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Enantioselective divergent total syntheses of fawcettimine-type *Lycopodium* alkaloids

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ABSTRACT

Enantioselective divergent total syntheses of (+)-fawcettimine, (+)-fawcettidine, (+)-lycoflexine, (+)-lycoposerramine Q, (−)-Huperzine Q and (+)-*N*-oxyhuperzine Q have been described from a common precursor. The syntheses feature a vinylogous Rubottom oxidation and several biomimetic transformations.

1. Introduction

The *Lycopodium* alkaloids are a group of natural products[1] with fascinating polycyclic structures and impressive biological activities.[2] The fawcettimine subclass, which usually possesses a *cis*-fused 6,5-carbocyclic framework with an all-carbon quaternary center and an azonane ring (Fig. 1), has attracted considerable attention from synthetic chemists in the past decade.[3]

Fawcettimine (**1**) was the first member of this type isolated from *Lycopodium fawcetti* by Burnell in 1959.[4] Subsequently, Burnell and co-workers also isolated fawcettidine (**2**) from *L. fawcetti* in 1963, which was proposed to be formed by dehydration of fawcettimine

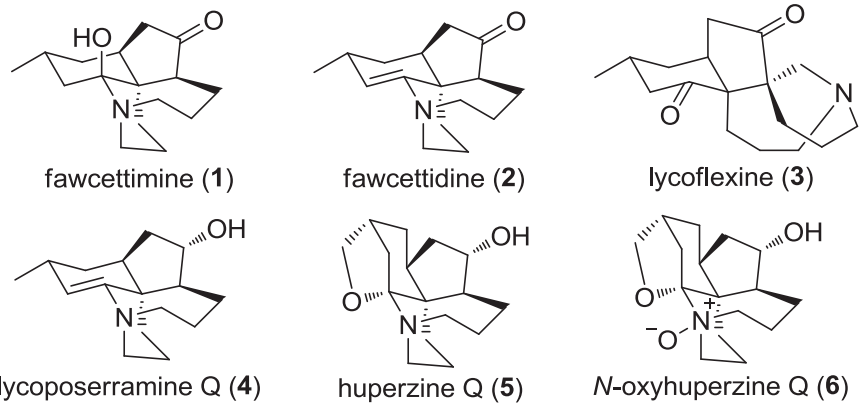

Fig. 1. Selected fawcettimine-type *Lycopodium* alkaloids.

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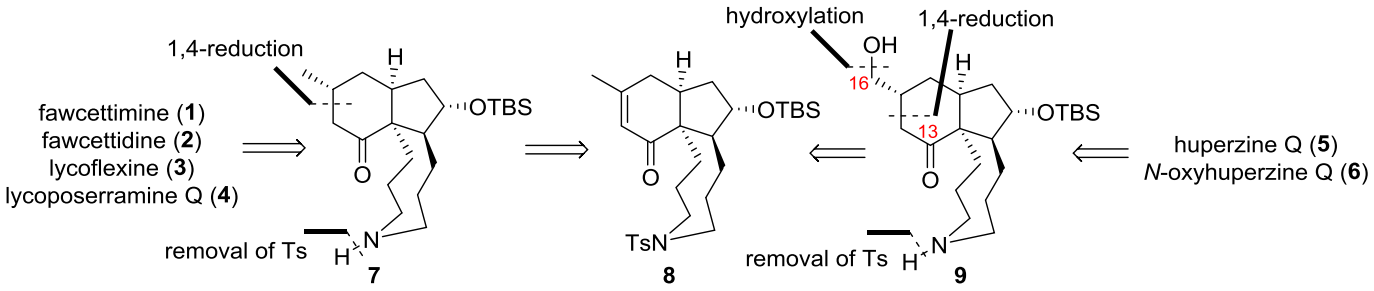
(**1**).[5] Lycoflexine (**3**) containing two adjacent all-carbon quaternary, was isolated from *Lycopodium clavatum var. inflexum.* in 1973 by Ayer and co-workers.[6] From a biosynthetic point of view, Lycoflexine (**3**) could be derived from fawcettimine (**1**) by an intramolecular Mannich reaction and this transformation was chemically achieved by Ayer and co-workers in their isolation paper. Lycoposerramine Q (**4**), isolated from the club moss *L. serratum* in 2002 by Takayama group, was supposed to be dihydrofawcettidine.[7] Huperzine Q (**5**) and *N*-oxyhuperzine Q (**6**), were isolated from *Huperzia serrata* by Zhu and co-workers in 2002.[8] From a structural perspective, **5** and **6** exhibit a unique pentacyclic ring system bearing a hemiaminal moiety and six stereogenic centers. Due to the relevance of molecular architectures, many elegant routes have been reported recently for the total syntheses of fawcettimine-type alkaloids, including **1**, **2**, **3**, and **4**.[3] Notably, the only total synthesis of huperzine Q (**5**) to date was accomplished by Takayama and co-workers in 2011[3f] and no total synthesis of *N*-oxyhuperzine Q (**6**) has been reported. Recently, we have completed the asymmetric total syntheses of (+)-fawcettidine (**2**) and (+)-lycoposerramine Q (**4**) in our previous studies.[9] The availability of this strategy for the syntheses of other fawcettimine-type alkaloids remains to be further explored. Herein, we describe the asymmetric syntheses of (+)-fawcettimine (**1**), (+)-lycoflexine (**3**), (−)-huperzine Q (**5**) and (+)-*N*-oxyhuperzine Q (**6**).

