Total Synthesis of Huperzine Q

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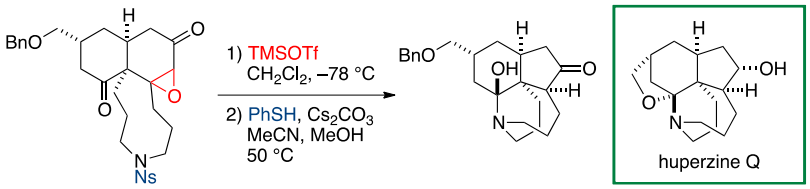
Supporting Information Placeholder



ABSTRACT: The total synthesis of huperzine Q was accomplished. The synthesis features the construction of the *cis*-hydrindane skeleton via a Diels–Alder reaction and a ring contraction reaction of an epoxyketone.

Huperzine Q (**1**, Figure 1) is an alkaloid isolated from *Lycopodium serratum* by Zhu and coworkers in 2002.[1,2] It is classified as a fawcettimine-type *Lycopodium* alkaloid. Although the core structure, *cis*-hydrindane, is identical to that of fawcettimine (**2**), the presence of an additional *N*,*O*-acetal moiety at C13 distinguished itself from **2**. The formation of the *N*,*O*-acetal moiety in huperzine Q was first achieved by Takayama and coworkers in 2011 via dehydration of the corresponding hemiaminal by treatment with CSA in refluxing toluene, leading to the total synthesis of huperzine Q.[3] Lei and coworkers reported the formation of the *N*,*O*-acetal moiety via bromination of an enamine in their synthesis of huperzine Q.[4]

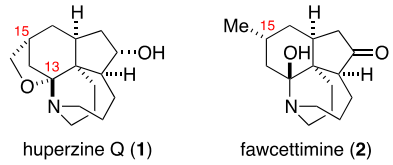
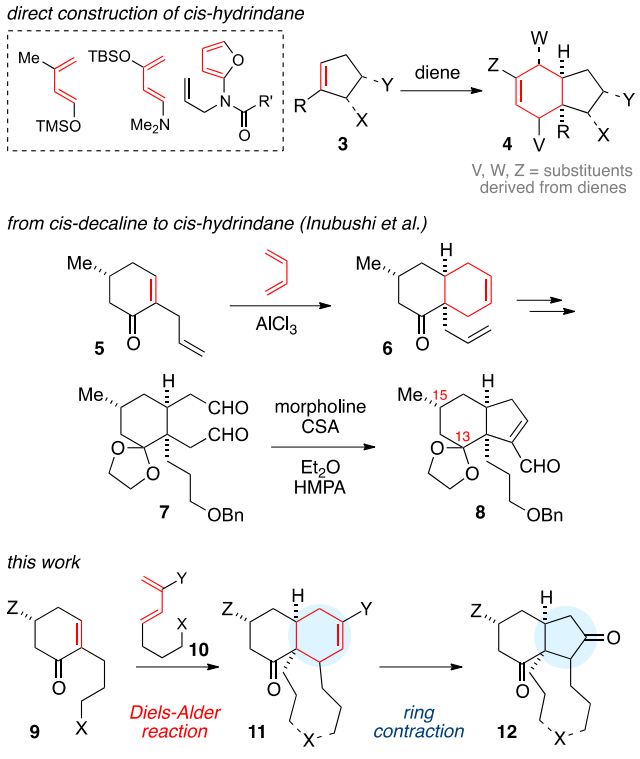


Figure 1. Structures of huperzine Q and fawcettimine.

