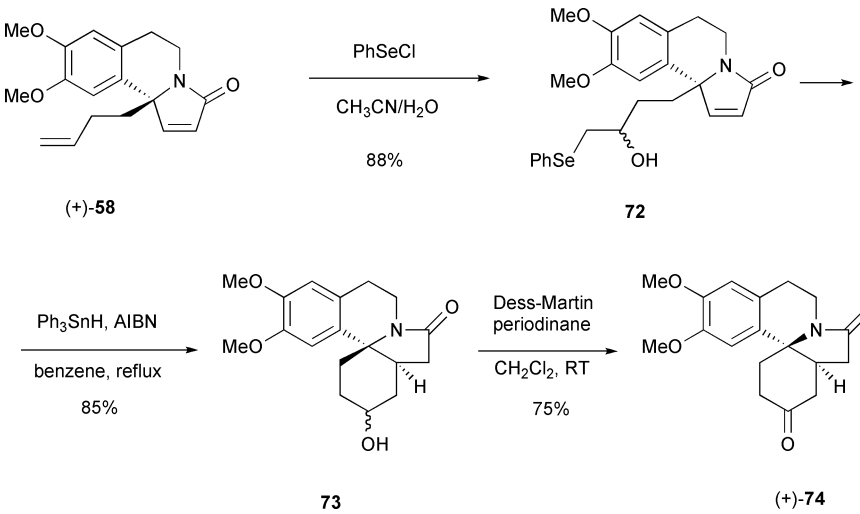
The cyclized secondary alcohol **73**, was also treated with Dess-Martin periodinane reagent to give another known compound, ketone (+)-**74**, Both this ketone, and the derived dioxolane, were synthesized in both enantiomeric forms by Allin and co-workers, and data for our ketone matched their spectroscopic and specific rotation data extremely well.[8] Thus, our synthesis of **74** constituted a formal synthesis of the natural product, since the dioxolane derived from ketone **74** had been previously converted into 3-demethoxyerythratidinone (**2**) by Tsuda *et al.*, although in racemic form.[45]

Total synthesis of 3-demethoxyerythratidinone by aldol ring-closure

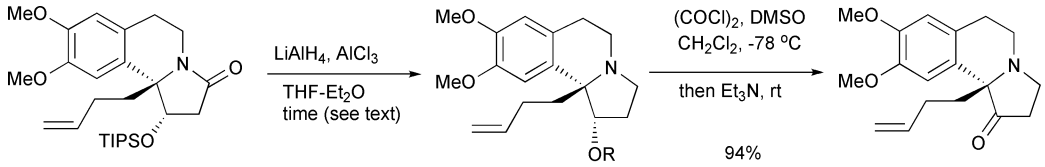
As outlined in Scheme 18 we also considered that the availability of various lactams, arising from diastereoselective *N*-acyliminium ion cyclisation, might enable access to erythrinan alkaloid natural products *via* intramolecular aldol reaction. Our initial attempts in this direction commenced by reduction of lactam **60** with $LiAlH_4$ in the presence of $AlCl_3$, Scheme 24.



Scheme 22



Scheme 23



60 **75** R = TIPS 69%; **76** R = H 90% **77**

Scheme 24

Lactam reduction to give TIPS protected hydroxy pyrrolidine **75** was reasonably efficient if the reaction time was limited to about 2 hours, but an even more effective reduction and in-situ deprotection ensued if the reaction was carried out overnight, providing the free alcohol **76**. This compound was efficiently oxidised, using typical Swern oxidation conditions, to give ketone **77**. Our plan with this compound was to effect Wacker oxidation of the alkenyl side-chain, followed by intramolecular aldol and dehydration to provide **2** directly. However, despite good precedent for Wacker oxidation of very similar alkenes we could not effect this transformation with **77**.[46]

