Asymmetric total synthesis of *Lycopodium* alkaloid (+)-lycopladine A

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ABSTRACT

Asymmetric total synthesis of (+)-lycopladine A (**1**) has been achieved. Key elements of the synthesis include an efficient Helquist annulation to assemble the cis-fused 6/5 bicycle, Stille coupling reaction to elongate the allylic side chain, and Kröhnke pyridine synthesis to set the pyridine core at the final stage.

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The *Lycopodium* alkaloids[1] are a diverse group of structurally complex natural products. Owing both to their appealing, synthetically challenging polycyclic systems with dense stereochemical array and wide-ranging biological activities, a cornucopia of total syntheses of *Lycopodium* alkaloids have been reported.[2] In the context of our ongoing synthetic endeavor on the complex polycyclic *Lycopodium* alkaloids,[3] lycopladine A, a pyridine-containing tricyclic *Lycopodium* alkaloid attracted our attention. Lycopladine A, isolated in 2006 from the club moss *Lycopodium complanatum* by Kobayashi and co-workers,[4] is a novel C16N type *Lycopodium* alkaloid possessing a pyridine-fused hydrindanone core, and it shows selective but modest cytotoxicity toward murine lymphoma L1210 cells (IC50 = 7 μg/mL). The unprecedented structure of lycopladine A has aroused interest of several synthetic groups. In 2006, Toste group[5] reported the first total synthesis of (+)-lycopladine A and assignment of the absolute configuration by taking advantage of a gold-catalyzed cyclization of a silyl enol ether onto an alkyne to install the key quaternary center of hydrindanone. Later in 2010, Martin and co-workers,[6] reported the second concise total synthesis of racemic (±)-lycopladine A via sequential conjugate addition and enolate arylation to construct the tricyclic framework. In 2011, Hiroya et al.[7] reported the third total synthesis of (+)-lycopladine A in 25 steps and formal synthesis of unnatural antipode (−)-lycopladine A utilizing diastereoselective protection of carbonyl group in a 1,3-cyclohexanedione derivative. The tricyclic structure of lycopladine A is quite different from those we accomplished recently[3] and the pyridine-fused structural hallmark is also ubiquitous in *Lycopodium* alkaloids such as lycodine[8] and

complanadine E[9] (Fig. 1). Herein we wish to report a facile, alternative approach to this alkaloid.
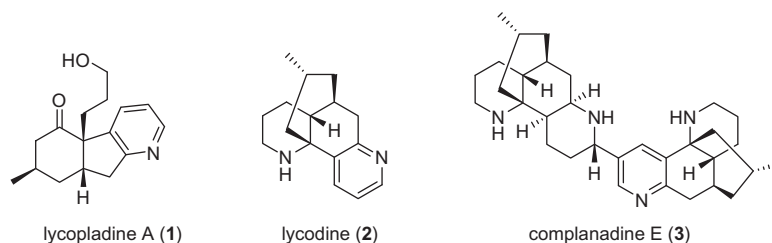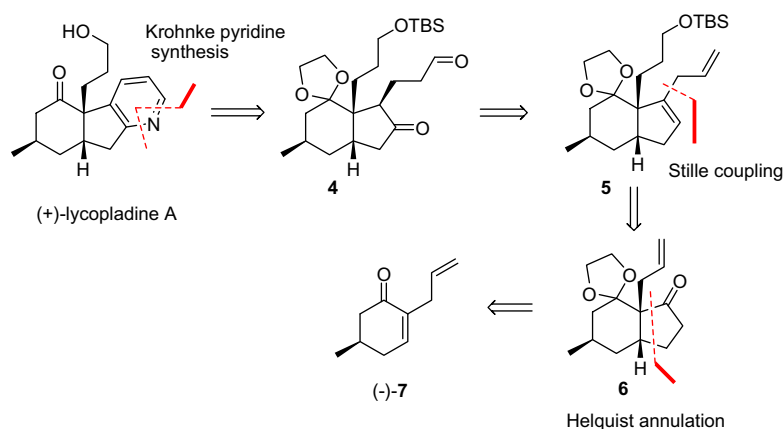
Our retrosynthetic analysis of (+)-lycopladine A (**1**) is outlined in Scheme 1. We conjectured that the Kröhnke pyridine synthesis[10] of 1,5-dicarbonyl compound **4** would set pyridine core in the natural product. Intermediate **4** would then in turn be accessed from diene **5** via hydroboration/oxidation and further oxidation of diol. Allylic side chain of **5** could be attached to the cis-fused 6/5 bicycle **6** from a highly efficient Stille coupling reaction. Eventually, the key cis-fused 6/5 bicycle **6** could be obtained through an efficient Helquist annulation[11] of optical enone (−)-**7**.[12]

