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Intramolecular Acylal Cyclisation (IAC) as an Efficient Synthetic Strategy towards the Total Synthesis of Erythrina Alkaloid Derivatives

Alessandra Monaco,[a] Abil E. Aliev,[b] and Stephen T. Hilton*[a]

Abstract: Compounds that comprise the erythrina alkaloid class of natural products are based on a tetracyclic spiroamine framework and exhibit a range of biological activities on the central nervous system. Herein, we report a new and efficient total synthesis of this multiple-ring system based on an intramolecular acylal cyclisation (IAC) approach. Using this methodology, the tetracyclic core was rapidly assembled over a two-step domino process catalysed by a Lewis acid. The effect of heteroatoms, substituents and ring size on the IAC has also been investigated, and the broad application of this procedure is demonstrated by the synthesis of a library of derivatives in good yields with excellent regioselectivity.

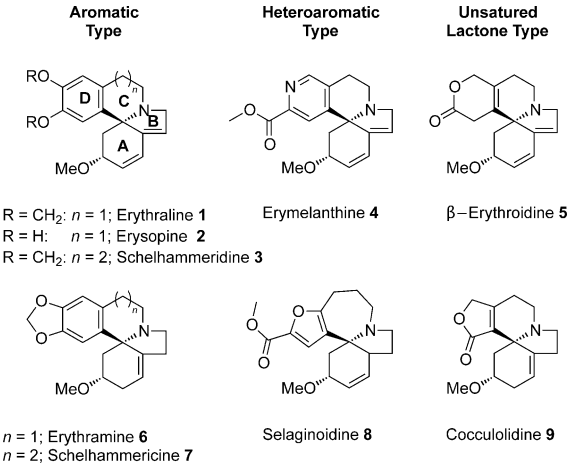

Figure 1. Classification of erythrina alkaloids depending on D ring (aromatic, heteroaromatic and unsaturated lactone types) and on the number of olefinic bonds (dienoid and alkenoid types).

The erythrina alkaloid family is a structurally diverse class of biologically active tetracyclic natural products that have been isolated from a number of tropical plant sources (Figure 1).[1] Many members of this family of compound display a potent effect on the central nervous system (CNS) and, as such, have been used in traditional medicine for their anxiolytic, anticonvulsant, sedative, antidepressive and antiepileptic effects.[2] The hydroalcoholic extract of *Erythrina mulungu* stem bark produces a nonopioid-like analgesic effect,[3] whereas neuroethological and neurochemical experiments have demonstrated that extracts of the flowers of *E. mulungu* produce an anxiolytic effect.[4] Several studies have also reported that oral administration of extracts (3, 10, 50, 100 and 200 mg kg^{-1}) produced anxiolytic effects in patients, which was analogous to the effects of diazepam.[5]

All members of the erythrina family possess a distinctive tetracyclic spiroamine core and can be classified by variations of the D ring, into three subclasses with aromatic, heteroaromatic or unsaturated lactone types as shown (Figure 1).[6] As a result of their potent biological activity and challenging structural features, the synthesis of the erythrina alkaloid core has attracted significant attention over a number of years through a variety of approaches, which have included radical- and Pummerer-mediated syntheses, intramolecular condensation and Diels–Alder reactions, to name but a few.[6,7]

Nearly all methods focus on one of two routes to generate the three aliphatic rings, either through a single cyclisation, or through a tandem cyclisation approach.[7,8] However, despite the reported potent biological activities, there has been a surprising lack of reports on structural variation of the tetracyclic core. Herein, we now wish to report on our novel approach towards the erythrina core and related structural derivatives.

Following our recent reports on the reactivity and use of acylals, we reasoned that the erythrina core could be obtained by a Lewis acid mediated intramolecular acylal cyclisation (IAC) to generate rings B and C in a two-step domino process triggered by acylal activation as outlined below (Scheme 1).

