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Total synthesis of (±)-protoemetinol

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ABSTRACT

A new approach to the benzo[*a*]quinolizidine alkaloid was described. Total synthesis of (±)-protoemetinol (**1**) was reported.

1. Introduction

(−)-Protoemetinol (**1**) is a benzo[*a*]quinolizidine alkaloid isolated from *Alangium lamarckii* by Battersby and co-workers.[1] This heterocyclic template is found in a number of alkaloids, such as psychotrine (**2**), emetine (**3**), and tubulosine (**4**) (Fig. 1). A number of their benzo[*a*]quinolizidine constituents have exhibited potent biological activity.[2] For instance, it was reported that psychotrine (**2**) is potent inhibitor of HIV-1 reverse transcriptase[3] and exhibit an unusual four-fold more potent inhibition of HIV-2 RT (9–10 μM) compared to HIV-1 RT.[4] Emetine (**3**) also shows antiamoebic properties,[5] shows activity against breast tumor cells,[6] and can be used as an emetic.[7]

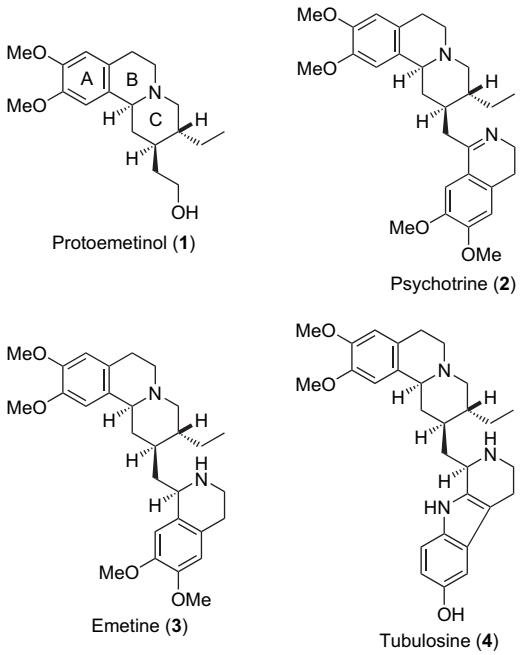

Figure 1. The benzo[*a*]quinolizidine alkaloids.

(−)-Protoemetinol (**1**) is an attractive synthetic target. Disconnection of psychotrine (**2**), emetine (**3**), and related alkaloids reveals the protoemetinol structure as essentially constituting the upper half of the molecular. A number of elegant syntheses of benzo[*a*]quinolizidine alkaloids have been reported.[8] Presently, we wish to report a new route to the benzo[*a*]quinolizidine alkaloids from glutarimide derivatives. Total synthesis of (±)-protoemetinol was also reported.

2. Results and discussion

2.1. Retrosynthesis of (±)-protoemetinol (1)

Our strategy for the synthesis of (±)-protoemetinol (**1**) was shown in Scheme 1. The benzo[*a*]quinolizidine alkaloid **1** was envisaged to arise from benzo[*a*]quinolizinone **5b**. The benzo[*a*]quinolizinone skeleton could then be formed via acid-catalyzed intramolecular cyclization of **6**. The enlactam **6** was anticipated to derive from [3+3] annulation adduct **7**.

2.2. Synthesis of enlactam 6

As shown in Scheme 2, glutarimide **7** was easily prepared via stepwise [3+3] annulation[9] of α-sulfonyl acetamide **8** with α,β-unsaturated ester **9**. Regioselective reduction of C-2 carbonyl group at **7** with sodium borohydride gave hydroxylactam **10**.[8k,10] Mesylation and elimination of **10** with methanesulfonyl chloride and triethylamine furnished **11**, which then further desulfonated with sodium amalgam to yield the corresponding enlactam **6**.

