Alkaloid Synthesis

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Total Synthesis of (+)-Fawcettidine**

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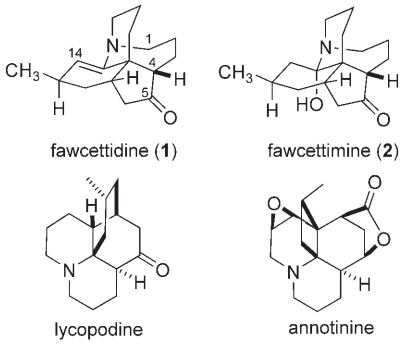
The structures of the *Lycopodium* family of alkaloids have inspired several examples of landmark total syntheses (Scheme 1).[1] Prominent examples include the constructions

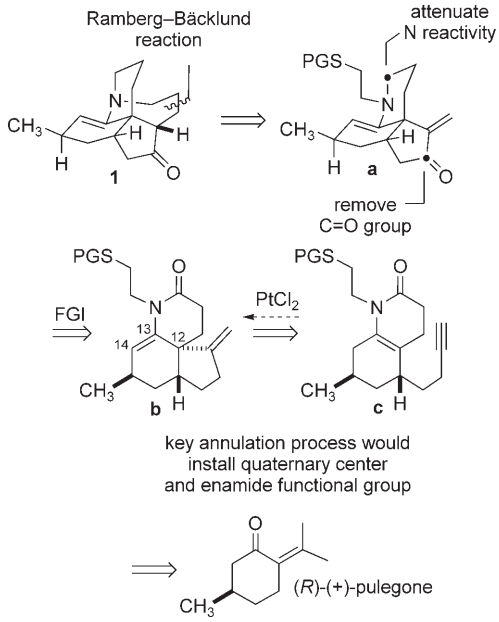


Scheme 1. *Lycopodium* alkaloids.

of lycopodine by the research groups of Stork,[2] Heathcock,[3] and Wenkert,[4] together with the investigation of annotinine by Wiesner and Poon,[5] as well as the synthesis of fawcettimine (**2**) by Inubushi and co-workers,[6] and by Heathcock et al.[7] A synthesis of (+)-**2** by using a gold(I)-catalyzed annulation was disclosed by the Toste research group last year.[8] Despite its near structural identity with **2**, a total synthesis of fawcettidine (**1**) has not yet been reported.

Fawcettidine (**1**) was isolated by Burnell et al. in the late 1950s from a Jamaican Lycopodium plant, *Lycopodium fawcetti*.[9] The structure of fawcettidine was established based on its semisynthesis from other members of the *Lycopodium* family.[10] In addition to their interesting tetracyclic structures, many *Lycopodium* alkaloids exhibit acetylcholine esterase (AChE) inhibition.[1b]

Our recent studies of platinum(II)-catalyzed annulations using enamides as nucleophiles indicated a direct approach towards the synthesis of **1**.[11] The retrosynthetic analysis of **1** is presented in Scheme 2. Previous syntheses of **2** essentially



Scheme 2. Retrosynthetic analysis of **1**. PG = protecting group, FGI = functional group interconversions.

left the formation of the C13–N bond until the last step.[6–8] Our strategy differs markedly from this path, where a critical disconnection leaves the formation of the seven-membered ring within **1** until a late stage of the synthetic sequence. A Ramberg–Bäcklund reaction emerged as a potential solution.[12] Functional group conversions of the hypothetical intermediate **a** generated tricycle **b**, that could undergo the key retro-annulation disconnection. We envisioned that alkyne **c** could be converted directly into **b** by using platinum(II) catalysis. If successful, this transformation would accomplish the formation of a critical tricyclic intermediate that would also install the quaternary center at C12 and the enamine functionality (C13–C14) within **1**. As noted, the exocyclic alkene that would be formed provides functionalization necessary to facilitate formation of the final ring of **1**. A major question at the outset was the identity of an effective thiol protecting group that would be compatible with the platinum(II)-catalyzed procedure. (*R*)-(+)-Pulegone was identified to be an appropriate chiral nonracemic starting material.

