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# Total Synthesis of (−)-Lycoperine A

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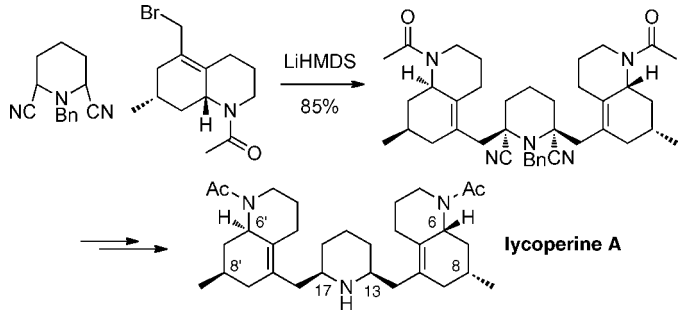
## ABSTRACT




**Lycoperine A was synthesized through a highly convergent route in which a double alkylation of 2,6-dicyano-*N*-benzylpiperidine with the octahydroquinoline moiety gave the lycoperine skeleton. The octahydroquinoline was prepared by a desymmetrization reaction of 5-methylcyclohexane-1,3-dione. Hydrolysis, reductive amination, and cyclization gave lycoperine A in 13 steps and 3% overall yield. The absolute configuration of lycoperine A was assigned as 6*R*,6′*R*,8*R*,8′*R*,13*S*,17*R*.**

*Lycopodium* alkaloids are an important class of natural products due to their diversity and their varied biological activities.[1] Several of these alkaloids inhibit acetylcholinesterase (AChE), which is responsible for the breakdown of the neurotransmitter acetylcholine. After the discovery of this significant biological activity around 1986,[2] there was a surge of interest in *Lycopodium* alkaloids, and subsequently numerous new alkaloids in this class were discovered and characterized.[1] In the time span from 1993 to 2004, 81 new *Lycopodium* alkaloids had been reported.[1] Of the *Lycopodium* alkaloids discovered in the 1980s, huperzine A (HupA) demonstrated the greatest inhibition of acetylcholinesterase, and its synthesis was first reported by Qian and Ji in 1989.[3] Recent studies subjecting rats to HupA have demonstrated increased efficiency in learning and memory and have been considered potential lead compounds for the treatment of Alzheimer's disease.[4]

*Lycopodium* alkaloids have also attracted significant interest from synthetic chemists due to their unique and complex structures. The four classes of *Lycopodium* alkaloids are the phelgmarine, lycodine, lycopodine, and fawcettimine (Figure 1).[1,5,6] Lycopodine was the first of this class discovered in 1881 by Bodecker.[7] Phlegmarine[8] is a representative of the most recently discovered class, described as the "miscellaneous group".[5] They are structurally related through their common quinolizine, quinoline, pyridine, or α-pyridone ring systems. They generally contain 16 carbons or as dimers 32 carbons.

(1) Ma, X.; Gang, D. R. *Nat. Prod. Rep.* **2004**, *21*, 752–772.
(2) (a) Tang, X. C.; Han, Y. F.; Chen, X. P.; Zhu, X. D. *Acta Pharmacol. Sin.* **1986**, *7*, 507–511. (b) Tang, X. C.; De Sarno, P.; Sugaya, K.; Giacobini, E. *J. Neurosci. Res.* **1989**, *24*, 276–285.
(3) Qian, L.; Ji, R. *Tetrahedron Lett.* **1989**, *30*, 2089–2090.
(4) (a) Zhang, R. W.; Tang, X. C.; Han, Y. Y.; Sang, G. W.; Zhang, Y. D.; Ma, Y. X.; Zhang, C. L.; Yang, R. M. *Acta Pharmacol. Sin.* **1991**, *12*, 250–252. (b) Jiang, H. L.; Luo, X. M.; Bai, D. L. *Curr. Med. Chem.* **2003**, *10*, 2231–2252.
(5) Ayer, W. A.; Trifonov, L. S. *Lycopodium Alkaloids*; Academic Press: San Diego, 1994.
(6) Bisai, A.; West, S. P.; Sarpong, R. *J. Am. Chem. Soc.* **2008**, *130*, 7222–7223.
(7) Bodeker, K. *Justus Liebigs Ann. Chem.* **1881**, *208*, 363.
(8) Nyembo, L.; Goffin, A.; Hootele, C.; Jean Claude, B. *Can. J. Chem.* **1978**, *56*, 851–856.