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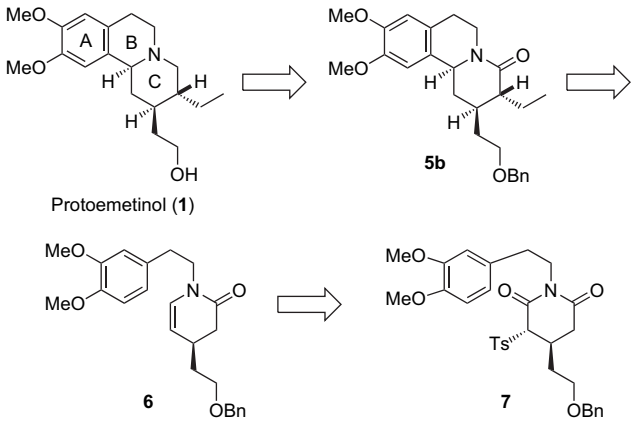
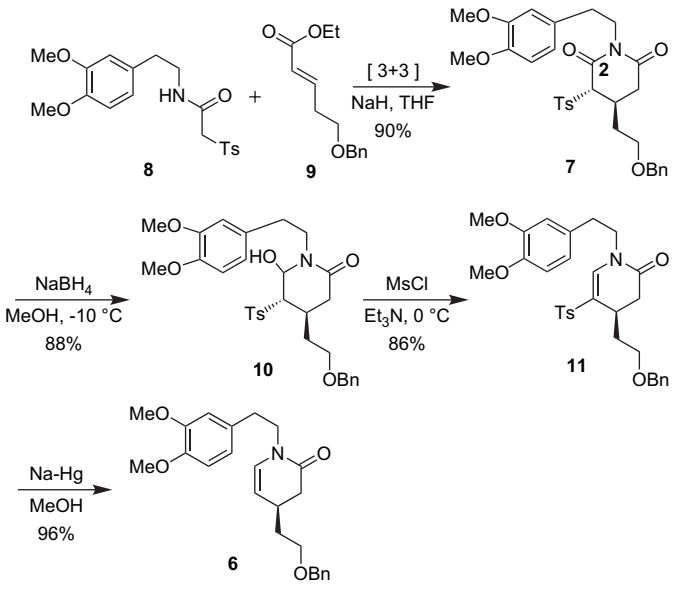


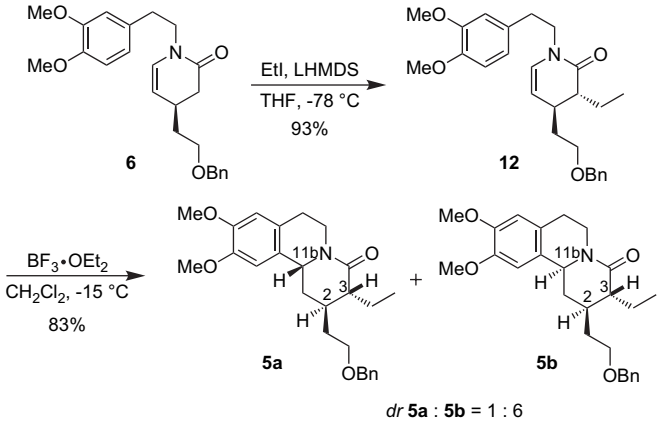
Scheme 1. Retrosynthesis of (±)-protoemetinol (**1**).



Scheme 2. Synthesis of enlactam **6**.

2.3. Total synthesis of (±)-protoemetinol (1)

With the key intermediate **6** in hand, we then focused our attention on the construction of ring B and three chiral centers in (±)-protoemetinol (**1**) (Scheme 3). Treatment of **6** with LHMDS and iodoethane provided alkylation product **12** as a single diastereomer in 93% yield. The stereochemistry of **12** was assigned as trans on the basis of NOESY data of the next reaction products **5a** and **5b**. Acid-catalyzed cyclization of **12** produced a 1:6 mixture of **5a** and **5b** in 83% yield. Their structures were determined by NOESY studies (Fig. 2). The NOESY experimental results of **5a** are similar to **5a′** as reported by Lete and co-workers.[11] Thus, for **5a**, an NOE enhancement between H-11b, H-3, and H-14 was observed. On the other hand, diastereomer **5b** showed an NOE enhancement between H-11b and H-2, whereas no NOE was observed between H-11b, H-3, and H-14. The diastereoselectivity observed in the cyclization of **12** could be rationalized on the basis of Takano's hypothesis.[12] The approach of the dimethoxyphenyl group to the 6-position of **12** from a pseudoaxial direction (a less hindered side) should give **5a** instead of **5b** as a main product. However, the 11b-β-H isomer (as **5a**) isomerized to the 11b-α-H isomer (as **5b**) via a B/C seco intermediate. Therefore, the thermodynamically more stable 11b-α-H isomer **5b** could be obtained through the isomerization of the 11b-β-H isomer **5a** on treatment with Lewis acid.



