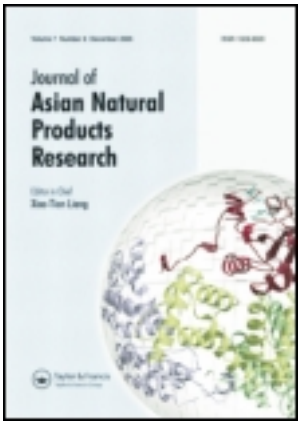

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Total synthesis of epiberberine

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Epiberberine, a natural bioactive protoberberine alkaloid, was totally synthesized in short, convenient and low-cost, four-step reactions including cyclization, condensation, reduction, and ring-closing, with an overall yield of 26.1%.

Keywords: epiberberine; protoberberine alkaloids; total synthesis

1. Introduction

Epiberberine is a natural quaternary berberine alkaloid isolated from *Coptis chinensis* [1] and other plants [2–5]. It exhibited broad biological activities, such as inhibition activity on CYP2D6 (one of cytochrome p450 isoforms) [6] and aldose reductase [7], α-adrenoceptor blocking action [8], *in vitro* hypoglycemic effect [9], etc. Recently, Jun *et al.* [10] have reported that epiberberine exhibited acetylcholinesterase (AChE), butyrylcholinesterase, and β-site amyloid precursor protein cleaving enzyme 1 inhibitory activities. The result indicated that epiberberine had beneficial use in the development of therapeutic and preventive agents for Alzheimer's disease (AD). The berberine structure has been used as a template to synthesize more potent AChE inhibitors [11]. However, low yields (0.5–2%) [12] made epiberberine mainly be used as reference substance in content determination and difficultly be purchased in market, which restricted the further study and application in pharmacology and clinic, and so on. So far only one literature reported the preparation of epiberberine [13]. However, this approach was uneconomical and tedious for the reactions of nine steps to form the side product epiberberine with low efficiency, as well as the use of expensive intermediates and several toxic reagents (CH_2N_2, PCl_5, etc.) (Scheme 1).

Therefore, increasing interest has been attracted by developing convenient synthetic route to get epiberberine and its natural and artificial derivatives in continuation of our ongoing program of the protoberberine and berberine alkaloids [14] on AD study. Herein, we report the total synthesis of epiberberine (Scheme 2).

2. Results and discussion

As shown in Scheme 2, intermediate **1** was formed by cyclization reaction of 2,3-dihydroxybenzaldehyde with CH_2Br_2 in 75.0% yield after column chromatography, and **2** was synthesized by condensation of **1** and 3,4-dimethoxyphenethylamine in 98.7% yield. Compound **3** was obtained by reduction reaction of **2** and $NaBH_4$. Ring-closing reaction of **3** and glyoxal

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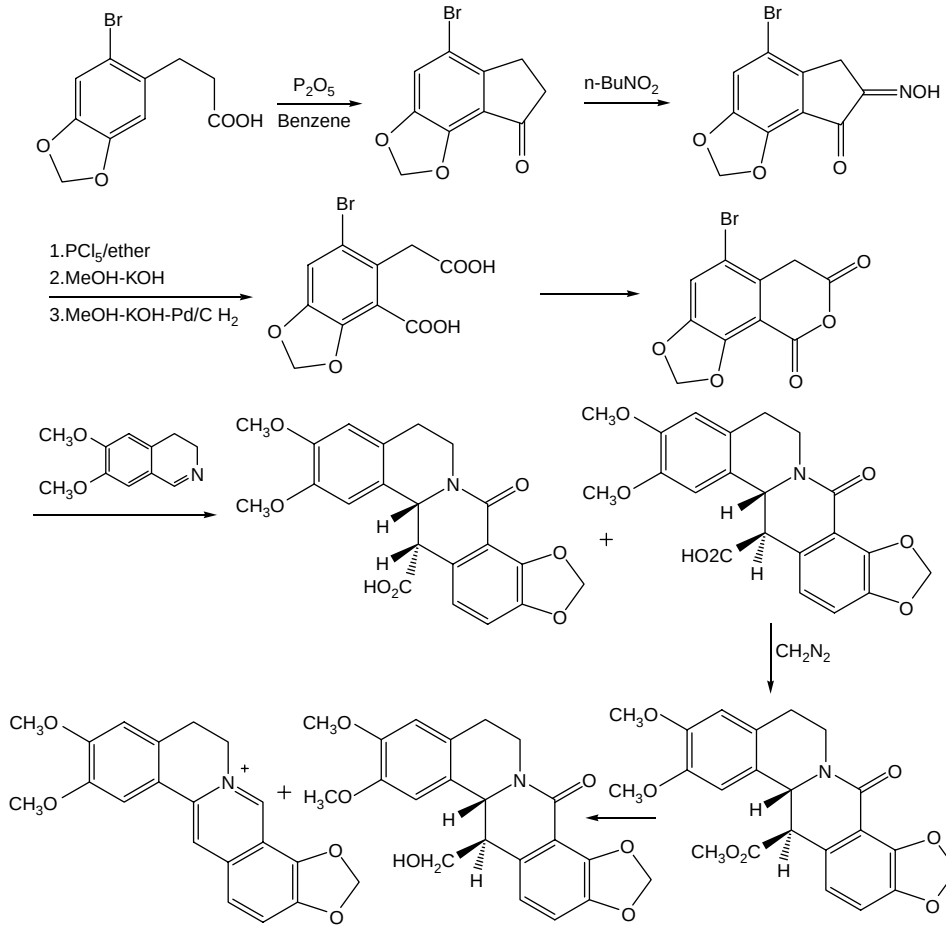


