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One-Carbon Insertion and Polarity Inversion Enabled a Pyrrole Strategy to the Total Syntheses of Pyridine-Containing *Lycopodium* Alkaloids: Complanadine A and Lycodine

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Abstract

Complanadine A and lycodine are representative members of the *lycopodium* alkaloids with a characteristic pyridine-containing tetracyclic skeleton. Complanadine A has demonstrated promising neurotrophic activity as well as potential for persistent pain management. Herein, we report a pyrrole strategy enabled by one-carbon insertion and polarity inversion for concise total syntheses of complanadine A and lycodine. The use of a pyrrole as the pyridine precursor allowed a rapid construction of their tetracyclic skeleton via a one-pot Staudinger reduction, amine-ketone condensation, and Mannich-type cyclization. The pyrrole group was then converted to the desired pyridine by the Ciamician-Dennstedt rearrangement via a one-carbon insertion process, which also simultaneously introduced a chloride at C3 for the next C-H arylation. Other key steps include a direct *anti*-Markovnikov hydroazidation, a Mukaiyama-Michael addition, and a Paal-Knorr pyrrole synthesis. Lycodine and complanadine A were prepared in 8 and 11 steps, respectively, from a readily available known compound.

Graphical Abstract

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DM and BSM contributed equally.

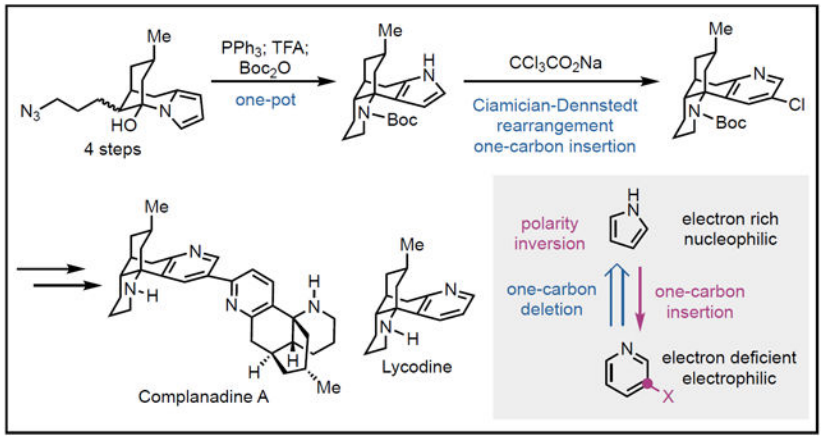
Supporting Information

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

Experimental procedures and spectra data (PDF file)

Cystallographic data for **36** (cif file)

The authors declare no competing financial interest.



Neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease continue to being insurmountable.[1] Recently, exciting progress has been made in amyloid beta-directed monoclonal antibodies for Alzheimer's disease treatment.[2] Meanwhile, naturally-occurring polypeptide neurotrophic factors, such as nerve growth factor (NGF) and brain-derived neurotrophic factor have shown significant therapeutic benefit in treating neurodegenerative disorders.[3] However, these natural biologics suffer from poor bioavailability and pharmacokinetics and require unique administration method. Therefore, there are strong interests in small molecules that can promote the production of natural neurotrophic factors or function like them. These efforts have led to the identification of a collection of natural products with neurotrophic activities.[4] Among them, the *lycopodium* alkaloids stood out because they are enriched with molecules having neurotrophic activities.[5] For examples, huperzine A, an acetylcholinesterase inhibitor, has entered human clinical trial for treating Alzheimer's disease;[6] lyconadin A[7] and complanadine A[8] (**1**, Figure 1A), isolated by Kobayashi and co-workers, demonstrated promising activity in enhancing the mRNA expression for NGF biosynthesis in 1321N1 human astrocytoma cells and the production of NGF in human glial cells. Our interest in the chemical synthesis and biological study of natural products with neurotrophic activities led us to these *lycopodium* alkaloids. In 2014, we reported the total syntheses of lyconadins A and C.[9] Herein, we report our total syntheses of complanadine A (**1**) and lycodine (**4**).

