Total Synthesis of Lyconesidine B, a *Lycopodium* Alkaloid with an Oxygenated, Amine-type Fawcettimine Core

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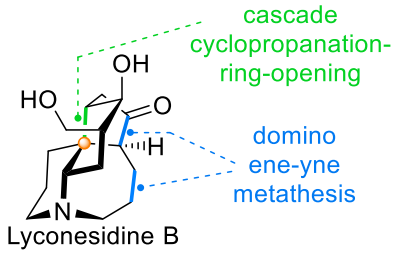
ABSTRACT: This report describes the total synthesis of the complex, oxygenated tetracyclic alkaloid, lyconesidine B. The key synthetic challenge involves diastereoselective generation of a decahydroquinoline ring with a quaternary carbon at the angular position via domino cyclopropanation, ring-opening, and reduction. Another crucial step is the domino ene-yne metathesis involving a quaternary ammonium ion, leading to the construction of a decahydroazaazulen framework. This synthesis requires minimizing catalyst deactivation and approaching the metal carbene with a double bond.



Lyconesidines A and B were first isolated from the club moss, *Lycopodium chinense*, by Kobayashi and co-workers in 2002 (Figure 1).[1] Their structures, including determination of the absolute stereochemistry, were verified using X-ray crystallography and extensive NMR analysis, including 2D-NMR and a modified Mosher's method. These alkaloids have a complex tetracyclic skeleton containing a *cis*-hydrindanone (BD ring; Figure 1a) and a hydroazonine with a quaternary carbon center at the angular position. This moiety is part of the basic skeleton of fawcettimine-type alkaloids, which are a major class of *Lycopodium* alkaloids.[2] The oxidation state of C13 (along the CD ring juncture, highlighted with a green sphere in Figure 1) in lyconesidines (i.e. amine-type alkaloids) is lower than that in typical aminal- and enamine-type analogs (fawcettimine and fawcettidine structures, respectively; Figure 1b,c). Therefore, the lyconesidines exhibit distinct D ring conformations, wherein the hydroxymethyl group is located at the axial position. In other words, lyconesidine B is characterized by an oxygen-functionalized amine-type skeleton. Lyconesidines A and B exhibited cytotoxicity against murine lymphoma L1210 cells (IC_{50} = 18.0 μg/mL and 9.5 μg/mL, respectively), and inhibited the polymerization of tubulin (IC_{50} = 300 μM and 250 μM, respectively). To our knowledge, there are currently no reports describing a total synthesis of lyconesidines; therefore, we have conducted a synthetic study involving these compounds with the aim of expanding our understanding of their three-dimensional structures and biological activities. Lyconesidine B, which exhibits relatively more potent activity, was used as a target to establish a synthetic route for obtaining analogs bearing oxygen-containing functional groups, ultimately to elucidate structure-activity relationships based on its three-dimensional framework. A synthetic method that allows introduction of functional groups at various positions in a certain skeleton enables synthesis of analogs with several interaction sites designed for a target protein. In this report, we describe the total synthesis of lyconesidine B, which contains a highly-oxygenated amine-type structure, by developing synthetic strategies that can be applied to analog synthesis.

