Synthesis of an isomer of lycoplanine A via cascade cyclization to construct the spiro-N,O-acetal moiety

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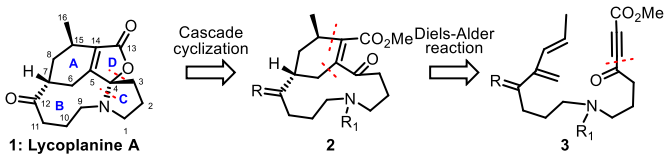
An isomer of lycoplanine A with a 6/10/5/5 tetracyclic skeleton was synthesized using D-A reaction and cascasde reaction to respectively construct the [9.2.2] pentadecane skeleton and the challenging 1-oxa-6-azaspiro[4.4]nonane spirocenter. Morever, detailed DFT calculations were conducted to explain the selectivity in the D-A reaction. This study may provide sufficient experience for the total synthesis of lycoplanine A and other alkaloids with similar spiro-N,O-acetal cores.

Lycopodium alkaloids, especially Huperzine A have shown great potential on the clinical treatment of Alzheimer's disease.[1-2] Up to now, over 300 Lycopodium alkaloids have been isolated,[3] and many beautiful total syntheses towards these alkaloids have been reported.[4] In 2017, lycoplanine A, a new type of Lycopodium alkaloid with a 6/9/5 tricyclic skeleton that is fused with the γ-lactone ring was firstly isolated and characterized by Zhao and co-workers.[5] Notably, in lycoplanine A, an unusual 1-oxa-6-azaspiro[4.4]nonane moiety is embedded, which is usually a core of bioactive natural products[6] and is generally obtained from oxidative spirocyclization of furan derivatives.[7] Biological studies show that lycoplanine A is a potent $Ca_v3.1$ T-type calcium channel (TTCC) inhibitor with the IC_{50} value of 6.06 μM.[5] In view of its unique structure and important biological activity, we herein explored the synthetic route to lycoplanine A, studied the rapid construction of the spiro-N,O-acetal moiety in lycoplanine A and accomplished the synthesis of an isomer of lycoplanine A with a 6/10/5/5 tetracyclic skeleton.

From the perspective of structure, the C and D rings in lycoplanine A (**1**) could be disassembled *via* an efficient tandem cyclization initiated from N-protected compound **2**, referring to the proposed biogenetic pathway between lycopladine H and lycoplanine A reported by Zhao et al. (Scheme 1).[5] The six-membered ring in **2** is proposed to be dissociated via intramolecular Diels-Alder reaction of **3**.[8] The key to synthesize D-A precursor **3** is the assembly of diene and dienophiles moieties.



Scheme 1 Retrosynthetic analysis of lycoplanine A.

With the above retrosynthetic analysis in mind, we started our synthesis via sequential installation of the diene and dienophile sections in D-A precursor **3** (Scheme 2). Starting from 1,3-dithiane **4**, the first C=C bond was effectively introduced employing Corey-Seebach reaction with the commercially available crotonaldehyde (E/Z>98%), giving alcohol **5** in 88% yield.[9] Sequentially, alcohol **5** was oxidized with Dess-Martin periodinane to deliver ketone **6** in 80% yield. To introduce the second C=C bond of D-A precursor **3**, numerous efforts were devoted, including Wittig reaction, Tebbe's reagent, and Nysted reagent. Only Nysted reagent gave methylenated product **7** in 63% yield.[10] At this stage, the diene moiety of D-A precursor **3** has been assembled, then attention was turned to the introduction of the dienophile moiety. Deprotection of the silane protecting group by TBAF and a typical Mitsunobu reaction with fragment A were conducted to lengthen the carbon chain as well as introduce the nitrogen atom, affording *o*-nitrobenzene sulfonyl protected amine **8**.[11] Before the late-stage introduction of the dienophile moiety, protecting group transformation of nitrogen atom from *o*-Ns to Boc and the ensuing deprotection of hydroxy group were performed to give alcohol **9**. After oxidation of the primary alcohol **9**, the *in-situ* generated anion of methyl propiolate was added onto the aldehyde moiety to deliver alcohol **10**, achieving the introduction of the dienophile section. Considering that alcohol **10** has possessed necessary structural features for D-A reaction,

