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

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An isomer of lycoplane A with a 6/10/5/5 tetracyclic skeleton was synthesized using D-A reaction and cascad reaction to respectively construct the [9.2.2] pentadecane skeleton and the challenging 1-oxa-6-azaaspiro[4.4]nonane spirocenter. Moreover, 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 lycoplane A and other alkaloids with similar spiro-N,O-acetal moieties.

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, lycoplane A, a new type of Lycopodium alkaloid with a 6/9/5 tricyclic skeleton that is fused with the y-lactone ring was firstly isolated and characterized by Zhao and co-workers.5 Notably, in lycoplane A, an unusual 1-oxa-6-azaaspiro[4.4]nonane moiety is embedded, which is usually a core of bioactive natural products6 and is generally obtained from oxidative spirocyclization of furan derivatives.7 Biological studies show that lycopane A is a potent Ca,3.1 T-type calcium channel (TTCC) inhibitor with the IC50 value of 6.06 μM.8 In view of its unique structure and important biological activity, we herein explored the synthetic route to lycopane A, studied the rapid construction of the spiro-N,O-acetal moiety in lycopane A and accomplished the synthesis of an isomer of lycopane A with a 6/10/5/5 tetracyclic skeleton.

From the perspective of structure, the C and D rings in lycopane A (1) could be disassembled via an efficient tandem cyclization initiated from N-protected compound 2, referring to the proposed biogenetic pathway between lycopaline H and lycopane 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.

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, Tebb’s reagent, and Nysted reagent. Only Nysted reagent gave methoxlated 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 silyl 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 sulfonfyl protected amine 8.11 Before the latest-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.
we directly subjected 10 to Lewis acid-catalyzed D-A conditions, such as Et$_3$AlCl, 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. 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$^3$ 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 Gaussian$^{13}$ 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$_3$·Et$_2$O 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.$^{40}$ 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$_3$N) 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...
on hAChE and eqBuChE inhibition. Unfortunately, 16 showed no inhibitory activity on cholinesterase (IC50 > 100 μM).

In conclusion, an isomer of lycoplane A with an unexpected 6/10/5/5 tetracyclic skeleton was synthesized during our synthetic route to the natural product lycopane A. Diels-Alder reaction and cascade cyclization were employed as the key steps to construct the [9.2.2] pentalenec 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 lycopane A, the challenging 1-oxa-6-azaspiro[4.4]nonane spirocenter in lycopane A was constructed by an efficient cascade reaction, which provided sufficient efficiency for the total synthesis of lycopane 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 lycopane H and lycopane A, which may further provide access to synthesize lycopane H and lycopane A. The total synthesis study on lycopane A is now underway in our laboratory.

Conflicts of interest
There are no conflicts to declare.

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