Research Signpost
37/661 (2), Fort P.O.
Trivandrum-695 023
Kerala, India

Recent Advances in Pharmaceutical Sciences IV, 2014: 143-163 ISBN: 978-81-308-0554-2
Editors: Diego Muñoz-Torrero, Manuel Vázquez-Carrera and Joan Estelrich

# 10. Synthetic approaches towards the *Lycopodium* alkaloids

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**Abstract.** The *Lycopodium* alkaloids are a structurally diverse group of natural products isolated from *Lycopodium* with important biological effects for the potential treatment of cancer and severe neurodegenerative diseases. To date, full biological studies have been hampered by lack of material from natural sources. Total synthesis represents a possible solution to meet this demand as well as the most effective way to design new compounds to determine structural activity relationships and obtain more potent compounds. The aim of this chapter is to summarise the work carried out in this field so far by presenting an overview of the synthetic strategies used to access each of the four key *Lycopodium* alkaloid types. Particular emphasis has been placed on methods that rapidly construct each nucleus utilizing tandem reactions.

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# 1. Introduction

The *Lycopodium* alkaloids, isolated from the *Lycopodium* genus of clubmosses belonging to the family of Lycopodiaceae, represent a diverse group of structures with important, wide-ranging biological effects. These compounds show great potential for the treatment of severe neurodegenerative diseases and cancers but to date biological studies have been hindered due to limited availability of material from natural sources. Attempts to access material via cultivation or fermentation have so far been unsuccessful [1] leaving total synthesis as the most promising way to access quantities of material for further biological testing. In addition, synthesis has the advantage that it easily enables structural modifications to be carried out to determine activity relationships and as a consequence design more potent analogues with improved biological profiles. The aim of this minireview is to give an overview of the synthetic strategies used to access each type of key Lycopodium alkaloids with particular emphasis on those synthetic approaches that feature tandem reactions enabling a rapid synthesis of each nucleus. Whilst a brief overview of the structures, biological properties and biosynthesis will be presented for contextual purposes, the authors direct the reader to the excellent review by Ma [1] for a more detailed coverage of these aspects.

## 1.1. Classification of the *Lycopodium* alkaloids

At the moment of writing this report almost 300 *Lycopodium* alkaloids have been discovered [2] which can be divided into four structural classes [3,4] based on the parent compound: phlegmarine (**1**), lycopodine (**2**), lycodine (**3**) and fawcettimine (**4**) (Fig. 1).

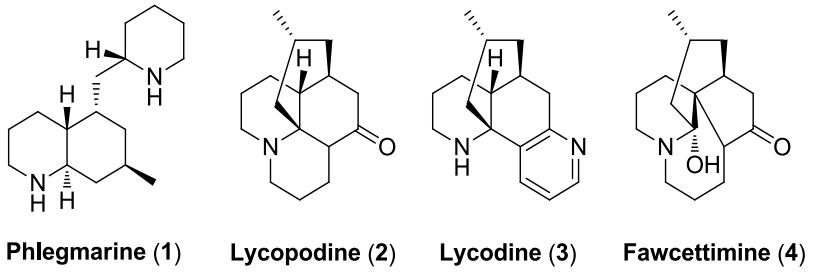



**Figure 1**. Representative examples of the four *Lycopodium* alkaloid classes.

## 1.2 . Bioactivities

An extensive biological investigation of the *Lycopodium* alkaloids has as yet not been carried out. However, from the limited studies undertaken so far it has been discovered that many of these compounds possess important biological activities that warrant further investigation and development. One key area of potential of these compounds is for the treatment of severe neurodegenerative diseases such as Alzheimer's. Examples include huperzine A [5] and lycoposerramine C [6], which act as inhibitors of the enzyme acetylcholinesterase (AChE), while lycodine-type complanadine B stimulates nerve growth factor (NGF) production in human glial cells [7]. Lycoposerramine Z from the phlegmarine structural class may potentially have neuroprotective properties due to the presence of the nitrone moiety, which can act as a free radical trap [8] helping prevent destructive cascades leading to brain deterioration (Fig. 2).

The *Lycopodium* alkaloids have also been shown to possess anticancer activities. For example, complanadine A was found to be cytotoxic against leukaemia cells in mice [9]. Lyconadine B, from the phlegmarine group exhibits biological activity against brain tumors [10] and lycopodine has the ability to bring about inhibition in the growth of HeLa55 cells [11].

