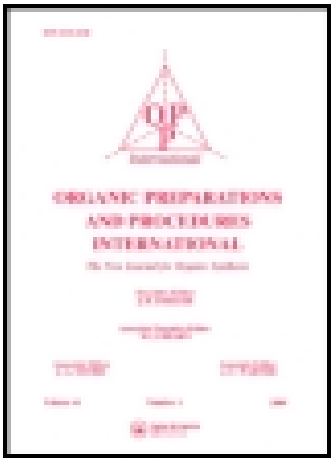

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PREPARATION OF METHYL 2-METHOXYCARBONYLMETHYL-6-OXO-1,6-DIHYDROPYRIDINE-3-CARBOXYLATE

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PREPARATION OF METHYL 2-METHOXYCARBONYLMETHYL-6-OXO-1,6-DIHYDROPYRIDINE-3-CARBOXYLATE

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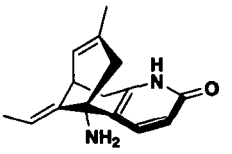
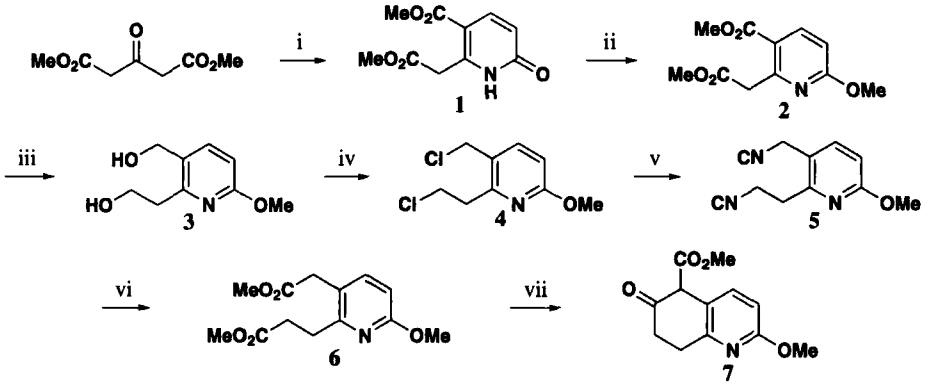
Huperzine A,[1] a *Lycopodium* alkaloid isolated from Chinese folk medicine, *Huperia serrata*(Thunb.) Trev., is a potent, reversible inhibitor of acetylcholinesterase. In China, it has been approved as a drug for the treatment of Alzheimer's disease. Several groups have achieved the total synthesis of huperzine A,[2-7] in which the protected tetrahydroquinolone β–keto ester **7** is a common key intermediate. A number of methods have been developed for the preparation of **7** from different starting materials. In the first total synthesis of huperzine A, compound **7** was prepared by Ji *et al.* from ethyl 2-methyl-6-hydroxynicotinate *via* a somewhat laborious sequence of reactions. Kozikowski's group[2,8] developed a one-pot, three-component condensation by simply admixing the mono-ethylene ketal of 1,4-cyclohexanedione, methyl propiolate in ammonia-saturated methanol in a Parr reactor,[10] followed by α-carbomethoxylation to obtain **7**.[3] Recently, Langlois *et al.*[6,9] reported that **7** was obtained from 2-methoxy-6-methylpyridine in five steps with a 43% overall yield. However, the overall yields of **7** obtained by these methods were not satisfactory, requiring the use of organometallic and expensive reagents and under critical reaction conditions. This paper describes a new approach to **7** from dimethyl acetone-1,3-dicarboxylate in 7 steps (*Scheme*).