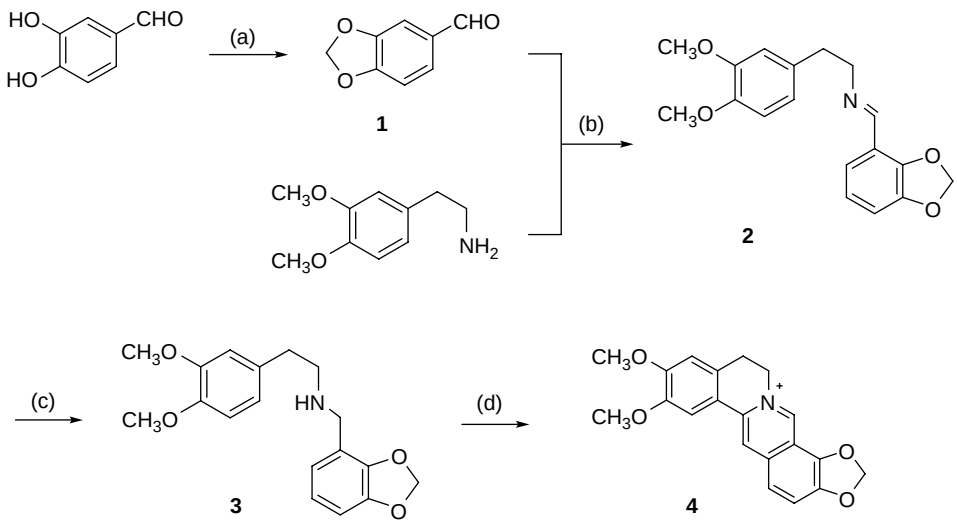
Scheme 1. Synthesis route of epiberberine in Ref. [13].

produced the target chemical agent **4**, epiberberine, and so on. Thus, a short, convenient and low-cost synthesis route of epiberberine including four-step reactions was established with an overall yield of 26.1%, and was suitable for synthesis in batch. Further pharmacokinetic profiles and *in vivo* pharmacology studies on AD are ongoing in our group. The synthesis of epiberberine derivatives is underway.

3. Experimental

3.1 General experimental procedures

All the reagents were obtained commercially and used without further purification. Melting points were determined on a Yanoco micro-melting apparatus (Yanagimoto Co., Tokyo, Japan) and are uncorrected. NMR spectra were recorded on Brucker AM-500 spectrometer (Bruker Instruments, Inc., Billerica, MA, USA). Chemical shifts of ^{1}H were referenced to the NMR solvents. Mass spectra were obtained on a VGZAB-2F spectrometer (VG Mircromas Ltd, Manchester, UK). TLC was carried out on silica gel (GF_{254}) (Yantai Chemical Industry Research Institute, Yantai, China). Column chromatography was run on silica gel (200–300 mesh) (Qingdao Ocean Chemical Factory, Qingdao, China). The samples were visualized by spraying with Dragendorff reagent to produce an orange spot.



Scheme 2. Conditions and reagents: (a) CH_2Br_2, anhydrous K_2CO_3, DMF, reflux, 24 h, 75.0%; (b) 3,4-dimethoxyphenethylamine, triethylamine, CH_2Cl_2, $MgSO_4$, reflux, 5 h, 98.7%; (c) $NaBH_4$, anhydrous ethyl alcohol, 10 h, 98.4%; (d) glyoxal, NaCl, $CuSO_4 \cdot 5H_2O$, 70°C, acetic anhydride, HAc, 20 h, 35.8%.

3.2 General procedures for the synthetic compounds

*3.2.1 Compound **1***

A mixture of 2,3-dihydroxy benzaldehyde (13.8 g, 100 mmol), anhydrous K_2CO_3 (20.8 g, 151 mmol), CH_2Br_2 (28.3 g, 163 mmol), and DMF (50 ml) were stirred and refluxed for 24 h. During the reaction, the detection was performed by TLC. EtOAc was used for extraction (3 × 150 ml). The organic phase was combined and dried over Na_2SO_4 over night and evaporated to give the crude product which was purified by column chromatography (PE:EtOAc; 20:1, v/v). Compound **1** was obtained as colorless needle (11.2 g, yield 75.0%). Compound **1**: m.p. 30–31°C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 10.09 (1H, s, 1-CHO), 7.25 (1H, d, J = 7.5 Hz, ArH), 7.02 (1H, d, J = 6.5 Hz, ArH), 6.95 (1H, dd, J = 7.5, 6.5 Hz, ArH), 6.11 (2H, s, —OCH_2O—) [15,16]. EI-MS *m/z*: 150.1 $[M]^+$.

