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Lycopodium Alkaloids

Total Synthesis of (+)-Fawcettimine**

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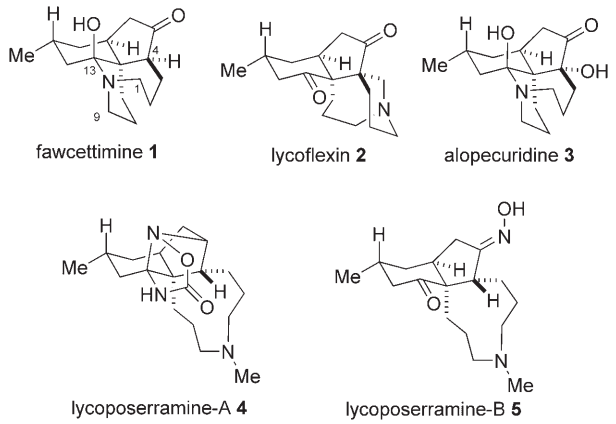
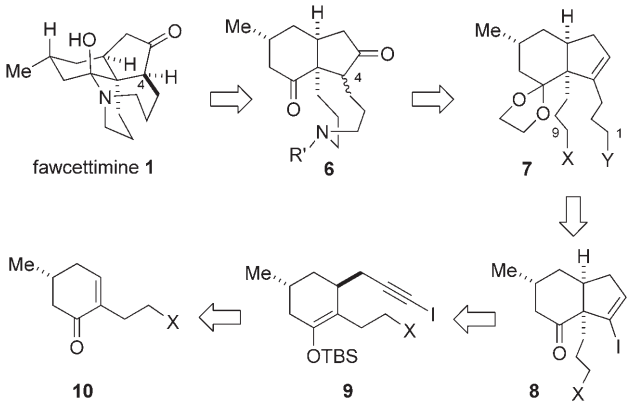
The fawcettimine class of *Lycopodium* alkaloids consists of over 60 natural products.[1] Typically, these tetracyclic compounds contain a single quaternary carbon center and are derived biosynthetically from the lycopodane core through an oxidative rearrangement reaction. In 1959, the first member of this class, fawcettimine (**1**), was isolated by Burnell in the Blue Mountain Range of Jamaica.[2] Inubushi and co-workers later confirmed the structure by chemical correlation through X-ray crystallography.[3] Heathcock and co-workers subsequently demonstrated that the carbinolamine **1** was in equilibrium with the corresponding ketone and therefore underwent facile epimerization at C-4.[4] Since the discovery of fawcettimine, a number of related compounds have also been isolated. For example, the C4-functionalized derivatives lycoflexin[5] (**2**) and alopecuridine[6] (**3**) were reported in 1973 and 1974, respectively. More recently, lycoposerramine-A[7] (**4**) with a 1,2,4-oxadiazolidin-5-one structure and lycoposerramine-B[8] (**5**) with a mono oxime functionality were discovered and proposed to be biosynthetically derived from fawcettimine (**1**).



Prior to the work presented herein, two syntheses of racemic (±)-fawcettimine have been reported. Inubushi and co-workers accomplished its total synthesis in 27 steps, proceeding in a 0.1% overall yield from commercially available 5-methyl-1,3-cyclohexanedione.[9,10] Later, the Heathcock group reported a more efficient synthetic route from the same commercially available compound, obtaining (±)-fawcettimine in 16 steps and 10% overall yield.[4,11]