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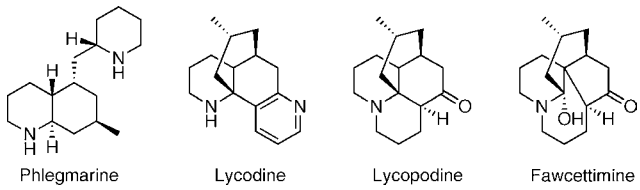
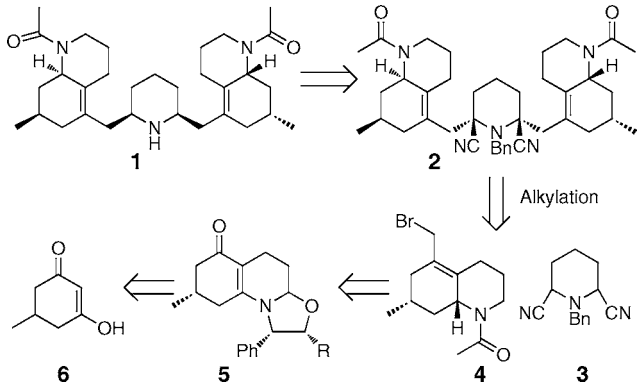



**Figure 1.** Classes of lycopodium alkaloids.

Lycoperine A (**1**) was recently isolated from the club moss *Lycopodium hamiltonii* in Japan by Kobayashi and coworkers from Hokkaido University.[9] This compound exhibited a moderate inhibitory activity against acetylcholine esterase from bovine erythrocyte. The structure and the relative stereochemistry of lycoperine A were determined by detailed 2D NMR studies after conversion to the *N*-diethyl analogue by the reduction of the acetamide moieties, but its absolute configuration was not determined. This compound has a characteristic pseudosymmetric structure in which two identical octahydroquinoline rings are linked to a central 2,6-*cis*-disubstituted piperidine ring. We report here the total synthesis of lycoperine A and its absolute configuration.

Our retrosynthetic analysis for lycoperine A is shown in Scheme 1. The plan called for the generation of lycoperine

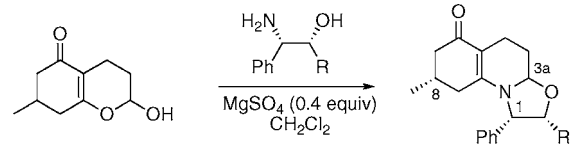
**Scheme 1.** Retrosynthetic Analysis for Lycoperine A




A by reductive decyanation of the dinitrile **2** and is based on precedent from Husson's program.[10] The dinitrile **2** would arise from a double alkylation of 2,6-dicyano-*N*-benzylpiperidine (**3**) with the octahydroquinoline **4**. The synthesis of **4** was envisioned to come from elaboration of vinylogous amide **5**, which itself would be prepared by a desymmetrization reaction. The starting material for the synthesis was 5-methylcyclohexane-1,3-dione (**6**). The configuration of the natural product would be derived from a chiral amino alcohol auxiliary.

Preparation of the octahydroquinoline segment was based on precedent from Lhommet and from Bosch.[11,12] Diketone **6** was combined with acrolein to produce hemiacetal **7**, a cyclic version of the underlying symmetric dione. Desymmetrization by condensation with amino alcohol auxiliaries **8** and **9** led to the formation of vinylogous amides **10** and **11**, respectively (Table 1). The condensation with **8** was

**Table 1.** Desymmetrization of Hemiacetal **7** with Amino Alcohols




**7** **8** (R = H) **9** (R = Ph) **10** (R = H) **11** (R = Ph)

| entry | auxiliary | Lewis acid[a] | conditions | yield | dr[b] |
|---|---|---|---|---|---|
| 1 | **8** (2 equiv) | $Zn(ClO_4)_2 \cdot 6H_2O$ | rt, 15 h | 100[c] | 2.7:1 |
| 2 | **8** (2 equiv) | $Sc(OTf)_3$ | 0 °C, 2 d | 96[c] | 2.7:1 |
| 3 | **8** (2 equiv) | $Cu(OTf)_2$ | 0 °C, 2 d | 92[c] | 4:1 |
| 4 | **9** (2 equiv) | $Cu(OTf)_2$ | 0 − 10 °C, 16 h | 95[d] | 20:1[f] |
| 5 | **9** (1.1 equiv) | $Cu(OTf)_2$[e] | 0 °C, 22 h | 96[d] | 20:1[f] |

