Alkaloids

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Total Syntheses of (−)-Huperzine Q and (+)-Lycopladines B and C**

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Abstract: *Utilizing a late-stage enamine bromofunctionalization strategy, the twelve-step total synthesis of (−)-huperzine Q was accomplished. Furthermore, the first total syntheses of (+)-lycopladines B and C are described. An unprecedented X-ray crystal structure of an unusual epoxyamine intermediate is also reported, and the synthetic application of this intermediate in natural product synthesis is demonstrated.*

The *Lycopodium* alkaloids are a large family of structurally unique natural products with nearly 300 compounds isolated to date.[1] Owing to their fascinating polycyclic architectures and diverse biological activities, these alkaloids have continued to serve as targets as well as inspirations to the synthetic community for decades.[2] Among them, the pentacyclic alkaloid (−)-huperzine Q (**1**), which was isolated in 2002 by Zhu and co-workers,[3] possesses a unique aminal moiety and six stereogenic centers (Figure 1). Its structure was initially determined by spectroscopic and single-crystal X-ray diffraction analysis. In 2011, Takayama and co-workers confirmed its absolute configuration through their 19-step first total synthesis.[4] On the other hand, (+)-lycopladines B (**2**) and C (**3**), which were isolated by Kobayashi and co-workers in 2006,[5] consist of a unique tetracyclic skeleton with a dienamine moiety. Their structures were elucidated based on spectral data and through a modified Mosher's method. However, no synthetic efforts towards these alkaloids have been reported thus far.

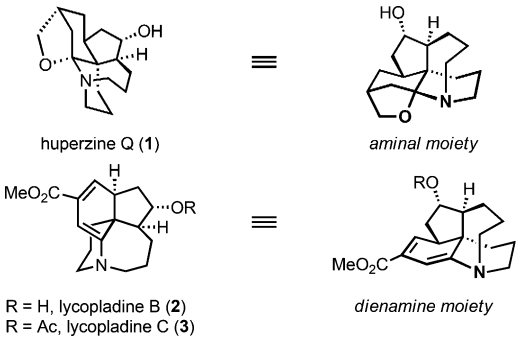

Figure 1. Huperzine Q (**1**) and lycopladines B (**2**) and C (**3**).

The halofunctionalization of alkenes, which proceeds mechanistically through the electrophilic addition to olefins via a halonium ion intermediate, has become one of the most classic and widely used organic transformations since its discovery (Scheme 1a).[6,7] Although various functionalized alkenes have been explored extensively for this transformation, enamines still present a formidable challenge with rare literature precedence presumably owing to their instability during or after the reaction. Based on our retrosynthetic analysis of (−)-huperzine Q (**1**) and (+)-lycopladines B (**2**) and C (**3**; Scheme 1b), we hypothesized that both the aminal moiety in **1** and the dienamine moiety in **2** and **3** could potentially be formed by a late-stage bromofunctionalization of an enamine (**1** from enamine **4**; **2** and **3** from enamine **5**). Both **4** and **5** could be derived from **6** through a C4-epimerization/cyclization sequence. A regioselective carbonyl–olefin metathesis was also conceived to forge the cyclopentanone ring in **6** from diketone **7**. Finally, starting from the known enantiopure enone **8**,[8] the key intermediate **7** would be rapidly assembled using our previously established Michael addition/aldol addition/C-alkylation method.[1g]

Our synthesis commenced with readily available (*R*)-**8** (Scheme 2).[9] Applying our established three-step method,[2q] the in situ generated allylic cuprate first reacted with **8**, followed by enolate trapping with iodoaldehyde **9**,[10] which smoothly afforded the secondary alcohol **10** as a mixture of two diastereoisomers in 73% yield. Oxidation of **10** with Dess–Martin periodinane followed by subsequent intramolecular C alkylation using DBU as the base in DMF afforded the desired diketone **7** with the correct stereochemistry.

