Total Synthesis of Lycoposerramine-R

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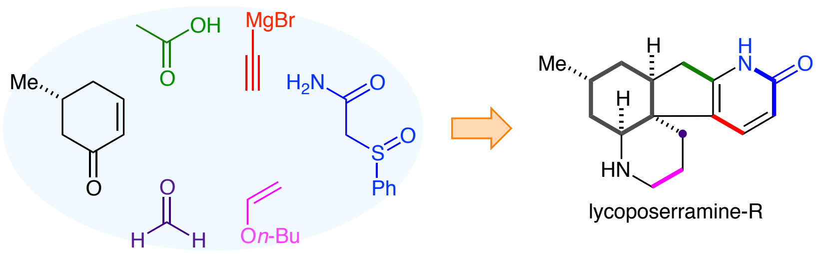

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Abstract The total synthesis of lycoposerramine-R was accomplished. The synthesis features a Claisen-Ireland rearrangement to install a two-carbon unit and a hetero-Diels-Alder reaction to form a cyclic enol ether, which reacted with an ethynyl group to construct the *cis*-hydrindane core containing a quaternary carbon. A 2-pyridone synthesis using 2-(phenylsulfinyl)acetamide was applied to the completion of the synthesis.

Key words alkaloids, Diels-Alder reaction, enone, gold catalyst, heterocycles, quaternary carbon, rearrangement

A variety of Lycopodium alkaloids have been isolated to date[1] and the proposed biosynthetic pathways assist in understanding the structural relationships of the diverse array of the molecules. The Lycopodium alkaloids thus can be classified into several groups. The fawcettimine-type skeleton features a [6-5] bicyclic core, *cis*-hydrindane (Figure 1). The lycodine-type skeleton has a pyridine or a 2-pyridone fused to the bicyclo[3.3.1]nonane core. Lycoposerramine-R (**1**), isolated by Takayama and coworkers in 2009,[2] includes both structural features. That is, it is a tetracyclic compound containing a *cis*-hydrindane fused with a 2-pyridone. A piperidine ring is also fused to the *cis*-hydrindane, sharing a quaternary carbon at C12. These characteristic structural features render lycoposerramine-R a good target for synthetic studies, and four total syntheses have been reported to date.[3] We also initiated our own synthetic program in this context.

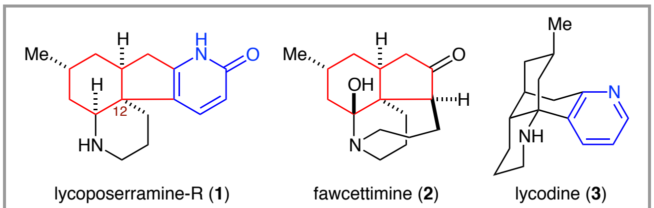
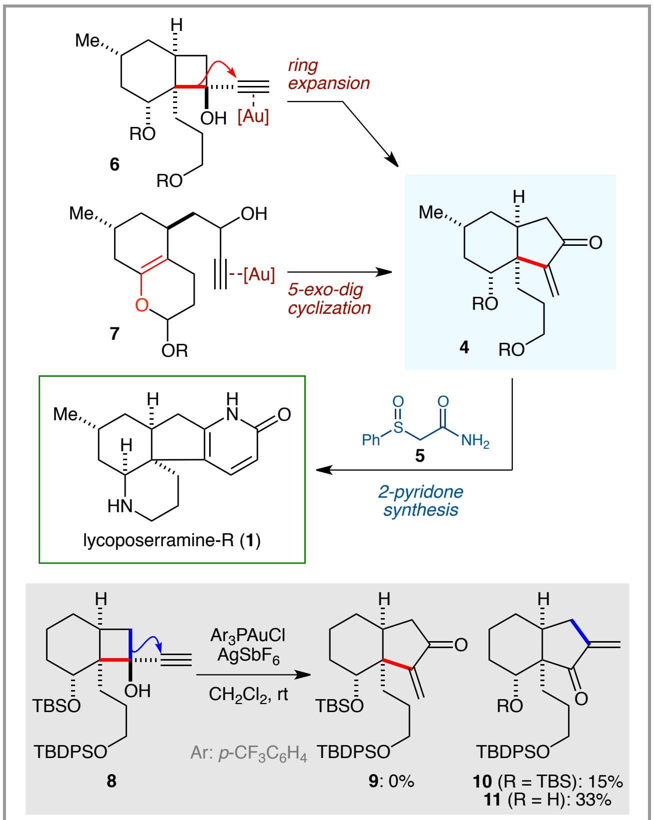