Huperzine A

Commercially available dimethyl acetone-1,3-dicarboxylate was treated with propiolyl amide in 5% Na_2CO_3 solution, affording 2-pyridone in 61% yield. After O-methylation of pyridone **1** with CH_3I/Ag_2CO_3 in $CHCl_3$, compound **2** was smoothly reduced with $LiAlH_4$ in THF furnishing diol **3** in 85% yield. Diol **3** was then transformed into **7** *via* the sequence of reactions reported by Qian *et al.*[8] Diol **3** was treated with $SOCl_2$ in $CHCl_3$ for 2.5 h, leading to dichloride **4**

in 92% yield. Reaction of **4** with sodium cyanide in DMSO gave cyanide a 99% yield of **6** which was esterified by refluxing in HCl-saturated CH_3OH for 3 h, to afford diester **6** in 85% yield. Finally, intramolecular Dieckmann condensation of **6** in a suspension of NaH in THF produced **7** regioselectively in 92% yield. The undesired regio-isomer was not detected. The overall yield of **7** is 33% in seven steps.



i) propioloyl amide, rt, 61%; ii) Ag_2CO_3, CH_3I, $CHCl_3$, 45°C, 90%; iii) LAH, THF, reflux, 85%; iv) $SOCl_2$, $CHCl_3$, reflux, 92%; v) NaCN, DMSO, 80°C, 99%; vi) dry HCl, CH_3OH, 60°C, 85%; vii) NaH (60%), THF, rt, 92%

In comparison to other approaches to **7**, a new 2-pyridone intermediate **1** was obtained by a novel method for the construction of 2-pyridone ring. All the reactions proceeded under mild conditions with satisfactory and reproducible yields and no organometallic and other expensive reagents were required.

EXPERIMENTAL SECTION

Mps were determined on a Büchi 510 apparatus and are uncorrected. Elemental analyses were performed on a Elementar vario EL instrument. IR spectra were taken on a Nicolet Magna 750 spectrophotometer. ^{1}H-NMR spectra were recorded in Bruker AMX-400 and GEMINI-300 spectrometers and the values of chemical shifts (δ) are given in ppm. Mass spectral data were obtained at MAT-711 and MAT-5 mass spectrometers. Column chromatography was performed using silica gel (200-300 mesh). All solvents were dried and redistilled before use.

Methyl 2-(Methoxycarbonylmethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (1).- To a stirred solution of dimethyl acetone-1,3-dicarboxylate (9.40 g, 5.4 mmol) in H_2O (10 mL), Na_2CO_3 was added to adjust the pH of the solution between 8-9, then propiolyl amide (3.11 g, 4.5 mmol) in H_2O (3 mL) was added, and the reaction mixture was stirred at 0°C for 24 h. To the mixture acetic acid was added to adjust the pH to 6. The mixture was extracted with methylene chloride (3 x 50 mL). The combined organic layer was washed with brine (2 x 20 mL), dried over anhydrous Na_2SO_4, then concentrated under reduced pressure. The solid residue was recrystallized from ethyl acetate to afford **1** as white crystals (6.18 g, 61%), mp. 145-146°C. IR (KBr): 3428, 1749, 1718, 1649, 1433, 1286, 1213, 1134, 1009, 844 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 12.18

(br.s, 1H, NH), 7.85 (d, J = 9.6Hz, 1H, ArH), 6.33 (d, J = 9.9Hz, 1H, ArH), 3.99 (s, 2H, CH_2), 3.72 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3); EI-MS (m/z): 225 (M^+, 20%), 193 (100%), 136, 94. *Anal.* Calcd. $C_{10}H_{11}NO_5$: C, 53.33; H, 4.92; N, 6.22. Found: C, 53.35; H, 4.97; N, 6.22

Methyl 6-Methoxy-2-(methoxycarbonylmethyl)nicotinate (2).- A stirred mixture of **1** (4.01 g,1.8 mmol), CH_3I (2.8 mL) and Ag_2CO_3 (4.68 g), in $CHCl_3$ (35 mL) was warmed at 45°C for 8 h, then cooled to room temperature. A little silica gel was added to the mixture and then was removed by filtration. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (petroleum ether/EtOAc: 88/12) to afford compound **2** as a yellowish oil (3.8 g, 90%).[8] IR (film): 2995, 2953, 1743, 1720, 1595, 1483, 1425, 1263, 1136, 1074, 1032, 960 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 8.19 (d, J = 8.7 Hz, 1H, ArH), 6.69 (d, J = 8.7 Hz, 1H, ArH), 4.20 (s, 2H, CH_2), 3.96 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3); EIMS (m/z): 239 (M^+, 76%), 207, 179 (100%), 164, 150, 136.