With **7** in hand, a direct metathesis between the alkene and carbonyl moieties (carbonyl–olefin metathesis) was explored to furnish the desired cyclopentene ring.[11,12] After extensive reaction optimization, we were pleased to find that in the presence of ethylene gas (1 atm), **13** could be obtained in moderate yield (48% yield of isolated product, 75% based

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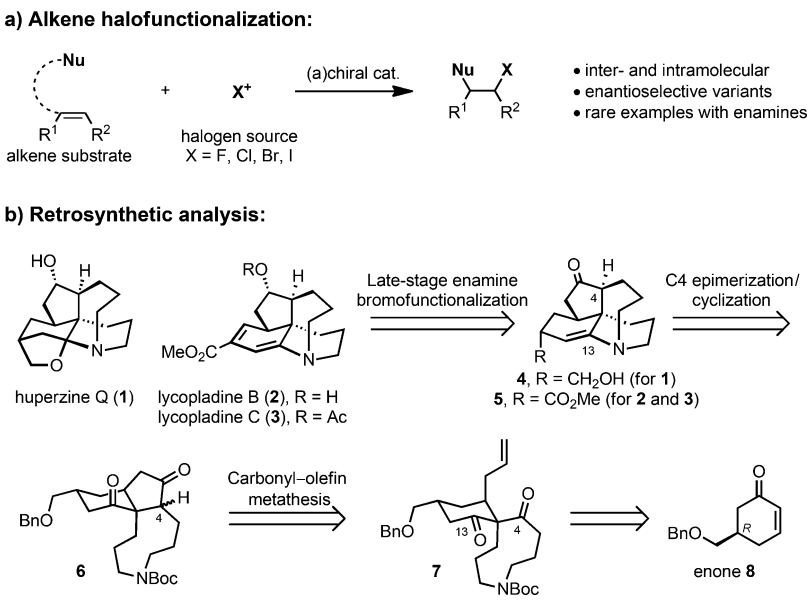


Scheme 1. Synthetic analysis.

on recovered starting material). Control experiments showed that ethylene probably played two crucial roles during the process: 1) It increased the catalyst reactivity by means of converting the bulky complex **11** into the more active species $\{Mo=CH_2\}$,[13] and 2) it reacted with the remaining molybdenum alkylidene intermediate **14** to avoid the formation of side products and to recover substrate **7**.[14] In all cases, a regiospecific metathesis reaction was observed, and only the desired product **13** was detected, presumably owing to the high torsional strain that exists in the disfavored bridged product **12**. Remarkably, to the best of our knowledge, only a few examples have been reported for the use of Schrock molybdenum alkylidene complex **11** for a carbonyl–olefin metathesis in natural product synthesis,[12] and our reaction is a rare example of ethylene-accelerated carbonyl–olefin metathesis.

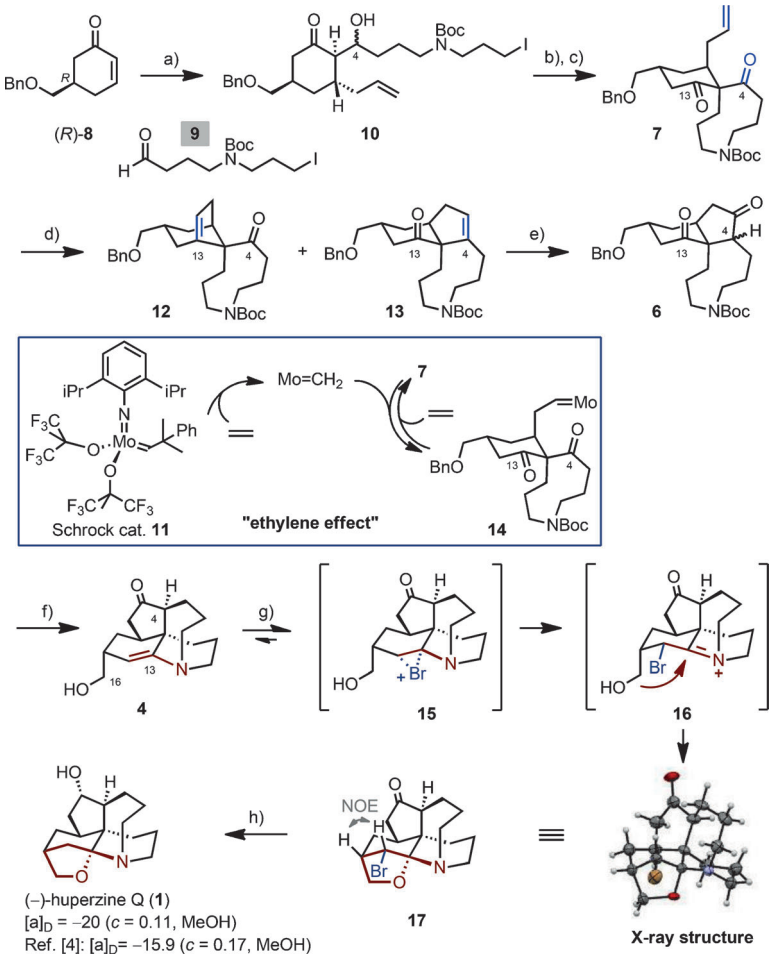
The cyclopentene moiety in ketone **13** was further smoothly elaborated into a cyclopentanone through a one-pot hydroboration/oxidation process.[15] Thus diketone **6** was obtained in 50% yield as a diastereoisomeric mixture (at the C4 position). Inspired by the pioneering work of the Heathcock group during their fawcettimine synthesis,[16] we anticipated that a single enamine product should be obtainable from the C4 isomers of **6** by a C4-epimerization/cyclization sequence. Indeed, after treatment of **6** with (+)-CSA at high temperature, which was followed by facile hydrogenolysis to remove the benzyl protecting group, enamine **4** was obtained in 84% yield as the sole product.