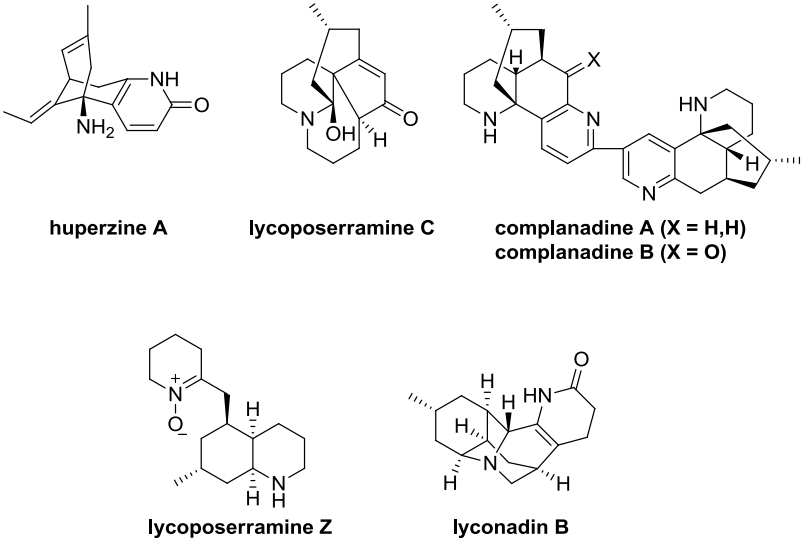
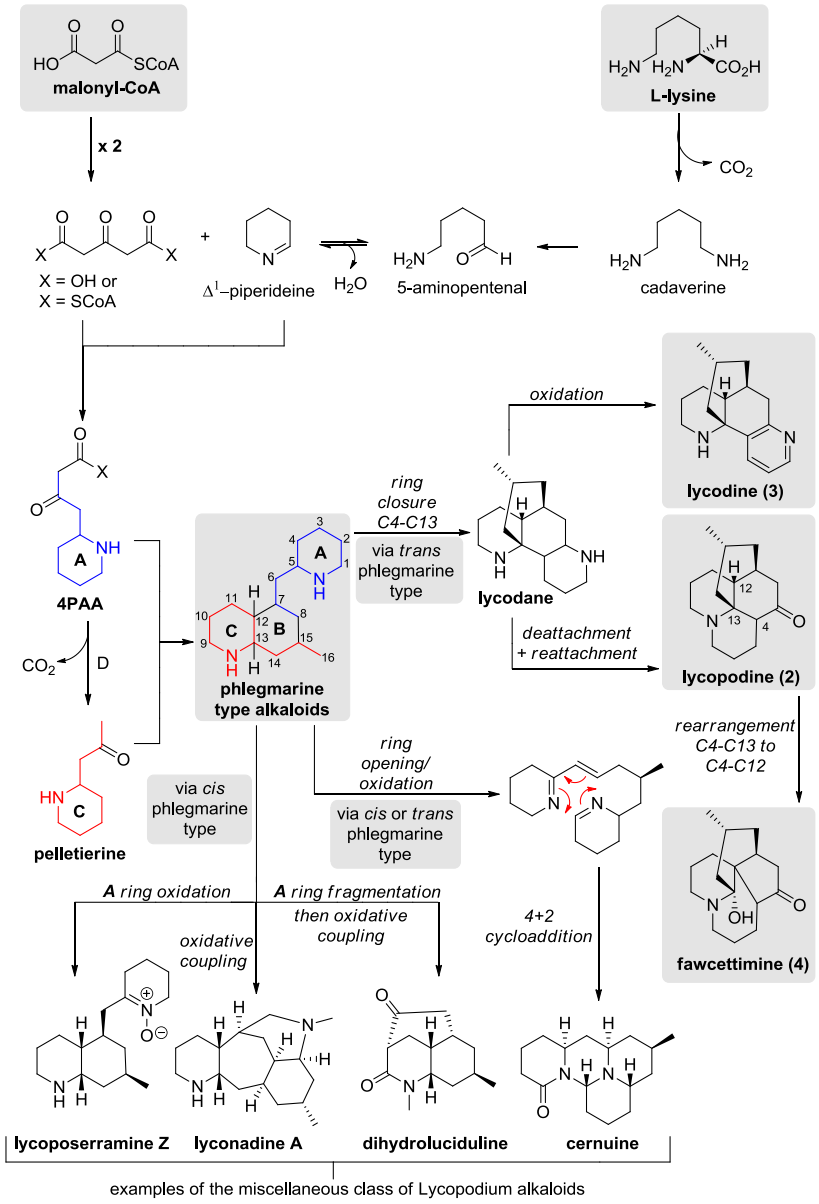



**Figure 2.** Some biologically active *Lycopodium* alkaloids.

## 1.3. Biosynthesis of the *Lycopodium* alkaloids

The biosynthetic pathway leading to all *Lycopodium* alkaloids is still not clear, although a basic overview is outlined in Scheme 1 based on the present knowledge [1]. The vast structural diversity encountered among the *Lycopodium* alkaloids is thought to derive from just two simple components, lysine and malonyl Co-A. The entry point into the pathway is through the decarboxylation of lysine to form cadaverine which is transformed to $\Delta^1$-piperideine. At the same time, two molecules of malonyl-CoA are condensed to form acetonedicarboxylic acid, whose union with $\Delta^1$-piperideine leads to 4-(2-piperidyl) acetoacetate (4PAA). This is then decarboxylated to form pelletierine, which is coupled to another molecule of 4PAA to form the phlegmarine-type *Lycopodium* alkaloids. These compounds are formed with multiple stereochemistries that can be separated into two main classes depending on whether the hydrogens at the ring fusion are arranged *cis* or *trans* (see section 2). It is assumed that on dimerisation slightly different pathways exist with different methods of control thus leading to the diverse range of stereochemistries observed. Phlegmarine (**1**) which is characterized by a *trans* fusion at the ring junction is considered to be the key intermediate from which the other three classes (**2**-**4**) of *Lycopodium* alkaloids are derived. Bond formation between C-4 and C-13 gives the lycodane skeleton, which after oxidation of the piperidine ring leads to lycodine (**3**). Detachment of C-1 from $N_\alpha$ of the lycodane skeleton and reattachment to $N_\beta$ then gives lycopodine (**2**). Rearrangement of (**2**) via migration of the C-4 to C-13 bond to C-12 forms the 5-membered ring of fawcettimine (**4**). Further complexity within each of these groups is arrived at by a series of modifications of these basic ring structures such as oxidations, ring fragmentations, dimerisations and additional skeletal rearrangements.