2-(2-Hydroxyethyl)-3-(hydroxymethyl)-6-methoxypyridine (3).- To a stirred suspension of $LiAlH_4$ (1.66 g, 42.6 mmol) in THF (40 mL) cooled in an ice-water bath, was added dropwise a solution of **2** (3.49 g, 14.6 mmol) in THF (10 mL) and the reaction mixture was heated to reflux for 1h. To the cooled mixture, H_2O (3.2 mL), 15% sodium hydroxide (1.6 mL) and H_2O (8 mL) were added successively and carefully. The mixture was stirred at room temperature for 2.5 h, the solid material formed was removed by suction and washed with THF (2 x 30 mL). The filtrate was evaporated *in vacuo* and the residue was purified by flash chromatography (petroleum ether/EtOAc: 50/50) to give **3** as a pale oil (2.65 g, 85%).[8] IR (film): 3330, 2928, 1597, 1477, 1421, 1294, 1263, 1043, 827 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.56 (d, J = 8.4Hz, 1H, ArH), 6.62 (d, J = 8.4 Hz, 1H, ArH), 4.60 (s, 2H, CH_2OH), 4.04 (t, J = 5.4Hz, 2H, CH_2OH), 3.91 (s, 3H, OCH_3), 3.00 (t, J = 5.3Hz, 2H, CH_2); 2.12 (br., 2H, OH); EI-MS(m/z): 183 (M^+, 55%), 168, 153, 150, 138 (100%), 136, 122, 104.

2-(2-Chloroethyl)-3-(chloromethyl)-6-methoxypyridine (4).- A mixture of thionyl chloride (10 mL), **3** (2.09 g,11.4 mmol) in $CHCl_3$ (100 mL) was stirred at room temperature for 1 h and heated to reflux for an additional 1.5 h, then cooled to room temperature. Crushed ice was added into the mixture, and its pH to 8-9 was adjusted with solid $NaHCO_3$. The aqueous layer was extracted with methylene chloride (3 x 50 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4. After concentration, the crude product was purified by column chromatography (petroleum ether/EtOAc: 80/20) to afford product **4** as a yellowish oil (2.30 g, 92%). IR(film): 2941, 1733, 1599, 1579, 1481, 1425, 1304, 1263, 1084, 1038, 829, 685 cm^{-1}; ^{1}H-NMR($CDCl_3$): δ 7.52 (d, J = 8.4Hz, 1H), 6.61 (d, J = 8.4Hz, 1H), 4.61 (s, 2H), 4.02 (t, J = 7.0Hz, 2H), 393 (s, 3H), 3.27 (t, J = 7.1Hz, 2H); EIMS (m/z): 220 (M^+, 12%), 186, 184 (100%), 148.

3-[(3-(Cyanomethyl)-6-methoxypyridin-2-yl)]propionitrile (5).- To a solution of sodium cyanide (1.34 g, 27 mmol) in DMSO (5 mL), **4** (2.01 g, 9.1 mmol) in DMSO (10 mL) was added dropwise at 50-70°C. The reaction mixture was stirred at 80-90°C for an additional 2 h, then was cooled to room temperature. Crushed ice (60 g) was slowly added at 0°C. The mixture was

extracted with diethyl ether (3 x 50 mL), the combined organic extracts were washed with brine (2 x 20 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuum. The crude product was purified by column chromatography (petroleum ether/EtOAc: 70/30) to afford the compound **5** as a colorless oil (1.83 g, 99%).[8] IR (film): 2943, 2249, 1718, 1599, 1479, 1427, 1302, 1269, 1088, 1036, 829 cm^{-1}; ^{1}H-NMR ($CDCl_3$: δ 7.55 (d, J = 8.4Hz, 1H), 6.69 (d, J = 8.4Hz, 1H), 3.96 (s, 3H), 3.65 (s, 2H), 3.08 (t, J = 6.9Hz, 2H), 2.94 (t, J = 6.8Hz, 2H); EIMS (m/z): 201(M^+, 100%), 184, 173, 161, 149, 131.

