Title: A Short Total Synthesis of (±)-Lycorane by a Sequential Intramolecular Acylic Cyclisation (IAC) and Intramolecular Heck Addition Reaction

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COMMUNICATION

A Short Total Synthesis of (±)-γ-Lycorane by a Sequential Intramolecular Acylal Cyclisation (IAC) and Intramolecular Heck Addition Reaction


Abstract: An intramolecular acylal cyclisation (IAC) approach to the synthesis of a range of bicyclic heterocycles is reported. As an example of the utility of the IAC reaction, the methodology was applied in a protecting-group free five-step total synthesis of (±)-γ-lycorane, incorporating a novel intramolecular Heck addition reaction to generate the pentacyclic core structure of the natural product in good yield.

Heterocycles based on indole and substituted hydroindole derivatives are found in an array of natural products and have been heavily exploited in medicinal chemistry due to their potent and wide-ranged biological activities. Examples of natural product alkaloids incorporating this bicyclic motif include the erythrina and lycorane alkaloid families which display potent and wide ranging biological activities.1,2 Erythrina derived compounds 1-3, display anxiolytic, anticonvulsant, sedative, antidepressive and antiepileptic effects,4,6 whilst lycorane derivatives as exemplified by 4-10 display central nervous system effects, acetylcholinesterase inhibition, antimalarial, analgesic and anti-inflammatory activity.2,7 Lycorane alkaloids have also been shown to display significant antipro liferative activity in various cancer cell lines including melanoma, multiple melanoma, leukaemia, carcinoma, lymphoma, glioblastoma and non-small cell lung cancer (Figure 1).7,8

Figure 1. Natural products based on the erythrin 1-3 and lycorane cores 4-10.

Due to their potent and wide ranging activities and their associated structural complexity, they have accordingly attracted significant efforts towards their syntheses,9,15 including radical cyclisation, aminocyclisation, intramolecular addition reactions and several metal-catalyzed amidations amongst others.9-16 Despite the structural diversity of both classes of compound and the wide array of synthetic methods used in their syntheses, many have focused on the synthesis of the dihydroindolone core 11, due to its ready elaboration to either of the core structures of erythrina (1-3) or lycorane alkaloids (4-10) (Figure 2).10,16,17

Figure 2. The dihydroindolone 11 intermediate used in the synthesis of both lycorane and erythrin.

As a result of the structural complexities and potent biological activities associated with each class of compound, we were interested in the development of novel methodology to access molecules related to the bicyclic core 11 as a route to both classes of compound.18,19 We were also cognizant of the need to develop a flexible route which would facilitate the synthesis of a range of analogues for biological testing. In a previous approach to the erythrin core 12, we had developed a facile two-step domino cyclisation process, which focused on a Lewis acid mediated intramolecular acylal cyclisation (IAC) via intermediate 13 (Scheme 1).18,19 We were therefore interested in the possibility that in the case of an N-benzyl substituted analogue (n = 1), the intermediate iminium ion 13 would not undergo a further intramolecular addition reaction with the aryl moiety, but would instead undergo tautomerisation to the intermediate 16, which with a suitably designed precursor could undergo radical cyclisation to generate the lycorane core 15 as per literature precedent and is outlined below (Scheme 1).16

Scheme 1. Proposed synthetic route to both the erythrin 12 and lycorane 15 cores.

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To investigate our hypothesis that both classes of compound could be accessed using this approach via simple variation of the N-substituent and to explore the synthesis of a range of bicyclic heterocycles related to compound 16, we first reacted benzylamine 17 with cyclohexanone under Dean and Stark water removal conditions. Intermediate 18 was subsequently reacted with diacetoxyacetyl chloride 19, in the presence of pyridine using our previously published methodology to give the intramolecular acylal cyclisation precursor 20a in 86% yield. On reaction with BF₃·OEt₂ (5 equiv.) and heating the reaction mixture in the microwave (Biotage Initiator) at 65 °C for 15 minutes, the reaction did not give the expected bicyclic heterocycle 16, but instead led to formation of dihydroindolenone 21a in good yield (78%) (Scheme 2).

Whilst obtention of the dihydroindolenone 21a was unexpected as we had anticipated that product 16 would be predominant, it is likely that the intermediate bicyclic acetate - 24 (obtained after reaction of the nucleophilic enamine with the oxonium ion) is unstable and readily undergoes hydride loss to give 25. Further activation via BF₃ and loss of acetate followed by tautomerisation provides a ready mechanistic route to the dihydroindolenone core 21a.