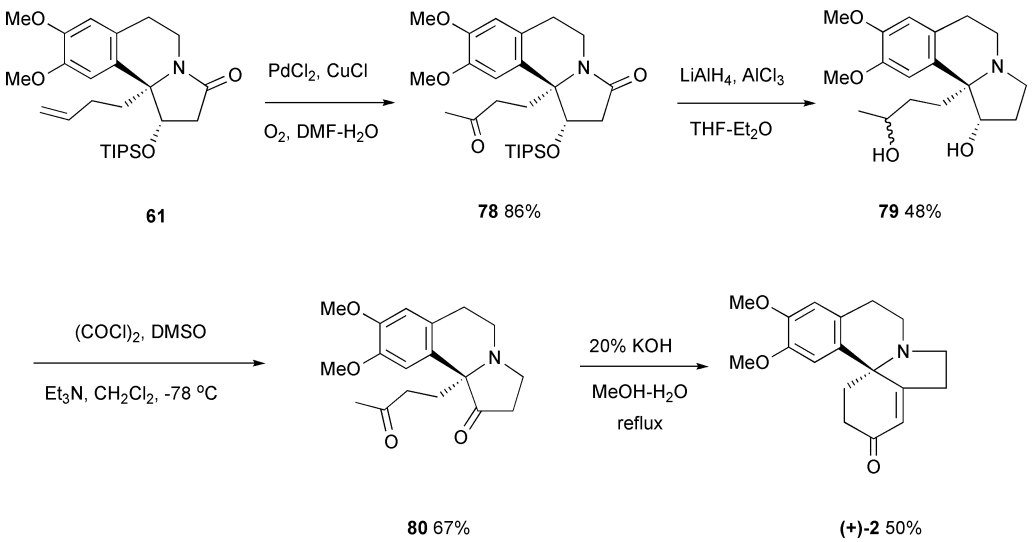
After further experimentation, we established that our earlier intermediates **60** and **61**, in which the ring nitrogen is part of a lactam, rather than a basic tertiary amine, participated well in Wacker oxidations. We were then in a position to conclude our proposed new access to 3-demethoxyerythratidinone **4**. Initially, in order to match our synthetic material with the alkaloid *in the natural enantiomeric series* we used the *minor* product **61** generated from the cyclisation shown in Scheme 20 for further transformations, Scheme 25.

Wacker oxidation of diastereomerically pure **61** gave ketolactam **78** in good yield and subsequent reduction with $LiAlH_4$–$AlCl_3$ provided diol **79**, which had been prepared previously by Wasserman and Amici in their synthesis of racemic 3-demethoxyerythratidinone.[47] Application of the final two steps from their synthesis to **79**, involving Swern oxidation to give **80** and then aldol cyclisation, gave (+)-3-demethoxyerythratidinone (**2**) with spectroscopic data consistent with the structure shown and the previous published data.[48] As anticipated, the use of **61** as starting material resulted in the formation of the final alkaloid as its natural antipode, with $[\alpha]_D^{26}$ +316 (*c*, 0.4, $CHCl_3$), compared to $[\alpha]_D^{20}$ +325 (*c*, 0.25, $CHCl_3$).[49] We also applied the sequence shown in Scheme 25 to the diastereomeric starting lactam **60** and obtained similar yields for each step (in parentheses) and were able to access the natural product as the unnatural (–)-antipode.

The total synthesis of alkaloid **2** proceeds in only 7 steps from the readily available starting imide **54**. However, access to the natural product as its natural antipode is hindered by the fact that the key *N*-acyliminium ion cyclisations are either poorly selective (*O*-acetyl series), or highly selective for the wrong epimeric series (*O*-TIPS compounds).

Summary and Conclusion

We were successful in establishing a concise new asymmetric total synthesis of (+)-erysotramidine (**1**) in highly enantiomerically enriched form by application of the chiral lithium amide base approach. The type of imide desymmetrisation employed should be a useful method for the synthesis of other naturally occurring alkaloids, both erythrinans and other types, although the requirement for a stoichiometric amount of chiral base is



61 **78** 86% **79** 48%

80 67% **(+)-2** 50%

Scheme 25

at present a disadvantage. There remain opportunities for new asymmetric (preferably catalytic) transformations of cyclic imides, both in terms of enolisation and additions to the imide carbonyl functions, which we hope to explore in the future.

Our alternative procedure for constructing the skeleton of *Erythrina* alkaloids using the ring-opening/ring-closing metathesis provides another example of this powerful ring-rearrangement procedure. Although ultimately unsuccessful, the route also provided examples of chiral base selectivity and diastereocontrolled *N*-acyliminium ion cyclisation in the unusual context of a cyclobutene-fused imide system.