The *cis*-fused phlegmarine alkaloids comprise the entry point to the miscellaneous class of the lycopodium alkaloids, including compounds such as lyconadine A or dihydroluciduline which maintain the same *cis* stereochemistry relationship as the parent compound. Cernuine and related quinazoline *Lycopodium* alkaloids are speculated to arise from an opening of the B ring of the phlegmarine skeleton, additional oxidation, followed by a 4+2 cycloaddition reaction. Due to the loss of the fusion stereochemistry, these compounds may arise via the *trans* or *cis* phlegmarine group intermediates.




**Scheme 1**. Overview of the biosynthesis of the *Lycopodium* alkaloids.

## 2. Phlegmarine class

Phlegmarine is the parent member of the miscellaneous group of the *Lycopodium* alkaloids and as mentioned above, is considered to play a key role in the biosynthesis of all the lycopodium alkaloids. While phlegmarine (**1**) is characterized by a *trans* substitution pattern at the ring fusion carbons, other compounds belonging to this group feature a *cis* relationship between the ring fusion hydrogens (e.g lycoposerramine Z and cermizine B). In addition to the wide variety of stereochemistries observed, other key variations are the oxidation of the nitrogen containing rings leading to pyridines (lycoposerramine V and W), nitrones (huperzine M and lycoposerramine Z) or N-oxides (huperzine N) (Fig. 3).

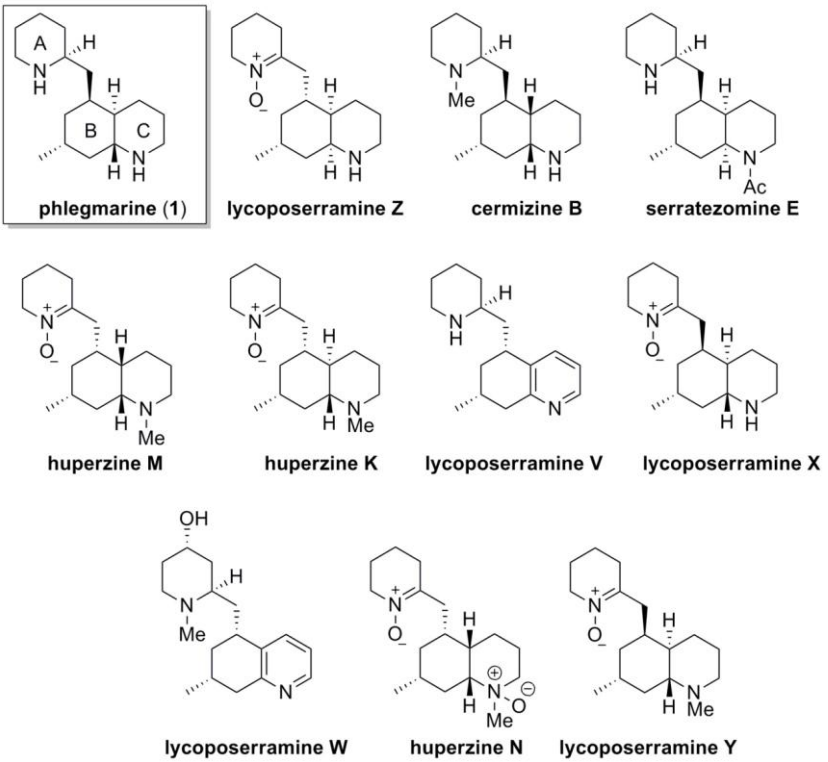



**Figure 3.** Representative compounds of the miscellaneous class based on the phlegmarine skeleton.

## 2.1. Previous synthesis of Phlegmarine type alkaloids

Despite the importance of this class of compounds from a biosynthetic point of view and their potential for use as biomimetic precursors of the other classes of *Lycopodium* alkaloids, the phlegmarine type has been one of the least studied (Table 1). Although the relative configuration of phlegmarine was established in 1981 [12] the absolute configuration of a phlegmarine derivative was not determined until 1999 [13] when Comins *et al* carried out the first asymmetric total synthesis of $N_{\alpha}$-acetyl-$N_{\beta}$-methylphlegmarine using a pyridine auxiliary for the construction of both the C and A nitrogen-containing rings. Takayama's enantioselective syntheses of lycoposerramines V, W [14], X and Z [15] were accomplished using (5*R*)-methyl-2-cyclohexenone as the source of chirality. Comins then completed the synthesis of phlegmarine in 2010 [16] based on his original methodology and finally, the Bonjoch group utilized organocatalysis to form the decahydroquinoline ring system as the key step.[17]