2. Results and discussion

2.1. Retrosynthetic analysis

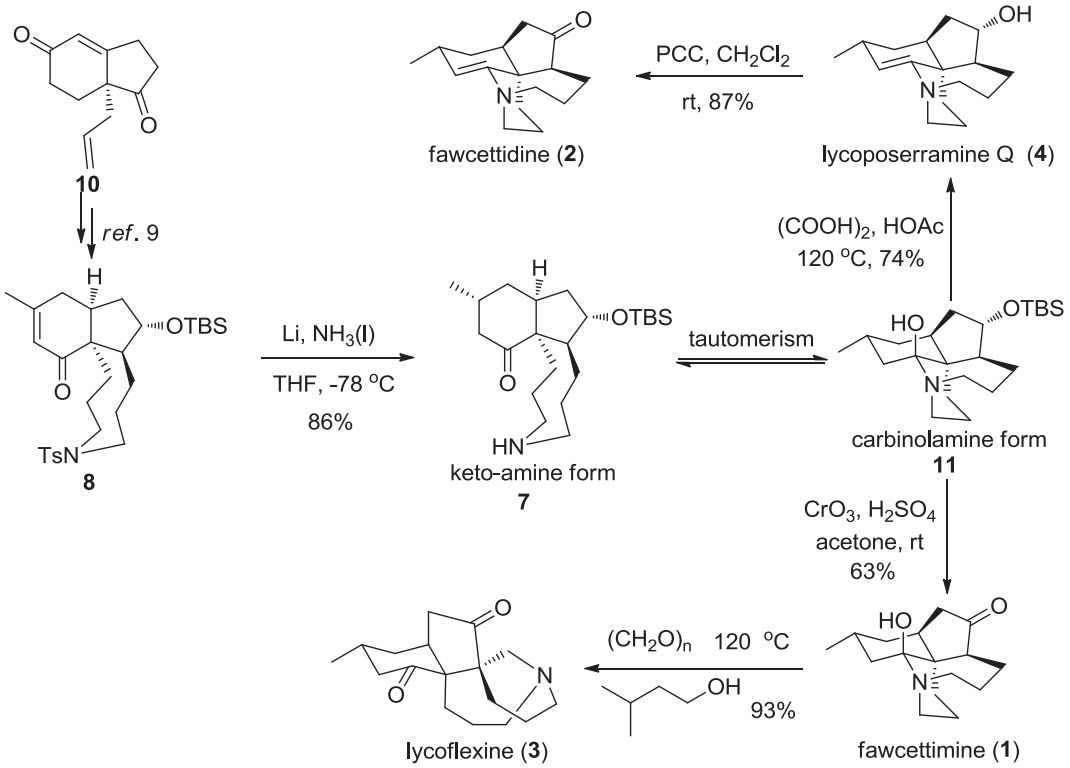
Based on our previous work, the retrosynthetic analysis is detailed in Scheme 1. We imagined that **1**, **2**, **3**, and **4** could be arised from precursor **7**, which in turn would be derived from intermediate **8** by a stereoselective 1,4-reduction and removal of the *N*-tosyl protecting group. The hemiaminal skeletons in **5** and **6** were expected to be constructed from compound **9** through intramolecular biomimetic hemiaminal formation,[3f] which possesses a free hydroxyl group at *C*-16, a secondary amine and a carbonyl group at *C*-13. We envisioned the free hydroxyl group in **9** could be constructed from the same intermediate **8** by hydroxylation of the allylic methyl group.



Scheme 1. Retrosynthetic analysis.

2.2. Syntheses of 1, 2, 3 and 4

As outlined in Scheme 2, our syntheses began with intermediate **8**, which was prepared from Hajos–Parrish-like diketone (*R*)-**10**.[9]



Scheme 2. Synthesis of **1**, **2**, **3**, and **4**.

Compound **8** was subjected to lithium in liquid ammonia to afford **7** by reductive cleavage of the *N*-tosyl amide and stereocontrolled Birch reduction of the conjugated double bond. The resulting α-oriented methyl group was the thermodynamic product, which occupied an equatorial position. The keto-amine **7** was in rapid equilibrium with its carbinolamine tautomer **11**, which could be proved by the absence of carbonyl peak and carbinolamine peak in the ^{13}C NMR spectrum.[10]

With **11** in hand, we were able to access **1**, **2**, **3**, and **4** in just two steps. Simultaneous dehydration and removal of *tert*-butyldimethylsilyl (TBS) protecting group by treatment of **11** with oxalic acid in AcOH at reflux provided lycoposerramine Q (**4**). Oxidation of **4** with PCC at room temperature proceeded cleanly to afford fawcettidine (**2**). Moreover, deprotection of TBS group of **11** with 3.0 M H_2SO_4 followed by oxidation of the resulting free hydroxyl with CrO_3 in one pot delivered fawcettimine (**1**) in 63% yield.[11] Upon treatment with paraformaldehyde in isoamyl alcohol at 120 °C for 20 minutes, the biomimetic conversion of **1** to lycoflexine (**3**) was achieved in 93% yield.[3e,6]