We envisaged that the cyclisation precursor could be obtained through condensation between a primary amine, cyclohexanone and diacetoxyacetyl chloride (Scheme 1). Under Lewis acid mediated IAC conditions, the enamine would cyclise onto the oxonium species **11** to generate the intermediate iminium ion **12**, which would react with the aromatic ring to form the tetracyclic erythrina core **13**. Simple variation of the ketone would therefore provide ready access to a range of analogues in this manner.[9] We decided to use BF_3 as the Lewis acid in

[a] *Dr. A. Monaco, Dr. S. T. Hilton*
UCL School of Pharmacy, University College London
29–39 Brunswick Square, London, WC1N 1AX (UK)
E-mail: s.hilton@ucl.ac.uk

[b] *Dr. A. E. Aliev*
Department of Chemistry, University College London
20 Gordon Street, London, WC1H 0AJ (UK)

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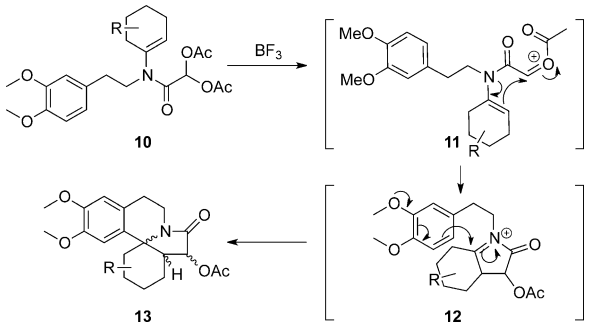


Scheme 1. Cyclisation to generate the tetracyclic core **18**.

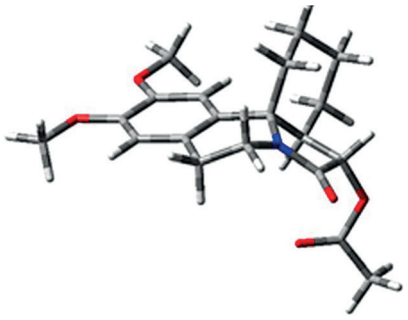
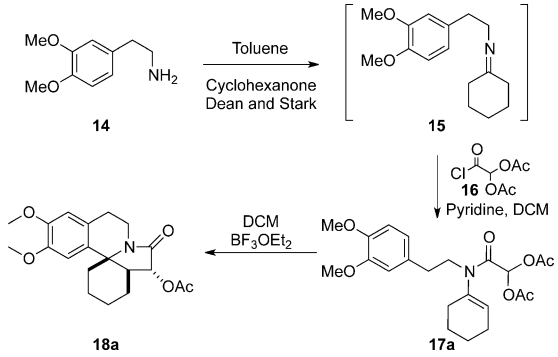


Figure 2. Determination of the relative configuration of the cyclised tetracyclic core structure **18a** showing *trans* configuration around the pyrrolidinone ring.

our cyclisations, due to its mild nature and our previous experience with its reactivity towards diacetoxyamides.[11–14]

To investigate our hypothesis, we carried out initial condensation of cyclohexanone and 2-(3,4-dimethoxyphenyl)ethanamine **14** under Dean and Stark water-removal conditions.[10] The intermediate imine was reacted immediately with 2-chloro-2-oxoethane-1,1-diyl diacetate[11] **16** in the presence of pyridine to afford the key cyclisation precursor **17a** in 63% yield. Pleasingly, on reaction with $BF_3{\cdot}OEt_2$ (5 equiv) and microwave heating of the reaction mixture at 65 °C for 15 min the tetracyclic core **18a** was obtained in good yield (61%) and as a single diastereoisomer (Scheme 2).



Scheme 2. Mechanism of cyclisation to generate the tetracyclic core **18a**.

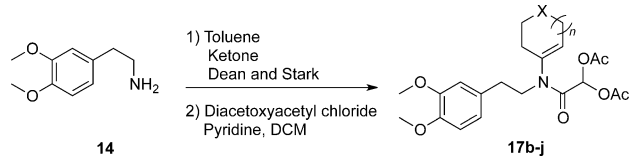
Although it could be anticipated that out of the four potential diastereoisomers, one would be predominant, we were surprised by obtention of a single diastereoisomer in this instance. In order to understand this perhaps surprising selectivity, the relative configuration of the three contiguous chiral centres was determined by NMR J coupling and NOE measurements of the single diastereoisomer **18a**. In combination with computational analysis of the four potential diastereoisomers,[15] the results from energy minimisation calculations and the values from the NMR parameters demonstrated that the hydrogen atoms at C2 and C3 of the pyrrolidine ring would be configured in a *trans* relationship as this diastereoisomer is approximately 5.9 kcal mol^{-1} more stable than its closest related congener (see Supporting Information for full details of NMR and computational analysis). The results from the NOE studies confirmed these results where the two hydrogen atoms are *trans* to each other, with a large J coupling of 10.0 Hz (Figure 2).