**Table 1.** Previous synthesis of some Phlegmarine-type *Lycopodium* alkaloids (*denotes enantioselective synthesis).

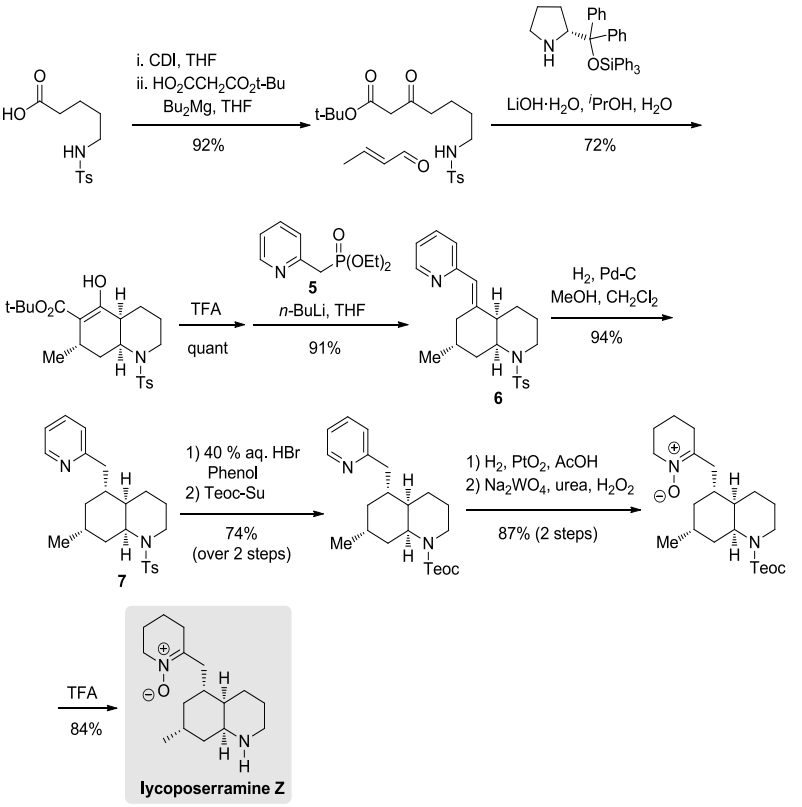
| *Year* | *Natural Product* | *Author* | *Ring Construction Strategy* |
|---|---|---|---|
| 1981 [12] | $N_{\alpha}$-methyl-$N_{\beta}$-acetylphlegmarine | Maclean | B→C→A |
| 1999 [13] | $N_{\alpha}$-acetyl-$N_{\beta}$-methylphlegmarine | Comins | C→B→A* |
| 2007 [14] | Lycoposerramine-V +(Lycoposerramine W) | Takayama | B→C→A* |
| 2009 [15] | Lycoposerramine-X +(Lycoposerramine Z) | Takayama | B→C→A* |
| 2010 [16] | (−)-Phlegmarine and derivatives | Comins | C→B→A* |
| 2013 [17] | Lycoposerramine-Z | Bonjoch | acyclic→BC→A* |

## 2.2. Bonjoch's synthesis of Lycoposerramine Z [17]

Bonjoch's group developed an asymmetric synthesis of lycoposerramine Z, where the decahydroquinoline core was assembled via an organocatalyzed diastereo and enantioselective one-pot tandem procedure (Scheme 2). Removal of the *tert* butyl ester group with TFA and coupling with pyridine phosphonate **5** assembled the complete carbon

skeleton in a rapid manner. Hydrogenation of alkene **6** took place exclusively from the top face leading to **7**, which has all the stereocentres required for lycoposerramine Z in place. The sensitive nature of the nitrone unit necessitated exchange of the tosyl group for the more readily labile Teoc group (trimethylsilylethylcarbonate), which was previously used in Takayama's synthesis of the same compound. Finally reduction of the pyridine ring followed by oxidation with $Na_2WO_4$ in the presence of urea peroxide installed the nitrone unit. Treatment with TFA smoothly removed the Teoc group to complete the synthesis.

It was also later shown that this method can be adapted to access all the different core decahydroquinoline stereochemistries present in the phlegmarine group via a series of controlled equilibration reactions [18].




**Scheme 2.** Bonjoch's total synthesis of Lycoposerramine Z.

## 3. Lycodine class

The lycodine (**3**) group comprises around 30 of the 300 known *Lycopodium* alkaloids. Some examples are shown in Fig. 4. Complanadine A is a dimer of two lycodine units. Hydroxypropyllycodine is the first *Lycopodium* alkaloid found to possess a 19-carbon skeleton [19]. In some compounds such as huperzines A and B the D ring is unsaturated whilst in the former the C ring has been cleaved. Casuaririne I features an unprecedented 5-membered tetrahydropyrrole ring and is believed to derive from huperzine A [20].

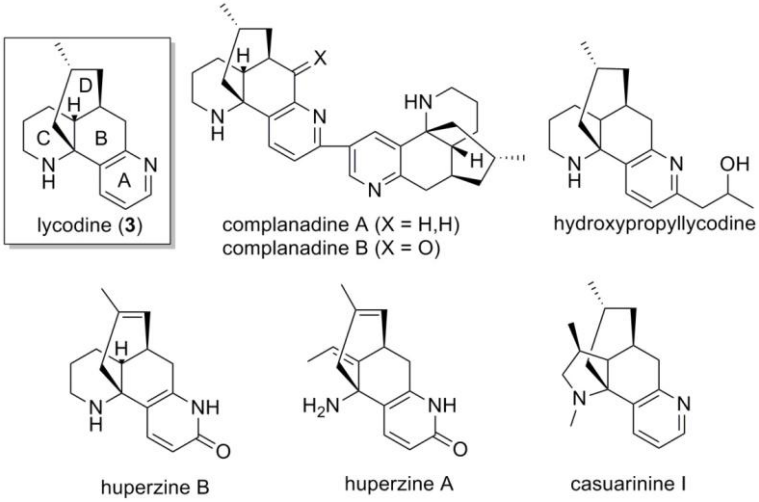



**Figure 4.** Representative compounds of the Lycodine group.

### 3.1. Previous synthesis of Lycodine and related compounds

Along with the phlegmarine group, the synthesis of the lycodine class has been the least studied. The D→C→B→A ring strategy is the most commonly used to construct the lycodine nucleus. The first synthesis of (±)-lycodine was performed by Heathcock [21], who closed the DCB skeleton in a one-pot diastereoselective Mannich condensation. Another racemic synthesis of lycodine was developed by Hirama [22] and involved a Diels-Alder cycloaddition followed by an intramolecular Mizoroki-Heck reaction to furnish the complete skeleton. In Sarpong's complanadine A synthesis [23] Boc-protected lycodine was prepared as a key intermediate en route to the

**Table 2**. Previous syntheses of Lycodine and its dimer's Complanadine A and B. (* denotes enantioselective synthesis).