Next, the key late-stage enamine bromofunctionalization was carefully examined with enamine **4**. To our delight, upon treatment of **4** with NBS in the presence of (+)-CSA, bromide **17** was formed in 96% yield. The structure of **17** was determined by two-dimensional NMR spectroscopy and further confirmed by single-crystal X-ray diffraction analysis.[17] Enamine **4** might first undergo a reversible bromination to form a single bromonium ion **15**, followed by subsequent ring opening of the bromonium ion to afford α-bromoiminium ion **16**, which underwent an intramolecular aminal formation to generate **17**. Finally, **17** was efficiently converted into the natural product huperzine Q (**1**) in 95% yield through SmI_2 mediated concurrent debromination and ketone reduction in the presence of Et_3N and H_2O.[18] The synthetic (−)-huperzine Q (**1**) with an $[\alpha]_D$ value of −20 ($c = 0.11$, MeOH), exhibited ^1H and ^{13}C NMR spectra indistinguishable from those reported for the natural isolate.[3] Thus, a twelve-step total synthesis of (−)-huperzine Q (**1**) has been accomplished starting from commercially available 3,5-dioxocyclohexanecarboxylic acid.

Following the C4-epimerization/cyclization strategy, another biomimetic approach was also investigated (Scheme 3). Hydrogenolysis of **6** with $Pd(OH)_2/C$ in the presence of H_2 afforded free alcohol **18** in 91% yield. **18** was also obtained as two diastereoisomers with different configurations at the C4 position. Treatment of **18** with (+)-CSA at high temperature gave a mixture of enamine **4** and the desired cyclized product **19** (1:1, 43% yield for **19**). Resubjecting either **19** or **4** to the same reaction conditions provided the same mixture of **19** and **4** (1:1.2), which clearly indicated that an iminium ion intermediate was involved in the cyclization. Aminal **19** was further reduced with SmI_2 to afford (−)-huperzine Q (**1**) in quantitative yield, whereas the epimer **20** was exclusively formed in 72% yield when Superhydride was used as the reducing agent.

After the synthesis of (−)-huperzine Q (**1**), further efforts then focused on the syntheses of lycopladines B and C (Scheme 4), which required the efficient preparation of the key precursor enamine **5**. Initial attempts to oxidize alcohol **4** to **5** under various conditions (pyridine chlorochromate, 2-iodoxybenzoic acid, Swern oxidation) all led to the same C16 oxidative-cleavage side product.[19] Thus we decided to revise the synthetic route, which began with a one-pot oxidation of **18** to provide ester **21** in 86% yield.[20] Then, upon the treatment of ester **21** with (+)-CSA at 160 °C for 30 minutes, enamine **5** was formed smoothly along with partial epimerization at the C15 position ($\alpha/\beta = 3.2:1$).[21] At this stage, **5** could either be isolated (95% yield) or further treated in situ with NBS in $THF/H_2O/HOAc$ at 0 °C. Much to our delight, after this one-pot sequence, bromide **22** and epoxyamine **23** were isolated in 33% and 53% yield, respectively. Their structures were unambiguously established by single-crystal X-ray diffraction analysis.[22]

Although epoxides are one of the most versatile building blocks and most commonly used intermediates in organic synthesis,[23] epoxyamines, which were initially isolated and characterized by Stevens and co-workers,[24] have received much less attention owing to their facile nitrogen-assisted ring opening and polymerization. In fact, very few stable epoxyamines have been documented thus far.[25,26] Based on the X-

