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Concise Total Synthesis of (±)-Lycodine

Chihiro Tsukano,*[a] Le Zhao,[b] Yoshiji Takemoto,[a] and Masahiro Hirama*[b]

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Lycodine is a representative *Lycopodium* alkaloid, which features a bicyclo[3.3.1]nonane core and pyridine and piperidine rings. Stereoselective total synthesis of lycodine was achieved using Diels–Alder and intramolecular Mizoroki–Heck reactions.

Introduction

Lycodine (**1**, Figure 1) is a representative *Lycopodium* alkaloid that was first isolated from *L. annotinum* by Anet and Eves.[1,2] The structure of **1** was elucidated by using spectroscopic methods and derivatization from the related *Lycopodium* alkaloid β-obscurine.[2,3] This class of alkaloids is structurally characterized by a bicyclo[3.3.1]nonane skeleton with pyridine and piperidine rings. Recently, new dimeric alkaloids with lycodine-type skeletons have been reported. Complanadines (e.g., **2** and **3**) are the most fascinating molecules in this class and were isolated from *L. complanatum* by Kobayashi et al.[4a] These molecules induce secretion of neurotrophic factors (NTF) from 1321N1 cells, which promotes neuronal differentiation of PC-12 cells and enhances expression of mRNA for nerve growing factor (NGF).[4b,4c] The only one total synthesis of racemic **1**, based on an intramolecular Mannich condensation strategy, was developed by Heathcock et al.,[5] whereas several groups have focused on huperzines (e.g., **4**) as a synthetic target.[6,7] Very recently, the total synthesis of complanadine A was reported by Sarpong et al. and Siegel et al. independently.[8] Sarpong et al. also reported the asymmetric synthesis of Boc-protected lycodine.[8a] As a result of the unique structure and interesting biological activities of the lycodine class of alkaloids, we started synthetic studies.

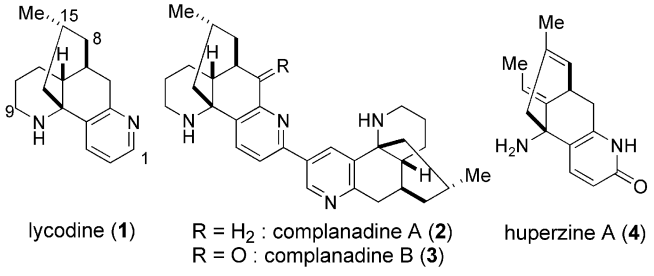
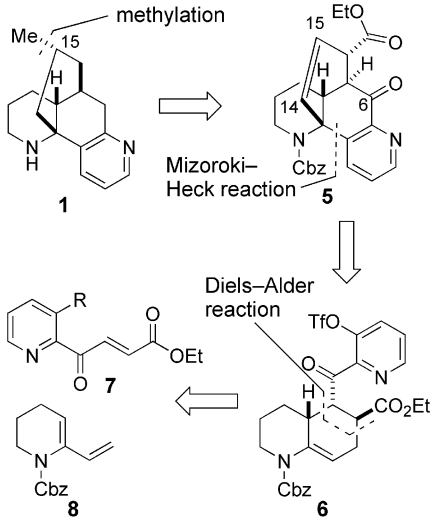


Figure 1. Lycodine and structurally related *Lycopodium* alkaloids.

Here we describe an efficient strategy for the synthesis of lycodine (**1**, Scheme 1). The key features are: (1) 6-*exo*-*trig* intramolecular Mizoroki–Heck cyclization to construct bicyclo[3.3.1]nonane core **5**[9,10] and (2) regio- and stereoselective Diels–Alder reaction of dienophile **7** and diene **8**, leading to octahydroquinoline skeleton **6**.[11,12]



Scheme 1. Retrosynthetic analysis for lycodine (**1**).

Results and Discussion

Our synthesis commenced with the preparation of dienophile **7a** for the Diels–Alder reaction (Scheme 2). TIPS protection of methyl 3-hydroxypicolinate (**9**)[13] followed by

[a] Department of Organic Chemistry, Graduate School of Pharmaceutical Sciences
Kyoto University
Yoshida, Sakyo-ku, Kyoto, Japan
Fax: +81-75-753-4532
E-mail: tsukano@pharm.kyoto-u.ac.jp
[b] Department of Chemistry, Graduate School of Science
Tohoku University
6-3 Aramaki-Aza-Aoba, Aoba-ku, Sendai, Japan
Fax: +81-22-795-6566
E-mail: hirama@mail.tains.tohoku.ac.jp