The final part of our study provided significant new information concerning the stereochemical issues related to *N*-acyliminium ion reactions of malic acid derived lactams, and particularly the unusual *syn*-effect seen with a TIPS protected compound. Based on these new results the formal syntheses of (+)-erysotramidine and (+)-3-demethoxyerythratidinone were achieved using radical cyclisation reaction for the final bond formation of the *Erythrina* skeleton. Also the total synthesis of (+)-3-demethoxyerythratidinone using *N*-acyliminium cyclisation and aldol condensation reactions as the key steps represents only the third asymmetric access to this compound, and at eight steps from commercial material is one of the shortest of the routes established to date.

Experimental part

General procedures - see ESI.† The preparation and spectral data of compounds **6**, **7**, (+)-**8**, (−)-**11**, (−)-**12**, (−)-**13**, (+)-**14**, (+)-**15**, can be found in our previous paper.[11]

(1*S*,5*R*)-3-(3,4-Dimethoxyphenethyl)-1-(trimethylsilyl)-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (29) (Scheme 7)

The *bis*-lithium chiral base **10** solution was prepared by addition of *n*-BuLi (1.6 M in THF, 0.66 mL, 1.05 mmol) to the solution of corresponding chiral amine (253 mg, 0.6 mmol) in THF (4 mL). After cooling to −100 °C, the chiral base was added dropwise by cannula to the solution of imide **24** (143 mg, 0.5 mmol) and TMSCl (0.64 mL, 5 mmol) in THF (8 mL). The resulting reaction mixture was stirred at the same temperature for 4 hours. Saturated aqueous $NaHCO_3$ (5 mL) solution was added and diluted with EtOAc (100 mL). The organic phase was washed with water (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica column chromatography (eluent: petroleum ether/AcOEt = 2/1 to 1/1) to give the product **29** (88 mg, 88%) as a yellow oil: $[\alpha]_D^{25}$ +131 (*c* 4.50, $CHCl_3$); $\nu_{max.}$ ($CHCl_3$)/cm^{-1} 2938, 2838, 1755, 1682, 1593, 1387, 1357, 986; δ_H (500 MHz, $CDCl_3$) 0.09 (s, 9 H, $Si(CH_3)_3$), 2.77 (t, *J* 7.5, 2 H, $PhCH_2$), 3.47 (d, *J* 1.0, 1 H, NCOCH), 3.59–3.69 (m, 2 H, NCH_2), 3.69 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 6.31 (dd, *J* 2.5, 1.0, 1 H, C*H*=CH), 6.39 (d, *J* 2.5, 1 H, CH=C*H*), 6.69–6.74 (m, 3 H, ArH); δ_C (125 MHz, $CDCl_3$) −3.5 ($SiCH_3$), 33.0 ($ArCH_2$), 39.7 (NCH_2), 50.0 (CH), 52.4 (CSi), 55.9 (OCH_3), 55.9 (OCH_3), 111.2 (ArCH), 112.1 (ArCH), 121.0 (ArCH), 130.3 (ArC), 136.0 (CH=), 142.6 (CH=), 147.7 (ArC), 148.8 (ArC), 174.3 (NC=O), 176.6 (NC=O); HRMS (ESI) found $[M + H]^+$, 360.1626. $C_{19}H_{25}NO_4Si$ requires *[M + H]*, 360.1590; The ee was determined as > 99% by HPLC (chiral OD column, 4% ^{i}PrOH in hexane, 0.6 ml/min), the retention times were 29.5 min (major), and 32.4 min (minor). The absolute configuration of this product was assigned by analogy with known examples.

(4a*S*,5*R*,13b*S*)-11,12-Dimethoxy-5-vinyl-1,2,4a,5,8,9-hexahydroindolo[1-*a*]-isoquinolin-6-one (21) (Scheme 9)

