

## TOTAL SYNTHESIS OF (±)-LYCODINE

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(±)-Lycodine (1) has been synthesized in five steps from cyanoenone 4. The approach has also been applied to a new synthesis of (±)-lycopodine (2). Both alkaloids are available in better than 20% overall yield from enone 4.

Lycodine (1), first isolated by Anet and Eves from *Lycopodium annotinum*<sup>1</sup> and subsequently from numerous other species,<sup>2</sup> is the simplest example of the small group of dinitrogen lycopodium alkaloids which includes N-methyllycodine,<sup>3</sup> α-obscurine,<sup>4</sup> and β-obscurine.<sup>4</sup> Utilizing methodology which was previously developed for our total synthesis of (±)-lycopodine (2),<sup>5</sup> we have now accomplished the first total synthesis of racemic 1.

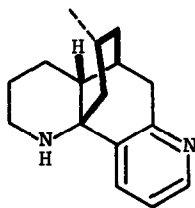
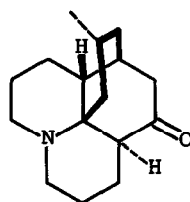
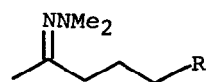
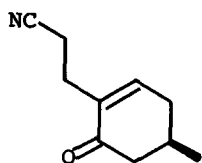
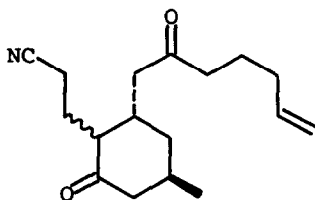
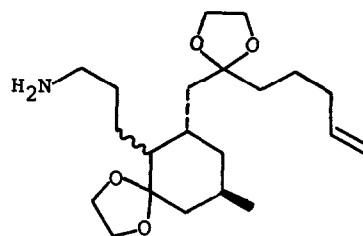
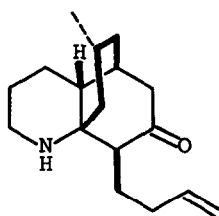
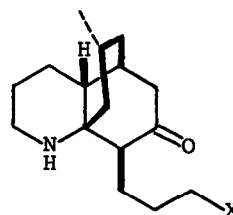
Hydrazone 3 is prepared in 62% yield by alkylation<sup>6a</sup> of the lithium enolate of the N,N-dimethylhydrazone of acetone with 4-bromo-1-butene. The enolate of 3, formed by reaction with n-butyllithium in THF at -70°C, is treated with thiophenoxycopper to produce a cuprate reagent<sup>6b,c</sup> which adds to cyanoenone 4<sup>7</sup> to afford, after hydrolysis (CuCl<sub>2</sub>, THF, H<sub>2</sub>O, pH 7, 25°C), cyanodione 5 in 65% yield. Ketalization of 5 (HOCH<sub>2</sub>CH<sub>2</sub>OH, p-TsOH, benzene, reflux) and subsequent reduction of the cyano function (LiAlH<sub>4</sub>, ether, 25°C) provides amine 6 in 85% yield. As expected, compound 6 is an epimeric mixture at the aminopropyl position. Treatment of 6 with 3N HCl in methanol at reflux for seven days furnishes the tricyclic amino ketone 7 in 53% yield. As in our previous intramolecular Mannich condensations,<sup>5</sup> only one stereoisomer is produced. The pyridine ring is elaborated by the following "one-pot" process. A methanol solution of 7 containing 10 equivalents of H<sub>2</sub>SO<sub>4</sub> is ozonized at -78°C. The resulting solution is treated directly with 20 equivalents of hydroxylamine

hydrochloride<sup>8</sup> at  $-78^{\circ}\text{C}$ , followed by a large excess of dimethylsulfide at  $0^{\circ}\text{C}$ , and is then refluxed for 48 hours. ( $\pm$ )-Lycodine (1), mp  $86-87^{\circ}\text{C}$ , is obtained in 75% yield. The synthetic material prepared in this manner is identical by infrared and 180-MHz  $^1\text{H-NMR}$  with an authentic sample of the alkaloid supplied.

An adaptation of this sequence provides a route to ( $\pm$ )-lycopodine which is even more efficient than that we previously published.<sup>5</sup> Alkylation of the *N,N*-dimethylhydrazone of acetone with 1-bromo-3-methoxypropane provides hydrazone 8, which is employed in a sequence of operations identical to that just discussed to obtain the tricyclic amino ketone 9 in 35% overall yield. Intermediate 9 is converted directly into ( $\pm$ )-lycopodine by treatment for 16 hours at  $25^{\circ}\text{C}$  with 25% HBr in glacial acetic acid, followed by alkaline work-up. It appears that the intermediate bromo ketone 10 spontaneously cyclizes to lycopodine upon being liberated from its salt. The reaction provides analytically pure ( $\pm$ )-lycopodine (mp  $128-129^{\circ}\text{C}$ ) in 59% yield.

Thus, we have devised five-step syntheses of ( $\pm$ )-lycodine and ( $\pm$ )-lycopodine from the key cyanoenone 4. In the former case, the overall yield is 22%; in the latter, it is 20.5%.

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123: R = CH=CH<sub>2</sub>8: R = CH<sub>2</sub>OCH<sub>3</sub>45679: X = OCH<sub>3</sub>10: X = Br

NOTES AND REFERENCES

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