Structurally, complanadine A is an unsymmetrical dimer of lycodine connected via a C2-C3' linkage. Its mono-oxidized analog complanadine B (**2**) and partially reduced analogs complanadines D (**3**) and E were isolated as well.[10] Additionally, lycopladine G (**5**), lycopladine F (**6**), and others featuring a pyridine C3-linkage with an amino acid or its derivative were identified.[11] Biosynthetically, the complanadines and lycodine are proposed to be synthesized from lysine by going through intermediates including pelletierine (**7**) and phlegmarine (**9**, Figure 1B).[12]

Both lycodine and the complanadines have attracted a significant amount of synthetic attention. The groups of Heathcock,[13] Hirama/Tsukano,[14] and Takayama[15] completed elegant total syntheses of lycodine. The reported complanadine A total syntheses are highlighted in Figure 1C. In 2010, the groups of Siegel[16] and Sarpong[17] reported their

total syntheses simultaneously. The Siegel synthesis (18 LLS steps) features two remarkable Co-mediated [2+2+2] cyclizations to form the C2-C3' bipyridine moiety. Their synthesis also led to lycodine. The Sarpong synthesis (15 LLS steps) employed a biomimetic tandem 1,4-addition/Mannich cyclization/amide-ketone condensation to form key intermediate **13**, which was then advanced to triflate **14**. After triflate reduction, an Ir(I)-catalyzed C-H borylation was used to produce boronic ester **15** for the next Suzuki cross coupling with **14** and completion of their complanadine A total synthesis. The Tsukano synthesis (20 LLS steps)[18] reported in 2013 used an intramolecular Heck reaction to build the tetracyclic core (**16→17**) and a Pd-catalyzed C-H arylation between **18** and **19** to forge the C2-C3' linkage. Notably, Siegel et al. identified complanadine A as a selective agonist for the Mas-related G protein-coupled receptor X2, a G protein-coupled receptor that is highly expressed in neurons and functions as a modulator of pain.[19] Thus, complanadine A is also a potential lead compound for persistent pain management.

Retrosynthetically, we deleted one carbon (1C) atom from the pyridine group of complanadine A and lycodine and envisioned a pyrrole as its precursor (Figure 1D). This 1C-deletion strategy is critical for our synthesis because it would invert an electron deficient (electrophilic) pyridine to an electron rich (nucleophilic) pyrrole and enable chemistries that are impossible for the pyridine group. In the forward sense, a 1C-insertion tactic would be needed to convert the pyrrole group to a pyridine, ideally functionalized with a handle for the next C-C bond formation step. In this scenario, the Ciamician-Dennstedt rearrangement[20] would serve the purpose. It goes through a dihalocarbene cycloaddition on a pyrrole followed by ring expansion to provide a 3-halopyridine. Despite its discovery in 1881, the development of the Ciamician-Dennstedt rearrangement is very limited[21] and it has not been used in total synthesis yet. The pyridine to pyrrole retrosynthetic analysis led us to key intermediate **24**, which could be converted to chloropyridine **26** via the Ciamician-Dennstedt rearrangement, then to lycodine and complanadine A. While attractive, we were aware of the potential issues associated with the proposed Ciamician-Dennstedt rearrangement. The rearrangement generally has harsh reaction conditions and the dihalocarbene would prefer the more substituted pyrrole double bond instead of the less substituted one. We were hoping that the steric effect would force the [2+1] cycloaddition on the less substituted double bond. Furthermore, the Reimer-Tiemann formylation is always a competing pathway.[22] In spite of these challenges, we decided to proceed because this unprecedented strategy once successful would provide a new retrosynthetic analysis for pyridine-containing natural products. More importantly, the use of the pyrrole group would enable a quick synthesis of **24** from **22** via an intramolecular Staudinger-aza-Wittig reaction[23] followed by Mannich-type cyclization. The nucleophilicity of the pyrrole group is essential for the proposed Mannich-type cyclization.

Our synthesis started with known enone **27** (Scheme 1), which can be prepared in large scale from chiral pool molecule (*R*)-(+)-pulegone (~ 1$/g) in three steps[24] or via a one-pot asymmetric organ ocatalytic approach in one step.[25] While the terminal olefin can be converted to an alkyl azide via a 3-step sequence (hydroboration-oxidation, activation of the resulting primary alcohol, and nucleophilic substitution with NaN_3), we decided to explore the possibility of installing the azide group via a hypervalent iodine-catalyzed