Our synthesis commenced with (−)-enone **7**, as shown in Scheme 2. The cis-fused 6/5 bicycle **6** bearing a quaternary center was synthesized in 60% yield from (−)-enone **7** through our reported three-step protocol including Helquist annulation, oxidation, as well as selective acetalation with ethylene glycol.[3b] With this compound in hand, the stage was set to the introduction of the third ring. First of all, enol triflation of the cis-fused 6/5 bicycle **6** gave vinyl triflate **8** in nearly quantitative yield. Hydroboration/ oxidation of the terminal olefin of **8** with 9-BBN and sodium perborate delivered the primary alcohol **9** (82% yield), which was subjected to silyl protection affording a TBS silyl ether protected vinyl triflate **10** in 96% yield. Stille coupling of this vinyl triflate with allyl-tributyl stannane under Pd(PPh3)4/LiCl conditions yielded the coupling product **5** quantitatively.
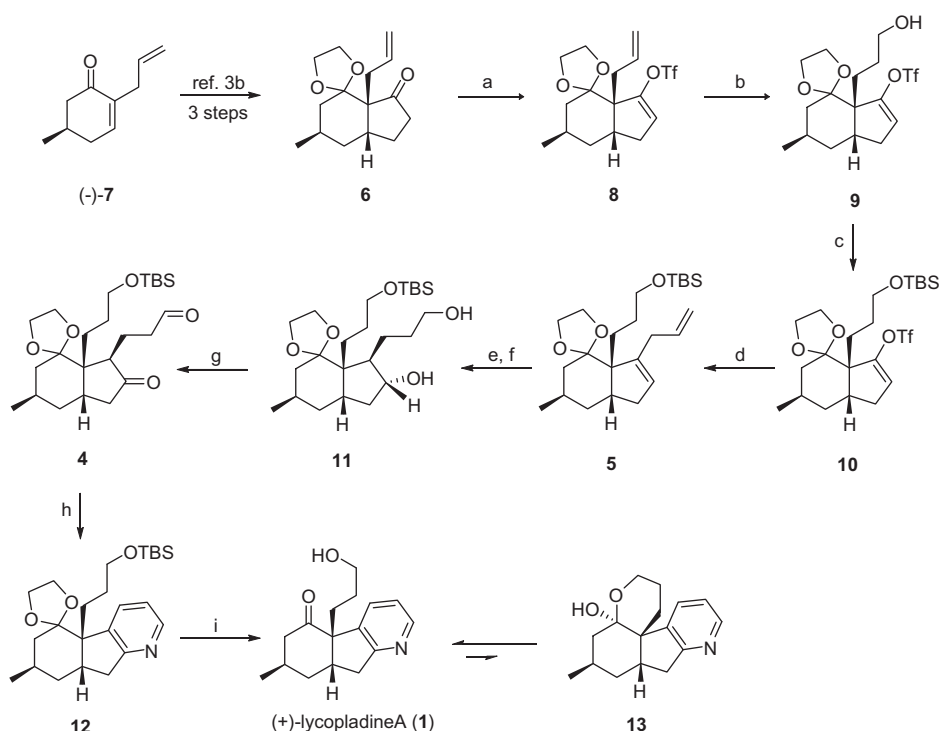
For installation of the two oxygen atoms for the Kröhnke pyridine synthesis, hydroboration/oxidation of the diene **5** was required. At the outset, we tried a sequential addition of 9-BBN, hoping to selectively form a trialkylborane at the allylic position first, and then addition of BH3 and oxidation altogether in one-pot, while this manipulation gave a lower yield than two separate operations outlined in Scheme 2. Diol **11** was obtained in pure