(*R*)-(+)-Pulegone was elaborated to give sulfoxide **3** in three steps as reported (Scheme 3).[13] Sulfoxide **3** was converted into δ keto ester **4** through a one-pot procedure. Sequential treatment of **3** with DBU followed by methyl acrylate at −40 °C then warming to 40 °C smoothly generated **4** in approximately 60 % yield on a multigram scale. The sulfinyl group proved very useful as it enabled high site selectivity (for enolate generation) and provided a means for

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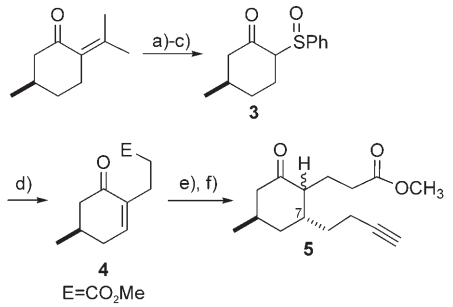
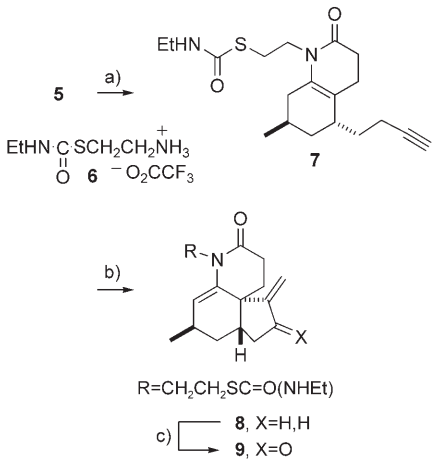


Scheme 3. Reagents and conditions: a) H_2O_2, LiOH (96%); b) NaH, HSPh; c) $NaBO_3 \cdot 4H_2O$, AcOH (88%, over 2 steps); d) 1. DBU, DMF, −40 °C; 2. methyl methacrylate; 3. warming to 40 °C (63%, over 3 steps); e) $BrMgCH_2CH_2CCSi(CH_3)_3$, CuBr·DMS, THF, −78 to −40 °C (83%); f) $(C_4H_9)_4NF$, THF (96%). Ac = acetyl, DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, DMF = *N*,*N*-dimethylformamide, DMS = dimethyl sulfide.

installation of the double bond. Formation of **4** by this procedure was more efficient than vinylogous Baylis–Hilman-type reactions. A cuprate addition followed by desilylation was used to produce **5** as an (ultimately inconsequential) mixture of epimers. Importantly, the conjugate addition was highly diastereoselective at C7 (fawcettidine numbering).[7,14]

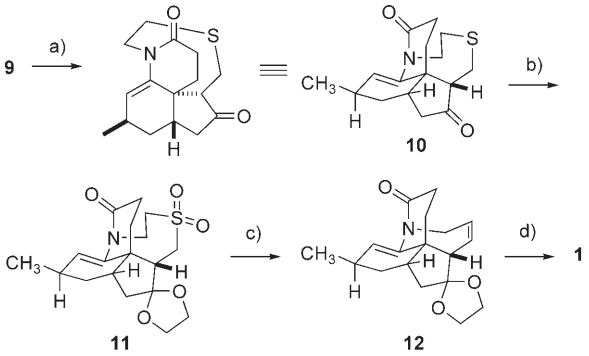
At this point the substrate required elaboration to install both the enamide functional group and the protected sulfide moiety prior to annulation. To this end, amine salt **6**[15] was condensed with the epimeric mixture **5** to produce enamide **7** in 70% yield as a 10:1 mixture of enamide isomers (Scheme 4). This mixture was carried forward without further separation as these isomers interconvert in the next reaction. Enamide **7** could be considered a potentially disastrous substrate for a reaction involving platinum catalysis, considering the affinity of sulfur atoms towards platinum. Even though the sulfur atom was protected as a thiocarbamate, this step was approached with some trepidation. These fears proved to be unfounded, however, as subjecting **7** to platinum(II) chloride (10 mol%) led to smooth annulation and formation of tricycle **8** in good yields, even on a gram



Scheme 4. Reagents and conditions: a) **6**, AcOH, toluene, 110 °C (70%); b) $PtCl_2$ (10 mol%), toluene, 90 °C (87%); c) SeO_2, 1,4-dioxane, 85 °C (54%).

scale. When lower catalyst loadings (5 mol%) were used these reactions were much slower, although the overall yields were similar. Somewhat surprisingly, the platinum-catalyzed procedure appeared to be unaffected by the thiocarbamate functionality, thus highlighting the robust nature of this reaction.[16] A chemoselective allylic oxidation was then required. Much experimentation established that essentially classical conditions (SeO_2, 1,4-dioxane, 85 °C) achieved this transformation in adequate yield.[17] Given our difficulties in achieving this conversion in high yield, effective methods for the allylic oxidation of complex organic structures are still required.