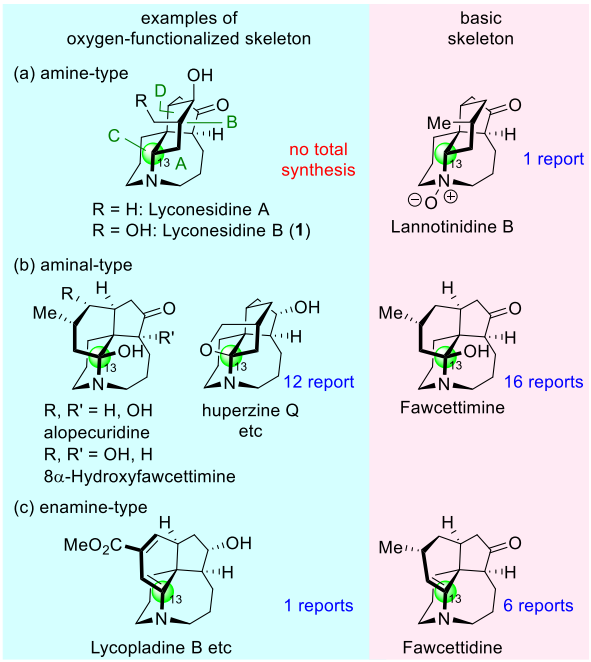


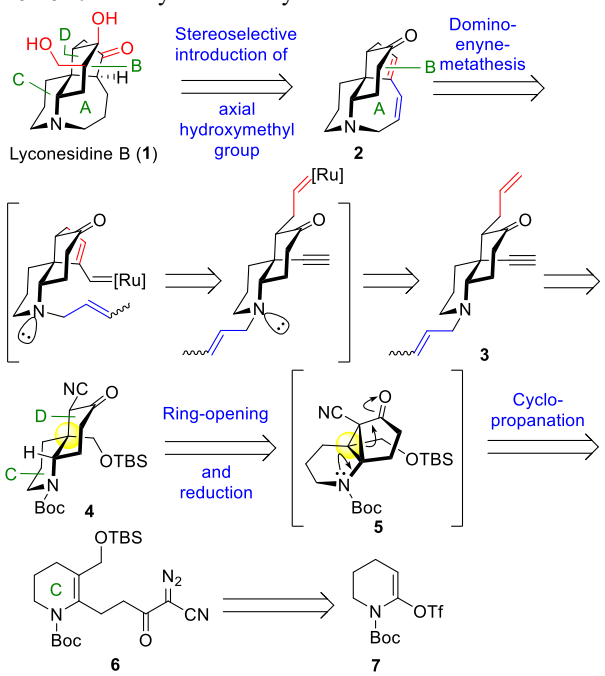
Figure 1. Examples of basic and oxygenated fawcettimine-type alkaloids, noting the number of total synthesis literature reports. (a) Lyconesidines and related amine-type alkaloids, (b) Fawcettimine and related aminal-type alkaloids, and (c) Fawcettidine and related enamine-type alkaloids.

Fawcettimine-type alkaloids have attracted the attention of numerous synthetic organic chemists because of their distinctive structures and biological activities.[3-5] Inubushi and Heathcock reported the pioneering total synthesis of the basic fawcettimine framework, which comprised a *cis*-hydrindanone (BD ring) fused with hydroazonine.[4a,b] Although various fawcettimine-type alkaloid syntheses have been reported to date, most of the strategies focus on the aminal- and enamine-type

structures (Figure 1b,c).[5] To our knowledge, there is only one synthetic study regarding the basic amine-type skeleton, specifically, lannotinidine B.[6] There are no known synthetic reports for the oxygen-functionalized amine-type skeleton, likely because the functional groups on the tetracyclic framework and the relatively lower oxidation state of C13 limit the strategies and reactions that can be applied to produce these structures. Therefore, a new synthetic approach is required to obtain lyconesidine B.

The synthesis of lyconesidine B poses several challenges, including the construction of a complex, oxygenated, tetracyclic skeleton, as well as the introduction of a quaternary carbon and six contiguous stereocenters, including an axial hydroxymethyl group on the D ring. The lyconesidine B (**1**) synthetic plan presented herein is based on a domino ene-yne metathesis reaction,[7,8] which generates a decahydroazaazulen structure (AB ring), in combination with a cyclopropanation ring-opening method to obtain the decahydroquinoline (CD ring) (Scheme 1).[9,10] We propose that the tetracyclic skeleton can be modified in a relatively late stage of the synthesis. Specifically, **1** is obtained from a tetracyclic compound **2** by stereoselectively introducing a hydroxymethyl group. The AB ring framework is constructed from dieneyne **3**, which is derived from compound **4**. To control the reactivity of the double bonds in **3** during the metathesis, a crotyl group is introduced on one side. The decahydroquinoline skeleton (CD ring) of **4** is constructed via intramolecular cyclopropanation of tetrahydropyridine **6**, ring-opening of cyclopropane **5**, and reduction of the resulting iminium ion. This one-pot transformation generates the *trans* ring juncture, including the quaternary carbon center. The cyclization precursor **6** is prepared from a known enol triflate **7**.[11] While many approaches involve synthesizing the tetracyclic skeleton from the BD ring, then forming the azonine ring to construct the AC ring, the synthetic route described herein is unique because the CD ring is constructed first, followed by the AB ring.