Scheme 3. Synthesis of benzo[*a*]quinolizinone **5b**.

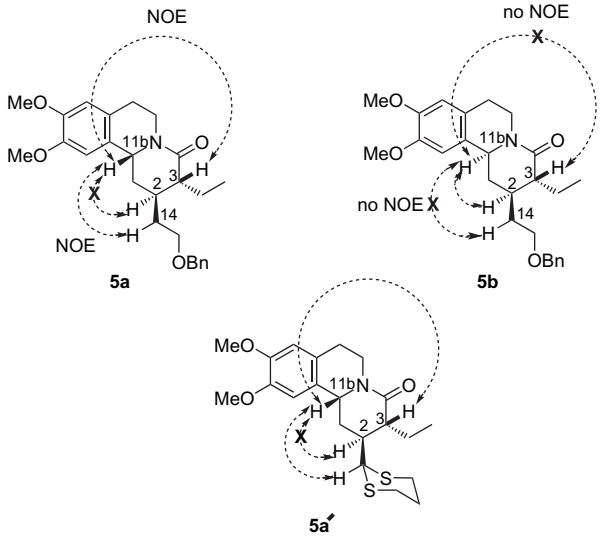
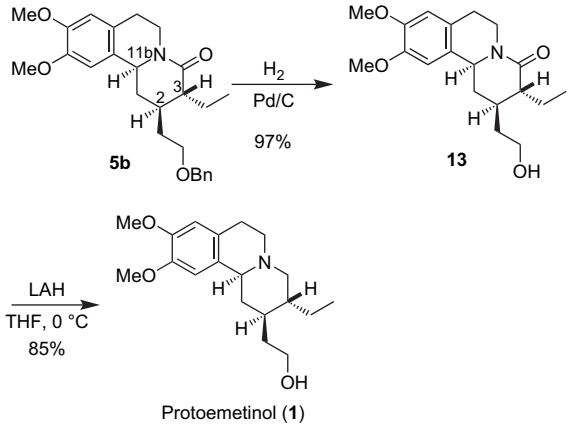


Figure 2. Selected NOE enhancements for **5a** and **5b**.

Finally, treatment of benzo[*a*]quinolizinone **5b** with palladium on carbon and hydrogen provided debenzylation product **13**, which was further reduced with lithium aluminum hydride to produce the desired reduced product (±)-protoemetinol (**1**) in 85% yield (Scheme 4).



Scheme 4. Completion of the total synthesis of (±)-protoemetinol (**1**).

3. Conclusion

Starting from easily available α-sulfonyl acetamide **8**, a concise eight-step synthesis of (±)-protoemetinol (**1**) has been achieved in a total of 35.7% yield. Further application of the present strategy to the synthesis of benzo[*a*]quinolizidine alkaloids are currently underway in our laboratory and will be reported in future.

4. Experimental

4.1. General

Melting points were determined with melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR were recorded on Varian VRX 500 spectrometer. NMR spectra were recorded in $CDCl_3$ (^{1}H at 500 MHz and ^{13}C at 125 MHz), and chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si.

Tetrahydrofuran was distilled prior to use. All other reagents and solvents were obtained from commercial sources and were used without any further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Solutions of products in organic solvents were dried over anhydrous magnesium sulfate before concentration under vacuum.