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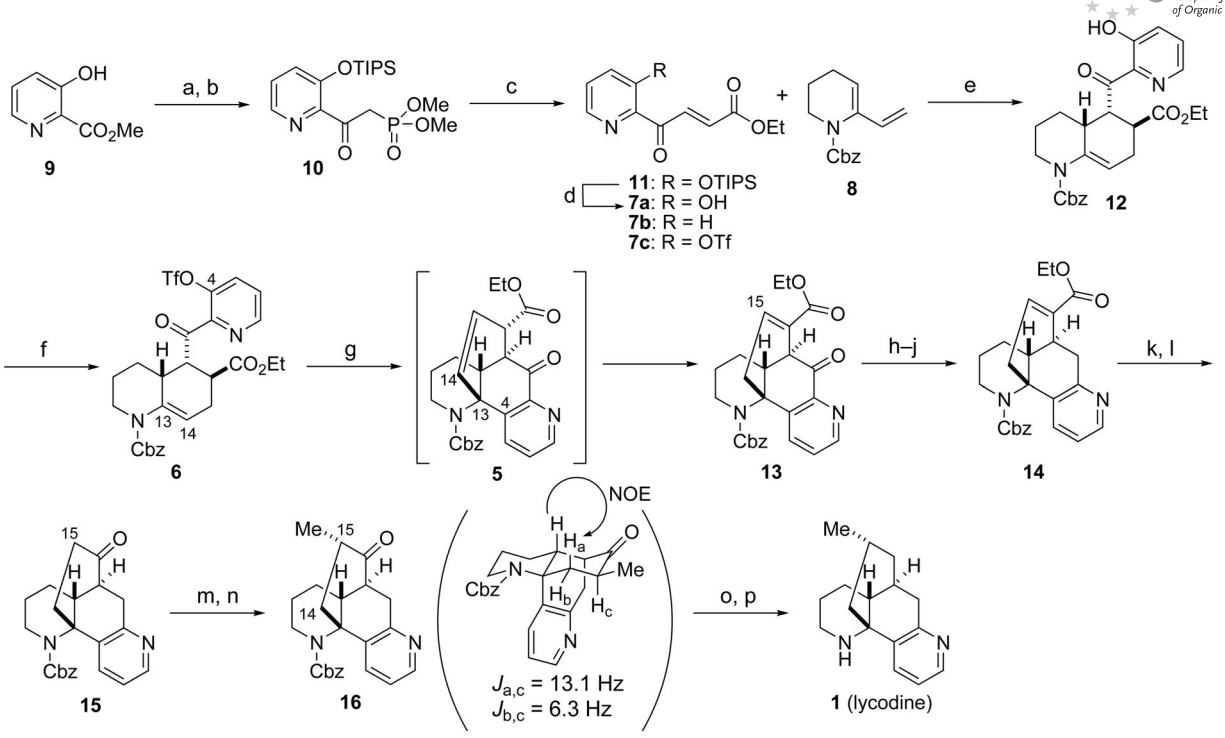

Scheme 2. Total synthesis of lycodine (**1**). Reagents and conditions: (a) TIPSCl, imid., DMF, room temp., 77%; (b) $CH_3P(O)(OMe)_2$, *n*BuLi, THF, –78 °C, 85%; (c) ethyl glyoxylate, *t*BuOK, DME, –30 °C; (d) TBAF, THF, 0 °C to room temp. 42% (2 steps); (e) $NaH_2PO_4{\cdot}2H_2O$, CH_3CN, room temp., 56%, (three isomers, 32%); (f) Tf_2O, Et_3N, CH_2Cl_2, 0 °C to room temp. 91%; (g) $PdCl_2(PPh_3)_2$, Et_3N, DMA, 120 °C, 73%; (h) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C to room temp. 86% (11:1); (i) NaH, CS_2 then MeI, THF, 0 °C to room temp. 84%; (j) nBu_3SnH, AIBN, toluene, 100 °C, 79%; (k) $LiOH{\cdot}H_2O$, MeOH/THF/H_2O, 50 °C; (l) $(PhO)_2P(O)N_3$, Et_3N, toluene/CH_3CN, 0 °C then H_2O, reflux, 98% (2 steps); (m) LiHMDS, TMSCl, Et_3N, THF, –78 °C, 98%; (n) MeI, BTAF, 4 Å MS, THF, 0 °C to room temp. 64%; (o) ethanedithiol, $BF_3{\cdot}OEt_2$, 0 °C to room temp. 93%; (p) Raney Ni (W-2), EtOH, reflux, 85%. TIPS = triisopropylsilyl, DMF = *N*,*N*-dimethylformamide, DME = 1,2-dimethoxyethane, TBAF = tetra-*n*-butylammonium fluoride, Tf = trifluoromethanesulfonyl, Cbz = benzyloxycarbonyl, Boc = *tert*-butoxycarbonyl, DMA = *N*,*N*-dimethylacetamide, AIBN = 2,2′-azobisisobutylnitrile, HMDS = hexamethyldisilazane, TMS = trimethylsilyl, BTAF = benzyltrimethylammonium fluoride.

treatment with dimethyl methylphosphonate and *n*BuLi gave β-ketophosphonate **10** in 65% yield for the two steps. Horner–Wadsworth–Emmons reaction of **10** and ethyl glyoxalate furnished α,β-unsaturated γ-keto esters **11** and **7a** (6:1) and a small amount of *cis*-olefin. TIPS deprotection and separation of the *cis*-isomer gave dienophile **7a** as a single isomer.

