

A TOTAL SYNTHESIS OF (+-)-HUPERZINE A

LIGANG QIAN AND RUYUN JI

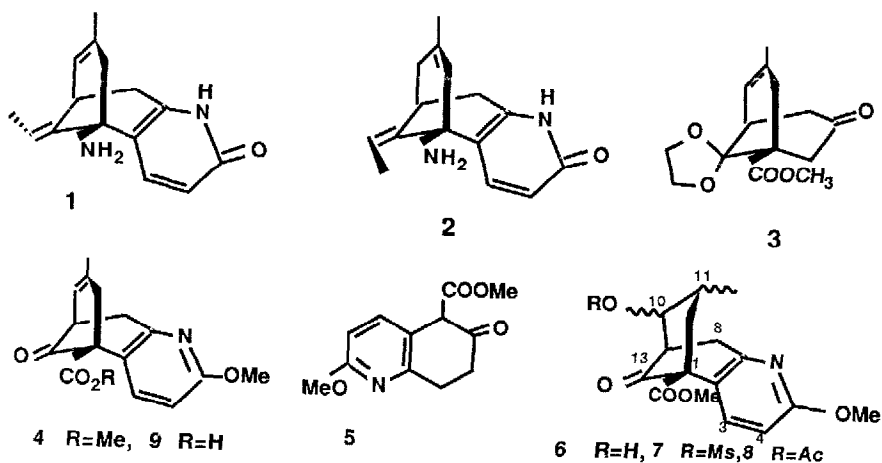
SHANGHAI INSTITUTE OF MATERIA MEDICA, CHINESE ACADEMY
OF SCIENCES, SHANGHAI 200031, CHINA

ABSTRACT The first total synthesis of (+-)-huperzine A, a new lycopodium alkaloid is described.

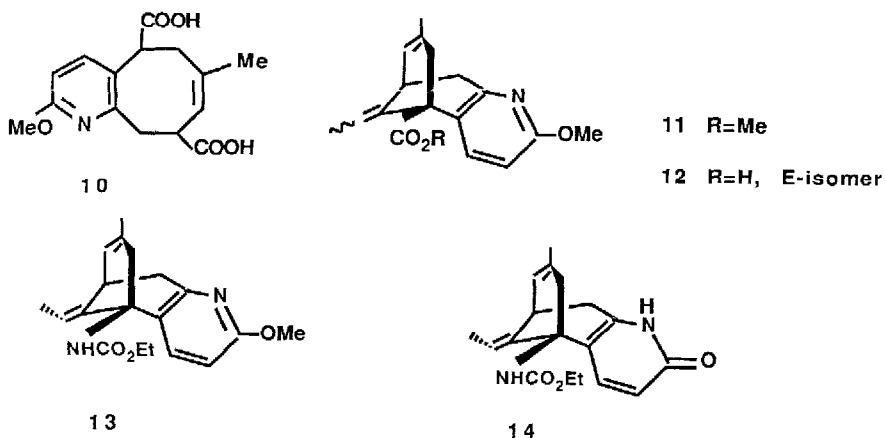
Huperzine A (**1**) is a new lycopodium alkaloid from *Lycopodium serratum* (Thunb) Trev. isolated by Liu¹ and has a structure similar to that of selagine (**2**) which was established in 1960 by Wiesner.² The alkaloid **1** has been shown to possess potent anticholinesterase activity in pharmacological studies, and used in clinic to treat myasthenia gravis, and Alzheimer's dementia and to improve senile memory loss. In this communication we report the first total synthesis of racemic **1**.

Previous endeavours toward the synthesis of **2** were made by Kende³ and Gravel.⁴ Kende constructed the skeleton of **2** from the bridged ring **3**; Gravel designed a synthetic route to **2** based on the reaction of α -carbomethoxy- β -tetralone. They, however, still left this subject an open challenge.

Our construction of bridged-ring compound **4** followed the similar route taken by Raphael et al in the synthesis of lycopodine.⁵ The starting material, tetrahydroquinoline **5** was made in several steps (39% overall yield) from 5-ethoxycarbonyl-6-methyl-2-pyridone.⁶ **4** was treated with methacrolein in methanol at -70°C to room temperature in the presence of sodium methoxide to give **6** (96% yield, gum). Mesylation of **6** with methanesulfonyl chloride at 0°C afforded the mesylate **7** (62.5%). Treatment of **7** with AcOH-AcONa at 130°C for 6-16 hr gave the olefin **4** (mp 123°C , 30%) and the by-product, acetate **8**, and recovered some unreacted material **7**.



Attempt to prepare the keto acid **9** by hydrolyzing **4** in aqueous alkaline solution was unsuccessful, mainly the pyridocyclooctenedioic acid **10** (mp 206°C) being obtained. Wittig reaction of **4** with ethylidene triphenylphosphorane ($\text{Ph}_3\text{P}^+\text{CH}_2\text{CH}_3 \text{ Br}^-/\text{BuLi}/\text{ether}$, 73.6%) at ambient temperature gave a mixture **11** of Z/E isomers, the ratio of which ranged from 95:5 to 85:15 under different reaction conditions. The mixture was treated with KOH-MeOH, by which E-isomer **11** was preferentially hydrolyzed into the acid **12** (mp 171°C), whereas the Z-isomer remained unchanged. **12** was easily converted into the urethane **13** (72% yield) by the modified Curtius reaction with $(\text{PhO})_2\text{P}(\text{O})\text{N}_3$ in ethanol.⁷ Cleavage of methyl ether of **13** by $\text{Me}_3\text{SiCl}/\text{NaI}/\text{CHCN}$ at 60-70°C afforded the α -pyridone derivative **14**, which was heated under reflux with KOH in toluene in the presence of 18-crown-6 ether to give the racemic **1**, identical to the natural specimen in MS,¹HNMR and IR.



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