4.2. Preparation of a key intermediate, enlactam 6

*4.2.1. 4-(2-Benzyloxyethyl)-1-[2-(3,4-dimethoxyphenyl)-ethyl]-3-(toluene-4-sulfonyl)piperidin-2,6-dione (**7**)*

A solution of α-toluenesulfonyl acetamide **8** (1.50 g, 4.00 mmol) in dry THF (40.0 mL) was added to a rapidly stirred suspension of sodium hydride (336 mg, 8.40 mmol, 60%) in dry THF (20.0 mL). After the reaction mixture was stirred at room temperature for 30 min, a solution of α,β-unsaturated ester **9** (731 mg, 4.20 mmol) in dry THF (20.0 mL) was slowly added over 1 h. The resulting mixture was stirred for 4 h, quenched with saturated ammonium chloride solution (25.0 mL) in an ice bath, and concentrated under reduced pressure. The residue was diluted with water (25.0 mL) and extracted with ethyl acetate (3×70.0 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. Purification on silica gel (*n*-hexane/ethyl acetate=4:1 to 2:1) produced glutarimide **7** (2.02 g, 90%) as a yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, *J*=8.5 Hz, 2H), 7.35–7.26 (m, 7H), 6.76 (s, 3H), 4.44 (s, 2H), 4.22 (s, 1H), 4.09–3.96 (m, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 3.51–3.45 (m, 2H), 3.40 (dd, *J*=6.0, 18.0 Hz, 1H), 3.18 (dd, *J*=6.5, 13.0 Hz, 1H), 2.79 (t, *J*=8.0 Hz, 2H), 2.62 (d, *J*=18.0 Hz, 1H), 2.46 (s, 3H), 1.56–1.53 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.26, 164.41, 148.80, 147.65, 145.62, 137.67, 135.18, 130.68, 129.87 (2C), 128.79 (2C), 128.51 (2C), 127.80, 127.66 (2C), 121.02, 111.17, 111.11, 73.27, 70.30, 67.28, 55.86, 41.23, 34.79, 33.51, 33.25, 29.69, 27.15, 21.78; IR ($CHCl_3$, cm^{-1}): 3027, 1689; HRMS (EI, M^+) calcd for $C_{31}H_{35}NO_7S$ 565.2129, found 565.2111.

*4.2.2. 4-(2-Benzyloxyethyl)-1-[2-(3,4-dimethoxyphenyl)-ethyl]-6-hydroxy-5-(toluene-4-sulfonyl)piperidin-2-one (**10**)*

A solution of glutarimide **7** (1.13 g, 2.00 mmol) in a co-solvent of THF (10.0 mL) and HPLC-grade MeOH (40.0 mL) was stirred at −10 °C. Sodium borohydride (136 mg, 4.00 mmol) was added at −10 °C. The mixture was stirred for 2 h at that temperature. Saturated sodium bicarbonate solution (10.0 mL) was added to the mixture and concentrated under reduced pressure. The residue was diluted with water (15.0 mL) and extracted with ethyl acetate (3×40.0 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. Purification on silica gel (*n*-hexane/ethyl acetate=2:1 to 1:1) produced **10** (1.02 g, 90%) as a yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, *J*=8.0 Hz, 2H), 7.47–7.36 (m, 7H), 6.87–6.74 (m, 3H), 5.06 (br, 1H), 4.51 (AB, 2H), 3.99–3.95 (m, 1H), 3.97 (s, 3H), 3.94 (s, 1H), 3.92 (s, 3H), 3.56–3.50 (m, 3H), 3.07–2.84 (m, 5H), 2.54 (s, 3H), 2.36 (dd, *J*=3.5, 16.5 Hz, 1H), 1.82–1.76 (m, 1H), 1.55–1.49 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3, 149.0, 147.7, 145.2, 138.1, 135.0, 131.3, 129.8 (2C), 128.7 (2C), 128.3 (2C), 127.56 (2C), 127.53, 120.8, 111.7, 111.2, 79.9, 72.8, 67.8, 66.8, 55.9, 55.7, 48.4, 35.2, 35.0, 33.9, 26.5, 21.6; IR ($CHCl_3$, cm^{-1}): 3459, 1647, 1596; HRMS (ESI, M^++1) calcd for $C_{31}H_{38}NO_7S$ 568.2369, found 568.2370.