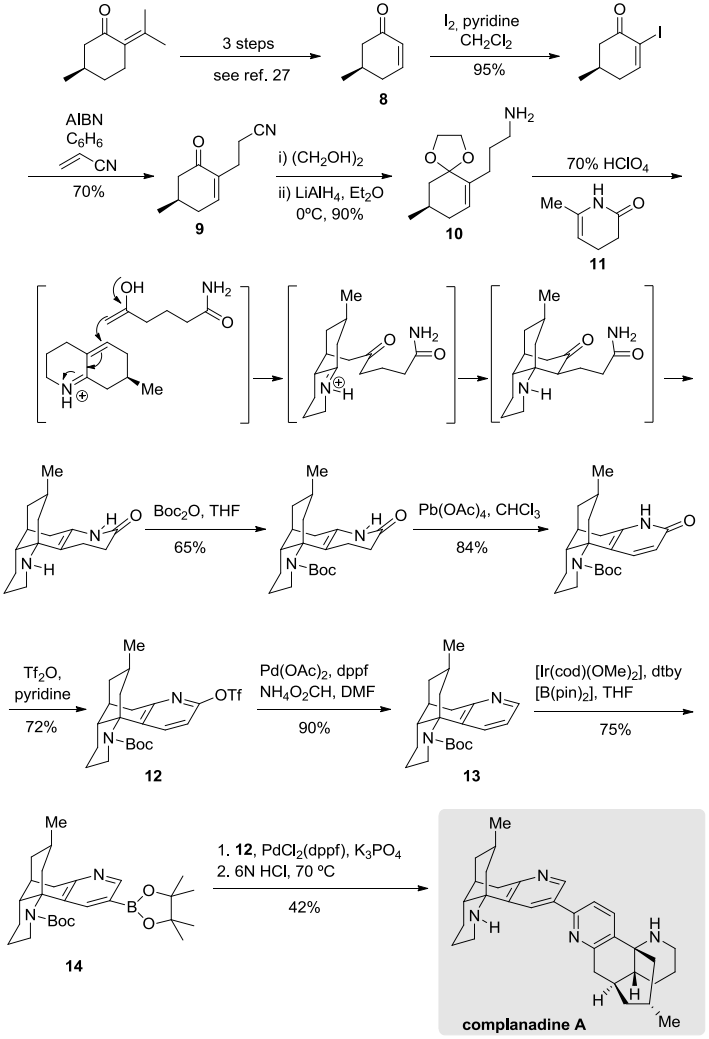
| *Year* | *Natural Product* | *Author Strategy* | *Ring Construction* |
|---|---|---|---|
| 1982 [21] | Lycodine | Heathcock | D→C→B→A |
| 2010 [22] | Lycodine | Hirama | acyclic→CD→BA |
| 2010 [23] | Complanadine A | Sarpong | D→DCBA* |
| 2010 [25] | Complanadine A | Siegel | D→C→B→A* |
| 2013 [24] | Complanadine B | Sarpong | D→DCBA |
| 2013 [26] | Complanadines A/B | Hirama | acyclic→CD→BA |

final product in enantiopure form (see Scheme 3). This same key intermediate was later used in his synthesis of complanadine B [24]. Seigel [25] made use of two Co-mediated [2+2+2] cycloaddition reactions to furnish complanadine B starting from a thioether derivative of (5*R*)-methyl-2-cyclohexenone. While as yet no enantioselective synthesis of lycodine has been described, recently Hirama [26] and co-workers reported the synthesis of Complanadines A and B starting from enantiopure (−)-lycodine, which was obtained by chiral HPLC separation.

## 3.2. Sarpong's synthesis of complanadine A [23]

Sarpongs´s synthesis of complanadine A takes advantage of the symmetry of the product to construct the dimer from two lycodine units via a palladium-based coupling reaction as the key step. Preparation of the (5*R*)-methyl-2-cyclohexenone starting material **8** was accomplished in 3 steps from *R*-(+)-pulegone using a reported procedure [27]. Iodination and radical addition to acrylonitrile gave **9** which after acetalization and reduction of the nitrile gave **10** the key material for the subsequent tandem cyclisation reaction. Treatment of this compound with perchloric acid led to an intermediate that was trapped with an enamide **11** via a Michael-Mannich tandem procedure to furnish the DCB core [28] followed by condensation of the amide to the carbonyl formed the A ring giving a rapid synthesis of the complete lycodine skeleton (Scheme 3). Protection of the resulting compound followed by oxidation with lead tetraacetate and triflation of the pyridone ring provided **12**. Removal of the triflate group gave Boc-protected lycodine

**13** to which was introduced a boronic ester with an iridium-catalyzed functionalization at the 3 position to give **14**. Finally, Suzuki cross-coupling of **12** and **14** followed by cleavage of the Boc protecting groups completed the synthesis.




**Scheme 3**. Sarpong's total synthesis of complanadine A.

## 4. Lycopodine class

Lycopodine (Fig. 5), the first isolated *Lycopodium* alkaloid [29], is the most widespread and can be found in several different *Lycopodium* species. Out of the 300 known *Lycopodium* alkaloids discovered so far, 100 belong to the lycopodine class.