The construction of the *cis*-hydrindane core of the *Lycopodium* alkaloids, which contains a quaternary carbon, has received significant attention, and a variety of synthetic strategies have been explored.[2i-m] A Diels–Alder reaction was employed to construct the *cis*-fused bicyclic system in one such strategy. Diels–Alder reactions between a diene and cyclopentene derivative **3** can directly provide *cis*-hydrindane **4** (Scheme 1).[5] Inubushi and coworkers carried out a Diels–Alder reaction of cyclohexenone **5** with 1,3-butadiene to produce a *cis*-decaline **6**, which was converted the *cis*-hydrindane skeleton **8** via oxidative cleavage of the cyclohexene moiety in a later step, followed by the intramolecular aldol condensation of the resulting dialdehyde **7**.[6] Although Inubushi's strategy required a subsequent ring contraction to form the *cis*-hydrindane skeleton, the carbonyl group at C13 and the stereogenic center at C15, both of which originated from the cyclohexenone, could be directly used for the synthesis of fawcettimine and related molecules. We envisioned that the side chain on the *cis*-hydrindane core might be installed as a part of the diene unit.[7] Herein, we disclose our total synthesis of huperzine Q by means of a Diels–Alder reaction between **9** and **10** and a subsequent ring contraction reaction.

Scheme 1. Construction of the *cis*-Hydrindane Core via a Diels–Alder Reaction



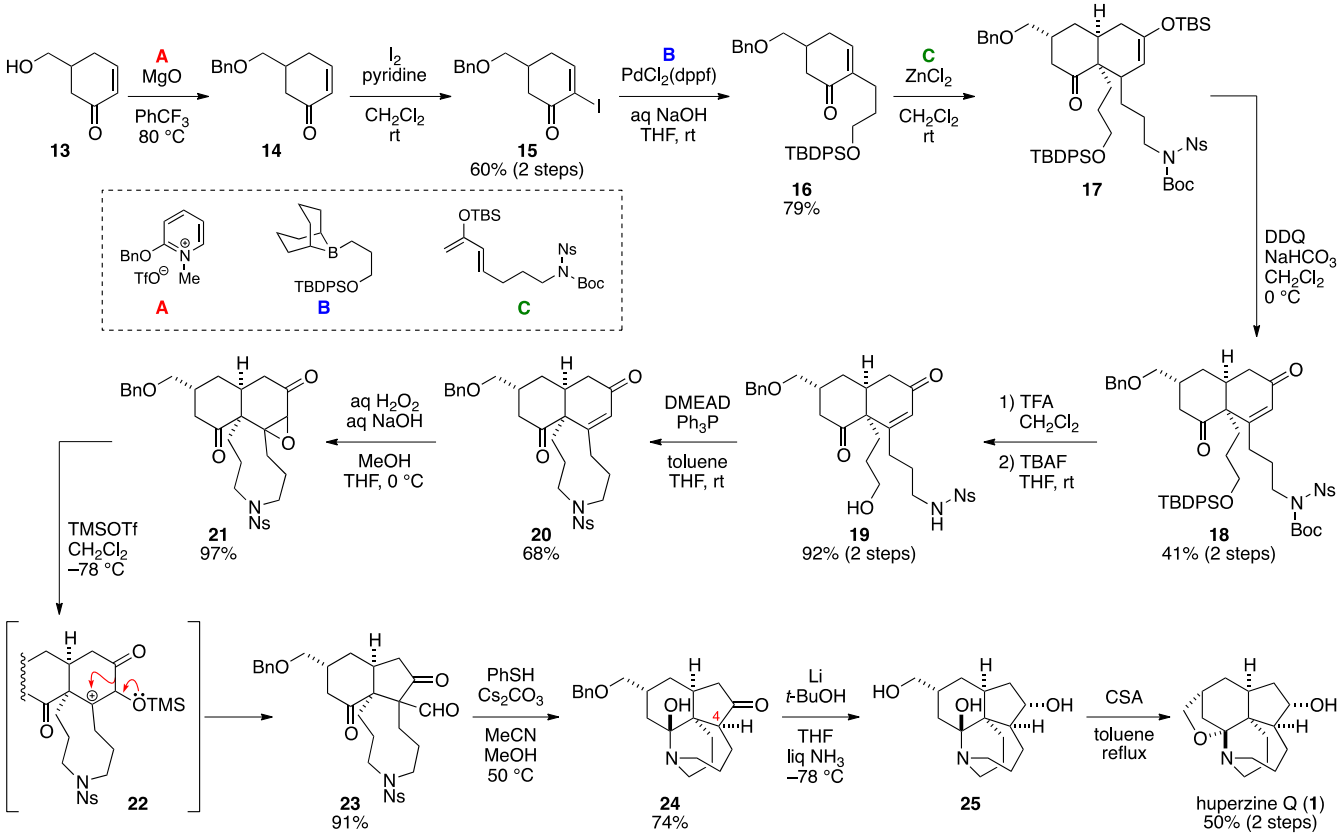
Our synthesis commenced with the benzylation of the known hydroxyketone **13**[8] according to Dudley's protocol by using the reagent **A** (Scheme 2).[9] α-Iodination, followed by Suzuki–Miyaura coupling[10] with alkylborane **B**, afforded the coupling product **16**. The crucial Diels–Alder reaction of **16** with diene **C**[11] in the presence of zinc chloride occurred at the opposite side of the benzyloxymethyl group on the cyclohexenone ring to furnish *cis*-decaline **17** as an inseparable mixture of the *endo*- and *exo*-isomers (dr = 1.5:1).[12,13]