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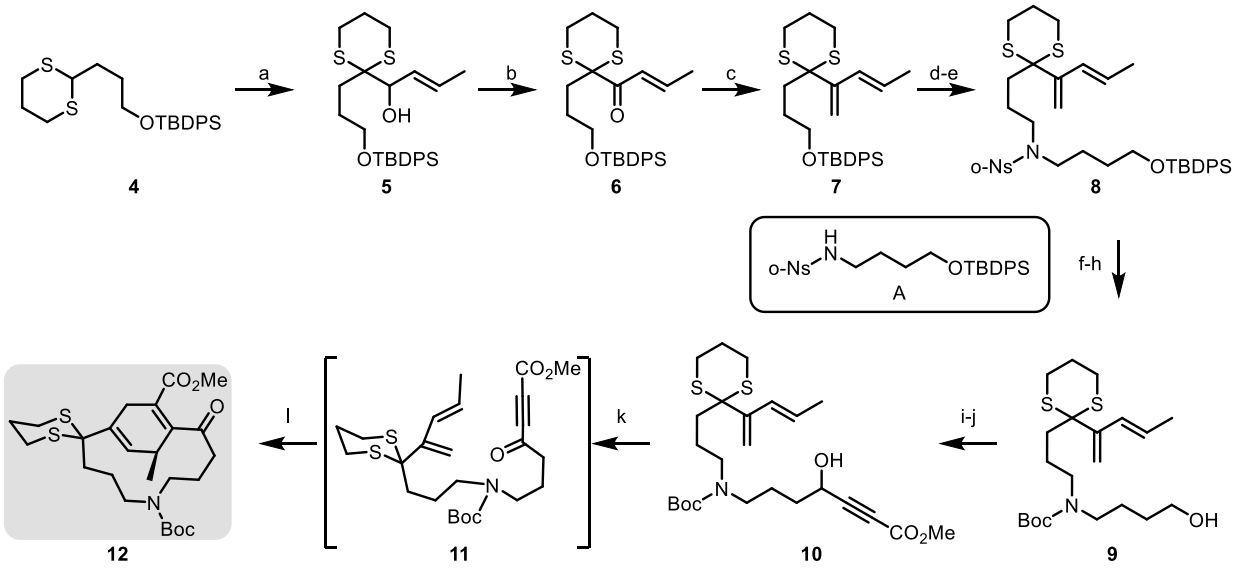


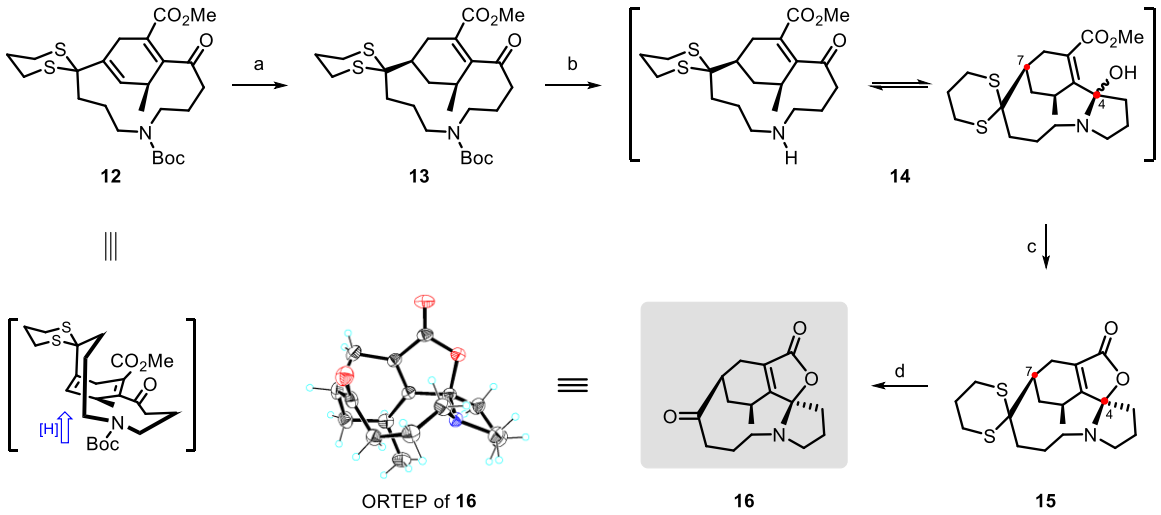
Scheme 2 Synthetic route to the Diels-Alder Product **16**. Reagents and conditions: (a) *t*-BuLi, Et_2O, crotonaldehyde, -78 °C to -20 °C, 88%; (b) Dess-Martin periodinane, CH_2Cl_2, r.t., 80%; (c) Nysted reagent, $TiCl_4$, THF, -20 °C to 50 °C, 63%; (d) TBAF, THF, r.t., 91%; (e) fragment A, PPh_3, DIAD, THF, -20 °C to r.t., 86%; (f) Cs_2CO_3, PhSH, acetonitrile, r.t., 86%; (g) $(Boc)_2O$, Et_3N, acetonitrile, r.t.; (h) TBAF, THF, r.t., 79%(2 steps); (i) Dess-Martin periodinane, CH_2Cl_2, r.t., 60%; (j) LiHMDS, methyl propiolate, THF, -78 °C, 83%; (k) Dess-Martin periodinane, CH_2Cl_2, r.t.; (l) BHT, toluene, 80 °C, 48%(2 steps).

we directly subjected **10** to Lewis acid-catalyzed D-A conditions, such as Et_2AlCl, $ZnCl_2$ and $Sc(OTf)_3$, however, no any D-A product was detected. In addition, heating **10** in toluene at reflux could not generate the desired D-A product. Afterwards, a more reactive D-A precursor—ketone **11**, which was obtained via DMP oxidation of alcohol **10**, was tested under the reaction conditions of 80 °C without the addition of any catalyst.[12] Unfortunately, rather than giving the expected [9.3.1] pentadecane skeleton, this reaction produced an undesired [9.2.2] pentadecane skeleton **12** in 48% yield over two steps from **10**. The structure of **12** was indirectly identified by the X-ray crystal structure of the final product (vide infra). We proposed that the existence of the two newly formed sp^2 bridge carbons in the desired D-A product may increase the ring tension of the pentadecane skeleton, thus leading to a relatively high regioselectivity to form the 13-membered [9.2.2] rather than the 12-membered [9.3.1] pentadecane skeleton to reduce the ring tension.