Following the success in the formation of the bicyclic dihydroindolenone core 21a, we next elected to explore the scope of this reaction in the synthesis of a range of closely related analogues through simple variation of the initial ketone component in order to explore the scope of the reaction with variation of ring size and incorporation of substituents on the aryl ring in order to develop an advanced intermediate towards the synthesis of the lycorane core 15. The desired cyclisation precursors 20b-20h were prepared in good yields (55-97%) as shown below (Scheme 3).

Scheme 3. Formation of bicyclic heterocycle cyclisation precursor analogues.

Compounds 20b and 20d were chosen to explore the effect of different ring sizes on the reaction outcome, whilst other cyclisation precursors were selected to explore the effects of electron-donating substituents on the aromatic ring as an approach towards the total synthesis of (±)-γ-Lycorane 5. All reactions were heated in the microwave at 65 °C for 15 minutes as per the formation of the initial bicyclic dihydroindolenone 21a and the results are shown below (Scheme 4).
As can be seen above, all compounds gave good yields of the bicyclic core structures (21b-21h) following intramolecular acylal cyclisation. The formation of the bicyclic fused [3.3.0] and [5.3.0] ring systems in compounds 21b and 21d showed a reduction in yield (65% and 60% respectively) when compared with the initial cyclisation to give 21a. The extended conjugated tricyclic compound was also obtained in good yield (71%), with the double bond undergoing a hydride shift to give the more thermodynamically stable compound 21f. Incorporation of an electron donating group on the N-benzyl substituent as exemplified by 21c and others was also very well tolerated with good yields obtained in all cases 45-75%. Pleasingly, compound 21g which is an advanced synthetic intermediate towards (±)-γ-lycorane 5, was also obtained in excellent yield (75%).

Initial reaction of the cyclisation precursor 33 under Heck cyclisation conditions using palladium diacetate as catalyst in dioxane, gave the cyclized product 34 albeit in low yield (5%) (Table 1, Entry 1). Optimization of the reaction conditions via use of triphenylphosphine palladium dichloride as catalyst and heating the reaction in the microwave at 150 °C for one hour afforded the Heck cyclisation product in good yield (74%) (Table 1, Entry 4).

Table 1. Heck cross-coupling optimization.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time</th>
<th>Catalyst</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dioxane</td>
<td>30 min</td>
<td>Pd(OAc)₂</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>DMF</td>
<td>1 h.</td>
<td>Pd(OAc)₂</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>DMF</td>
<td>1 h.</td>
<td>Pd(OAc)₂</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>DMF</td>
<td>1 h.</td>
<td>(PPh₃)₂PdCl₂</td>
<td>74</td>
</tr>
</tbody>
</table>

Attempts to synthesize lycorane from the bicyclic precursor 33 under previous analogous radical conditions led to degradation of the starting material in all cases. We attributed this to the inherent stability of the conjugated double bond and therefore sought an alternative approach. We were therefore intrigued by a novel palladium-mediated intramolecular Heck reaction with the conjugated amidic carbonyl and as such, elected to explore a range of Heck coupling conditions with 33 (Scheme 6).
Following efficient formation of the pentacyclic core of lycorane, we next sought to complete the total synthesis of (±)-Lycorane 5. Hydrogenation of the conjugated double bonds in 34 via use of an H-cube hydrogenation flow reactor using a mixture of ethanol and ethyl acetate as solvent to aid solubility, with a flow rate of 0.5 mL/min and 10% palladium on charcoal as catalyst at 65 °C and 60 bar pressure gave the reduced product 35 in almost quantitative yield (97%). Reduction following literature precedent using lithium aluminium hydride completed the synthetic route to give the total synthesis of (±)-Lycorane 5 in 85% yield (Scheme 7).16a

Scheme 7. Total synthesis of (±)-lycorane 5.

In summary, we have developed a novel five-step route to the total synthesis of (±)-Lycorane 5, which is based on a novel sequential intramolecular acyl cyclisation/ Heck addition approach. In addition, we have shown that by variation of the starting ketone or the N-benzylo substituent of the precursor, we will be able to generate a number of substituted analogues as demonstrated by the efficient formation of the bicyclic core. Our approach is readily adaptable to incorporation of heteroatom substituents and further studies on these are under way in our laboratories and will be reported in due course.

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Keywords: Erythrina • Lewis acid • Lycorane • tandem cyclisation • Heck


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A novel approach to the total synthesis of \(\gamma\)-lycorane: The pentacyclic structure of the natural product \((\pm)\-\gamma\)-lycorane was synthesized via a novel sequential Lewis acid mediated intramolecular acylal cyclisation (IAC)/ Heck coupling approach. Using this methodology, a range of bicyclic heterocycles were also synthesised in good yields demonstrating the potential of the IAC reaction to access complex heterocycles.