Our synthetic plan is shown in antithetic format in Scheme 1. On the basis of Heathcock's finding that fawcettimine is predominantly the thermodynamic isomer, we rationalized that the C-4 configuration could be established by equilibration to the correct isomer in the deprotection and carbinolamine-forming step (**6** to **1**). We envisioned that the C-5 ketone could be prepared from the C4–C5 olefin. Disconnection to this olefin allows for formation of the hydrindanone core, containing a quaternary carbon atom, through a transition-metal-catalyzed 5-*endo*-*dig* cyclization.[12] We envisioned cyclization onto an alkynyl iodide leading to a vinyl iodide, which could then be functionalized through cross-coupling. This route allows for flexibility in the functional groups (X and Y) that could be employed for construction of the azepine ring (**7** to **6**). Therefore, disconnection of the C3–C4 bond provides bicyclic vinyliodide **8** that in turn could be prepared by the gold(I)-catalyzed cyclization of silyl enol ethers developed by our laboratory (**9** to **8**).[12b,13] As previously described, this approach allows for the diasteroselective construction of *cis*-fused 5,6-bicyclic ketones. Finally, construction of the acetylenic cyclization precursor could be completed by a Michael addition to a 2-functionalized cyclohexen-3-one (**10**), presumably forming the *trans* diastereomer.



Scheme 1. Retrosynthetic analysis of **1**. TBS = *tert*-butyldimethylsilyl.

To achieve an asymmetric synthesis of (+)-fawcettimine, we first pursued a robust method for the formation of enantioenriched 2-functionalized cyclohexen-3-ones (Scheme 2). To this end, iodide **11**[14] was smoothly transformed through a Suzuki–Miyaura cross-coupling reaction into enones **10a**,**b** with pendant oxygen or nitrogen functionalities (X in Scheme 1) that could ultimately be employed to

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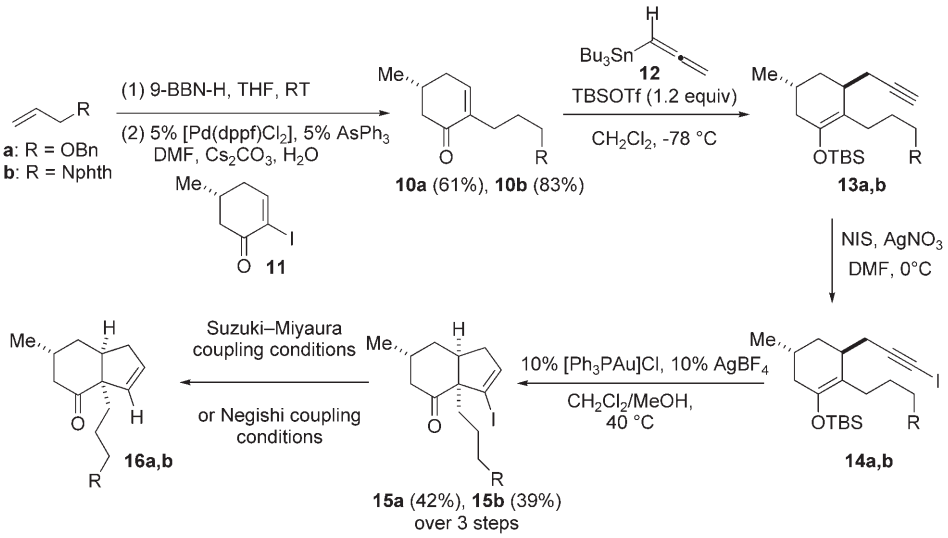


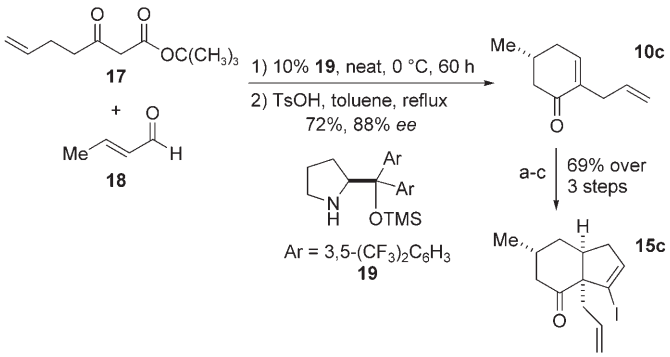
Scheme 2. Cross-coupling route to the hydridanone core of **1**. phth = phthaloyl; dppf = 1,1′-bis(diphenylphosphino)ferrocene, 9-BBN-H = 9-borabicyclononane, DMF = dimethylformamide.