direct intermolecular *anti*-Markovnikov hydroazidation developed by Xu[26] and Liu[27] independently. After tunings of the reaction conditions developed by Xu et al., **27** was converted to **29** in 42% yield at gram scale with 0.5 equiv. of benziodoxole (**28**). Our unsuccessful attempts to install the pyrrole group directly prompted us to use 1,4-dicarbonyl **32** as the precursor of pyrrole **22**. In this case, an intermolecular Mukaiyama-Michael addition of **30** to **29** was investigated. We were aware that introduction of the azide group at an early stage (cf. **29**) could be problematic due to the potential Schmidt-Aube-type rearrangement.[28] For example, while TBSOTf was able to promote the conjugate addition on a similar substrate without the azide group, it failed on **29**. Eventually, we identified that the azide group could survive the use of triflimide as the promoter at −78 °C. After the reaction was quenched with HCl, product **31** was produced in 70% yield as a 1:1 mixture of epimers at the α position. The 1,4-addition occurred exclusively on the opposite face of the methyl group. This mixture was then subjected to ozonolysis to cleave the terminal olefin for the Paal-Knorr pyrrole synthesis. To our surprise, after **32** was treated with NH_4OAc, the isolated product was not **22**; instead, **33** was obtained as a 1.2:1 epimeric mixture. It turned out that the newly formed pyrrole further reacted with the ketone to form a stable hemiaminal. We decided to push forward with **33** with the hope that the hemiaminal formation is reversible. Staudinger reduction of azide **33** with PPh_3 produced amine **34**. After concentration, **34** was treated with trifluoroacetic acid. Under the acidic conditions, the hemiaminal did open to release the ketone, which further underwent condensation with the primary amine to form iminium ion **23**. The next Mannich-type cyclization afforded tetracyclic product **24**, which was further protected as Boc carbamate **35**. Overall, **35** was obtained in 96% yield from **33** in a one-pot procedure. Notably, both epimers of **33** were funneled to the same product **35**. The structure of **24** was confirmed by X-ray crystallographic analysis of its derivative **36** (CCDC: 2101755).[29]

With multiple grams of **35** in hand, we next concentrated on the Ciamician-Dennstedt rearrangement. Chloropyridine **37** could be obtained in 17% yield with a combination of $CHCl_3$ and KOH to generate the dichlorocarbene, but the major identifiable side product (23%) was produced via the Reimer-Tiemann formylation. The use of $CHBr_3$ and KOH is much less effective while bromopyridine is more reactive for the next cross coupling reaction. After further exploration, we identified that the use of CCl_3CO_2Na to release dichlorocarbene under thermal conditions (70 °C) performed better than the basic conditions and product **37** was obtained in 23%. Further increasing the reaction temperature to 90 °C enhanced the yield to 31%. When the reaction was scaled up to 1 mmol (330 mg) of **35**, **37** was obtained in 27% yield.

With sufficient amount of **37** in hand, we proceeded to complete the total synthesis of lycodine and complanadine A. After removal of the chlorine atom and the Boc protecting group, lycodine was prepared in 8 steps from **27**. For the synthesis of complanadine A, we first tried to prepare a C2 functionalized intermediate such as **39** via C-H stannation of **38**,[30] but failed. Thus, **38** was oxidized to pyridine **N**-oxide **40**. In the Tsukano synthesis, a bromopyridine derivative (**18**, Figure 1C) was used to react with **19**, an analog of **40**. In our case, chloropyridine **37** is much less reactive than bromopyridine **18**. Indeed, when we used the conditions reported by Tsukano et al., C-H arylation of **40** with **37** produced **41** in

low yield. Considering the slow oxidative addition with chloropyridine, we switched to more electron rich ligands and identified the conditions developed by Fagnou and co-workers,[31] which was recently modified and used by Stoltz and co-workers in their total synthesis of jorunnamycin A and jorumycin.[32] Under the Stoltz conditions [$Pd(OAc)_2$, t-$Bu_2MePHBF_4$, Cs_2CO_3, and CsOPiv in toluene at 130 °C], desired product **41** was produced in 66% yield with a 1/3 ratio of**37**/**40** or 78% yield with a 1/4 ratio of **37**/**40**. The excess amount of **40** can be recovered in almost quantitative yield to avoid loss of material. After pyridine **N**-oxide reduction and deprotection, the total synthesis of complanadine A was completed in 11 steps from known compound **27**.