2.3. Syntheses of 5 and 6

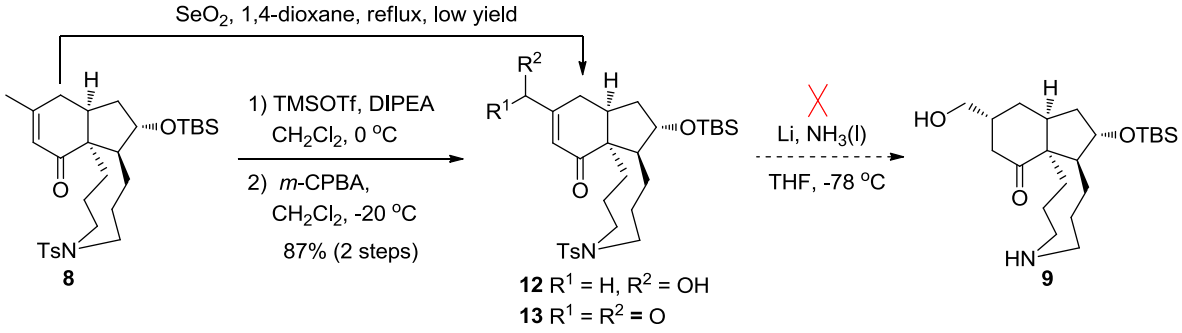
With an efficient route to **1**, **2**, **3**, and **4** secured, we set out to complete the syntheses of **5** and **6**. The first task we met is to convert the allylic methyl of **8** to a hydroxymethyl group and we explored a variety of approaches to form the desired product (Scheme 3). Direct allylic oxidation in the presence of Cr(VI)-based reagents such as CrO_3-3,5-dimethylpyrazole[12] resulted in no reaction. Treatment of **8** with SeO_2 (4 equiv) in 1,4-dioxane for 2 h at reflux produced only ca. 28–40% yield of the desired compound **12** with the corresponding aldehyde **13**, the formation of which might be ascribed to the further oxidation of **12** by SeO_2, and 12% starting material was recovered.[13] We were unable to obtain **12** in satisfactory yield despite evaluating numerous conditions, including alternative solvents, additives, temperatures, equivalent of SeO_2 due to the low reactivity of **8** and instability of **12** under the harsh conditions employed. To surmount this obstacle, we designed an alternative stepwise approach for this conversion, which was the regioselective formation of a dienol silyl ether and subsequent vinylogous Rubottom oxidation of this resulting intermediate.[14] Thus, enol silylation of the methyl group in **8** with TMSOTf in the presence of Hünig's base at 0 °C followed by oxidation with *m*-CPBA at −20 °C occurred smoothly to obtain the desired γ-hydroxylated product **12** in 87% yield for two steps.[15]

existence of compound **7**, the formation of which presumably was attributed to the cleavage of the allylic alcohol under the reductive conditions. Next, we investigated a few more selective protocols to reduce the double bond, by which the allylic hydroxyl group was intact. Finally, we observed that **12** was elaborated into **14** with complete stereoselectivity and chemoselectivity via $NiCl_2/NaBH_4$ reduction[16] in 92% yield (Scheme 4). The stereochemistry of **14** at *C*-15 position was quite opposite to what we had expected, which revealed that the reduction conducted under kinetical control. In order to invert the stereochemistry at *C*-15, **14** was oxidized to aldehyde **15** by treatment with Dess–Martin periodinane, which was isomerized at alpha position of aldehyde group to **16** in the presence of DBU. This conversion could be also achieved in a one pot operation in 83% yield. With all of the requisite stereochemical information established, efforts were made to selectively reduce the aldehyde group in the presence of ketone group. Initial attempts to reduce **16** via $NaBH_4$ in MeOH or EtOH were plagued by the formation of lots of over-reduced diol byproducts. To avoid the side reaction, THF was used as solvent to dissolve the starting material and lower the reactivity of $NaBH_4$, and primary alcohol **17** could be obtained in 89% yield. Removal of the *p*-toluenesulfonyl group from nitrogen by the use of sodium naphthalenide as reducing agent furnished **9**. At the end, we turned our attention to the formation of the hemiaminal moiety. To our delight, this key biomimetic transformation[3f] was achieved by treatment of compound **9** with (+)-camphorsulfonic acid in toluene at 120 °C followed by removal of the TBS group in the presence of 2.0 M HCl in one pot at room temperature to give huperzine Q (**5**). Oxidation of **5** with *m*-CPBA at −10 °C proceeded smoothly to lead to *N*-oxyhuperzine Q (**6**) in 83% yield.

The spectral data of our synthetic (+)-fawcettimine (**1**), (+)-fawcettidine (**2**) (+)-lycoflexine (**3**), (+)-lycoposerramine Q (**4**), (−)-huperzine Q (**5**) and (+)-*N*-oxyhuperzine Q (**6**) were identical to those reported, including ^1H NMR, ^{13}C NMR data, mass spectra and optical rotation.[3b-l]

3. Conclusion

In summary, we have accomplished the syntheses of (+)-fawcettimine (**1**), (+)-fawcettidine (**2**), (+)-lycoflexine (**3**), (+)-lycoposerramine Q (**4**), (−)-huperzine Q (**5**) and (+)-*N*-oxyhuperzine Q (**6**) from known compound **8** by a divergent path. Highlights of the syntheses include a vinylogous Rubottom oxidation to install a hydroxyl group and several biomimetic transformations.