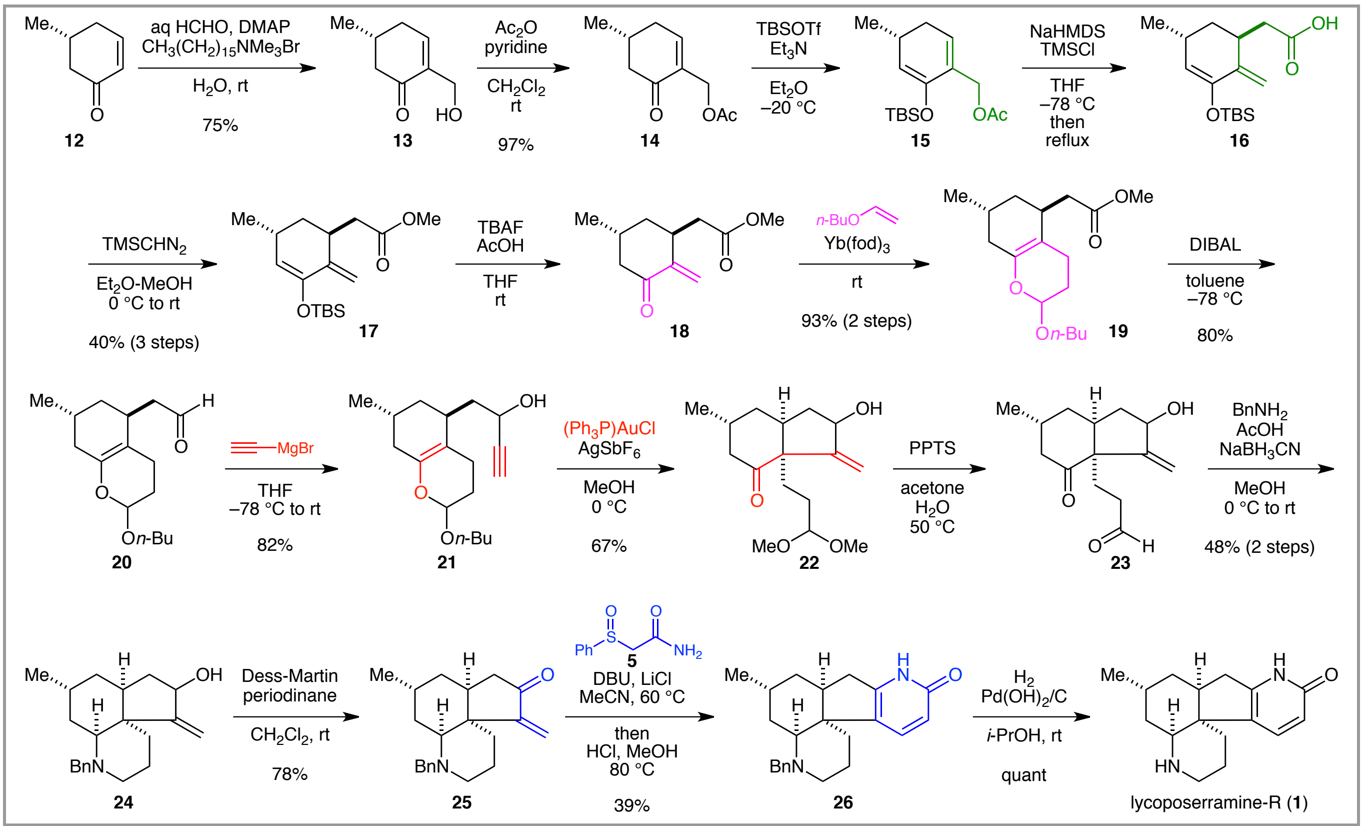
Figure 1 Structures of selected Lycopodium alkaloids.