Cyclobutene imide **22** (233 mg, 0.72 mmol) was dissolved in dry CH_2Cl_2 (50 mL) so that the concentration reached approximately 0.01 M. This solution was degassed under argon. Ethylene was then bubbled through the solution for 5 min. Grubbs' first generation catalyst **18** (59 mg, 0.07 mmol) was then added. Ethylene was again passed through the solution for 5 min, and the solution was then stirred under an ethylene atmosphere (fitted balloon) at 35 °C until TLC revealed completion of the reaction. The mixture was cooled to room temperature and ethyl vinyl ether (2 mL) was added. The reaction mixture was stirred for another 1 hour then concentrated. The crude product was purified by silica column chromatography (eluent: petroleum ether/AcOEt = 3/1 to 1/1) to give the major product **21** (144 mg, 62%): $\nu_{max.}$ ($CHCl_3$)/cm^{-1} 2996, 2846, 1662, 1463, 1362, 1106, 908; δ_H (400 MHz, $CDCl_3$) 1.74–1.81 (m, 1 H), 2.00–2.06 (m, 2 H), 2.16–2.22 (m, 1 H), 2.72–2.78 (ddd, 1 H, *J* 16.4, 6.0, 3.2, $ArCH_AH_B$), 2.94–3.02 (m, 1 H, $ArCH_AH_B$), 3.10 (d, *J* 8.0, 1 H, C*H*CH=CH), 3.29–3.36 (m, 2 H, C*H*CO, NCH_AH_B), 3.82 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 4.10–4.21 (ddd, *J* 13.2, 7.2, 3.2, 1 H, NCH_AH_B), 5.26–5.32 (m, 2 H, CH=CH_2), 5.73–5.86 (m, 2 H, C*H*=CH_2, C*H*=CHCH), 6.05–6.12 (m, 1 H, CH=C*H*CH), 6.61 (s, 1 H, ArH), 6.73 (s, 1 H, ArH); δ_C (100 MHz, $CDCl_3$) 22.2 (CH_2), 27.1 (CH_2), 33.3 (CH_2), 35.1 (CH_2), 43.3 (CH), 50.8 (CH), 55.9 (OCH_3), 56.0 (OCH_3), 61.0 (C), 108.1 (ArCH), 111.8 (ArCH), 119.3 (CH_2=), 125.2 (ArC), 126.5 (CH=), 128.8 (CH=), 133.5 (ArC), 133.8 (CH=), 147.6 (ArC), 148.0 (ArC), 172.8 (NC=O); ESIMS *m/z* (%) 326.2 ($[M + H]^+$, 100); HRMS (ESI) found M^+, 325.1670. $C_{20}H_{23}NO_3$ requires *M*, 325.1678.

2-((4a*S*,5*R*,13b*S*)-11,12-Dimethoxy-6-oxo-1,2,4a,5,8,9-hexahydroindolo-[1-*a*]isoquinolin-5-yl)acetaldehyde (41) (Scheme 14)

A suspension of $PdCl_2$ (17.4 mg, 0.1 mmol) and CuCl (40.3 mg, 0.4 mol) in DMF (2.0 mL) and water (0.4 mL) was degassed with oxygen. The mixture was then stirred at room temperature for 4 hours. A solution of imide **21** (145 mg, 0.45 mmol) in DMF (0.8 mL) was added and the resulting reaction mixture was stirred under oxygen atmosphere for 20 h. The reaction mixture was diluted with EtOAc (100 mL). The organic phase was washed with water (3 × 10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica column chromatography (eluent: petroleum ether/AcOEt = 1/1) to give the product as a colourless oil **41** (119 mg, 78%): $\nu_{max.}$ ($CHCl_3$)/cm^{-1} 2935, 2835, 1723, 1694, 1456, 1392, 1361, 1120, 870; δ_H (500 MHz, $CDCl_3$) 1.73–1.78 (m, 1 H), 1.94–2.13 (m, 3 H), 2.64–2.71 (m, 2 H), 2.83–3.02 (m, 2 H), 3.12–3.28 (m, 3 H), 3.79 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 4.10–4.19 (m, 1 H, NCH_AH_B), 5.57–5.60 (m, 1 H, CH=), 6.01–6.04 (m, 1 H, CH=), 6.56 (s, 1 H, ArH), 6.66 (s, 1 H, ArH), 9.82 (s, 1 H, CHO); δ_C (125 MHz, $CDCl_3$) 21.7 (CH_2), 26.8 (CH_2), 33.8 (CH_2), 35.0 (CH_2), 39.9 (CH), 41.4 (CH), 42.6 (CH_2), 55.8 (OCH_3), 56.0 (OCH_3), 61.5 (C), 108.0

(CH), 111.8 (CH), 125.1 (C), 125.4 (CH), 130.0 (CH), 133.0 (C), 147.6 (C), 148.0 (C), 174.7 (NC=O), 200.4 (CHO); HRMS (ESI) found M^+, 341.1627. $C_{20}H_{23}NO_4$ requires *M*, 341.1626.