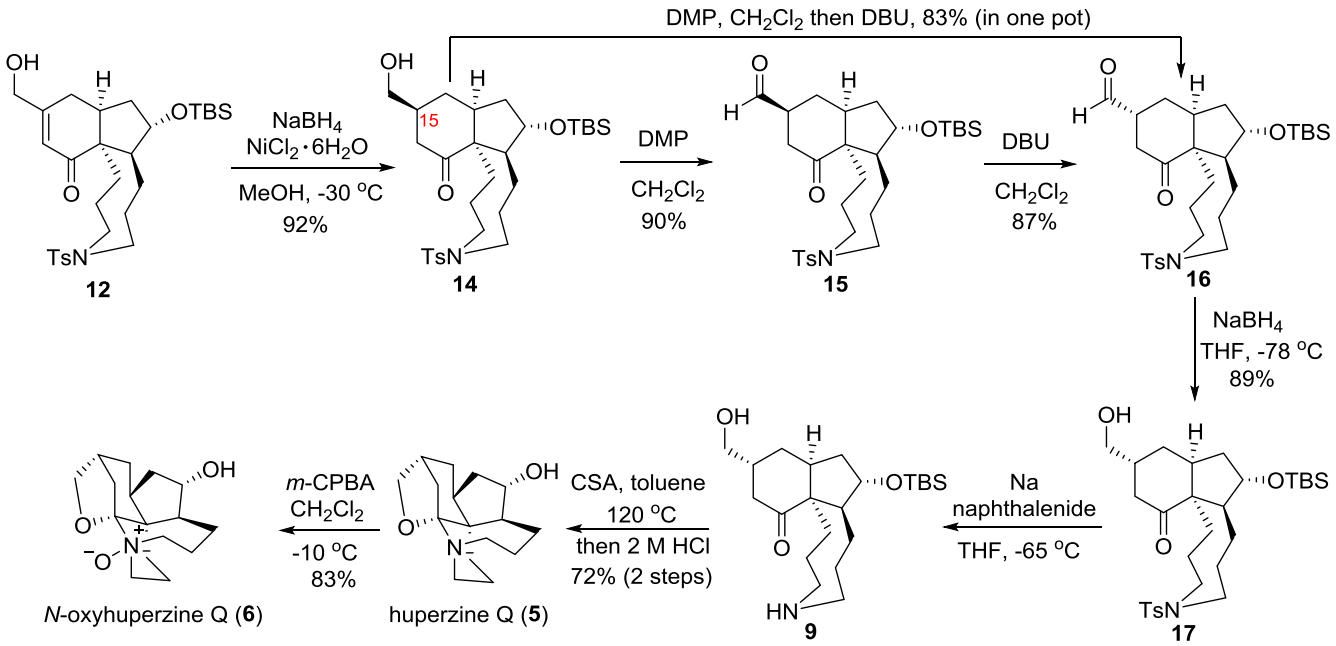
Scheme 3. Synthesis of intermediate **12**.

Having forged the key hydroxyl group into **12**, the last challenge was to remove the *N*-tosyl group and reduce the conjugated double bond as we have encountered above. Unfortunately, no desired product **9** could be detected in the reaction mixture upon exposure of **12** to lithium in liquid ammonia, although **12** disappeared completely. The ESI-MS of the crude mixture indicated the

4. Experimental section

4.1. General

^1H and ^{13}C NMR spectra were recorded on a Bruker AMX-400 spectrometer at ambient temperature with $CDCl_3$ as the solvent



Scheme 4. Synthesis of **5** and **6**.

and TMS as the internal standard unless otherwise stated. Chemical shifts are reported in parts per million relative to chloroform (^{1}H, δ 7.26; ^{13}C, δ 77.16). Data for ^{1}H NMR are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad), coupling constants and integration. IR spectra were collected on Avatar 330 FT-IR spectrometer. Optical rotations were determined on JASCO P-1030 Polarimeter in the solvent indicated. High-resolution mass spectra were recorded on IonSpec 4.7 Tesla FTMS or Bruker Daltonics, Inc. APEXIII 7.0 TESLA FTMS. All reactions were carried out in oven-dried glassware under an argon atmosphere unless otherwise noted. THF was purified by sodium/benzophenone. CH_2Cl_2 was distilled from calcium hydride before use. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates visualized with UV light or by staining with ethanolic phosphomolybdic acid (PMA). Flash column chromatography was performed on silica gel (300–400 mesh).

4.2. (7a*S*,8*S*,9a*S*,11*R*,13a*S*)-8-((*tert*-Butyldimethylsilyl)oxy)-11-methyldodecahydro-1*H*-indeno[1,7a–e]azonin-13(2*H*)-one (7)

Small pieces of lithium (90 mg, 13.0 mmol) were added to condensed ammonia (40 mL) at −78 °C and the deep blue mixture was stirred for 20 min. A solution of **8** (0.69 g, 1.3 mmol) in THF (10 mL) was added and stirred for 30 min at −78 °C before solid NH_4Cl was slowly added to quench the reaction. It was warmed up to room temperature and diluted with saturated Na_2CO_3. The mixture was extracted with $CHCl_3$, dried over $MgSO_4$ and concentrated. The resulting residue was purified by flash chromatography ($CHCl_3$–MeOH=40:1) to give **7** (0.42 g, 86%) as a yellow oil.