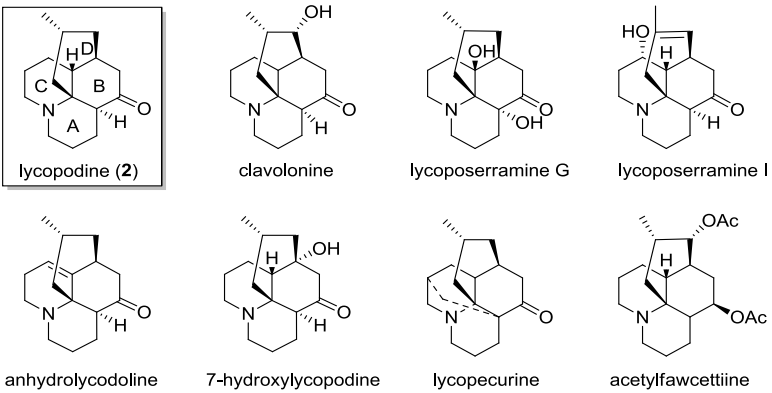



**Figure 5**. Some representative alkaloids belonging to the Lycopodine class.

### 4.1. Previous synthesis of Lycopodine and related compounds

Along with the Fawcettimine nucleus, the synthesis of lycopodine has been one of the most intensively studied, with most of the approaches reported to date relying on a common D→C→B→A ring construction strategy. The key ring-forming step usually involves the manner of formation of the B ring, which can be divided into two main approaches. The first, described by Stork, involves an intramolecular Pictet-Spengler cyclization onto an iminium group located between the D and C rings. The aromatic ring is then fragmented and used to form the required carbon atoms of the A ring. Padwa and Mori later arrived at the same key intermediate precursor in their synthetic approaches albeit by very different methods. The other key strategy to form the B ring involves an intramolecular diastereoselective Mannich cyclization approach which was first reported by Heathcock (see Scheme 4). This strategy, and variations thereof, has been the most commonly employed in subsequent synthetic approaches. The first enantioselective synthesis of a lycopodine related compound, clavolonine A was described by Evans and used a similar Mannich strategy. However, instead of following Heathcock and starting from a racemic D ring building block, a chiral auxiliary strategy

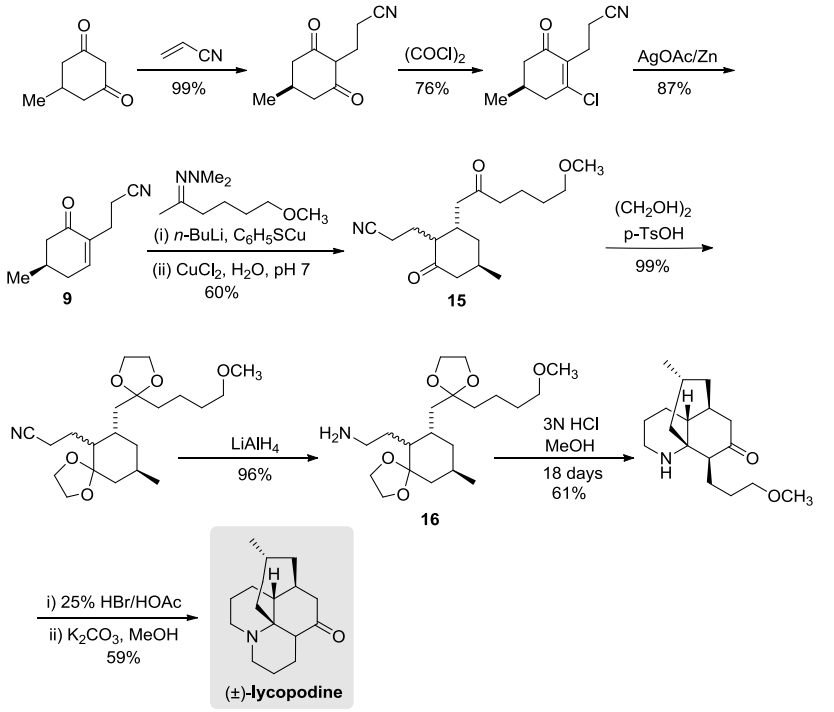
was used to form an acyclic chain which was then cyclised to form the D ring in enantiopure form. A few years later, Carter achieved the first enantioselective synthesis of lycopodine using an analogous approach to Evans employing a chiral auxiliary and a Mannich cyclisation as the key steps. Whilst a number of strategies do not fall into the categories described above, the methods employed have usually required a significant amount of additional functional group manipulation steps and consequently these strategies have not been exploited in further synthetic approaches.

**Table 3**. Summary of the most relevant previous syntheses of Lycopodine and its derivatives. (* denotes enantioselective synthesis).

| *Year* | *Natural Product* | *Author* | *Ring Construction Strategy* |
|---|---|---|---|
| 1967 [30] | 12-epi-Lycopodine | Weisner | D→C→B→A |
| 1968 [31] | 12-epi-Lycopodine | Weisner | D→C→A→B |
| 1968 [32] | Lycopodine | Stork | D→C→B→A |
| 1968 [33] | Lycopodine | Ayer | BC→A→D |
| 1978 [34] | Lycopodine | Heathcock | D→C→B→A |
| 1978 [35] | Lycopodine | Kim | D→B→C→A |
| 1982 [28] | Lycopodine | Schumann | D→C→B→A |
| 1982 [21] | Lycopodine | Heathcock | D→C→B→A |
| 1984 [36] | Lycopodine | Wenkert | C→A→B→D |
| 1985 [37] | Lycopodine | Kraus | D→B→C→A |
| 1998 [38] | Lycopodine | Mori | D→B→C→A |
| 1998 [39] | Lycopodine | Grieco | B→D→CA |
| 1997 [40] | Lycopodine | Padwa | acyclic→CD→B→A |
| 2005 [41] | Clavolonine | Evans | acyclic→D→C→B→A* |
| 2008 [42] | Lycopodine | Carter | acyclic→D→C→B→A* |
| 2010 [43] | Acetylfawcettiine | Breit | D→C→B→A* |
| 2011 [44] | Clavolonine | Fujioka | D→C→B→A* |
| 2012 [45] | 7-hydroxylycopodine | Snider | D→C→B→A |