Scheme 1. Retrosynthesis of lyconesidine B.

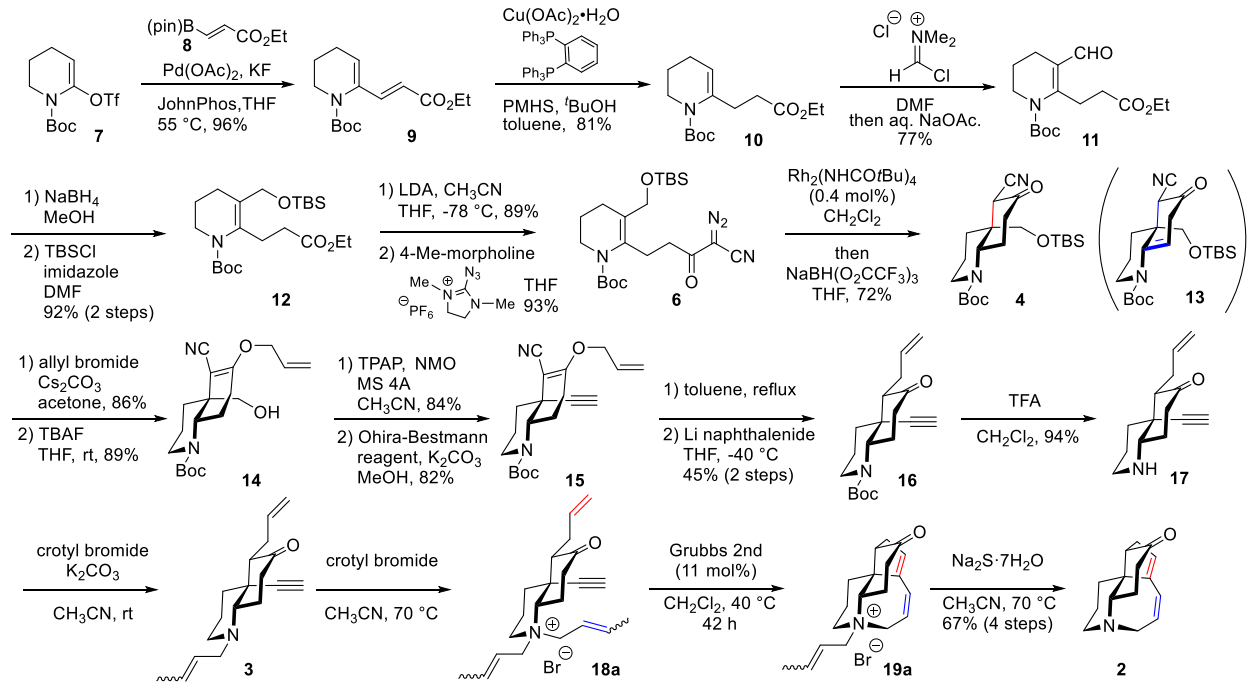


The synthesis began with a Suzuki-Miyaura coupling of enol triflate **7**, which was prepared from δ-valerolactam in two steps,[11] with vinyl boronic ester **8** (Scheme 2).[12] The resulting unsaturated ester **9** was converted to **11** by Cu-catalyzed 1,4-reduction[13] and introduction of an aldehyde moiety using the Vilsmeier reagent. Following the reduction of aldehyde **11** and silylation of the resulting alcohol, the diazonitrile unit was introduced by treating with deprotonated acetonitrile and performing diazotransfer with 2-azido-1,3-dimethylimidazolinium hexafluorophosphate[14] to afford the cyclization precursor **6**. This compound can be converted into decahydroquinoline **4** using a one-pot process. Applying our previously developed procedure,[9] tetrahydropyridine **6** was treated with bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)] (Rh_2(esp)$_2$),[15] then trifluoroacetic acid (TFA) and $NaBH(OAc)_3$. The reaction proceeded through cyclopropanation, ring-opening of the unstable intermediate **5**, and finally, reduction of an iminium ion to generate decahydroquinoline **4** in 45% yield, along with a small amount of enecarbamate **13** as a byproduct. Because **13** could not be converted to **4**, various reducing agents and Rh catalysts were investigated to improve the yield and suppress the formation of byproduct **13**. It was determined that the combination of $Rh_2(NHCOtBu)_4$,[16] bearing an amide ligand, and $NaBH(O_2CCF_3)_3$ (1 equiv.), prepared from $NaBH_4$ and TFA (1:3),[17] provided better results. The reaction under these optimized conditions proceeded smoothly to afford **4** in 72% yield as the single product. These conditions were reliable and could be applied for decagram-scale synthesis of **4**.