R_f=0.65 ($CHCl_3$–MeOH=10:1); $[\alpha]_D^{25}$ 12.3 (*c* 0.25, $CHCl_3$); IR (film): 3315, 2952, 2927, 2856, 1461, 1254, 1047 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96–3.85 (m, 1H), 3.55–3.40 (m, 1H), 3.14 (t, *J*=12.0 Hz, 1H), 2.85 (dd, *J*=4.0, 14.0 Hz, 1H), 2.75–2.64 (m, 1H), 2.25–2.14 (m, 1H), 2.13–1.90 (m, 6H), 1.89–1.70 (m, 4H), 1.57–1.34 (m, 4H), 1.32–1.15 (m, 3H), 0.87 (d, *J*=6.4 Hz, 3H), 0.85 (s, 9H), 0.00 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 81.0, 61.6, 52.9, 50.0, 49.3, 47.1, 44.7, 40.2, 36.9, 32.9, 31.6, 29.8, 26.0, 25.0, 23.1, 22.3, 18.1, -4.4; HRMS (ESI): Calcd for $C_{22}H_{42}NO_2Si^+$ $[M+H]^+$ 380.2979, found 380.2982.

4.3. (+)-Lycoposerramine Q (4)

To a solution of **7** (29 mg, 0.076 mmol) in HOAc (1 mL) was added $(COOH)_2$ (45 mg, 0.5 mmol). The reaction mixture was stirred at 120 °C for 25 h. After cooling, the mixture was concentrated in vacuo. To a solution of the residue in CH_2Cl_2 (2 mL) was added K_2CO_3 (138 mg, 1 mmol) and the mixture was stirred at room temperature for 0.5 h. Then the suspension was filtered off and the filtrate was concentrated under reduced pressure. Purification of the residue by flash chromatography ($CHCl_3$–MeOH=30:1) to provide **4** (14 mg, 74%) as a colorless powder.

R_f=0.31 ($CHCl_3$–MeOH=12:1); $[\alpha]_D^{25}$ 85.7 (*c* 0.55, $CHCl_3$); IR (film): 3366, 2923, 2851, 1655, 1455 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56 (d, *J*=3.6 Hz, 1H), 3.96 (q, *J*=4.8 Hz, 1H), 3.13–3.04 (m, 1H), 3.02–2.91 (m, 3H), 2.27–2.19 (m, 1H), 2.16–2.08 (m, 1H), 1.96–1.88 (m, 2H), 1.87–1.79 (m, 3H), 1.77–1.67 (m, 3H), 1.58 (dd, *J*=4.0, 12.4 Hz, 1H); 1.54–1.47 (m, 2H), 1.34 (q, *J*=12.8 Hz, 1H), 1.28–1.24 (m, 1H), 0.98 (d, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 127.7, 80.1, 60.0, 57.9, 52.4, 47.2, 43.2, 40.9, 38.4, 33.2, 33.1, 31.5, 27.0, 24.2, 21.3; HRMS (ESI): Calcd for $C_{16}H_{24}NO^+$ $[M+H]^+$ 248.1862, found 248.1846.

4.4. (+)-Fawcettidine (2)

Compound **4** (10.1 mg, 0.04 mmol) was dissolved in CH_2Cl_2 (2 mL) at room temperature, followed by the addition of PCC (22 mg, 0.1 mmol) and Celite. After stirring at room temperature for 2 h, the suspension was filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by flash chromatography ($CHCl_3$–MeOH=40:1) to give **2** (8.5 mg, 87%) as a colorless powder.

R_f=0.46 ($CHCl_3$–MeOH=12:1); $[\alpha]_D^{25}$ 65.7 (*c* 0.80, EtOH); IR (film): 2924, 2851, 1736, 1449 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68 (d, *J*=5.2 Hz, 1H), 3.16–3.08 (m, 1H), 3.07–2.94 (m, 3H), 2.72 (dd, *J*=7.2, 16.8 Hz, 1H), 2.34–2.22 (m, 2H), 2.18–2.02 (m, 3H), 1.98–1.82 (m, 2H), 1.75–1.55 (m, 3H), 1.40–1.31 (m, 2H), 1.29–1.18 (m, 2H), 1.04 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.9, 146.1, 127.4, 60.5, 56.4, 52.1, 46.3, 44.2, 39.3, 37.4, 34.3, 31.5, 29.3, 27.8, 23.9, 20.9; HRMS (ESI): Calcd for $C_{16}H_{24}NO^+$ $[M+H]^+$ 246.1852, found 246.1854.