(*S*)-10b-(But-3-enyl)-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-one (−)-(58) (Scheme 19)

To a stirred suspension of NaH (2.6 g, 64 mmol, 60% dispersion in mineral oil) in THF (20 mL) was added dropwise a solution of mixture **57** (1.6 g, 4.3 mmol) in THF (10 mL). The resulting solution was then stirred overnight under nitrogen atmosphere. The reaction mixture was added dropwise to the ice-water and extracted with EtOAc (200 mL). The organic phase was washed with water (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica column chromatography (eluent: petroleum ether/AcOEt = 2/1) to give a viscous yellow oil (−)-**58** (1.2 g, 95%): $[\alpha]_D^{25}$ −108 (*c* 2.20, $CHCl_3$); $\nu_{max.}$ ($CHCl_3$)/cm^{-1} 2937, 2847, 2936, 1681, 1360, 1108; δ_H (400 MHz, $CDCl_3$) 1.86–1.95 (m, 2 H, CCH_2), 2.01–2.10 (m, 2 H, CH_2CH=), 2.67 (dd, *J* 16.1, 4.0, 1 H, $ArCH_AH_B$), 2.94 (ddd, *J* 16.1, 12.0, 6.6, 1 H, $ArCH_AH_B$), 3.18 (ddd, 1 H, *J* 13.3, 12.0, 4.0, NCH_AH_B), 3.83 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 4.40 (dd, *J* 13.3, 6.6, 1 H, NCH_AH_B), 5.00 (m, 2 H, CH_2=), 5.70–5.80 (m, 1 H, CH=CH_2), 6.18 (d, *J* 5.8 Hz, 1H, CH=), 6.60 (s, 1 H, ArH), 6.70 (s, 1 H, ArH), 7.29 (d, *J* 5.8, 1 H, CH=); δ_C (100 MHz, $CDCl_3$) 27.6 (CH_2), 29.1 (CH_2), 34.8 (CH_2), 37.9 (NCH_2), 56.0 (OCH_3), 56.3 (OCH_3), 68.4 (C), 109.2 (CH=), 112.2 (CH=), 115.2 (CH_2=), 125.3 (ArC), 126.4 (CH=), 129.4 (ArC), 137.5 (CH=), 147.7 (ArC), 148.3 (ArC), 151.7 (CH=), 170.9 (C=O); ESIMS *m/z* (%) 322.1 ([M + Na]$^+$, 100), 300.2 ([M + H]$^+$, 76); HRMS (ESI) found M^+, 299.1522. $C_{18}H_{21}NO_3$ requires *M*, 299.1521; The ee was determined as 47% by HPLC (Chiracel OD Column, 20% ^{i}PrOH in hexane, 0.4 mL/min); the retention times were 23.4 min (minor) and 31.2 min (major).

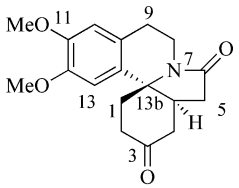
(*R*)-10b-(3-Butenyl)-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-one (+)-(58) (Scheme 20)

TBAF (0.2 mL, 0.2 mmol, 1 M in THF) was added to the solution of lactam **60** (65 mg, 0.14 mmol) in THF (2 mL). The resulting reaction mixture was then stirred at rt for 3 h. The mixture was extracted with EtOAc (50 mL), the organic phase was washed with H_2O (10 mL), brine (10 mL), then dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica chromatography (eluent: petroleum ether/AcOEt = 2/1 then pure EtOAc) gave the alcohol corresponding to **60** (39 mg, 91%) as a colorless oil: $[\alpha]_D^{25}$ +182 (*c* 1.89, $CHCl_3$).