Following the success in the formation of the erythrina core, we turned our attention towards formation of a range of closely related analogues through simple variation of the initial ketone component in order to explore the scope of the reaction by variation of ring size and incorporation of heteroatom substituents. The desired cyclisation precursors **17b**–**17j** were prepared in good yields (17–67%) analogous to the formation of the erythrina core as shown below (Table 1).

Compounds **17c** and **17d** were selected to explore the effect of ring size on diastereoselectivity, whilst the various heteroatom and substituted cyclohexyl rings were chosen to explore the scope of the reaction for the formation of potentially biologically active moieties. All compounds gave good yields of the cyclisation precursors, with the exception of the trifluoromethyl analogue **17j**, which was a result of the volatility of the starting ketone. Having the cyclisation precursors in hand we focused on their cyclisation to generate erythrina analogues, the results of which are shown below (Table 2).

All reactions were heated in the microwave at 65 °C for 15 min as per the initial reaction with the cyclohexenyl cyclisation precursor **17a**. Following purification, it can be readily observed that the cyclised products were obtained in good to excellent yield with good control over diastereoselectivity in most cases. Examination of the results for both the cyclopentyl **18c** and cycloheptyl **18d** erythrina analogues demonstrated that the calculations of their respective minimised energies are an effective predictor of the outcome of the diastereoselectivity of cyclisation. In the case of the cyclopentyl analogue **18c**, the *trans* diastereoisomer is 3.9 kcal mol^{-1} more stable than the corresponding *cis* diastereoisomer and, as such, the ratio of *trans/cis* is 85/15. In the case of the cycloheptyl product **18d**, the *trans* diastereoisomer is 0.4 kcal mol^{-1} more stable than the corresponding *cis* diastereoisomer and, as such, the ratio deteriorates to give a *trans/cis* ratio of 60/40, clearly highlighting that the effect of reducing or increasing ring size leads to a lowering of diastereoselectivity. Incorporation of heteroatom six-membered analogues of the erythrina core was well-tolerated with compounds **18b**, **18g** and **18h** all obtained in good yields (30–61%) and as single diastereoisomers. Substitution of

Table 1. Formation of erythrina cyclisation precursor analogues.