4.5. (+)-Fawcettimine (1)

To a solution of **7** (38 mg, 0.1 mmol) in acetone (1 mL) was added H_2SO_4 (0.1 mL, 3.0 M, 0.3 mmol) at room temperature. This solution was stirred for 1 h before a solution of CrO_3 (20 mg, 0.2 mmol) in H_2SO_4 (0.4 mL, 3.0 M, 1.2 mmol) was added to the reaction mixture. After stirring the reaction at room temperature for 6 h, saturated $NaHCO_3$ was added and the mixture was extracted with $CHCl_3$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash chromatography ($CHCl_3$–MeOH=30:1) to give **1** (16 mg, 63%) as a yellow foam.

R_f=0.58 ($CHCl_3$–MeOH=10:1); $[\alpha]_D^{25}$ 89.0 (*c* 0.40, MeOH); IR (film): 3315, 2922, 2864, 1732, 1456, 1144 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.50–3.34 (m, 1H), 3.22 (td, *J*=4.0, 14.4 Hz, 1H), 2.88 (dd, *J*=5.2, 14.4 Hz, 1H), 2.72 (dt, *J*=4.8, 14.4 Hz, 1H), 2.62 (dd, *J*=13.6, 17.6 Hz, 1H), 2.28–2.00 (m, 8H), 1.94–1.82 (m, 4H), 1.62 (d, *J*=14.0 Hz, 1H), 1.49–1.36 (m, 3H), 1.18–1.12 (m, 1H), 0.94 (d, *J*=6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.3, 60.2, 53.4, 50.1, 48.3, 44.7, 43.3, 42.0, 36.0, 31.9, 28.9, 28.3, 23.7, 22.7, 21.8; HRMS (ESI): Calcd for $C_{16}H_{26}NO_2^+$ $[M+H]^+$ 264.1958, found 264.1953.

4.6. (+)-Lycoflexine (3)

To a solution of **1** (16 mg, 0.063 mmol) in isoamyl alcohol (1 mL) was added paraformaldehyde (18 mg, 0.60 mmol). The mixture was stirred for 20 min at 120 °C, cooled to room temperature, filtered, and concentrated. The crude product was purified with flash column chromatography ($CHCl_3$–MeOH=20:1) to provide **3** (16 mg, 93%) as a white solid.

R_f=0.52 ($CHCl_3$–MeOH=10:1); $[\alpha]_D^{25}$ 9.5 (*c* 0.40, CH_2Cl_2); IR (film): 2924, 2853, 1726, 1698, 1457, 1174 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.22–3.06 (m, 2H), 3.01–2.91 (m, 1H), 2.89–2.76 (m, 2H), 2.70–2.58 (m, 2H), 2.35 (dd, *J*=8.8, 10.0 Hz, 1H), 2.30–2.03 (m, 7H), 2.00–1.70 (m, 5H), 1.62–1.53 (m, 1H),1.36–1.29 (m, 1H), 1.02 (d, *J*=6.0 Hz, 3H), 0.03 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.2, 213.8, 60.6, 58.3, 56.6, 53.5, 53.3, 46.7, 40.3, 40.0, 36.1, 31.2, 29.2, 28.0, 25.9, 22.3, 19.3; HRMS (ESI): Calcd for $C_{17}H_{26}NO_2^+$ $[M+H]^+$ 276.1958, found 276.1955.

4.7. (7a*S*,8*S*,9a*S*,13a*S*)-8-((*tert*-Butyldimethylsilyl)oxy)-11-(hydroxymethyl)-4-tosyl-3,4,5,6,7,7a,8,9,9a,10-decahydro-1*H*-indeno[1,7*a*–*e*]azonin-13(2*H*)-one (12)

To a solution of **8** (850 mg, 1.6 mmol) in CH_2Cl_2 (10 mL) were added DIPEA (0.42 mL, 2.4 mmol) and TMSOTf (0.36 mL, 2.0 mmol) at 0 °C. The mixture was stirred for 15 h at 0 °C before the mixture was diluted with water and extracted with EtOAc. The combined organic phase were dried over Na_2SO_4 and concentrated in vacuo. The resulting oil was used for the next step without further purification.

To a solution of crude silyl enol ether in CH_2Cl_2 (15 mL) were added $NaHCO_3$ (403 mg, 4.8 mmol) and *m*-CPBA (75%, 550 mg, 2.4 mmol) at −20 °C. The mixture was stirred for 1 h at same temperature before it was quenched with saturated $Na_2S_2O_3$. The aqueous layer was extracted with EtOAc, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (hexanes–EtOAc=3:2) to afford **12** (761 mg, 87% for two steps) as a white solid.

R_f=0.50 (PE:EA=1:1); $[\alpha]_D^{25}$ 8.9 (*c* 0.50, $CHCl_3$); IR (film): 3497, 3054, 2926, 2856, 1652, 1339, 1159 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J*=8.0 Hz, 2H), 7.28 (d, *J*=8.0 Hz, 2H), 6.02 (s, 1H), 4.18 (s, 2H), 3.58–3.51 (m, 1H), 3.45 (t, *J*=11.2 Hz, 1H), 3.28 (d, *J*=14.4 Hz, 1H), 2.80–2.61 (m, 2H), 2.55–2.47 (m, 1H), 2.45–2.19 (m, 7H), 2.17–2.07 (m, 1H), 2.01 (d, *J*=18.4 Hz, 1H), 1.87–1.60 (m, 8H), 0.87 (s, 9H), 0.00 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.2, 159.5, 143.2, 135.2, 129.6, 127.5, 123.5, 77.9, 65.0, 54.2, 53.6, 51.2, 50.4, 38.4, 37.8, 30.1, 27.5, 27.2, 26.5, 25.9, 22.6, 21.5, 18.0, −4.2, −4.7; HRMS (MALDI): Calcd for $C_{29}H_{45}NO_5SSiNa^+$ $[M+Na]^+$ 570.2679, found 570.2676.