construct the azepine ring. Utilizing the modified method of the Haruta group,[15] *tert*-butyldimethylsilyltriflate (TBSOTf) promoted 1,4-addition of allenyltributylstannane **12** to cyclohexenones **10a**,**b** gave *trans* silyl enol ethers **13a**,**b** with excellent diastereoselectivity (d.r. > 95:5). Iodination of the terminal C≡C bond with *N*-iodosuccinimide (NIS) and silver nitrate afforded iodoacetylenes **14a**,**b**.[16] 5-*Endo-dig* carbocyclization of **14a,b** proceeded smoothly, catalyzed by (triphenylphosphine)gold(I) tetrafluoroborate, to furnish the hydrindanone core (**15a**,**b**) of fawcettimine (Scheme 2). Notably, both the [4.3.0] bicyclic structure and carbon quaternary center were installed in a single step.

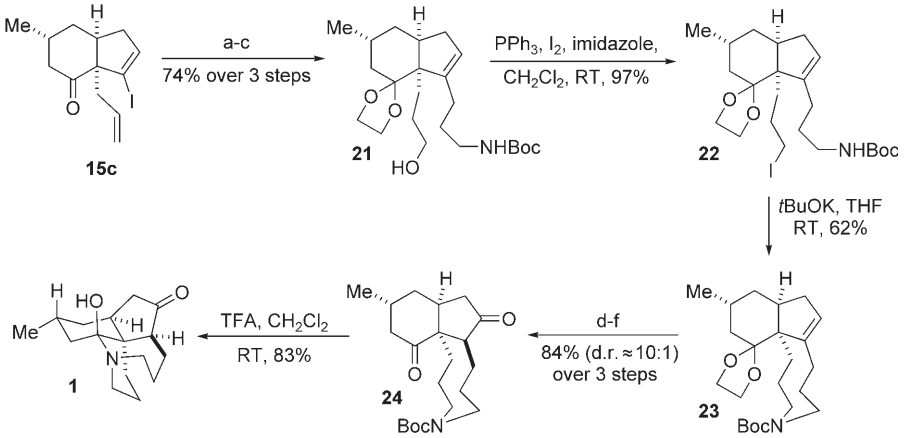
With vinyl iodides **15a**,**b** in hand, we attempted to employ transition-metal-catalyzed cross-coupling reactions to introduce the C1–C3 carbon atoms with an appropriate functional group (Y in Scheme 1) at C1. Unfortunately, Suzuki–Miyaura and Negishi coupling methods, under various reaction conditions, produced dehalogenated compounds (**16a**,**b**) as the major product without significant amounts of the desired cross-coupling products (Scheme 2).

Given the failure of heteroatom-substituted hydridanones to participate in the cross-coupling reaction, we considered an approach wherein the C9 functionality would be introduced by hydroboration of a C–C double bond. While this compound could be prepared by the cross-coupling route described in Scheme 2, a direct catalytic enantioselective approach was developed using an organocatalytic Robinson annulation reaction between ketoester **17** and crotonaldehyde (**18**), which gave 2-allylcyclohexenone **10c** in 88% *ee* and 72% yield (Scheme 3).[17] This reaction performed well on a multigram scale, providing nearly 10 g of dienone **10c** in a single run. This dienone was converted into **15c** in 69% yield as a single diastereomer using a sequence of conjugate propargylation, acetylene iodination and gold(I)-catalyzed cyclization analogous to that described in Scheme 2.

We were pleased to find that allyl-substituted vinyl iodide **15c** underwent smooth palladium-catalyzed cross-coupling reactions with a variety of sp^3-carbon–zinc and –boron species.[18,19] As shown in Scheme 4, protection of the carbonyl group as the cyclic ketal and cross-



Scheme 3. Organocatalytic/gold-catalyzed cyclization approach to the hydridanone core of **1**. a) **12**, TBSOTf, CH_2Cl_2, −78 °C; b) NIS, $AgNO_3$, DMF, 0 °C; c) 10% $[Ph_3PAu]Cl$, 10% $AgBF_4$, CH_2Cl_2/MeOH 10:1. 40 °C. Ts = *p*-toluenesulfonyl.