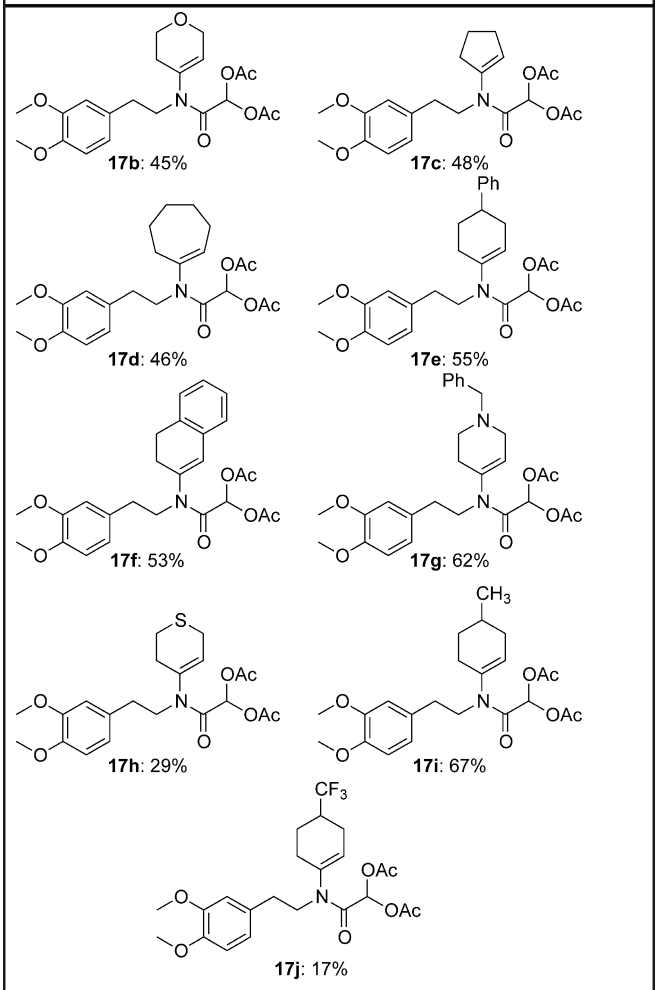
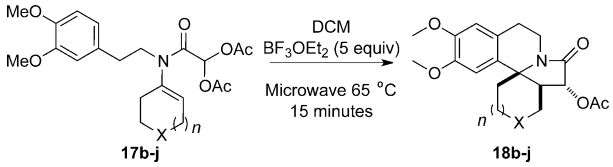
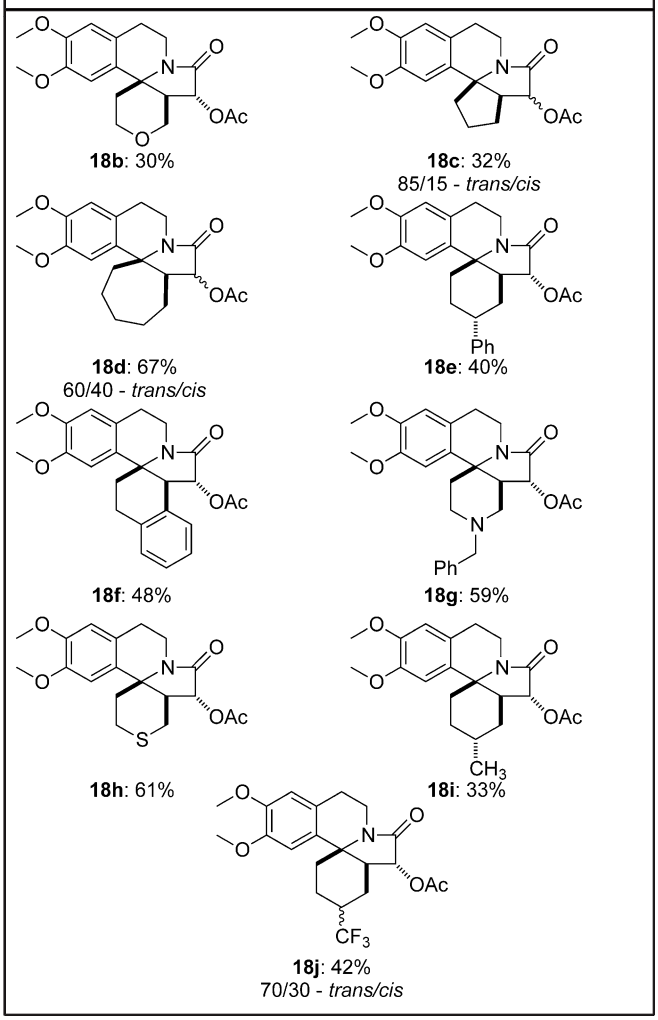


Table 2. Formation of erythrina tetracyclic analogues.





the cyclohexyl ring in the 4-position was also well-tolerated with a phenyl group leading to a single diastereoisomer **18e** in reasonable yield (40%), whereas the methyl-substituted analogue **18i** and the trifluoromethyl analogue **18j** afforded reasonable yields of the cyclised products. In the case of **18j**, the trifluoromethyl group led to a 70/30 mixture of diastereoisomers at the trifluoromethyl position. As per previous six-membered ring-containing examples, the diastereoselectivity at the pyrrolidinyl ring was not affected. Pleasingly, we were also able to generate pentacyclic derivatives of the erythrina core with compound **18f** obtained as a single diastereoisomer in 48% yield and no evidence of any regioisomers.

In summary, we have developed a novel two-step route to the erythrina core, which is based on an intramolecular acylal cyclisation (IAC) approach. In addition, we have shown that, by simple variation of the starting ketone, we can generate a range of substituted analogues with good stereocontrol. Our approach is readily adaptable to incorporation of heteroatom substituents and related pentacyclic derivatives. Further studies on variation of the D ring of the erythrina core are under way in our laboratories and will be reported in due course.

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Keywords: acylal · erythrina alkaloids · intramolecular acylal cyclisation · Lewis acid · tandem cyclisation

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