Figure 1. Selected *Lycopodium* alkaloids

Scheme 1. Retrosynthetic analysis of (+)-lycopladine A

Scheme 2. Synthesis of (+)-lycopladine A. Reagents and conditions: (a) KHMDS (1.6 equiv), PhNTf$_2$ (1.6 equiv), THF, −78 °C to −30 °C, 1.5 h, 99%; (b) 9-BBN (3.0 equiv), THF, 0 °C to rt, 2.5 h, then aq NaBO$_3$, 82%; (c) TBSCl (4.0 equiv), imidazole (6.0 equiv), 4-DMAP (0.1 equiv), DMF, rt, 6 h, 96%; (d) allyl–tributyl stannane (2.0 equiv), Pd(PPh$_3$)$_4$ (0.1 equiv), LiCl (6.0 equiv), DMF, 65 °C, 8 h, 100%; (e) 9-BBN (2.5 equiv), THF, rt to 35 °C, 3 h, then 3 N NaOH, 30% H$_2$O$_2$; (f) BH$_3$·Me$_2$S (8.0 equiv), THF, 0 °C to rt, 12 h, then 3 N NaOH, 30% H$_2$O$_2$, 80% in two steps; (g) PCC (3.5 equiv), CH$_2$Cl$_2$, rt, 1 h, 56%; (h) NH$_4$OAc (6.0 equiv), ethanol, 60 °C, 12 h, 50%; (i) 2N HCl, THF, rt, 24 h, 92%.

form and the stereochemistry of the newly generated two stereo-centers was determined by ROESY analysis.[13] Oxidation of diol **11** with PCC furnished 1,5-dicarbonyl compound **4** (56% yield). The next Kröhnke pyridine synthesis was performed uneventfully,

and upon treatment with ammonium acetate in ethanol, this dicarbonyl compound **4** was converted into pyridine **12** smoothly. Global deprotection of pyridine **12** with 2N HCl afforded (+)-lycopladine A (**1**) in excellent yield (92%). The spectral data and

optical rotation for the synthetic lycopladine A were consistent with those reported in the literature.[14] Additionally, as Martin described,[6] we also observed tiny amounts of what appear to be the isomeric lactol **13** (ca. 7% as calculated by ^{1}H NMR spectroscopy) coexisting with lycopladine A.

In summary, a novel efficient synthetic route to (+)-lycopladine A was achieved in 12 steps from enone **7** with 10% overall yield. In the early stage, the cis-6/5 bicyclic system of the target was assembled by the application of Helquist annulation. In the later stage, the pyridine ring was set smoothly through the facile manipulation of Stille coupling reaction, hydroboration/oxidation, and Kröhnke pyridine synthesis. The application of this strategic approach to the synthesis of other *Lycopodium* alkaloids is currently under investigation.

Acknowledgments

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.03.097.

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13. See the Supplementary data section for the ROESY analysis.

14. See the Supplementary data section for a more detailed comparison of the spectral data for synthetic (+)-Lycopladine A compared with the natural (+)-Lycopladine A. The reported optical rotation for natural (+)-lycopladine A by Kobayashi is ($[\alpha]_D^{23}$ + 102, *c* 1.0, MeOH). Our synthetic sample exhibited a rotation of $[\alpha]_D^{22}$ + 130, (*c* 0.4, MeOH). Toste reported $[\alpha]_D^{23}$ + 144, (*c* 0.7, MeOH), and Hiroya documented $[\alpha]_D^{27}$ + 156, (*c* 1.1, MeOH).