*3.2.2 Compound **2***

A mixture of **1** (8.51 g, 57 mmol), 2,3-dimethoxyphenethylamine (10.6 g, 58 mmol), CH_2Cl_2 (100 ml), triethylamine (6.82 g, 67 mmol), and anhydrous $MgSO_4$ (10 g) were stirred and refluxed for 5 h. The reaction progress was monitored by TLC. After the completion of reaction, the mixture was filtered, and the filtrate was evaporated and cooled for crystallization. The precipitate was washed well with methanol. Compound **2** was obtained as white square crystal (17.6 g, yield 98.7%). Compound **2**: m.p. 41–43°C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 8.23 (1H, s, N═CH-Ar), 6.86 (1H, d, J = 8.0 Hz, ArH), 6.85 (1H, J = 8.0 Hz, ArH), 6.79 (1H, t, J = 8.0 Hz, ArH), 6.76 (2H, d, J = 8.0 Hz, ArH), 6.04 (1H, s, ArH), 5.90 (2H, s, —OCH_2O—), 3.85 (3H, s, —OCH_3), 3.82 (3H, s, —OCH_3), 3.85 (2H, t, J = 7.0 Hz, CH_2), 2.96 (2H, t, J = 7.0 Hz, CH_2). EI-MS *m/z*: 313.1 $[M]^+$.

*3.2.3 Compound **3***

Compound **2** (17.6 g) was heated and dissolved in anhydrous ethanol (100 ml). $NaBH_4$ (5.0 g, 66 mmol) was added in batches. After the addition, the mixture was refluxed for 10 h and monitored by TLC. Then, the reaction product was

evaporated to remove the solvent. To the residue, water (150 ml) and EtOAc (3 × 150 ml) were added which were used for extraction. The organic phase was combined and dried over Na_2SO_4 over night and evaporated. Compound **3** was obtained as yellow oil (17.4 g, yield 98.4%). Compound **3**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 6.71–6.80 (6H, m, ArH), 5.90 (2H, s, —OCH_2O—), 3.85 (3H, s, —OCH_3), 3.84 (3H, s, —OCH_3), 3.79 (2H, s, N—CH_2—Ar), 2.87 (2H, t, $J = 7.0$ Hz, CH_2), 2.77 (2H, t, $J = 7.0$ Hz, CH_2). EI-MS *m/z*: 315.1 $[M]^+$.

3.2.4 *Epiberberine*

In 500 ml three-necked bottle, $CuSO_4 \cdot 5H_2O$ (16.1 g), NaCl (16.3 g), and 40% glyoxal (24.1 g) were added under stir, and the mixture was heated to 70°C for 2 h. Following the addition of compound **3** (17.4 g, 55 mmol), acetic anhydride (30 ml) and HAc (100 ml) were added. The mixture was stirred and heated to 100°C for 20 h. Additional water (250 ml) was added, and the mixture was kept at 90°C and stood for 1 h. After the mixture was removed from the bottle, it was neutralized to pH 7 with saturated $NaCO_3$ solution. The precipitate was collected and washed with water till the washing water showed light yellow. Then, the precipitate was added in HCl–95% ethanol (5:95, v:v, 20 ml), and heated for 1 h, then cooled and filtered. The cake was purified by column chromatography ($CHCl_3$:MeOH; 9:1, v:v). Epiberberine was obtained by recrystallization in 95% ethanol as hydrochlorate of orange amorphous powder (7.3 g, yield 35.8%), and it showed the identical TLC behavior with the reference substance. Epiberberine: m.p. 259–260°C (dec.) ([13], 260°C(dec.)). ^{1}H NMR (DMSO-d_6): δ (ppm) 9.91 (1H, s, H-8), 9.04 (1H, s, H-13), 8.03 (1H, d, $J = 8.4$ Hz, H-11), 7.86 (1H, d, $J = 8.4$ Hz, H-12), 7.71 (1H, s, H-l), 7.09 (1H, s, H-4), 6.55 (2H, s, —OCH_2O—), 4.94 (2H, t, $J = 5.6$ Hz, H-6), 3.95 (3H, s, 2-OCH_3), 3.88 (3H, s, 3-OCH_3), 3.22 (2H, t, $J = 5.6$ Hz, H-5). EI-MS *m/z*: 339.1 $[M]^+$ [5,13].

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