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Stereocontrolled Total Syntheses of (±)-Fawcettimine, (±)-Lycoflexine, and (±)-Lycoflexine *N*-Oxide

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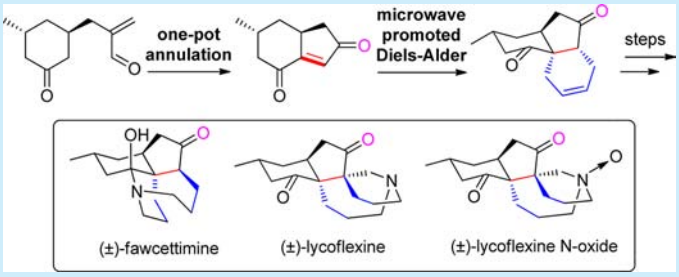
Supporting Information



ABSTRACT: New stereocontrolled total syntheses of (±)-fawcettimine, (±)-lycoflexine, and (±)-lycoflexine *N*-oxide have been accomplished. The highlights include a one-pot annulation to construct the enedione and a microwave-promoted Diels–Alder reaction.

Since the isolation of fawcettimine (**1**) from *Lycopodium fawcetti* by Burnell in 1959,[1] about 90 members of *Lycopodium* alkaloids[2] have been discovered over the past decades (Figure 1).

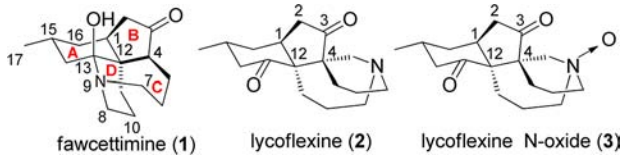


Figure 1. Structures of **1**–**3**.

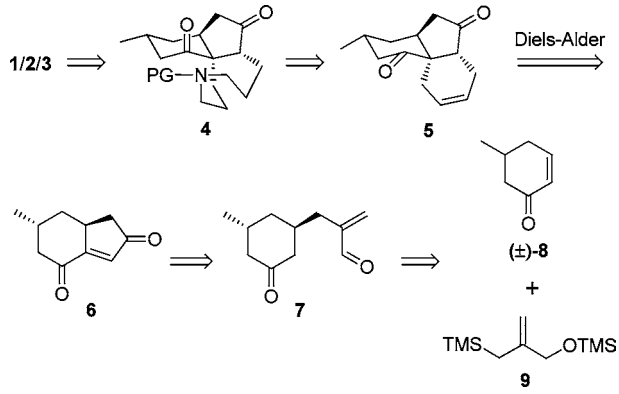
Fawcettimine, an important biogenetic precursor of other *Lycopodium* alkaloids, possesses a unique 6/5/7/6 tetracyclic skeleton embedded with five stereogenic centers including an all-carbon quaternary one. Due to its structural complexity and potent acetylcholine esterase inhibitory activity,[3] this alkaloid has become an attractive target for the synthetic community. To date, 11 total syntheses,[4a−k] one formal synthesis,[4l] and one synthetic study[4m] have been reported.

Lycoflexine (**2**) was proposed to be derived biogenetically from fawcettimine via Mannich cyclization and was first isolated from *Lycopodium clavatum* var. *Inflexum*.[5] Its intriguing structure consists of a 6/5/7/6 tetracyclic skeleton and four stereogenic centers including two adjacent quaternary carbons. Since the first total synthesis by Ramharter and co-workers,[6] three unified routes have been developed for the total syntheses of fawcettimine and lycoflexine in 16–22 steps.[4g,i,j]

Lycoflexine *N*-oxide (**3**) was recently isolated from three species of *Lycopodium* (i.e., *Lycopodium clavatum*, *Lycopodium serratum*, and *Lycopodium squarrosum*) and a semisynthesis of **3** has been accomplished by Takayama and co-workers.[7]

In this paper, we report a unified strategy for the stereocontrolled assembly of fawcettimine (**1**), lycoflexine (**2**), and lycoflexine *N*-oxide (**3**). As outlined in Scheme 1, alkaloids **1**–**3** could be derived from the common intermediate **4**. We envisioned that **4** should be accessible through Diels–Alder reaction of **6** followed by a formal three-atom ring