4.8. (7a*S*,8*S*,9a*S*,11*S*,13a*S*)-8-((*tert*-Butyldimethylsilyl)oxy)-11-(hydroxymethyl)-4-tosyldodecahydro-1*H*-indeno[1,7*a*–*e*]azonin-13(2*H*)-one (14)

To a solution of **12** (656 mg, 1.2 mmol) in CH_3OH (20 mL) were sequentially added $NiCl_2 \cdot 6H_2O$ (475 mg, 2.0 mol) and $NaBH_4$ (75 mg, 2.0 mol) at −30 °C. The mixture was stirred for 1 h at −30 °C before the mixture was diluted with water and extracted with EtOAc. The combined organic phase were dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (hexanes–EtOAc=1:1) to afford **14** (606 mg, 92%) as a white foam.

R_f=0.46 (PE:EA=1:1); $[\alpha]_D^{25}$ 15.8 (*c* 0.50, $CHCl_3$); IR (film): 3527, 2927, 2856, 1701, 1592, 1463, 1339, 1159 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J*=8.0 Hz, 2H), 7.29 (d, *J*=8.0 Hz, 2H), 3.75 (q, *J*=8.4 Hz, 1H), 3.49 (d, *J*=6.4 Hz, 2H), 3.47–3.39 (m, 1H), 3.36–3.23 (m, 1H), 2.76–2.56 (m, 3H), 2.41 (s, 3H), 2.41–2.34 (m, 1H), 2.32–2.08 (m, 3H), 2.06–1.60 (m, 11H), 1.57–1.48 (m, 1H), 1.08–0.98 (m, 1H), 0.88 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.7, 143.3, 135.4, 129.7, 127.6, 77.3, 67.3, 57.8, 54.7, 51.7, 51.4, 43.3, 41.9, 40.6, 37.0, 34.5, 31.8, 29.9, 26.6, 26.0, 22.5, 21.6, 18.1, -4.1, -4.6; HRMS (MALDI): Calcd for $C_{29}H_{47}NO_5SSiNa^+$ $[M+Na]^+$ 572.2836, found 572.2841.

4.9. (7a*S*,8*S*,9a*S*,11*R*,13a*S*)-8-((*tert*-Butyldimethylsilyl)oxy)-13-oxo-4-tosyltetradecahydro-1*H*-indeno[1,7*a*–*e*]azonine-11-carbaldehyde (16)

To a solution of **14** (439 mg, 0.8 mmol) in CH_2Cl_2 (10 mL) at room temperature was added DMP (382 mg, 0.9 mmol). After 2 h of stirring at room temperature, to the mixture were added CH_3OH (1 mL) and DBU (0.3 mL, 2 mmol). The reaction was stirred at room temperature for 14 h before it was quenched with saturated $Na_2S_2O_3$. The aqueous layer was extracted with Et_2O, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (hexanes–EtOAc=3:1) to give **16** (363 mg, 83%) as a yellow oil.

R_f=0.56 (PE:EA=3:2); $[\alpha]_D^{25}$ 39.3 (*c* 0.60, $CHCl_3$); IR (film): 2927, 2850, 2718, 1724, 1704, 1592, 1470, 1339, 1256, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.64 (s, 1H), 7.65 (d, *J*=10.8 Hz, 2H), 7.28 (d, *J*=10.8 Hz, 2H), 3.93–3.80 (m, 1H), 3.30–3.15 (m, 1H), 3.10–2.97 (m, 1H), 2.94–2.80 (m, 2H), 2.79–2.69 (m, 1H), 2.65–2.50 (m, 2H), 2.40 (s, 3H), 2.36–2.22 (m, 2H), 2.02–1.58 (m, 12H), 0.87 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.2, 201.1, 143.3, 134.7, 129.6, 127.4, 77.9, 59.2, 53.8, 50.9, 48.9, 47.1, 43.3, 38.4, 36.3, 29.7, 29.0, 25.9, 23.7, 21.5, 20.6, 18.0, −4.3, −4.7; HRMS (MALDI): Calcd for $C_{29}H_{45}NO_5SSiNa^+$ $[M+Na]^+$ 570.2680, found 570.2698.

4.10. (7a*S*,8*S*,9a*S*,11*R*,13a*S*)-8-((*tert*-Butyldimethylsilyl)oxy)-11-(hydroxymethyl)-4-tosyldodecahydro-1*H*-indeno[1,7*a*–*e*]azonin-13(2*H*)-one (17)

To a solution of **16** (344 mg, 0.63 mmol) in THF (10 mL) was added $NaBH_4$ (25 mg, 0.66 mol) at −78 °C. The mixture was stirred for 2 h at −78 °C before the mixture was diluted with water and extracted with EtOAc. The combined organic phase were dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (hexanes–EtOAc=1:1) to afford **17** (308 mg, 89%) as a white foam.