Scheme 1 Synthetic Plan toward Lycoposerramine-R

We envisioned that the 2-pyridone ring could be formed by means of our protocol,[4] which requires enone **4** as the substrate (Scheme 1). In order to achieve the concurrent construction of the enone moiety and the bicyclic carbon skeleton containing a quaternary carbon at the ring juncture, we employed two Au-mediated strategies: ring expansion and 5-*exo-dig* cyclization.[5,6,7] Unfortunately, the former strategy resulted in the opposite selectivity, giving **10** and **11** as the only products. Therefore, we investigated the latter strategy for the 5-*exo-dig* cyclization. Recent total synthesis of lycoposerramine-R by Trauner and coworkers via a related cyclization reaction under basic conditions[3d] prompted us to disclose our total synthesis of lycoposerramine-R. The present synthesis is characterized by a Au-mediated cyclization between an ethynyl group and a cyclic enol ether moiety that could be derived via a hetero-Diels-Alder reaction of an enone.

Our synthetic route to lycoposerramine-R is shown in Scheme 2. A Morita-Baylis-Hillman reaction of the known enone **12**[8] in an aqueous cationic micellar solution afforded hydroxy ketone **13**,[9] which was acetylated to give acetate **14**. After protecting the ketone moiety as its silyl enolate, a Claisen-Ireland rearrangement was conducted.[10] Thus, **15** was treated with NaHMDS and TMSCl, and the resulting mixture was refluxed in THF to furnish carboxylic acid **16**, which was esterified with trimethylsilyldiazomethane, giving methyl ester **17** in 40% yield in three steps. Removal of the silyl group in **17** using TBAF and acetic acid liberated labile enone **18**, which was immediately reacted with *n*-butyl vinyl ether in the presence of a catalytic amount of Yb(fod)$_3$ to afford cyclic enol ether **19** in 93% yield.[11,12] In addition to the introduction of a two-carbon unit, this hetero-Diels-Alder reaction realized both protection and regioselective activation of the ketone moiety as its enol ether. The ester moiety in **19** was reduced with DIBAL to furnished aldehyde **20**, into which an ethynyl group was introduced. When the resultant propargyl alcohol **21** was treated with a gold catalyst in methanol, a cyclization reaction between the ethynyl group and the enol ether moiety occurred in the 5-*exo-dig* manner. Subsequently, the pyrane ring was cleaved to form a dimethyl acetal moiety, resulting in the production of **22** in 67% yield.[13] Acidic hydrolysis of the dimethyl acetal afforded aldehyde **23**, which was subjected to reductive amination with benzylamine to give tricyclic compound **24**.[3a] Dess-Martin oxidation of **24** furnished enone **25**,[14] which was converted into 2-pyridone **26** according to our procedure.[4] Thus, conjugate addition of 2-(phenylsulfinyl)acetamide (**5**) into the enone moiety, followed by cyclization and sulfoxide elimination under acidic conditions, produced **26**.[15] Finally, hydrogenolysis of the benzyl group on the nitrogen atom gave lycoposerramine-R (**1**).[16]



Scheme 2 Total Synthesis of Lycoposerramine-R.