Treatment of **9** with 1M sodium hydroxide cleanly removed the carbamate group from the sulfur atom (Scheme 5). As expected, the thiolate thus generated sponta-



Scheme 5. Completion of the synthesis of **1**. Reagents and conditions: a) 1M NaOH (76%); b) 1. ethylene glycol, PPTS, benzene (87%); 2. *m*CPBA, CH_2Cl_2 (98%); c) CBr_2F_2, KOH·alumina, *t*BuOH, CH_2Cl_2 (46%); d) 1. H_2, Pd/C, EtOH/THF (57%); 2. $LiAlH_4$, THF (71%); 3. 1M HCl, THF (60%). *m*CPBA = *meta*-chloroperbenzoic acid, PPTS = pyridinium *para*-toluenesulfonate.

neously added to the enone functionality in a conjugate fashion to produce sulfide **10** in 76% yield. The protection of the carbonyl group of **10** followed by sulfide oxidation with *m*CPBA to give sulfone **11** proceeded uneventfully.

Our attempts to carry out the Ramberg–Bäcklund process by using two-step procedure failed. The "one-step" procedure disclosed by Chan et al. turned out to be successful.[18] Treatment of **11** with dibromodifluoromethane in a *tert*-butanol/dichloromethane solvent mixture and in the presence of potassium hydroxide adsorbed onto alumina enabled the isolation of alkene **12** in 46% yield. Interestingly, crystals of **12** were amenable to X-ray diffraction analysis, and a solid-state molecular structure was obtained (Figure 1).[19] The conversion of **12** into **1** was subsequently carried out by hydrogenation over palladium on carbon, reduction of the enamide to the enamine with lithium aluminum hydride, and conversion of the ketal into its corresponding ketone with aqueous hydrochloric acid.

As the original structural elucidation of **1** was defined by conversion from other members of the *Lycopodium* family, high-field NMR spectroscopic data are not available for comparison. We note that **1** has spectroscopic features in common with recently isolated hydroxylated derivatives of **1**.[20] Specifically, key spectroscopic data include the ^{1}H NMR

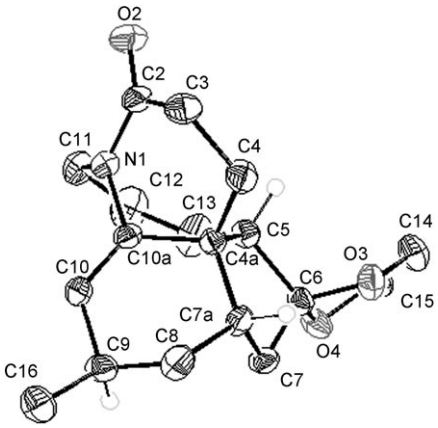


Figure 1. Solid-state molecular structure of compound **12** shown with ellipsoids at 50% probability.

signal attributable to the enamine vinyl proton of **1** ($\delta =$ 5.69 ppm, d, $J = 5.2$ Hz), and the corresponding IR stretches (1741, 1663 cm^{-1}), both sets of which are consistent with data from the original isolation report and with those of recently reported fawcettidine relatives. Unfortunately, the optical rotation data (in ethanol) for synthetic (+)-**1** is at odds with that reported in the original article.[9b,21] Our data (in chloroform) compares well with the reported optical rotation data for synthetic and natural (+)-**2**.[8]

The first total synthesis of (+)-fawcettidine (**1**) has been carried out in 16 steps by using (*R*)-(+)-pulegone as the chiral starting material. Key features of this synthesis include a platinum(II)-catalyzed annulation reaction of a highly functionalized enamide, and a one-pot Ramberg–Bäcklund reaction to form a seven-membered ring. The tolerance of platinum(II) chloride catalysis to the functional groups present in this study bodes well for the use of the annulation strategy in the synthesis of other complex natural products.

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[1] a) T. A. Blumenkopf, C. H. Heathcock, *Alkaloids: Chemical and Biological Perspectives*, *Vol. 3* (Ed.: S. W. Pelletier), Wiley, New York, **1985**, pp. 185–240; b) X. Ma, D. R. Gang, *Nat. Prod. Rep.* **2004**, *21*, 752–772.

[2] G. Stork, R. A. Kretchmer, R. H. Schlessinger, *J. Am. Chem. Soc.* **1968**, *90*, 1647–1648.