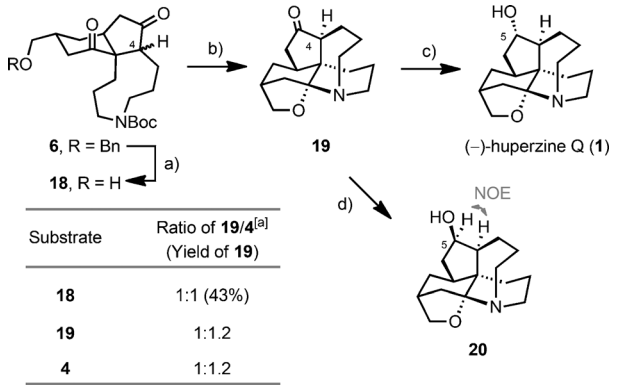


Scheme 2. A twelve-step synthesis of (–)-huperzine Q (**1**). Reagents and conditions: a) AllylMgBr, CuI, Me_2S, THF, −78 °C, 1 h; then aldehyde **9**, −78 °C, 3 h, 73 %; b) Dess–Martin periodinane, CH_2Cl_2, RT, 1.5 h, 82 %; c) DBU, DMF, RT, 72 h, 51 %; d) **11** (1.0 equiv), ethylene balloon, benzene, reflux, 5 h, **12** (not observed), **13** (48 %, 75 % brsm); e) $BH_3{\cdot}Me_2S$, Et_2O, reflux, 10 h; then NMO, 4 Å M.S., TPAP, CH_2Cl_2, 50 %; f) (+)-CSA, dichlorobenzene, 160 °C, 0.5 h; then $Pd(OH)_2/C$, H_2 balloon, EtOH, RT, 15 h, 84 % (one pot); g) (+)-CSA, NBS, CH_2Cl_2, RT, 1.5 h, 96 %; h) SmI_2, Et_3N, THF/H_2O (5:1 v/v), RT, 10 min, 95 %. Bn = benzyl, Boc = *tert*-butyloxycarbonyl, brsm = based on recovered starting material, CSA = camphorsulfonic acid, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMF = dimethylformamide, M.S. = molecular sieves, NBS = *N*-bromosuccinimide, NMO = *N*-methylmorpholine *N*-oxide, NOE = nuclear Overhauser effect, TPAP = tetrapropylammonium perruthenate.

ray structure of the epoxyamine that we obtained herein, it is noteworthy that the bond length of the C13–N bond is much shorter (1.431 Å) than the other two C–N bonds (1.471 Å for the C9–N bond and 1.479 Å for the C1–N bond), which implies that the C13–N bond might have a more sp^2-hybridized character and thus be prone to iminium ion formation during the ring opening of the epoxyamine. This hypothesis was later confirmed by the $pTsOH{\cdot}H_2O$ promoted ring opening of epoxyamine **23** at 120 °C, which presumably formed the α,β-unsaturated iminium ion intermediate **24**. Subsequent rearrangement afforded dienamine **25** in 62 % yield. Luche reduction of ketone **25** at −78 °C furnished the natural product (+)-lycopladine B (**2**), and acetylation of **2** smoothly afforded (+)-lycopladine C (**3**).[5] The spectroscopic data of the synthetic compounds **2** and **3** fully matched the data previously reported by Kobayashi and co-workers.[1c,5] Thus we have achieved the first total syntheses of (+)-lycopladines B (**2**) and C (**3**) and established the absolute configurations of both natural products.