Having constructed the *cis*-decaline system, we next focused on the conversion into the *cis*-hydrindane core. We found that a ring contraction reaction of an epoxyketone was effective for this purpose.[14] The silyl enolate moiety in **17** was oxidized with DDQ to afford enone **18**.[15] Sequential cleavage of the Boc and TBDPS groups gave hydroxy nosylamide **19**, which, upon subjection to the Mitsunobu reaction conditions[16] with di(2-methoxyethyl) azodicarboxylate (DMEAD),[17] underwent cyclization to produce the tricyclic compound **20**.[18] Nucleophilic epoxidation of the enone moiety in **20** afforded epoxyketone **21** under standard conditions.[14a,19] Upon treatment with TMSOTf in dichloromethane at –78°C, **21** underwent a selective cleavage of the epoxide, followed by a 1,2-shift of the carbonyl group, to give a ring-contracted product **23** in 91% yield.

Transformation of ketoaldehyde **23** into huperzine Q (**1**) proceeded uneventfully. Under the conditions for removal of the nosyl group, cleavage of the formyl group occurred concomitantly by the addition of methanol to afford hemiaminal **24**. The stereochemistry at C4 was thermodynamically controlled during the formation of the hemiaminal moiety.[20] Cleavage of the benzyl group and the stereoselective reduction of the ketone moiety in **24** were simultaneously achieved via the Birch reduction, leaving the hemiaminal moiety intact. Finally, the formation of the *N*,*O*-acetal moiety was carried out according to Takayama's procedure to furnish huperzine Q (**1**).[3a]

In summary, we have achieved a total synthesis of huperzine Q in the racemic form. The Diels–Alder reaction constructed the *cis*-decaline system, which was converted into the *cis*-hydrindane core of the natural product via a ring contraction reaction of the epoxyketone.

Scheme 2. Total Synthesis of Huperzine Q



ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, spectroscopic data, and ^{1}H and ^{13}C NMR spectra (PDF)

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ACKNOWLEDGMENTS

This work was financially supported by JSPS KAKENHI (Grant Numbers 25221301, 26713001, and 16H01141) and by the Platform Project for Supporting Drug Discovery and Life Science Research (Platform for Drug Discovery, Informatics, and Structural Life Science) from the Ministry of Education, Culture, Sports, Science and Technology of Japan (MEXT) and the Japan Agency for Medical Research and Development (AMED).

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(11) Diene **C** was prepared from *N*-Boc-*N*-(4-penten-1-yl)-nosylamide in 3 steps. For details, see Supporting Information.

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(13) When the Diels–Alder reaction time was extended from 2 to 24 hours, the mixture of **17** converged to a single isomer perhaps via either Lewis-acid-mediated cleavage of the C–C bond between the α-position of the ketone and the allylic position of the silyl enolate or retro Diels-Alder reaction.

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