The obtained decahydroquinoline skeleton **4** was then converted to the domino ene-yne cyclization precursor **3**. Following *O*-allylation, the *tert*-butyldimethylsilyl (TBS) group was removed to afford the alcohol **14**. Oxidation of that alcohol with tetra-*n*-propylammonium perruthenate (TPAP)[18] and introduction of an alkyne moiety using the Ohira-Bestmann reagent generated compound **15**. It was essential to introduce the alkyne unit at this stage to avoid steric congestion. After a Claisen rearrangement, the nitrile and *tert*-butoxycarbonyl (Boc) groups were removed under Birch and acidic conditions, respectively. The resulting amine **17** was treated with crotyl bromide and a base (K_2CO_3) to afford the cyclization precursor **3**, which was used for initial attempts of domino ene-yne metathesis.

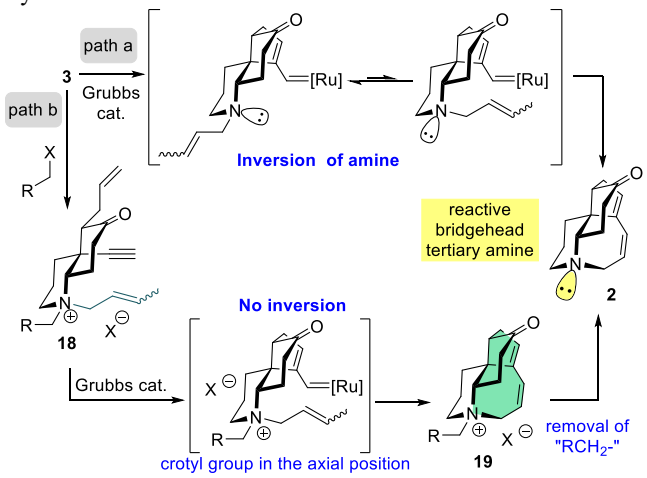
First, **3** was treated with 5 mol% Grubbs 2nd generation catalyst, but the desired cyclized product **2** was only obtained in 5% yield. When 50 mol% of Grubbs 2nd catalyst was used, **2** was produced in up to 50% yield, depending on the amount of the catalyst. These results suggested that the catalyst was deactivated by the bridge-head tertiary amine of the product (Scheme 3, path a). Therefore, the addition of Lewis and Brønsted acids, including Ti(O*i*Pr)$_4$[19] and HCl,[8h] was examined as a method to prevent the deactivation of the Grubbs catalyst. However, these conditions did not improve yields, because the crotyl group avoided inversion and remained at the equatorial position. Therefore, to achieve the domino ene-yne metathesis, it is necessary to minimize the tertiary amine's deactivation of the Grubbs catalyst while positioning the crotyl group in the axial conformation for the second cyclization.

Scheme 2. Synthesis of the tetracyclic core of lyconesidine B.



JohnPhos = 2-(di-tert-butylphosphino)biphenyl, PMHS = polymethylhydrosiloxane, LDA = lithium diisopropylamide, TBAF = tetra-*n*-butylammonium fluoride, NMO = *N*-methylmorpholine *N*-oxide, MS 4A = molecular sieves 4Å.

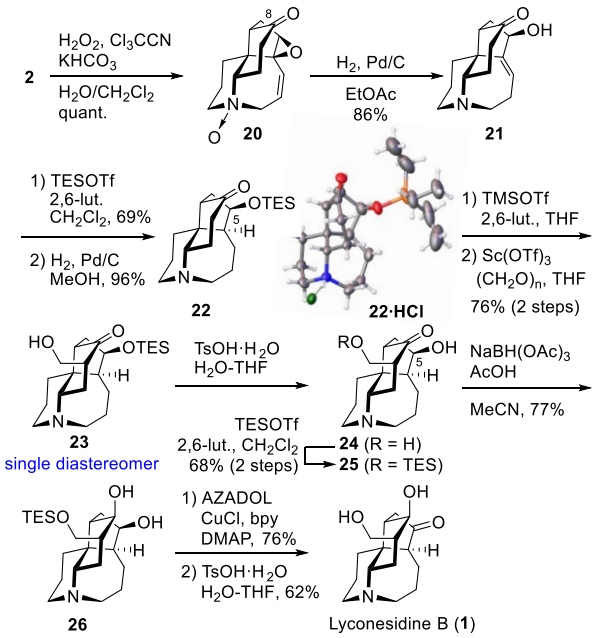
Scheme 3. Constructing of the tetracyclic skeleton via domino ene-yne metathesis.