*4.2.3. 4-(2-Benzyloxyethyl)-1-[2-(3,4-dimethoxyphenyl)-ethyl]-5-(toluene-4-sulfonyl)-3,4-dihydro-1H-pyridin-2-one (**11**)*

Triethylamine (0.60 mL, 4.20 mmol) was added to the solution of **10** (990 mg, 1.70 mmol) in dry THF (10.0 mL) and the mixture was stirred at room temperature. After 0.5 h, the resulting mixture was poured into methanesulfonyl chloride (205 mg, 1.80 mmol) in an ice bath for 12 h. Saturated sodium bicarbonate solution (10.0 mL) was added to the mixture and concentrated under reduced pressure. The residue was diluted with water (15.0 mL) and extracted with ethyl acetate (3×40.0 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. Purification on silica gel (*n*-hexane/ethyl acetate=4:1 to 2:1) produced **11** (800 mg, 86%) as a yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (d, *J*=8.5 Hz, 2H), 7.35–7.27 (m, 7H), 7.16 (s, 1H), 6.82 (d, *J*=8.0 Hz, 1H), 6.74 (dd, *J*=2.0, 8.0 Hz, 1H), 6.67 (d, *J*=2.0 Hz, 1H), 4.46 (d, *J*=12.0 Hz, 1H), 4.39 (d, *J*=12.0 Hz, 1H), 3.94–3.88 (m, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.71–3.65 (m, 1H), 3.41 (t, *J*=6.0 Hz, 2H), 2.90–2.81 (m, 2H), 2.74–2.72 (m, 1H), 2.59 (d, *J*=16.5 Hz, 1H), 2.42 (s, 3H), 2.35 (dd, *J*=7.5, 16.5 Hz, 1H), 1.75–1.71 (m, 1H), 1.44–1.39 (m,, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.07, 149.02, 147.89, 144.08, 138.86, 138.19, 137.39, 129.90, 129.84 (2C), 128.31 (2C), 127.61 (2C), 127.54 (3C), 120.87, 120.72, 111.99, 111.43, 72.49, 66.48, 55.88, 55.81, 48.71, 33.55, 34.39, 31.17, 28.56, 21.56; IR ($CHCl_3$, cm^{-1}): 3030, 1649; HRMS (EI, M^+) calcd for $C_{31}H_{35}NO_6S$ 549.2180, found 549.2185.

*4.2.4. 4-(2-Benzyloxyethyl)-1-[2-(3,4-dimethoxyphenyl)-ethyl]-3,4-dihydro-1H-pyridin-2-one (**6**)*

Sodium amalgam (6%, Na/Hg, 3.00 g) and sodium phosphate (40.0 mg) were added to a stirred solution of **11** (853 mg, 1.55 mmol) in MeOH (40.0 mL), and vigorously stirred for 2 h at room temperature. The residue was filtered and washed with MeOH (2×10.0 mL). The combined organic layers were concentrated to obtain the crude product. The crude product was purified by silica gel chromatography (hexane/ethyl acetate=4:1 to 2:1) to afford enlactam **6** (590 mg, 96%) as colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.27 (m, 5H), 6.79 (d, *J*=8.5 Hz, 1H), 6.72 (d, *J*=8.5 Hz, 1H), 6.69 (s, 1H), 5.79 (dd, *J*=3.0, 8.0 Hz, 1H), 5.06 (dd, *J*=2.0, 8.0 Hz, 1H), 4.52 (dd, *J*=3.5, 15.5 Hz, 2H), 3.77–3.74 (m, 1H), 3.68–3.60 (m, 2H), 3.59–3.56 (m, 1H), 2.82 (dd, *J*=7.0, 14.5 Hz, 2H), 2.58–2.54 (m, 1H), 2.19–2.12 (m, 1H), 1.76–1.71 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.18, 148.94, 147.76, 138.38, 130.63, 128.35 (2C), 127.94, 127.62 (2C), 127.54, 120.78, 112.03, 111.30, 110.23, 72.91, 70.87, 67.95, 55.88, 55.86, 48.33, 36.78, 34.32, 31.49; IR ($CHCl_3$, cm^{-1}): 3027, 1641; HRMS (ESI, M^++1) calcd for $C_{24}H_{30}NO_4$ 396.2175, found 396.2175.