Computational studies were carried out using Gausssian[13] to understand the regioselectivity of the D-A reaction from **11** to **12** (See SI). Unfortunately, these DFT calculations suggest that our desired 12_[9.3.1] should be the kinetic product, although the experimentally observed product 12_[9.2.2] is calculated to be thermodynamically more stable. Considering that this D-A reaction is calculated to be irreversible, hence the possibility of transformation from 12_[9.3.1] to 12_[9.2.2] could be excluded. From the results of these calculations, our desired product 12_[9.3.1] should be formed. We envisage the reason for us to only detect 12_[9.2.2] is because 12_[9.3.1] is instable, leading to a trace amount and the difficulty in its detection, and thus the thermodynamically stable 12_[9.2.2] was the only obtained product, indicating that the D-A reaction may be a thermodynamically controlled process.

Considering that the 1,4-diene moiety in D-A product **12** was easily aromatized into a benzene ring, **12** was simply purified via a flash silica gel chromatography and was directly subjected to the hydrogenation conditions. To selectively hydrogenate the trisubstituted C=C bond without affecting the tetrasubstituted C=C bond, Wilkinson's catalyst and Crabtree's catalyst were investigated. Only Crabtree's catalyst could give trisubstituted C=C bond hydrogenated product **13** in 47% yield with absolute regio- and stereoselectivities, while the reaction did not proceed under the conditions of Wilkinson's catalyst. This excellent stereoselectivity may attribute to that the steric hindrance of the *β*-face of the boat conformation of the 1, 4-diene cyclohexane is larger than that of the *α*-face, thus resulting in the completely facial selective cis-hydrogenation towards the less hindered *α*-face. Then the hydrogenated product **13** was treated with $BF_3{\cdot}Et_2O$ at -30 °C to remove the Boc protecting group to render amine **14**, as well as a trace amount of cascade cyclization product **15** detected by LC-MS, which inspired us to use other acids to facilitate this cascade reaction.[4n] After extraction of the reaction mixture, amine **14** was directly subjected to AcOH, stimulating a cascade reaction, and rendering cyclized product **15** stereo-specifically in 35% yield. We deduced that this satisfying stereoselectivity may be affected by the stereochemistry at C7. Subsequently, we explored other basic conditions (pyridine and Et_3N) to improve the yield, but no cyclized product **15** was detected. The thioketal group in **15** was then removed under the promotion of PIFA, affording **16** as the isomer of lycoplanine A in 83% yield, the structure of which was unambiguously confirmed by the X-ray single crystal diffraction to be a tetracyclic compound with a 3-azabicyclo[6.2.2]dodecane unit (CCDC: 1947434).

In view of the biological activities of Lycopodium alkaloids previously reported, we conducted a biological evaluation of **16**



Scheme 4 Synthetic route to the isomer of lycoplanine A. Reagents and conditions: (a) Crabtree's catalyst, H_2, DCE, 80 °C, 47%; (b) $BF_3 \cdot Et_2O$, DCM, -30 °C; (c) AcOH, toluene, 90 °C, 35% (2 steps); (d) PIFA, MeCN-H_2O, 83%. Non-hydrogen atoms are shown as 30% ellipsoids.

on EeAChE and eqBuChE inhibition. Unfortunately, **16** showed no inhibitory activity on cholinesterase (IC_{50} > 100 μM).

In conclusion, an isomer of lycoplanine A with an unexpected 6/10/5/5 tetracyclic skeleton was synthesized during our synthetic route to the natural product lycoplanine A. Diels-Alder reaction and cascade cyclization were employed as the key steps to construct the [9.2.2] pentadecane skeleton and the challenging 1-oxa-6-azaspiro[4.4]nonane spiro moiety, respectively. In addition, we evaluated the preliminarily inhibitory activity of synthesized isomer on cholinesterase but the result was unsatisfactory. Although the final product we synthesized was a complex isomer of lycoplanine A, the challenging 1-oxa-6-azaspiro[4.4]nonane spirocenter in lycoplanine A was constructed by an efficient cascade reaction, which provided sufficient experience for the total synthesis of lycoplanine A and natural products with a similar spiro-N,O-acetal moiety.[14] In addition, this work may be helpful for studying the proposed biogenetic pathway between lycopladine H and lycoplanine A, which may further provide access to synthesize lycopladine H and lycoplanine A. The total synthesis study on lycoplanine A is now underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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