## 4.2. Heathcock's synthesis of Lycopodine [21]

Key to Heathcock's synthesis is an equilibrating Mannich cyclisation reaction which assembles the DCB tricyclic in a single step. The requisite material required for the cyclisation was prepared from 5-methylcyclohexane-1,3-dione, which underwent Michael addition to acrylonitrile followed by formation of the cyclohexenone. Conjugate addition of a tosyl hydrazine to **9** followed by hydrolysis of the hydrazone gave **15**. Protection of the ketone moieties as acetals then allowed the nitrile to be reduced to the primary amine. Treatment of **16** with strong acid over an extended period resulted in a diastereoselective Mannich cyclization to forming the DCB tricyclic system via equilibration to the most stable structure. Removal of the methoxyether group with HBr resulted in subsequent formation of the primary alkyl bromide, which was then cyclised onto the nitrogen under basic conditions giving lycopodine.




**Scheme 4**. Heathcock's total synthesis of Lycopodine.

## 5. Fawcettimine class

About a third of all the known lycopodium alkaloids are of the fawcettimine type. Key structural variations to the parent structure include skeletal oxidations as well as the formation of dimeric products. The fawcettimine nucleus can be simplified to the three-ring DBA system since the C ring forms spontaneously via the free amine condensing with the carbonyl to form the hemiaminal unit.

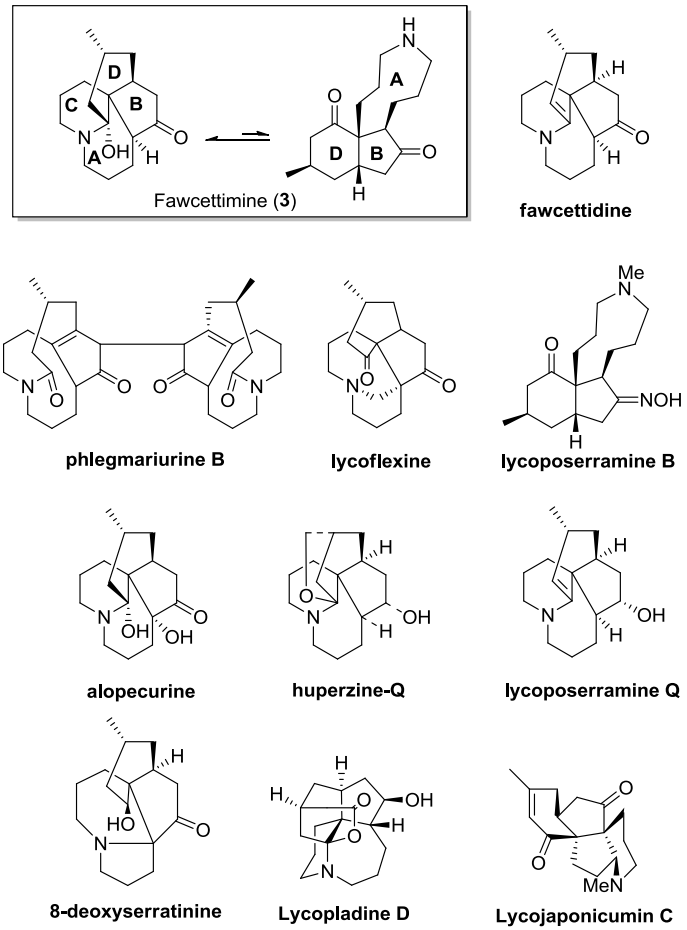



**Figure 6**. Representative compounds of the Fawcettimine class.

## 5.1. Previous synthesis of Fawcettimine and related compounds

Fawcettimine-type products have been the area of most intensive synthetic research in the field of *Lycopodium* alkaloids, with the vast majority of syntheses being reported from 2007 onwards [46].