Et_3N (76 mg, 0.75 mmol), Ac_2O (55 mg, 0.53 mmol) and DMAP (6.0 mg, 0.05 mmol) were added to the solution of secondary alcohol (160 mg, 0.5 mmol) in CH_2Cl_2 (4 mL). The resulting solution was then stirred at rt for 4 h. The reaction mixture was then extracted with Et_2O (100 mL). The organic phase was washed with water (10 mL), brine (10 mL), then dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica chromatography (eluent: petroleum ether/AcOEt = 1/1) to give the acetate corresponding to **60** (130 mg, 78%) as a colourless oil: $[\alpha]_D^{25}$ +112 (*c* 0.85, $CHCl_3$); $\nu_{max.}$ ($CHCl_3$)/cm^{-1} 2938, 2836, 1738, 1682, 1463, 1363, 1042, 907; δ_H (400 MHz, $CDCl_3$) 1.58 (s, 3 H, $COCH_3$), 1.92–2.14 (m, 4 H, CH_2CH_2), 2.38 (d, *J* 17.6, 1 H, CH_AH_BPh), 2.65 (dd, *J* 15.6, 3.2, 1 H, CH_AH_BCON), 2.80–2.88 (m, 1 H, CH_AH_BPh), 3.00–3.11 (m, 2 H, CH_AH_BCON, CH_AH_BN), 3.83 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 4.44 (dd, *J* 13.2, 5.6, 1 H, CH_AH_BN), 4.95–5.01 (m, 2 H, CH=CH_2), 5.67–5.73 (m, 2 H, CH=CH_2, $CHOAc$), 6.51 (s, 1 H, ArH), 6.59 (s, 1 H, ArH); δ_C (100 MHz, $CDCl_3$) 20.7 (CH_3), 28.6 (CH_2), 28.8 (CH_2), 36.4 (CH_2), 38.6 (CH_2), 39.8 (NCH_2), 55.8 (OCH_3), 56.0 (OCH_3), 68.6 (C), 73.4 (CH), 108.8 (ArCH), 111.4 (ArCH), 115.5 (CH_2=), 126.5 (ArC), 127.1 (ArC), 137.0 (CH=), 147.4 (ArC), 147.8 (ArC), 169.9 (NC=O), 171.0 (C=O); ESIMS *m/z* (%) 382.2 ([M + Na]$^+$, 100); HRMS (ESI) found [M + H]$^+$, 360.1803. $C_{20}H_{25}NO_5$ requires *[M + H]*, 360.1811.

To a stirred suspension of NaH (2.6 g, 64 mmol, 60% dispersion in mineral oil) in THF (20 mL) was added dropwise a solution of acetate (1.6 g, 4.3 mmol) in THF (10 mL). The resulting solution was then stirred overnight under a nitrogen atmosphere. The reaction mixture was added dropwise to ice-water and extracted with EtOAc (200 mL). The organic phase was washed with water (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica column chromatography (eluent: petroleum ether/AcOEt = 2/1) to give a viscous yellow oil (+)-**58** (1.2 g, 95%): $[\alpha]_D^{27}$ +242 (*c* 1.57, $CHCl_3$). The spectral data were identical with (−)-**58**. The ee was determined as >99% by HPLC (Chiracel OD Column, 20% ^{i}PrOH in hexane, 0.4 mL/min); the retention time was 23.4 min (major) and 31.2 min (minor).

(4a*R*,13b*R*)-11,12-Dimethoxy-1,2,4a,5,8,9-hexahydroindolo[1-*a*]-isoquinoline-3,6-dione (+)-(74)