Diels–Alder reaction of dienophile **7a** with known diene **8**[10] proceeded smoothly in toluene at 110 °C to give a mixture of four isomers without double bond isomerization in good yield (87%, 6:2:3:1).[14] Desired major product **12** could be isolated by silica gel column chromatography, and the stereochemistry of **12** was determined by extensive NMR spectroscopic analysis including NOESY experiments.[15] When dienophile **7b** or **7c**[16] was employed for the Diels–Alder reaction, lower regioselectivity was observed. We explored the effects of reaction temperature, solvent, and additives with the use of **7a**. The addition of $NaH_2PO_4{\cdot}2H_2O$ (1 equiv.) in acetonitrile at room temperature gave an 88% yield with good selectivity (9:1:3:1.5).

After triflation of Diels–Alder product **12**, intramolecular Mizoroki–Heck reaction was investigated for constructing the bicyclo[3.3.1]nonane core. Compound **6** was treated with a catalytic amount of $PdCl_2(PPh_3)_2$ and triethylamine in dimethylacetamide at 120 °C. The reaction afforded α,β-unsaturated ester **13** in 18% yield via putative 6-*exo*-*trig* product **5**, which was immediately isomerized under the reaction conditions. The low yield was anticipated to be due to deactivation of the palladium catalyst by chelation of the pyridyl ketone unit of two molecules of **6**. Therefore, dilute conditions (0.005 M) were employed to optimize the yield (73%).

After synthesis of valuable intermediate **13**, the goal was to stereoselectively introduce the C15 methyl group to complete the total synthesis. Reduction of ketone **13** under Luche conditions afforded a mixture of epimeric alcohols (*dr* = 11:1). Subsequent formation of the xanthate followed by Barton–McCombie deoxygenation[17] produced compound **14** in 58% overall yield. Introduction of the C15 methyl group was unsuccessful with α,β-unsaturated ester **13** and **14** with the use of various organocopper reagents.[18] Therefore, ester **14** was hydrolyzed under basic conditions, and the resultant carboxylic acid was decarboxylated by Curtius rearrangement by using diphenylphosphoryl azide (DPPA)[19] followed by hydrolysis to give ketone **15** in 98% yield. After formation of the silyl enol ether, the methyl group was introduced stereoselectively by treatment with iodomethane, benzyltrimethylammonium fluoride (BTAF), and 4 Å molecular sieves to afford methyl ketone **16** in 63% yield for the two steps.[20] The stereochemistry was con-

firmed by extensive NMR spectroscopic analysis including NOESY experiments. Thioacetalization of ketone **16** with ethanedithiol and $BF_3{\cdot}OEt_2$ and subsequent one-pot reduction and deprotection of the Cbz group by using Raney Ni (W-2) resulted in completion of the total synthesis of (±)-lycodine (**1**). Spectroscopic (^{1}H NMR, ^{13}C NMR, UV, IR) and high-resolution mass spectrometric data of the synthetic sample were identical to those of the natural product.[21]

Conclusions

In conclusion, we established a convenient synthetic route to (±)-lycodine (**1**) by using Diels–Alder and intramolecular Mizoroki–Heck reactions [total 15 steps from methyl 3-hydroxypicolinate (**11**)]. This strategy will be readily applicable to the total syntheses of related natural products including complanadines and synthetic analogues for structure–activity relationship studies.

Experimental Section

Supporting Information (see footnote on the first page of this article): Experimental details and copies of the ^{1}H and ^{13}C NMR spectra of all new compounds.

Acknowledgments

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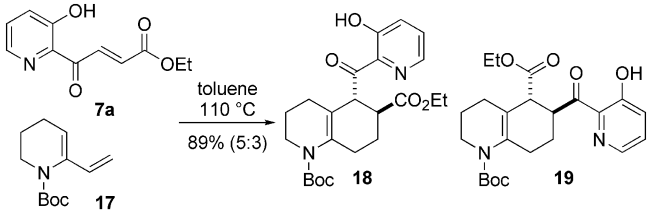
[14] Diels–Alder reaction of **7a** and **17** produced a mixture of isomerized products **18** and **19** in 89% yield (5:3).



[15] We also determined the stereochemistry of the other three isomers of **15** by extensive NMR spectroscopic analysis. See the Supporting Information.
[16] Dienophile **7b** was prepared from methyl picolinate in two steps including Horner–Wadsworth–Emmons reaction. Dienophile **7c** was obtained by triflation of **7a**.
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