[a] The Lewis acid was used in 5 mol % quantities unless otherwise noted. [b] The dr between C1 and C8 is reported and was estimated from NMR spectroscopy. Epimers at C3a were also observed in roughly a 10:1 dr with amino alcohol **8**. [c] The product was **10**. [d] The product was **11**. [e] Only 3 mol % of the Lewis acid was used. [f] The crude mixture was ca. 92:5:2:1 by NMR analysis, but the two minor isomers were removed on chromatography.

efficient using several different Lewis acids, but the desymmetrization to set the C8 methyl center resulted in very modest selectivities (entries 1−3). Switching to the amino alcohol **9** led to much more effective desymmetrization, with ca. 95:5 dr at the C8 stereogenic center. Copper triflate was the best catalyst, and 3 mol % of the catalyst was effective (entry 5). Minor diastereomers were produced with both auxiliaries, but in the case of **9** they could be separated on silica gel chromatography to deliver the vinylogous amide **11** in 96% yield. The relative configuration of compound **11** was confirmed by X-ray crystallography.[13] This unusual desymmetrization strategy[12d] allowed the C8 stereogenic center to be introduced efficiently from a racemic precursor.

Synthesis of the octahydroquinoline **4** is presented in Scheme 2. Optimized conditions for the desymmetrization

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(10) Husson, H.-P.; Royer, J. *Chem. Soc. Rev.* **1999**, *28*, 383–394.

(11) (a) Noël, R.; Vanucci-Bacque, C.; Fargeau-Bellassoued, M.-C.; Lhommet, G. *J. Org. Chem.* **2005**, *70*, 9044–9047. (b) Noel, R.; Fargeau-Bellassoued, M. C.; Vanucci-Bacque, C.; Lhommet, G. *Synthesis* **2008**, 1948–1954. (c) Noel, R.; Vanucci-Bacque, C.; Fargeau-Bellassoued, M. C.; Lhommet, G. *Eur. J. Org. Chem.* **2007**, 476–486.

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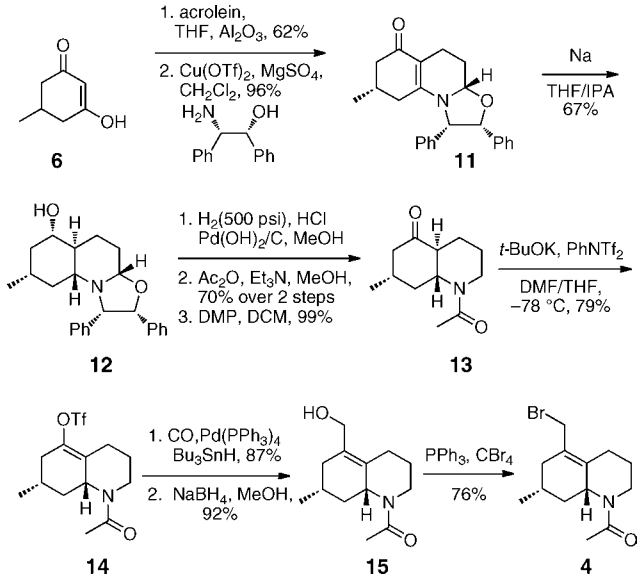
(13) Details of the X-ray structures for compounds **11**, **12**, and **13** are included in Supporting Information.