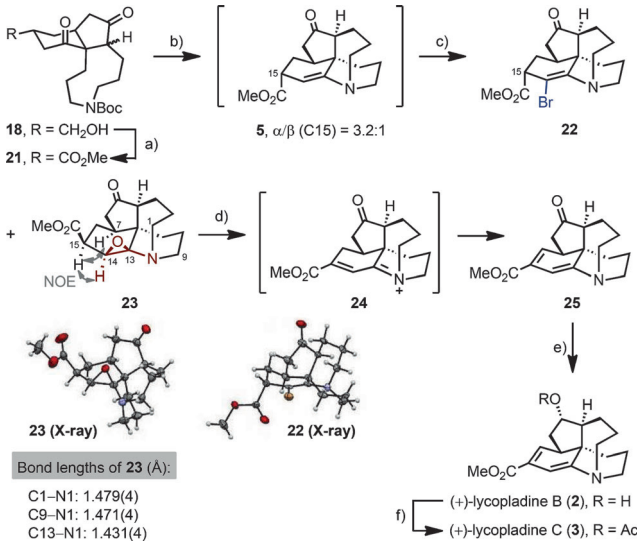
To rationalize the stereochemical outcome of the formation of **22** and **23** from **5**,[27] a dynamic kinetic epimerization process is suggested (Scheme 5): α-**5** is in equilibrium with β-**5** under acidic conditions. By treatment with NBS, both isomers are converted into the corresponding bromonium ions **26** and **27**, which further undergo sequential ring opening (to form α-bromoiminium ions), hydration (leading to keto-amines), and eventually ring–chain tautomerization[28] to afford hemiaminals **28** and **29**, respectively. Whereas dehydration of **28** under acidic conditions provided α(C15)-bromide **22**, hemiaminal **29** underwent an intramolecular S_N2 reaction and afforded β(C15)-epoxyamine **23** as a single isomer.

In summary, the power of enamine bromofunctionalization has been exemplified by the twelve-step total synthesis of (–)-huperzine Q (**1**) as well as the first total syntheses of (+)-lycopladines B (**2**) and C (**3**). Other notable features of the syntheses include 1) an ethylene-accelerated carbonyl–olefin metathesis using Schrock molybdenum complex **11**, 2) a biomimetic synthesis of **1** based on a C4-epimerization/cyclization strategy, and 3) an unprecedented X-ray crystal structure of an unusual epoxyamine intermediate and its first synthetic application in complex natural product synthesis. Further investigations towards the development of a general and effective method for the synthesis of epoxyamines as well as their applications in organic synthesis are currently underway and will be reported in due course.

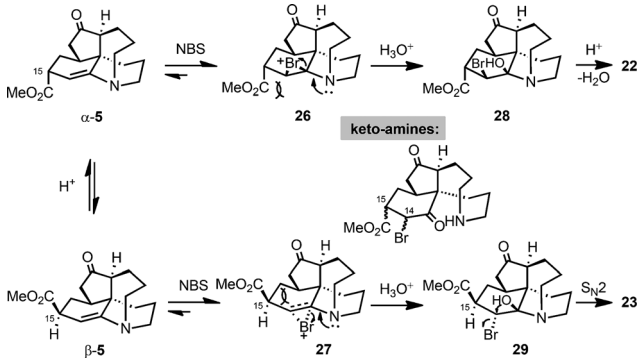


Substrate	Ratio of **19**/**4**[a] (Yield of **19**)
18	1:1 (43 %)
19	1:1.2
4	1:1.2

Scheme 3. Biomimetic cyclization approach to **1**. Reagents and conditions: a) $Pd(OH)_2/C$, H_2 balloon, EtOH, RT, 18 h, 91 %; b) (+)-CSA, dichlorobenzene, 160 °C, 2 h, 43 % for **19**, 43 % for **4**; c) SmI_2, THF/H_2O (5:1 v/v), RT, 10 min, quant.; d) $LiBHEt_3$, −78 °C, 1 h, 72 %. [a] Determined by ^1H NMR analysis of the crude reaction product.



Scheme 4. Total syntheses of (+)-lycopladines B (**2**) and C (**3**). Reagents and conditions: a) IBX, EtOAc, reflux; then Br_2, MeOH/H_2O (9:1 v/v), $NaHCO_3$, RT, 3 h, 86%; b) (+)-CSA, dichlorobenzene, 160°C, 0.5 h, 95% for **5** (α/β (C15) = 3.2:1); c) NBS, THF/H_2O/HOAc (1:1:1.5 v/v/v), 0°C, 15 min, 33% for **22**, 53% for **23**; d) pTsOH·H_2O, toluene, 4 Å M.S., 120°C, 36 h, 62%; e) $NaBH_4$, $CeCl_3$·7H_2O, MeOH, −78°C, 0.5 h, 80%; f) pyridine, Ac_2O, DMAP, RT, 7 h, 88%. DMAP = 4-dimethylaminopyridine, IBX = 2-iodoxybenzoic acid, pTsOH = *para*-toluenesulfonic acid.



Scheme 5. Proposed dynamic kinetic epimerization for the synthesis of epoxyamine **23**.

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