Scheme 1. Retrosynthetic Analysis of 1–3



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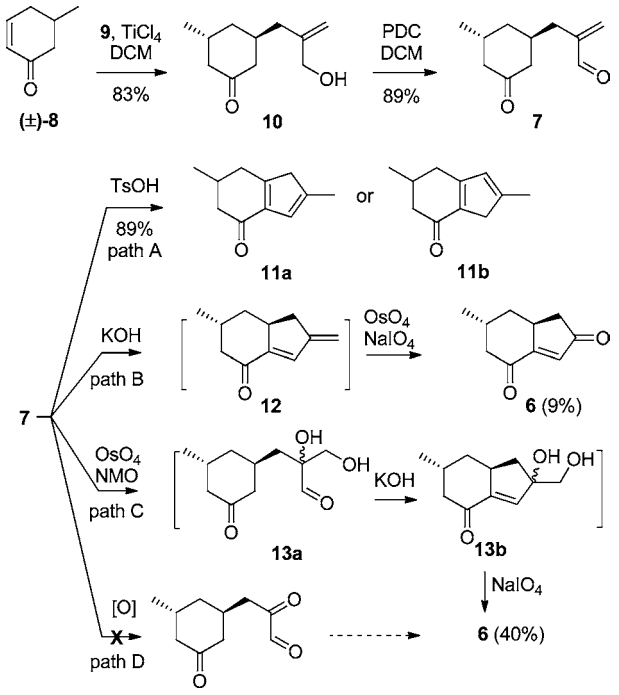
expansion. Dienophile **6** may be generated from aldehyde **7**, which could be readily prepared from enone **8** and bis-silane **9**. It is worth noting that the Diels–Alder reaction has been utilized to construct the A ring[4i] (see Figure 1 for the ring codes) and B ring[4a] of fawcettimine. However, this cycloaddition reaction has never been used for assembling the C ring within fawcettimine or its related alkaloids.

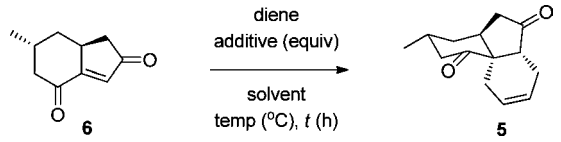
Sakurai alkylation[4c,d,8] of **8**[9] with **9**[10] was utilized to introduce a desirable side chain at C1, providing alcohol **10** essentially as a single isomer (Scheme 2). Oxidation of **10** with PDC in DCM furnished aldehyde **7** in high yield. The hydrindanone core of **6** could potentially be obtained from **7** via an intramolecular aldol reaction. The transformation was initially carried out with a Brønsted acid (TsOH or camphorsulfonic acid) as a catalyst, but an undesired product (either **11a** or **11b**) was formed (path A). When compound **7** was treated with KOH in EtOH and H_2O followed by a selectively oxidative cleavage of the terminal olefin within **12** (path B), the desired product **6** could be obtained but only in 9% overall yield. After various attempts, we were pleased to find that the overall yield of enedione **6** could be increased to 40% if **7** was subjected sequentially to dihydroxylation, aldol reaction, and oxidative cleavage of the vicinal diol unit in a one-pot fashion (path C). In contrast, **6** could not be generated from aldehyde **7** through sequential alkene cleavage (OsO_4/$NaIO_4$ or O_3)/aldol reaction, presumably due to the poor stability of the α-carbonyl aldehyde intermediate (path D).[11]

Scheme 2. Synthesis of 6



With compound **6** in hand, the Diels–Alder reaction was extensively investigated under a series of conditions (Table 1). Initially, 3-sulfolene was chosen as a diene precursor, from which 1,3-butadiene could be produced in situ.[12a] Unfortunately, enedione **6** was completely decomposed in various solvents (PhH, DCM, or MeOH), even in the presence of an excess amount of base, presumably due to the adverse effect of SO_2, the byproduct of the thermal cracking of 3-sulfolene at high temperature (Table 1, entries 1–4). 1,3-Butadiene was subsequently used in the reaction instead of 3-sulfolene.[12b] No reaction took place when a low concentration (c = 1.5 mM) of 1,3-butadiene was heated with **6** in PhMe at 120 °C; however, adduct **5** could be stereoselectively formed in 39% yield (or 84%, brsm) with higher 1,3-butadiene concentration (c = 30 mM) at the same temperature (entries 5–6). The stereoselectivity observed for the formation of **5** should result from steric control. A much higher temperature (140 °C) and longer reaction time (50 h) led to an even better yield (58%, entry 7). Gratifyingly, the yield could be further improved to 79% by performing the cycloaddition in a microwave reactor while the reaction time was reduced to 11 h (entry 8).[12c] Note that the Diels–Alder reaction of **6** with 1,3-butadiene conducted in the presence of either a Brønsted acid (CF_3CO_2H) or a Lewis acid ($TiCl_4$, TMSOTf, or Me_2AlCl) proved to be unsuccessful.[12d]