R_f=0.46 (PE:EA=1:1); $[\alpha]_D^{25}$ 27.0 (*c* 0.55, $CHCl_3$); IR (film): 3491, 2927, 2856, 1701, 1592, 14,693, 13,409, 1159 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J*=8.0 Hz, 2H), 7.28 (d, *J*=8.0 Hz, 2H),

3.93–3.82 (m, 1H), 3.54 (d, J=4.4 Hz, 2H), 3.26–3.10 (m, 1H), 3.05–2.85 (m, 2H), 2.82–2.70 (m, 1H), 2.50–2.42 (m, 1H), 2.40 (s, 3H), 2.38–2.24 (m, 2H), 2.17–2.06 (m, 2H), 2.02–1.92 (m, 3H), 1.90–1.81 (m, 2H), 1.76–1.50 (m, 8H), 0.86 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.37, 143.3, 135.0, 129.7, 127.6, 78.3, 67.2, 59.1, 54.0, 51.1, 49.1, 43.8, 42.5, 37.8, 36.9, 29.9, 29.3, 26.8, 26.0, 21.5, 20.8, 18.1, −4.2, −4.6; HRMS (MALDI): Calcd for $C_{29}H_{47}NO_5SSiNa^+$ $[M+Na]^+$ 572.2836, found 572.2828.

4.11. (−)-Huperzine Q (5)

A solution of sodium naphthalenide was prepared by adding sodium (18 mg, 0.8 mmol) to a solution of naphthalene (128 mg, 1 mmol) in THF (5 mL) and stirring the resulting mixture at room temperature for 1 h. To a stirred solution of **17** (88 mg, 0.16 mmol) in THF (2 mL) was added dropwise the sodium naphthalene solution at −65 °C until a light green color persisted. The reaction was quenched by addition of saturated $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was used for the next step without further purification.

The aforementioned oil was dissolved in dry toluene (2 mL) and (+)-camphorsulfonic acid (37 mg, 0.16 mmol) was added at room temperature. The reaction mixture was heated to reflux and stirred for 4 h. After cooling to room temperature, HCl (1 mL, 2.0 M, 2 mmol) was added to the solution. The mixture was stirred at room temperature for 2 h before it was diluted with saturated Na_2CO_3 and extracted with $CHCl_3$. The combined extracts was dried with $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash chromatography ($CHCl_3$–MeOH=20:1) to provide huperzine Q (30 mg, 72% for two steps) as a colorless solid.

R_f=0.42 ($CHCl_3$–MeOH=6:1); $[\alpha]_D^{25}$ −24.5 (c 0.60, MeOH); IR (film): 3375, 2929, 2860, 1452, 1079, 1059 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.05–3.84 (m, 2H), 3.73 (d, J=7.6 Hz, 1H), 3.43 (td, J=4.0, 14.0 Hz, 1H), 3.17–3.05 (m, 1H), 3.04–2.94 (m, 1H), 2.71 (dd, J=4.8, 14.0 Hz, 1H), 2.51–2.40 (m, 1H), 2.23–2.10 (m, 2H), 2.05 (d, J=11.2 Hz, 1H), 1.93–1.73 (m, 7H), 1.72–1.56 (m, 4H), 1.52–1.39 (m, 2H), 1.28–1.20 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 96.5, 79.8, 70.7, 54.0, 52.2, 47.9, 40.8, 40.4, 38.3, 37.8, 37.6, 36.6, 31.4, 29.7, 22.7; HRMS (ESI): Calcd for $C_{16}H_{26}NO_2^+$ $[M+H]^+$ 264.1958, found 264.1952.

4.12. (+)-*N*-Oxyhuperzine Q (6)

To a solution of **5** (9 mg, 0.032 mmol) in DCM (1 mL) was added *m*-CPBA (75%, 8 mg, 0.035 mmol) at 0 °C. The reaction mixture was stirred for 30 min and then directly subjected to flash chromatography ($CHCl_3$–MeOH=15:1) to give huperzine *N*-oxide (8 mg, 83%) as a white solid.

R_f=0.35 ($CHCl_3$–MeOH=6:1); $[\alpha]_D^{25}$ 2.56 (c 0.85, $CHCl_3$); IR (film): 3357, 2933, 2862, 1724, 1655, 1460, 1089, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16–4.06 (m, 1H), 4.03–3.90 (m, 1H), 3.82 (d, J=6.8 Hz, 1H), 3.77–3.66 (m, 1H), 3.59 (d, J=14.8 Hz, 1H), 3.46–3.37 (m, 1H), 3.30 (t, J=14.4 Hz, 1H), 2.90–2.75 (m, 1H), 2.51 (s, 1H), 2.33–2.23 (m, 1H), 2.20–1.94 (m, 4H), 1.87–1.71 (m, 3H), 1.69–1.50 (m, 5H), 1.40 (d, J=11.2 Hz, 1H), 1.33–1.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 106.7, 78.4, 73.3, 72.2, 66.1, 53.6, 53.1, 43.3, 37.7, 37.1, 36.6, 35.2, 33.3, 28.2, 26.1, 21.0; HRMS (ESI): Calcd for $C_{16}H_{26}NO_3^+$ $[M+H]^+$ 280.1907, found 280.1904.

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Supplementary data

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.tet.2014.11.041.

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