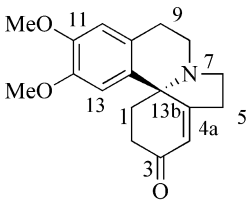


(+)-**74**

A solution of Dess-Martin periodinane (0.2 mL, 15 wt% in CH_2Cl_2) was added to a solution of secondary alcohols **73** (30 mg, 0.09 mmol) in CH_2Cl_2 (2 mL) at room temperature. The resulting solution was then stirred for 8 hours. Saturated $Na_2S_2O_3$ solution (6 mL) was added and the mixture was extracted with CH_2Cl_2 (10 mL). The organic phase was washed with water (6 mL) and brine (6 mL). After drying ($MgSO_4$), the organic layer was concentrated to yield the crude product, which was further purified by column chromatography (eluent: petroleum ether/AcOEt = 1/2, then 1/4) to give the desired product (+)-**74** (21 mg, 75%): $[\alpha]_D^{22}$ +45 (*c* 1.10, $CHCl_3$); $\nu_{max.}$ ($CHCl_3$)/cm^{-1} 2937, 1716, 1681, 1463, 1362, 1122; δ_H (500 MHz, $CDCl_3$) 2.10–2.16 (m, 1 H, 5-H_A), 2.24–2.35 (m, 3 H, 1-H, 2-H_A), 2.38–2.43 (m, 1 H, 2-H_B), 2.60–2.76 (m, 3 H, 4-H_A, 5-H_B, 9-H_A), 2.96–3.11 (m, 4 H, 4a-H, 4-H_B, 8-H_A, 9-H_B), 3.86 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 4.32–4.40 (m, 1 H, 8-H_B), 6.58 (s, 1 H, ArH), 6.69 (s, 1 H, ArH); δ_C (125 MHz, $CDCl_3$) 27.6 ($ArCH_2$), 33.6 (CCH_2), 34.8 (CH_2CH_2CO), 35.3 (NCH_2), 37.5 (CCH), 37.8 ($NCOCH_2$), 43.3 ($COCH_2CH$), 56.0 (OCH_3), 56.4 (OCH_3), 62.5 (C), 107.2 (ArCH), 111.7 (ArCH), 125.5 (ArC), 134.4 (ArC), 148.3 (ArC), 148.5 (ArC), 172.2 (NC=O), 210.2 (C=O); ESIMS *m/z* (%) 316.2 ([M + H]$^+$, 100), 338.1 ([M + Na]$^+$,

74); HRMS (ESI) found $[M + H]^+$, 316.1554. $C_{18}H_{21}NO_4$ requires *[M + H]*, 316.1532.

(*S*)-11,12-Dimethoxy-1,2,5,6,8,9-hexahydroindolo[1-*a*]isoquinolin-3-one (+)-(2)



(+)-**2**

A solution of diketone **80** (34 mg, 0.107 mmol) and 20% KOH (1.5 mL) in MeOH (30 mL) was heated at 120 °C under a nitrogen atmosphere for 10 hours. The reaction mixture was concentrated and extracted with CH_2Cl_2 (20 mL). The organic phase was washed with water (5 mL), brine (5 mL) and dried over anhydrous $MgSO_4$. After filtration and concentration, the crude product was purified by flash silica chromatography (eluent: CH_2Cl_2/MeOH = 10/1) to give a yellow oil (+)-**2** (15.9 mg, 50%): $[\alpha]_D^{26}$ +316 (*c* 0.40, $CHCl_3$); $\nu_{max.}$ ($CHCl_3$)/cm^{-1} 2936, 2852, 1666, 1463, 1360, 1107; δ_H (400 MHz, $CDCl_3$) 2.24–2.33 (m, 2 H, 1-H), 2.43–2.68 (m, 4 H, 2-H, 5-H_A, 9-H_A), 2.68–2.92 (m, 2 H, 5-H_B, 6-H_A), 3.03–3.12 (m, 2 H. 9-H_B, 6-H_B), 3.26 (dd, 1 H, *J* 14.4, 7.6, 8-H_A), 3.45–3.52 (m, 1 H, 8-H_B), 3.76 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 6.12 (s, 1 H, 4-H), 6.56 (s, 1 H, ArH), 6.66 (s, 1 H, ArH); δ_C (100 MHz, $CDCl_3$) 21.5 (9-CH_2), 28.6 (5-CH_2), 32.8 (2-CH_2), 35.9 (1-CH_2), 40.1 (8-CH_2), 45.7 (6-CH_2), 55.9 (OCH_3), 56.0 (OCH_3), 63.7 (13b-C), 110.2 (ArCH), 112.8 (ArCH), 123.9 (4-CH=), 124.4 (ArC), 125.4 (ArC), 146.9 (ArC), 148.4 (ArC), 168.5 (4a-C), 199.3 (C=O); ESIMS *m/z* (%) 300.2 ([M + H]$^+$, 100); HRMS (ESI) found $[M + H]^+$, 300.1586. $C_{18}H_{21}NO_3$ requires *[M + H]*, 300.1594.

Acknowledgements

We gratefully acknowledge the University of Nottingham and the ORS scheme for support of this work through a studentship to FZ.

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