Thus, we expected that the quaternary ammonium salt **18** would meet these requirements, although the additional substituent must be removed after the cyclization (path b). The second crotyl group would be best because there is no need to distinguish between the two substituents on the nitrogen atom. It was regioselectively introduced to compound **3** at elevated temperature, without using a base (K_2CO_3) to generate a thermodynamically-stable linear-crotyl product **18a** (Scheme 2). The obtained quaternary ammonium salt **18a** was treated with 11 mol% Grubbs 2nd catalyst, and the desired domino cyclization proceeded smoothly to give compound **19a** in good yield. The crotyl group could be readily removed by treating with Na_2S to obtain the tetracyclic compound **2**. The overall yield was 67% through crotylation, domino ene-yne metathesis, and de-crotylation. Although it takes 19 steps to access the key tetracyclic skeleton **2**, from the known triflate **7**, this synthetic route generates enough material (over 500 mg) to synthesize the natural product.

After construction of the tetracyclic compound **2**, the total synthesis of lyconesidine B requires regio- and stereoselective introduction of a hydroxymethyl group and an oxygen functionality. Epoxidation of **2** with H_2O_2 and trichloroacetonitrile[20] afforded **20** as a single diastereomer, along with oxidation of the bridge-head amine to an *N*-oxide (Scheme 4). After reductive ring-opening of the epoxide, the resulting allyl alcohol **21** was converted to **22** through silylation and diastereoselective hydrogenation. The newly generated stereochemistry of **22** was confirmed by X-ray crystallographic analysis of its salt (**22·HCl**), as shown in Scheme 4. Diastereoselective introduction of the axial hydroxymethyl group was achieved by Mukaiyama aldol reaction of a silyl enol ether, prepared from ketone **22**, with formaldehyde in the presence of $Sc(OTf)_3$.[21] The β-hydroxyketone **23** was produced as a single diastereomer by shielding one side of the silyl enol ether with a bulky siloxane group. After a protecting group manipulation, ketone **25** was reduced diastereoselectively using the hydroxy group on C5 as the directing group. Selective oxidation of the resulting diol **26** with 2-azaadamantane-*N*-oxyl (AZADO)[22] was followed by the removal of the triethylsilyl (TES) group to give lyconesidine B (**1**). The spectral data (high-resolution mass spectrometry (HRMS) and ^1H and ^{13}C NMR) obtained for the synthetic lyconesidine B matched well with those of the natural product. Thus, we achieved the total synthesis of lyconesidine B.[1]

Scheme 4. Total synthesis of lyconesidine B.



TMS = trimethylsilyl, DMAP = 4-dimethylaminopyridine.

In summary, we have accomplished the total synthesis of lyconesidine B by applying an original synthetic strategy employing domino reactions to generate a framework comprising decahydroquinoline (CD ring) and decahydroazaazulen (AB ring). The CD ring, which contains a quaternary carbon center at the angular position, was constructed via cyclopropanation of a tetrasubstituted enecarbamate, followed by ring-opening and diastereoselective reduction. The AB ring was obtained through a domino ene-yne metathesis, in which a quaternary ammonium ion played an important role in minimizing the deactivation of the Grubbs catalyst and positioning the crotyl group in the axial conformation to allow the second cyclization. The developed synthetic route enabled easy access to the oxygenated amine-type tetracyclic skeleton, which cannot be readily obtained using other established strategies. Follow-up studies are currently underway to investigate the biological activity of these synthetic analogs.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, spectral data (^{1}H and ^{13}C NMR, IR, and HRMS) (PDF).

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Notes

The authors declare no conflicts of interest.

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