**Scheme 2.** Synthesis of Allyl Bromide **4** for Double Alkylation

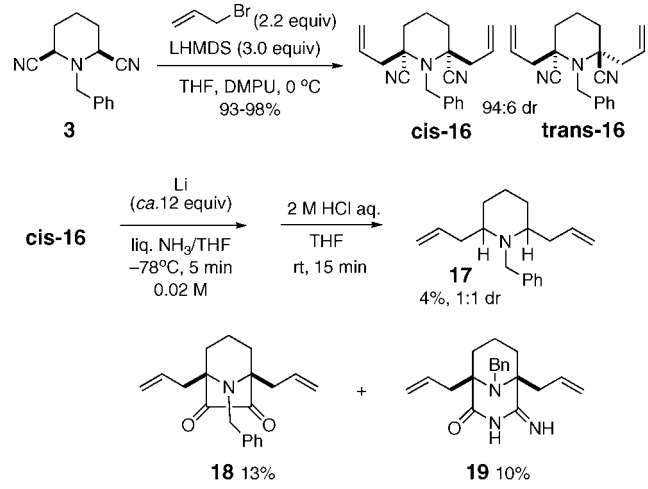



led to vinylogous amide **11** with excellent diastereoselectivity. Attempts to reduce the tetrasubstituted double bond by hydrogenation were unsuccessful, and so we turned to dissolving metal conditions. On the basis of Palmieri's precedent, we investigated sodium and isopropanol.[14] Optimized conditions delivered the amine **12** in 67% yield with >95:5 dr. The relative configuration of amine **12** was established by X-ray crystallography.[13] Hydrogenolysis of the auxiliary was accomplished under forcing conditions with 20% $Pd(OH)_2$/C in acidic methanol. The resulting amine was directly acylated to give an acetamide in 70% yield over two steps. Oxidation with Dess−Martin periodinane produced the crystalline ketone **13** as a single diastereomer. The relative configuration of **13** was confirmed by X-ray crystallography.[13] The octahydroquinoline **13** was assembled in six steps and 27% overall yield from commercially available diketone **6**.

The next goal was to introduce the tetrasubstituted double bond and a one-carbon substituent onto ketone **13**. A thermodynamic enolate is required, and a number of conditions were investigated to generate it. KHMDS and $PhNTf_2$ gave predominantly the less substituted enol triflate.[15] Potassium *tert*-butoxide led to more of the desired enol triflate, but it was accompanied by epimerization adjacent to nitrogen, presumably due to a reversible Michael addition of the amide. Selection of the solvent and reaction temperature turned out to be important, and going from THF to 2:1 DMF/THF gave predominantly the more hindered enol triflate **14** with no detectable epimerization adjacent to nitrogen.[16] Stille carbonylation was uneventful, and reduction delivered the allylic alcohol **15**.[17] Generation of the alkylating agent **4** used standard $PPh_3$ and $CBr_4$ conditions.[18] Allyl bromide **4** was set up to couple with the central piperidine ring.

The original plan called for the introduction of the two identical octahydroquinoline segments by alkylation of a piperidine dinitrile **3**, followed by reductive decyanation and deprotection. A single reductive decyanation has ample precedent from Husson's piperidine assembly.[10] Model studies for the double alkylation and reductive decyanation are outlined in Scheme 3. Dinitrile **3** was prepared from glutaraldehyde following Husson's procedure.[19] After some optimization, the double alkylation using just 2.2 equiv of allyl bromide worked extremely well, delivering predominantly the *cis*-**16** diastereomer in >90% yield.[20] Surprisingly, the reductive decyanation was not straightforward. Numerous attempts to cleave the nitriles did not produce the expected *cis*-2,6-disubstituted piperidine (**17** *cis*) but rather led to complex mixtures of products. A representative example is shown in Scheme 3, where the expected decyanation product **17** was produced in only 4% yield as a mixture of stereoisomers. Reductive coupling of the two nitriles generated diketone **18**, and addition of lithium amide and cyclization led to compound **19**. Clearly the reduction does not proceed one nitrile at a time, but rather the two nitriles interact and generate a variety of side products. The alkylation reaction was very effective, but the reductive decyanation was an utter failure.

**Scheme 3.** Alkylation and Decyanation of Dinitrile **3**




(14) Bartoli, G.; Cimarelli, C.; Palmieri, G. *J. Chem. Soc., Perkin Trans. 1* **1994**, 537–543. Hsung et al. utilized Palmieri's method for the total synthesis of (±)-tangutorine; see: (b) Luo, S.; Zificsak, C. A.; Hsung, R. P. *Org. Lett.* **2003**, *5*, 4709–4712.

(15) Mori, M.; Nakanishi, M.; Kajishima, D.; Sato, Y. *J. Am. Chem. Soc.* **2003**, *125*, 9801–9807.

(16) No epimerization was detected in the generation of enol triflate **14** at −78 °C, but significant epimerization was observed at −35 °C.

(17) Baillargeon, V. P.; Stille, J. K. *J. Am. Chem. Soc.* **2002**, *108*, 452–461.

(18) Mori, M.; Chiba, K.; Okita, M.; Kayo, I.; Ban, Y. *Tetrahedron* **1985**, *41*, 375–385.