Table 1. Diels–Alder Reaction of 6 with 1,3-Butadiene or Its Precursor[a]



entry	diene	solvent	temp (°C)	t (h)	additives (equiv)	yield[b] (%)
1	3-sulfolene	PhH	120	8	quinol (0.2)	–
2	3-sulfolene	DCM	120	8	quinol (0.2)	–
3	3-sulfolene	MeOH	120	8	quinol (0.2)	–
4	3-sulfolene	PhH	120	8	quinol (0.2), Py (3), $NaHCO_3$ (3)	–
5[c]	butadiene	PhMe	120	24	BHT (0.2)	NR
6[d]	butadiene	PhMe	120	10	BHT (0.2)	39
7[d]	butadiene	PhMe	140	50	BHT (0.2)	58
8[d,e]	butadiene	PhMe	110	11	BHT (0.2)	79

[a]All reactions were performed in a sealed tube. [b]Isolated yields. [c]Concentration of 1,3-butadiene in PhMe was 1.5 mM. [d]Concentration of 1,3-butadiene in PhMe was 30 mM. [e]Performed in a microwave reactor. BHT: 2,6-di-*tert*-butyl-4-methylphenol.

With the consideration of double N-alkylation at a later stage in mind, protection of both carbonyl groups in **5** gave bis-acetal **14**, the structure of which was confirmed by X-ray crystallographic analysis. Compound **14** was transformed into bisiodide **17** in 53% overall yield after a four-step reaction sequence: (a) oxidative cleavage of the carbon–carbon double bond, (b) Wittig reaction of both formyl groups, (c) hydroboration/oxidation of both terminal alkene units, and (d) iodination of both hydroxyl groups. However, the attempted double N-alkylation of $NsNH_2$ with **17** was unsuccessful; the diiodide substrate decomposed in the presence of a base such as K_2CO_3, NaOH, or Cs_2CO_3.

The acetal protecting groups might adversely affect the above-mentioned double alkylation of $NsNH_2$ with **17** (Scheme 3). Subsequently, we resorted to a different protection approach for the carbonyl groups in **5**. As described in Scheme 4, stereoselective reduction of diketone **5** with $NaBH_4$ afforded diol **18** (62%) and other stereoisomers (30%); the latter were oxidized with DMP to regenerate **5** for the purpose of recycling. Protection of both hydroxyl groups in **18** resulted in compound **19**, where the relative configurations of C3 and C13 were speculated on the basis of NOE experiments. Through similar transformations applied to **14**, alkene **19** was converted smoothly into diol **20** in three steps including (a) oxidative

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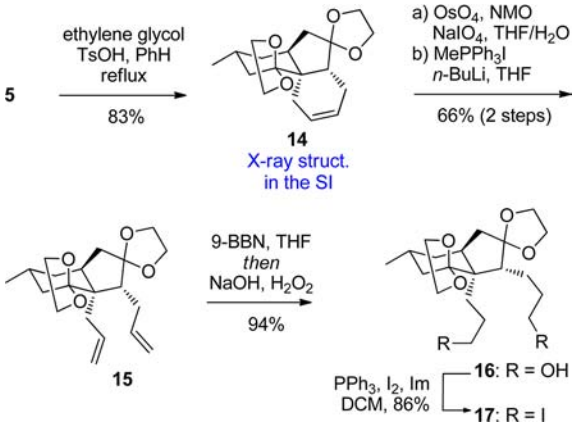
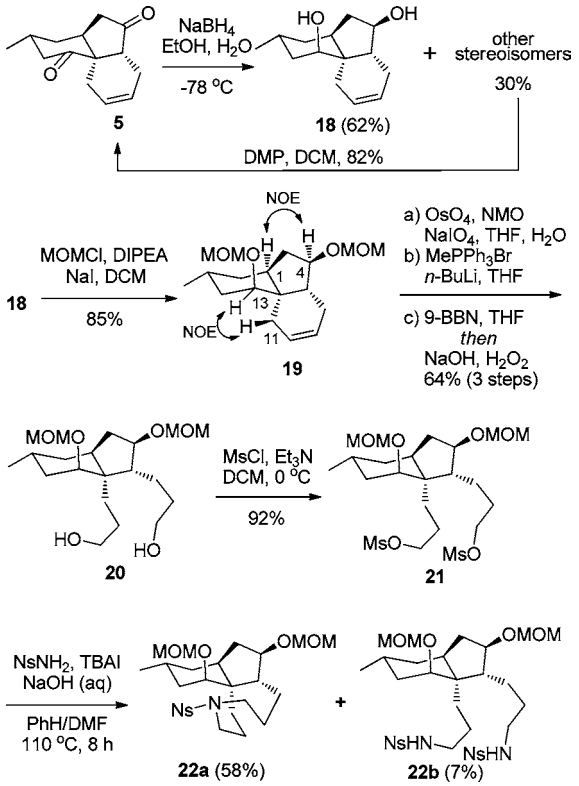
Scheme 3. Synthesis of Diiodide 17