In summary, we achieved a total synthesis of lycoposerramine-R, starting from a known enone. The Claisen-Ireland rearrangement introduced a two-carbon unit and a hetero-Diels-Alder reaction formed a cyclic enol ether. A Au-mediated cyclization reaction of the cyclic enol ether with an ethynyl group formed the bicyclic carbon skeleton having a quaternary carbon. The 2-pyridone ring was constructed via a reaction using 2-(phenylsulfinyl)acetamide.

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Supporting Information

Yes

Primary Data

No

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(13) **(3a*S*,6*R*,7a*S*)-3a-(3,3-Dimethoxypropyl)-2-hydroxy-6-methyl-3-methylenehexahydro-1*H*-inden-4(2*H*)-one (22)**: To a solution of propargyl alcohol **21** (173 mg, 0.591 mmol) in MeOH (6.0 mL) was added the supernatant of a suspension of gold triphenylphosphine chloride and silver hexafluoroantimonate (0.059 M in MeOH, 1.0 mL, 0.059 mmol) at 0 °C. After stirring for 11 h, the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc. The organic layer was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (hexane:EtOAc = 1:1) to give allyl alcohol **22** (113 mg, 0.400 mmol, 67%) as a pale yellow oil. This material was obtained as a 3:2 mixture of two diastereomers, containing a small amount of impurities. $[\alpha]_D^{21}$: 39.4° (*c* 0.97, $CHCl_3$); IR (film, cm^{-1}): 3445, 2955, 2359, 2249, 1698, 1456, 1383, 1191, 1128, 1053, 910; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.47 (d, *J* = 1.4 Hz, (3/5)1H), 5.45 (d, *J* = 2.3 Hz, (2/5)1H), 5.13 (m, 1H), 4.56 (m, (3/5)1H), 4.40 (m, (2/5)1H), 4.33 (m, 1H), 3.32 (s, (3/5)3H), 3.31 (s, (2/5)3H), 3.30 (s, (3/5)3H), 3.30 (s, (2/5)3H), 2.69 (m, (3/5)1H), 2.50-2.02 (m, 3H+(2/3)1H), 1.93-1.46 (m, 8H+(3/5)1H), 1.41 (m, (2/5)1H), 1.00 (d, *J* = 6.4 Hz, (2/5)3H), 0.98 (d, *J* = 6.4 Hz, (3/5)3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 211.8, 211.4 (C), 155.2, 154.4 (C), 113.8, 112.2 (CH_2), 104.5, 104.5 (CH), 73.7, 73.4 (CH), 61.0, 60.4 (C), 53.0, 52.8 (CH_3), 46.8, 46.6 (CH_2), 40.2, 40.1 (CH), 38.7, 38.1 (CH_2), 33.6, 33.2 (CH_2), 30.5, 30.4 (CH_2),

28.7, 28.7 (CH), 28.1, 27.9 (CH_2), 21.8, 21.1 (CH_3); HRMS (ESI+): 305.1731 (calcd for $C_{16}H_{26}NaO_4$ 305.1729).