4.3. Total synthesis of (±)-protoemetinol (1)

*4.3.1. 4-(2-Benzyloxyethyl)-1-[2-(3,4-dimethoxyphenyl)-ethyl]-3-ethyl-3,4-dihydro-1H-pyridin-2-one (**12**)*

A solution of lithium bis(triethylsilyl)amide (LHMDS, 1.06 M, 2.70 mL, 2.70 mmol) in THF was added to the solution of enlactam **6** (530 mg,1.30 mmol) in dry THF (15.0 mL) at −78 °C, and the mixture was stirred for 0.5 h. Iodoethane (310 mg, 2.00 mmol) was added; the resulting mixture was stirred for 10 h at −78 °C. Saturated ammonium chloride solution (15.0 mL) was added to the

mixture and concentrated under reduced pressure. The residue was diluted with water (10.0 mL) and extracted with ethyl acetate (3×40.0 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. Purification on silica gel (*n*-hexane/ethyl acetate=4:1 to 2:1) produced **12** (530 mg, 93%) as a yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34–7.25 (m, 5H), 6.79–6.69 (m, 3H), 5.80 (d, J=7.5 Hz, 1H), 4.96–4.91 (m, 1H), 4.48 (AB, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.60–3.71 (m, 2H), 3.46 (t, J=6.0 Hz, 2H), 2.83–2.73 (m, 2H), 2.40–2.34 (m, 1H), 2.21–2.17 (m, 1H), 1.65–1.45 (m, 4H), 0.93 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.4, 148.8, 147.6, 138.3, 131.1, 128.3 (2C), 128.2, 127.6, 127.6, 120.8, 112.0, 111.1, 108.2, 72.9, 67.2, 55.84, 55.79, 48.5, 47.7, 34.4, 34.0, 32.9, 23.7, 11.7; IR ($CHCl_3$, cm^{-1}): 1655, 1516, 1237; HRMS (ESI, M^++1) calcd for $C_{26}H_{34}NO_4$ 424.2488, found 424.2484.

4.3.2. 2-(2-Benzyloxyethyl)-9,10-dimethoxy-3-methyl-1,2,3,6,7,11b-hexahydropyrido[2,1-a]isoquinolin-4-ones (**5a**) and (**5b**)

A solution of **12** (440 mg, 1.00 mmol) in dry dichloromethane (20.0 mL) was treated with $BF_3{\cdot}OEt_2$ (0.15 mL, 1.10 mmol) at −15 °C. After 15 h, the resulting mixture was quenched with saturated sodium bicarbonate solution (20.0 mL) and extracted with dichloromethane (2×20.0 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. Purification on silica gel (*n*-hexane/ethyl acetate=6:1 to 2:1) produced **5a** (51.0 mg, 12%) and **5b** (300 mg, 71%). Compound **5a**: colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35–7.27 (m, 5H), 6.61 (s, 1H), 6.58 (s, 1H), 4.88–4.84 (m, 1H), 4.65 (dd, J=5.0, 11.0 Hz, 1H), 4.54 (s, 2H), 3.86 (s, 3H), 3.79 (s, 3H), 3.67–3.58 (m, 2H), 2.90–2.76 (m, 2H), 2.64–2.61 (m, 1H), 2.29 (td, J=4.0, 13.5 Hz, 1H), 2.21–2.18 (m, 1H), 2.13–2.11 (m, 1H), 1.95–1.73 (m, 4H), 1.55–1.46 (m, 1H), 0.96 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.7, 147.7, 147.6, 138.2, 129.4, 128.4 (2C), 127.63, 127.58 (2C), 127.2, 111.5, 107.8, 73.1, 68.2, 56.0, 55.8, 52.5, 47.8, 39.7, 33.0, 30.7, 29.9, 28.6, 25.5, 12.3; IR ($CHCl_3$, cm^{-1}): 1656, 1513; HRMS (ESI, M^++1) calcd for $C_{26}H_{34}NO_4$ 424.2488, found 424.2491.