Scheme 4. Completion of the synthesis of (+)-fawcettimine (**1**); reagents and conditions: a) ethylene glycol, TsOH, benzene, reflux; b) 1) $H_2C{=}CHCH_2NHBoc$, 9-BBN-H; 2) $[PdCl_2(dppf)]$, $AsPh_3$, Cs_2CO_3, DMF, RT; d) acetone/H_2O, pyridinium *p*-toluenesulfonate (PPTS), reflux; e) BH_3·THF, THF, 50 °C, then NaOH, H_2O_2, RT; f) Dess–Martin periodinane, CH_2Cl_2, 84% from **22** over 3 steps, d.r. ≈ 10:1.

coupling under Trost's conditions[20] provided the *tert*-butyloxycarbonyl (Boc) protected amine. The double bond was then converted into primary alcohol **21** using a hydroboration/oxidation sequence. We envisioned that the nine-membered ring could be constructed by an intramolecular S_N2 reaction. However, attempts to effect this intramolecular displacement with the mesylate or tosylate derivative of alcohol **21** and the Boc-protected amine group under basic conditions produced a complex mixture. On the other hand, transformation of alcohol **21** to iodide **22** allowed for intramolecular alkylation of the amine to furnish the desired nine-membered ring (**23**) in 62% yield.

With the entire fawcettimine skeleton installed, all that remained was to introduce the final oxygen atom and remove the protecting groups. After deprotection of the carbonyl group, the resulting enone was subjected to hydroboration and reduction to afford a diastereomeric mixture of diols. Their Dess–Martin oxidation provided diketone **24**. A 10:1 mixture of two diastereomers was observed in favor of the thermodynamic *trans* epimer, which is consistent with the studies of Heathcock's group.[4] Finally, removal of the Boc group with trifluoroacetic acid (TFA) followed by basic work-up gave (+)-fawcettimine (**1**) along with a small amount of the C4 epimer that slowly isomerized to the natural product over time. Treatment of the resulting amine with hydrogen bromide afforded fawcettimine hydrobromide in good yield. The spectral data (^{1}H and ^{13}C) for both fawcettime and its hydrobromide salt were consistent with those reported by Heathcock and co-workers.

In conclusion, the first asymmetric total synthesis of (+)-fawcettimine has been achieved in 13 steps from crotonaldehyde. Additionally, the absolute configuration of (+)-fawcettimine, which showed the same optical rotation as the natural product,[21] was established by a crystal-structure analysis of its hydrobromide (Figure 1). Ultimately this work demonstrates that organocatalytic annulation and gold(I)-catalyzed cyclization reactions are an effective combination for the synthesis of complex molecules.[22] A diverse synthesis of other members of the fawcettimine-type *Lycopodium* alkaloids using the strategies highlighted herein is a current focus of our research and will be reported in due course.

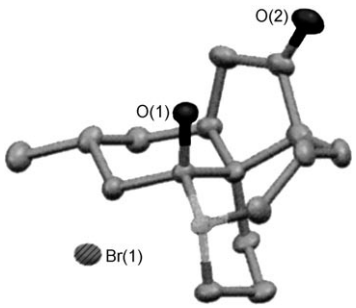


Figure 1. Structure of (+)-fawcettimine·HBr in the crystal.

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[18] We propose that the reactivity of **15c** might derive from intramolecular coordination of the alkene to palladium. This interaction results in occupation of the vacant site on the metal center, which is required for the β-hydride elimination that ulitmately leads to reduction of the vinyliodide.
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[22] For a review on organocatalysis in the synthesis of natural products, see: R. Marcia de Figueiredo, M. Christmann, *Eur. J. Org. Chem.* **2007**, 2575.