In summary, a pyrrole strategy was developed to synthesize lycodine and complanadine A. The nucleophilic pyrrole group was used as the precursor of an electrophilic pyridine. This polarity inversion strategy enabled an efficient approach featuring a one-pot Staudinger reduction, amine-ketone condensation, and Mannich-type cyclization to rapidly construct the tetracyclic core skeleton. The Ciamician-Dennstedt one-carbon insertion converted the pyrrole group to a chloropyridine for the next C-H arylation for the complanadine A synthesis. These novel chemistries together with an iodine(III)-mediated direct intermolecular *anti*-Markovnikov hydroazidation, a triflimide-promoted Mukaiyama-Michael addition, and a Paal-Knorr pyrrole synthesis enabled us to complete the total syntheses of lycodine in 8 steps and complanadine A in 11 steps from readily available known cyclohexenone **27**.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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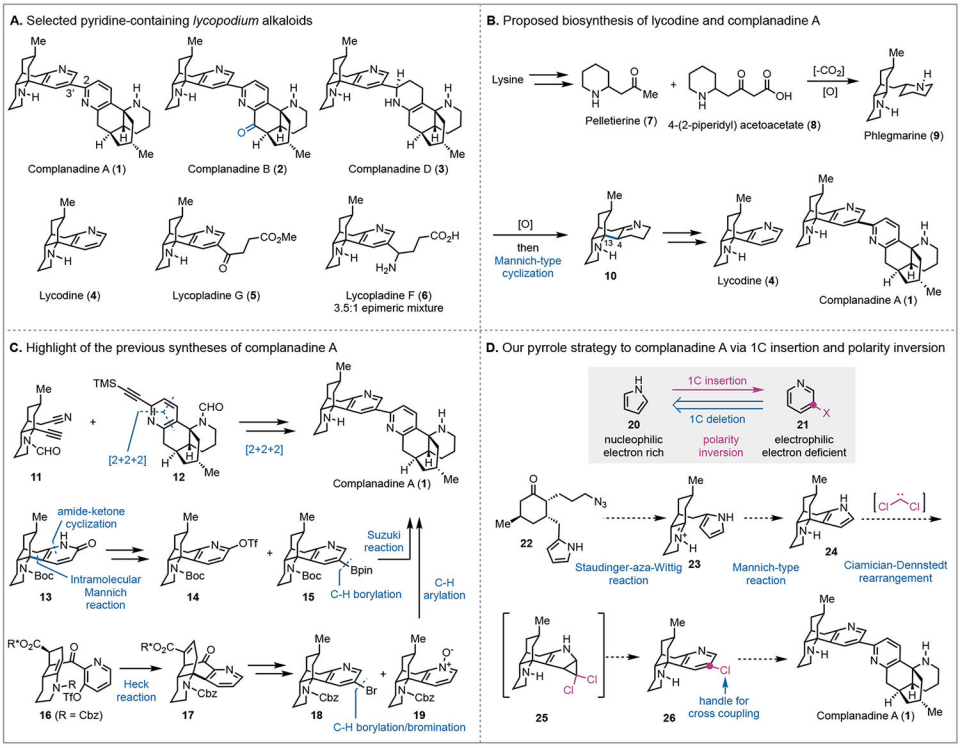
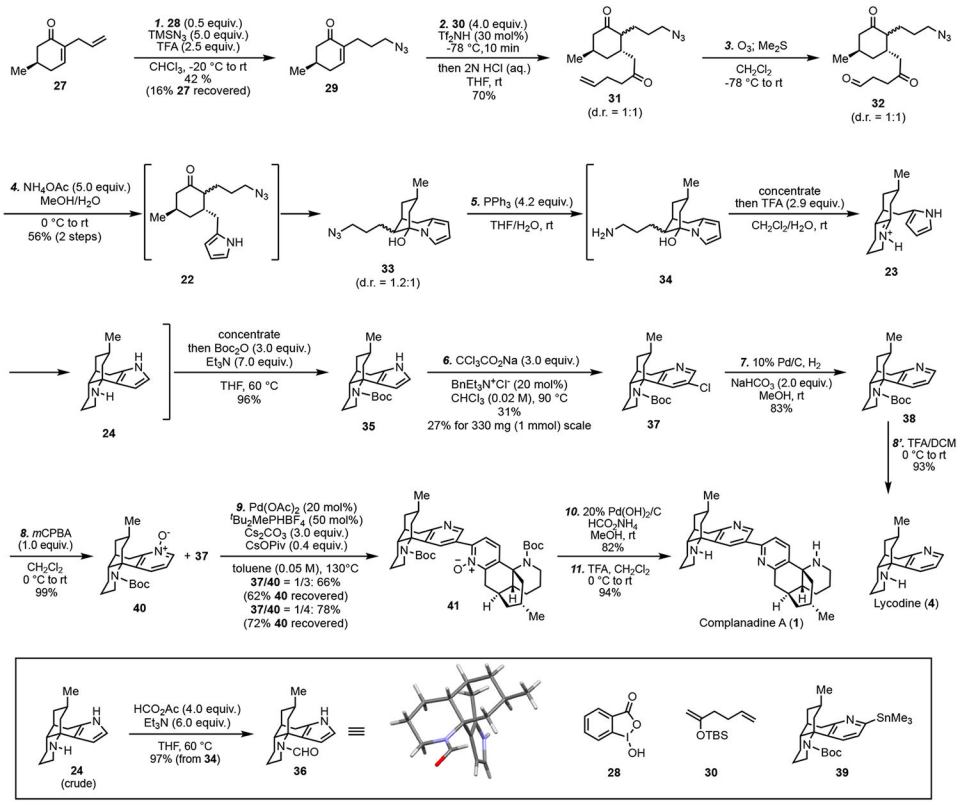


Figure 1.

Lycodine and complanadine natural products, proposed biosynthesis, prior total syntheses, and our synthetic plan.



Scheme 1.

Total synthesis of complanadine A and lycodine.