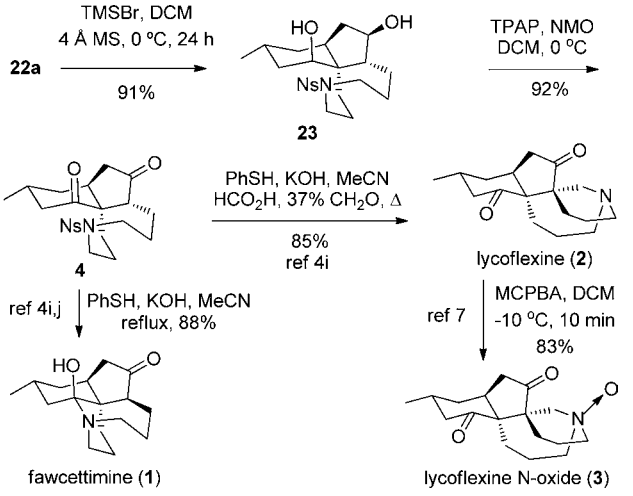
Scheme 4. Synthesis of 22a



cleavage, (b) Wittig reaction, and (c) hydroboration/oxidation. Unfortunately, all attempts to effect double Fukuyama–Mitsunobu reactions[13] of **20** under various conditions with $NsNH_2$ produced only a complex mixture. Then, sulfonation of both hydroxyl groups in **20** furnished dimesylate **21** in 92% yield. To our delight, double N-alkylation did take place when **21** was treated with $NsNH_2$ (1.4 equiv), aqueous NaOH solution, and tetrabutylammonium iodide in benzene/DMF at 110 °C. The desired tricycle **22a** was produced in 58% yield along with a small amount (7%) of bis-sulfonamide **22b**.[4g,i,j,14]

Removal of both MOM groups in **22a** followed by Ley oxidation of **23** led to the key intermediate **4** in 84% overall yield (Scheme 5). Upon desulfonation of **4**, fawcettimine (**1**) was afforded in 85% yield after spontaneous epimerization at C4 and aminal formation.[4i,j] Lycoflexine (**2**) was obtained from **4** in 88% yield via a one-pot desulfonation/Mannich reaction.[4i]

Scheme 5. Completion of the Total Syntheses of 1–3



Upon treatment with MCPBA in DCM (−10 °C), lycoflexine (**2**) was cleanly converted into lycoflexine *N*-oxide (**3**) in 10 min (as monitored by TLC).[7] The spectroscopic data of the synthetically obtained (±)-fawcettimine (**1**), (±)-lycoflexine (**2**), and (±)-lycoflexine *N*-oxide (**3**) were identical to those reported in the literature.[4a–k,5–7]

In summary, we have developed a unified strategy for the total syntheses of fawcettimine (**1**), lycoflexine (**2**), and lycoflexine *N*-oxide (**3**) from (±)-**8** in 14, 14, and 15 steps, respectively. Although the total syntheses reported herein are those of racemic **1**–**3**, it would be straightforward to realize their asymmetric syntheses by starting with optically active (5*R*)-5-methylcyclohex-2-enone [(5*R*)-**8**].[15] The key features of the current strategy include a one-pot annulation of **7** to construct fused 6/5 bicyclic enedione **6** and a microwave-promoted Diels–Alder reaction of **6** to assemble key intermediate **5** with the C12 quaternary center installed in place.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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