Methyl 3-[(6-Methoxy-3-(methoxycarbonylmethyl)pyridin-2-yl)]-propionate (6).- Cyanide **5** (1.70 g, 8.5 mmol) was added under stirring to MeOH saturated with HCl (20 mL). The mixture was heated to reflux for 8 h and cooled to room temperature. Solid $NaHCO_3$ was added in portions to basify the mixture to pH 8-9. The mixture was extracted with Et_2O (3 x 50 mL), the combined extracts were washed with brine, dried over anhydrous Na_2SO_4. The solvent was evaporated *in vacuo* and the residue was purified by short column chromatography (petroleum ether/EtOAc: 75/25) to yield compound **6** as a colorless oil (1.90 g, 85%).[8,9] IR (film): 2953, 1740, 1599, 1581, 1477, 1429, 1298, 1159, 1038, 816 cm^{-1}; ^{1}H-NMR($CDCl_3$: δ 7.39 (d, J = 8.2Hz, 1H), 6.56 (d, J = 8.4Hz, 1H), 3.88 (s, 3H), 3.69 (s, 3H), 3.67 (s, 3H), 3.61 (s, 2H), 3.05 (t, J = 6.9Hz, 2H), 2.85 (t, J = 6.9Hz, 2H); EIMS (m/z): 267 (M^+, 21%), 236, 208 (100%), 148.

Methyl 2-Methoxy 6-oxo-5,6,7,8-tetrahydro-5-quinolinecarboxylate (7).- To a suspension of NaH (60%; 0.84 g, 21 mm and the mixture was stirred at room temperature overnight. After quenching with saturated aqueous NH_4Cl, the solvent was evaporated in vacuum, and the residue was extracted into diethyl ether (3 x 50 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The solid reside was recrystallized from CH_3OH to give pyridone **7** as yellowish crystals (1.30 g, 92%), mp. 70-71°C, *lit.*[8,11] 70°C, 71-72°C. IR (KBr): 3423, 2960, 1739, 1635, 1606, 1570, 1479, 1448, 1425, 1315, 1240, 1200, 1122, 1036, 820 cm^{-1}; ^{1}H-NMR($CDCl_3$): δ 13.17 (s, 1H), 7.90 (d, J = 8.8Hz, 1H), 6.57 (d, J = 8.8Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 2.94 (t, J = 7.8, 2H), 2.63 (t, J = 7.9, 2H); EIMS (m/z): 255 (M^+, 35%), 203 (100%), 174, 146, 118.

Anal. Calcd. for $C_{12}H_{13}NO_4$: C, 61.66; H, 5.64; N, 5.91; Found: C, 61.27; H, 5.57; N, 5.95

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REFERENCES

1. D. L. Bai, X. C. Tang and X. C. He, *Curr. Med. Chem.*, **7**, 355 (2000).

2. L. Qian and R. Y. Ji, *Tetrahedron Lett.*, **30**, 2089 (1989).

3. Y. Xia and A. P. Kozikowski, *J. Am. Chem. Soc.*, **111**, 4116 (1989).

4. G. Campiani, L. Q. Sun, A. P. Kozikowski, P. Aagaad and M. McKinney, *J. Org. Chem.*, **58**, 7660 (1993).

5. S. Kaneko, T. Yoshino, T. Kotoh and S. Terashima, *Tetrahedron*, **54**, 5471 (1998).

6. A. Haudrechy, C. Chassaing, C. Riche and Y. Langlois, *Tetrahedron*, **56**, 3181 (2000).

7. X. C. He, B. Wang, G. Yu and D. L. Bai, *Tetrahedron: Asymmetry*, **12**, 3213 (2001).

8. L. Qian, K. Gu and R. Y. Ji, *Chin. J. Med. Chem.*, **2**, 1(1992).

9. C. Chassaing, A. Haudrechy and Y. Langlois, *Synth. Commun.*, **27**, 61 (1997).

10. A. P. Kozikowski, E. R. Reddy and C. P. Miller, *J. Chem. Soc. Perkin Trans.* 1, 195 (**1990**).

11. A. P. Kozikowski, Y. Xia, E. R. Eddy, W. Tueckmantel, I. Hanin and X. C. Tang, *J. Org. Chem.*, **56**, 4636 (1991).

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