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(15) **(4a*S*,6*R*,7a*S*,12b*S*)-4-Benzyl-6-methyl-1,2,3,4,4a,5,6,7,7a,8-decahydropyrido[2',3':4,5]cyclopenta[1,2-*e*]quinolin-10(9*H*)-one (26)**: To a solution of enone **25** (27.4 mg, 0.088 mmol), LiCl (37.5 mg, 0.885 mmol) and 2-(phenylsulfinyl)acetamide (**5**, 64.5 mg, 0.354 mmol) in MeCN (1.0 mL) was added DBU (0.13 mL, 0.88 mmol) at rt.The mixture was warmed up to 60 °C and stirred for 3 h. After cooling to rt, hydrogen chloride in MeOH (5~10%, 2.0 mL) was added to the mixture. The mixture was warmed up to 80 °C and stirred for 42 h. The reaction was quenched with saturated aqueous NaHCO3. The mixture was extracted with EtOAc. The organic layer was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The crude product was purified by PTLC (CH_2Cl_2:MeOH = 19:1) to give pyridone **26** (11.8 mg, 0.034 mmol, 39%). $[\alpha]_D^{21}$: –23.7° (*c* 0.59, $CHCl_3$); IR (film, cm^{-1}): 2926, 2859, 2790, 1652, 1604, 1551, 1467, 1093, 832; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.38 (d, *J* = 9.2 Hz, 1H), 7.38-7.23 (m, 5H), 6.38 (d, *J* = 9.2 Hz, 1H), 4.18 (d, *J* = 13.0 Hz, 1H), 3.32 (dd, *J* = 17.4, 7.3 Hz, 1H), 2.91 (m, 1H), 2.81 (d, *J* = 13.0 Hz, 1H), 2.52 (dd, *J* = 11.6, 5.2 Hz, 1H), 2.42 (d, *J* = 17.4 Hz, 1H), 2.29 (m, 1H), 1.88 (ddd, *J* = 12.0, 12.0, 3.2 Hz, 1H), 1.71-1.32 (m, 8H), 1.23 (m, 1H). 0.92 (d, *J* = 6.4 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 166.1 (C), 150.1 (C), 143.1 (CH), 140.3 (C), 128.9 (CH), 128.3 (CH), 126.7 (CH), 125.1 (C), 114.9 (CH), 62.6 (CH), 58.0 (CH_2), 54.1 (CH_2), 49.2 (C), 43.3 (CH), 39.1 (CH_2), 36.8 (CH_2), 36.0 (CH_2), 33.1 (CH_2), 24.6 (CH), 22.1 (CH_3), 21.8 (CH_2); HRMS (ESI+): 371.2099 (calcd for $C_{23}H_{28}N_2NaO$ 371.2099).

(16) **Lycoposerramine-R (1)**: To a solution of **26** (11.8 mg, 0.033 mmol) in *i*-PrOH (1.0 mL) was added 20% $Pd(OH)_2$/C (47.5 mg, 0.033 mmol) at rt. The mixture was stirred for 4.5 h at rt under 1.0 atm hydrogen. The mixture was filtered through a pad of NH_2 silica gel. The solvent was removed under reduced pressure. The crude product was purified by PTLC (CH_2Cl_2:MeOH = 19:1) to give lycoposerramine-R (**1**, 8.6 mg, 0.033 mmol, quant). $[\alpha]_D^{21}$: –28.6° (*c* 0.43, $CHCl_3$); IR (film, cm^{-1}): 2925, 2851, 2801, 1650, 1600, 1550, 1466, 1437, 1093, 832, 753; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.32 (d, *J* = 9.2 Hz, 1H), 6.34 (d, *J* = 9.2 Hz, 1H), 3.21 (dd, *J* = 16.8, 6.4 Hz, 1H), 3.17 (m, 1H), 2.90 (dd, *J* = 12.0, 4.8 Hz, 1H), 2.79 (ddd, *J* = 11.6, 11.6, 3.2 Hz, 1H), 2.33 (d, *J* = 16.8 Hz, 1H), 2.19 (ddd, *J* = 6.9, 6.9, 6.9 Hz, 1H), 1.78 (m, 1H), 1.68 (m, 1H), 1.60 (m, 1H), 1.52 (m, 1H), 1.46 (m, 1H), 1.45 (m, 2H), 1.43 (m, 1H), 1.24 (m, 1H), 1.18 (m, 1H), 0.97 (d, *J* = 7.6 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 166.1 (C), 150.3 (C), 143.3 (CH), 124.5 (C), 114.7 (CH), 57.1 (CH), 49.3 (C), 48.0 (CH_2), 41.7 (CH), 38.1 (CH_2), 36.1 (CH_2), 36.0 (CH_2), 34.8 (CH_2), 25.6 (CH), 22.9 (CH_2), 20.5 (CH_3); HRMS (ESI+): 281.1623 (calcd for $C_{16}H_{22}N_2NaO$ 281.1629).