[3] C. H. Heathcock, E. Kleinman, E. S. Binkley, *J. Am. Chem. Soc.* **1978**, *100*, 8036–8037.

[4] E. Wenkert, C. A. Broka, *J. Chem. Soc. Chem. Commun.* **1984**, 714–715.

[5] K. Wiesner, L. Poon, *Tetrahedron Lett.* **1967**, *8*, 4937–4940.

[6] T. Harayama, M. Takatani, Y. Inubushi, *Tetrahedron Lett.* **1979**, *20*, 4307–4310.

[7] C. H. Heathcock, T. A. Blumenkopf, K. A. Smith, *J. Org. Chem.* **1989**, *54*, 1548–1562.

[8] X. Linghu, J. J. Kennedy-Smith, F. D. Toste, *Angew. Chem.* **2007**, *119*, 7815–7817; *Angew. Chem. Int. Ed.* **2007**, *46*, 7671–7673.

[9] a) R. H. Burnell, *J. Chem. Soc.* **1959**, 3091–3093; b) R. H. Burnell, C. G. Chin, B. S. Mootoo, D. R. Taylor, *Can. J. Chem.* **1963**, *41*, 3091–3094.

[10] a) H. Ishii, B. Yasui, R.-I. Nishino, T. Harayama, Y. Inubushi, *Chem. Pharm. Bull.* **1970**, *18*, 1880–1888; b) Y. Inubushi, T. Harayama, K. Yamaguchi, H. Ishii, *Chem. Pharm. Bull.* **1981**, *29*, 3418–3421; c) Y. Inubushi, H. Ishii, T. Harayama, R. H. Burnell, W. A. Ayer, B. Altenkirk, *Tetrahedron Lett.* **1967**, *8*, 1069–1072.

[11] T. J. Harrison, B. O. Patrick, G. R. Dake, *Org. Lett.* **2007**, *9*, 367–370.

[12] a) L. Ramberg, B. Bäcklund, *Ark. Kemi Mineral. Geol.* **1940**, *13A*, 1–50; b) R. J. K. Taylor, G. Casy, *Org. React.* **2003**, *62*, 357–475.

[13] Adapted from: a) D. Caine, K. Procter, R. A. Cassell, *J. Org. Chem.* **1984**, *49*, 2647–2648; b) S. Mutti, C. Daubié, F. Decalogne, R. Fournier, P. Rossi, *Tetrahedron Lett.* **1996**, *37*, 3125–3128.

[14] For a similar procedure, see: T. W. Bell, *J. Am. Chem. Soc.* **1981**, *103*, 1163–1171.

[15] T. Anada, R. Karinaga, M. Mizu, K. Koumoto, T. Matsumoto, M. Numata, S. Shinkai, K. Sakurai, *e-J. Surf. Sci. Nanotechnol.* **2005**, *3*, 195–202.

[16] a) A. Fürstner, P. W. Davies, *Angew. Chem.* **2007**, *119*, 3478–3519; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410–3449; b) L. Zhang, J. Sun, S. A. Kozmin, *Adv. Synth. Catal.* **2006**, *348*, 2271–2296; c) B. M. Trost, G. A. Doherty, *J. Am. Chem. Soc.* **2000**, *122*, 3801–3810; d) T. J. Harrison, G. R. Dake, *Org. Lett.* **2004**, *6*, 5023–5026.

[17] G. Vincent, R. M. Williams, *Angew. Chem.* **2007**, *119*, 1539–1542; *Angew. Chem. Int. Ed.* **2007**, *46*, 1517–1520.

[18] T.-L. Chan, S. Fong, Y. Li, T.-O. Man, C.-D. Poon, *J. Chem. Soc. Chem. Commun.* **1994**, 1771–1772.

[19] CCDC 676469 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[20] K. Katakawa, A. Nozoe, N. Kogure, M. Kitajima, M. Hosokawa, H. Takayama, *J. Nat. Prod.* **2007**, *70*, 1024–1028.

[21] Synthetic (+)-**1**: $[\alpha]_D^{19} = +61\ deg\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.41\ g\,cm^{-3}$, EtOH); $[\alpha]_D^{21} = +92\ deg\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.41\ g\,cm^{-3}$, $CHCl_3$); reported data for natural (+)-**1**: $[\alpha]_D = +161\ deg\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.6\ g\,cm^{-3}$, EtOH).