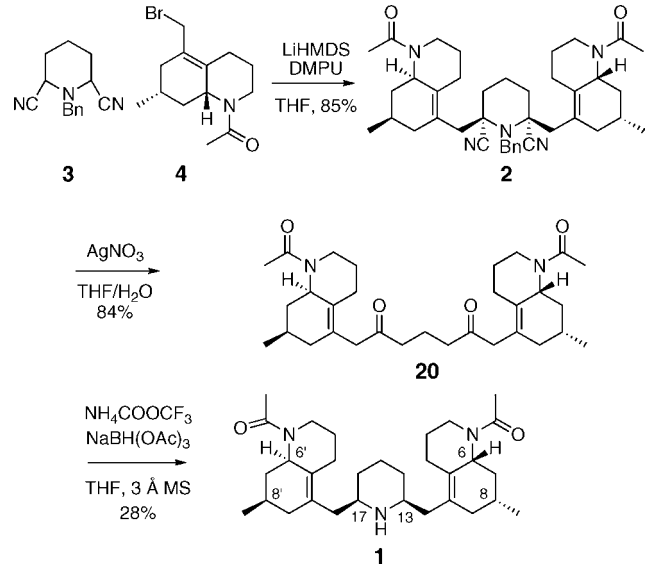
(19) Bonin, M.; Chiaroni, A.; Riche, C.; Beloeil, J.-C.; Grierson, D. S.; Husson, H.-P. *J. Org. Chem.* **1987**, *52*, 382–385.

(20) Takahashi et al. reported the bisalkylation of 1-benzyl-2,6-dicyanopiperidine in a stepwise manner; see: Takahashi, K.; Kurita, H.; Ogura, K.; Iida, H. *J. Org. Chem.* **1985**, *50*, 4368–4371.

An alternative approach to the central piperidine ring would be a reductive amination of a 1,5-diketone. A number of different routes to the desired 1,5-diketone **20** can be envisioned, but we decided to build upon the successful alkylation reaction in Scheme 3. The double alkylation was accomplished in good yield by mixing 1.0 equiv of **3** with 2.2 equiv bromide **4** in THF/DMPU and adding an excess of LiHMDS at reduced temperature. The dinitrile piperidine **2** was isolated in good yield. Deprotection to give the diketone **20** was initially attempted by treatment with HCl in MeOH, but the conditions led to subsequent alkene isomerization. Using $AgNO_3$ as a Lewis acid to promote the hydrolysis gave the desired diketone **20** in good overall yield.[21]

Reductive amination was first attempted using sodium cyanoborohydride as described by Abe and co-workers,[22] but the reaction was very slow and provided a mixture of the desired product and an undesired side product, the tetrahydropyran ring corresponding to piperidine **1**, which arose from reduction of the ketone and cyclization. Ketone reduction could be avoided by using a more selective reducing agent, sodium triacetoxyborohydride.[23] The reductive amination was still slow, gave incomplete conversion, and produced 28% yield of the piperidine **1** along with 50% of recovered diketone **20**. The NMR spectra and other physical data for piperidine **1** matched that reported for lycoperine A, including optical rotation.[24] LAH reduction of diamide **1** gave the diethyl compound, and its spectra compared favorably with that reported by Kobayashi's.[25]

**Scheme 4.** Double Alkylation and Preparation of Lycoperine A




Synthesis of lycoperine A was accomplished using a desymmetrization reaction that led to an efficient synthesis of the octahydroquinoline **4**. A double alkylation reaction and subsequent piperidine ring formation completed the synthesis and allowed the configuration of the natural product to be assigned as 6*R*,6′*R*,8*R*,8′*R*,13*S*,17*R*.

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**Supporting Information Available:** Characterization data and experimental procedures for all compounds described are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Abe, K.; Okumura, H.; Tsugoshi, T.; Nakamura, N. *Synthesis* **1984**, 597–598.

(23) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849–3862.

(24) Reported (ref 9): $[\alpha]^{24}_D$ −238 (*c* 0.1 MeOH). Observed: $[\alpha]^{24}_D$ −196 (*c* 0.14 MeOH).

(25) $^1$H NMR data and $^{13}$C NMR data for the diethyl compound show discrepancies with the reported values, presumably due to the variable protonation state of the triamine. The $^{13}$C NMR data shows all peaks within 0.5 ppm of reported values and an average difference of 0.14 ppm.