**Table 4**. Previous synthesis of Fawcettimine and related compounds. (* denotes enantioselective synthesis).

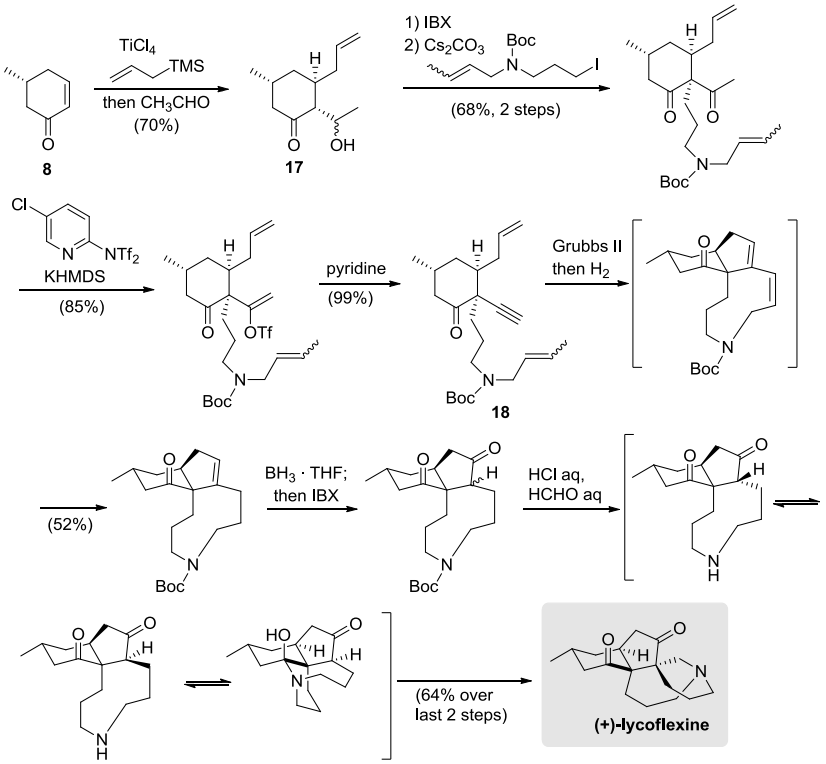
| *Year* | *Natural Product* | *Author* | *Ring Construction Strategy* |
|---|---|---|---|
| 1979 [47] | Fawcettimine | Inubushi | D→B→A→C |
| 1986 [48] | Fawcettimine | Heathcock | D→B→A→C |
| 1989 [49] | Fawcettimine | Heathcock | D→B→A→C |
| 2002 [50] | Magellanine | Liao | BC→ A→D |
| 2007 [51] | Fawcettimine | Toste | D→B→A→C* |
| 2008 [52] | Fawcettidine | Dake | D→C→B→A* |
| 2010 [53] | Fawcettimine (Fawcettidine) | Takayama | acyclic→DB→A→C* |
| 2010 [54] | Fawcettimine | Jung | D→B→A→C* |
| 2010 [55] | Fawcettimine (Lycoposerramine-B) | Mukai | acyclic→DB→A→C* |
| 2010 [56] | Fawcettimine +(Lycoflexine) | Yang | D→B→A→C* |
| 2010 [57] | Lycoflexine (Fawcettimine) | Mulzer | D→BA→C* |
| 2011 [58] | Huperzine-Q | Takayama | acyclic→DB→A→C* |
| 2010 [59] | Alopecuridine | Meng | D→A→B→C |
| 2012 [60] | Fawcettimine | Willliam | D→A→B→C* |
| 2012 [61] | Fawcettimine (Fawcettidine and Deoxyserratinine) | Lei | D→A→B→C* |
| 2013 [62] | Lycojaponicumin C 8-Deoxyserratinine Fawcettimine Fawcettidine | Zhao | D→B→A→C* |
| 2013 [63] | Lycopladine D, Fawcettidine Lycoposerramine Q | Tu | DB→A→C* |

As a consequence most of the syntheses carried out are enantioselective with 3-methyl cyclohexenone **8** (derived from pulgeone) as the most popular source of chirality. As in all the previous syntheses of the *Lycopodium* alkaloids one strategy dominates for the construction of the fawcettimine skeleton. Most methods employ the D→B→A→C order (see Table 4) with the key differences in strategy centring on the assembly of the 5-membered B ring. This usually involves a conjugate addition onto a suitably substituted cyclohexenone followed by a subsequent trapping of the nucleophile via the formed carbonyl enolate. In a number of cases the order is reversed, with the 6-membered D ring being appended onto a 5-membered B ring starting material precursor, for example, using a Diels-Alder [60] or a Robinson annulation reaction [62] Alternatively, the 6,5-bicycle (D-B) core has been constructed in a single step from an acyclic precursor using a Pauson-Khand reaction [53,55].

Subsequent closure of the 9-membered A ring usually involves a Mitsunobu-type reaction. Finally, deprotection of the nitrogen yields the free amine, which then spontaneously cyclises via the hemiaminal to close the C ring.

## 5.2. The Mulzer synthesis of Lycoflexine and Fawcettimine

Mulzer and co-workers [57] have reported an efficient route to construct the 6,5,9-tricylic framework of fawcettimine which features an enyne ring-closing-metathesis to construct the B and A rings in a single step. Like many *Lycopodium* syntheses it utilises 3-methylcyclohexenone **8** as the starting material and source of chirality. A Sakurai-aldol sequence gave substituted cyclohexanone **17** which after oxidation with IBX was alkylated with a nitrogen-containing side chain. Conversion of the methyl ketone to an alkyne prepared the starting material **18** for the tandem cyclization reaction. Treatment with Grubbs II catalyst initiated the enyne ring-closing-metathesis first forming the five-membered B ring followed by the 9-membered A ring. The resulting diene was hydrogenated in-situ to selectively remove the less substituted alkene. The remaining alkene then underwent a hydroboration-oxidation sequence using IBX as the oxidant to directly introduce the desired ketone in the cyclopentane ring system. Deprotection of the Boc group liberated the secondary amine which underwent spontaneous cyclisation to fawcettimine. The addition of formaldehyde precipitated a Mannich reaction to give lycoflexine.




**Scheme 5**. Mulzer's total synthesis of (+)-lycoflexine.

## 6. Conclusions

An overview of the synthetic approaches used to construct the four core structural types of the *Lycopodium* alkaloids has been presented. As can be seen, for each nucleus type one ring construction strategy tends to dominate for each nucleus type and there exists significant similarity between the starting materials and intermediates employed across the range of different approaches. There are now efficient procedures for the rapid construction of each nucleus type, using tandem reactions that construct many of the rings in a single step. It is hoped that continuing work within this field will lead to new and more efficient approaches to the *Lycopodium* alkaloids and their analogs that will enable a full investigation of their important biological activities for the treatment of serious diseases such as Alzheimer's or cancer.

## Acknowledgement

This work was supported by the Spanish Ministry of Economy and Competitiveness (Project CTQ2010-14846/BQU).

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