Compound **5b**: colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53–7.27 (m, 5H), 6.60 (s, 1H), 6.57 (s, 1H), 4.88–4.85 (m, 1H), 4.58–4.55 (m, 1H), 4.53 (AB, 2H), 3.86 (s, 3H), 3.79 (s, 3H), 3.65–3.58 (m, 2H), 2.88–2.74 (m, 2H), 2.62–2.59 (m, 1H), 2.48 (td, J=3.5, 13.5 Hz, 1H), 2.16–2.02 (m, 3H), 1.96–1.90 (m, 1H), 1.71–1.66 (m, 1H), 1.49–1.43(m, 1H), 1.32 (AB, 1H), 0.91 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.4, 147.6, 138.4, 129.1, 128.3 (2C), 127.62, 127.59, 127.5 (2C), 127.3, 111.4, 108.4, 72.9, 67.7, 56.1, 55.8, 55.7, 48.0, 39.5, 37.2, 34.0, 31.3, 28.5, 22.2, 10.0; HRMS (ESI, M^++1) calcd for $C_{26}H_{34}NO_4$ 424.2488, found 424.2489.

4.3.3. 3-Ethyl-2-(2-hydroxyethyl)-9,10-dimethoxy-1,2,3,6,7,11b-hexahydropyrido[2,1-a]isoquinolin-4-one (**13**)

Palladium on activated carbon (10%, 10.0 mg) was added to the solution of **5b** (80.0 mg, 0.20 mmol) in EtOH (15.0 mL) Hydrogen was bubbled into the mixture for 10 min, and the reaction mixture was continued to stir for 12 h at room temperature. The catalyst was filtered through a short plug of Celite and washed with EtOH (2×10.0 mL). The combined organic layers were concentrated to obtain the crude product. The crude product was purified by silica gel chromatography (hexane/ethyl acetate=4:1 to 2:1) to afford **13** (58.0 mg, 97%) as colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.66 (s, 1H), 6.61 (s, 1H), 4.88–4.85 (m, 1H), 4.60 (dd, J=3.5, 11.5 Hz, 1H), 3.87 (s, 6H), 3.84–3.78 (m, 2H), 2.89–2.75 (m, 2H), 2.63–2.60 (m, 1H), 2.53 (td, J=3.5, 13.0 Hz, 1H), 2.17–2.05 (m, 3H), 1.91–1.84 (m, 1H), 1.74–1.65 (m, 2H), 1.46–1.41 (m, 1H), 1.36 (AB, 1H), 0.91 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.5, 147.7, 138.4, 129.0, 127.3, 111.4, 108.5, 60.2, 56.2, 55.9, 55.7, 48.0, 39.6, 37.3, 37.1, 30.8, 28.6, 22.3, 10.0; IR ($CHCl_3$, cm^{-1}): 3459, 1653, 1597; HRMS (ESI, M^++1) calcd for $C_{19}H_{28}NO_4$ 334.2018, found 334.2020.

4.3.4. 2-(3-Ethyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl)ethanol (**1**)

A solution of **13** (170 mg, 0.50 mmol) in dry THF (10.0 mL) was added to the solution of lithium aluminum hydride (76.0 mg, 2.00 mmol) in dry THF (5.00 mL) in an ice bath. The resulting mixture was stirred for 24 h at 0 °C, quenched with saturated ammonium chloride solution (10.0 mL), and concentrated under reduced pressure. The residue was diluted with water (10.0 mL) and extracted with ethyl acetate (3×30.0 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. Purification on silica gel (*n*-hexane/ethyl acetate=2:1 to 1:1) produced protoemetinol (**1**) (138 mg, 85%) as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.69 (s, 1H), 6.57 (s, 1H), 3.92–3.73 (m, 4H), 3.85 (s, 3H), 3.84 (s, 3H), 3.14–3.03 (m, 3H), 2.99–2.95 (m, 1H), 2.64–2.60 (m, 1H), 2.47 (td, J=11.5, 4.0 Hz, 1H), 2.35–2.33 (m, 1H), 2.04–2.00 (m, 1H), 1.97–1.92 (m, 1H), 1.70–1.64 (m, 1H), 1.44–1.41 (m, 2H), 1.28–1.09 (m, 2H), 0.92 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.4, 147.1, 130.0, 126.6, 111.4, 108.2, 62.6, 61.4, 60.4, 56.1, 55.8, 52.4, 41.2, 37.6, 37.2, 35.8, 29.1, 23.4, 11.1; IR ($CHCl_3$, cm^{-1}): 3450, 1426, 1292; HRMS (ESI, M^++1) calcd for $C_{19}H_{30}NO_3$ 320.2226, found 320.2223.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2008.07.110.

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