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CONVENIENT SYNTHESIS OF THE KEY INTERMEDIATE FOR DIHYDROCORYNANTHEOL AND PROTOEMETINOL FROM THE MONOACETATE OF 4-CYCLOPENTENE-1,3-DIOL†

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Abstract – We invented an efficient method to obtain the key δ-lactone possessing the $(CH_2)_2$OTBDPS and Et groups at C3 and C4, respectively, starting with the acetate of 4-cyclopentene-1,3-diol, which was subjected to Pd-catalyzed allylation with malonate anion to attach the $(CH_2)_2$OTBDPS group. The Et group was then installed by 1,4-addition to the derived enone. Finally, the resulting enol TMS ether was oxidized to afford the lactone. Furthermore, the lactone was converted to dihydrocorynantheol and protoemetinol, both of which are typical examples of indoloquinolizidine and benzo[*a*]quinolizine alkaloids.

INTRODUCTION

Dihydrocorynantheol and protoemetinol are typical alkaloids possessing the indoloquinolizidine and benzo[*a*]quinolizine structures, respectively (Figure 1).[1] In addition to the interesting biological activities such as antiparasitic, antiviral, and analgesic activities, the structures have attracted much attention as synthetic targets, and thus various synthetic methods have been developed. Among them, δ-lactone **1a** (R = Bn) introduced by Ihara and Fukumoto[2] as the key intermediate for synthesis of these alkaloids attracted our attention because of its synthetic potency. The lactone **1a** was constructed by using intramolecular radical cyclization of the bromo cis-olefin. Although the cyclization is stereoselective, the preparation of the cis-olefin suffers from somewhat low stereoselectivity. As an alternative synthesis of lactone **1** we envisioned a synthetic method starting with the monoacetate **2** through stereoselective

† This paper is dedicated to Professor Albert Eschenmoser on the occasion of his 85th birthday.

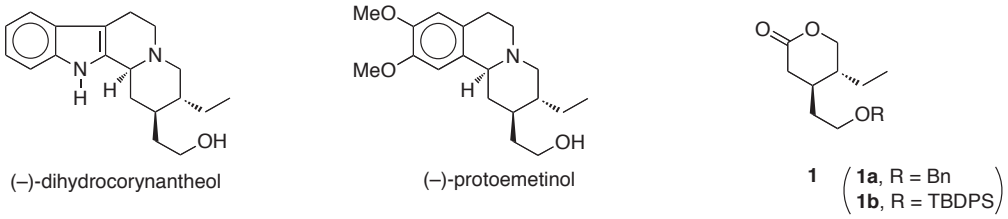
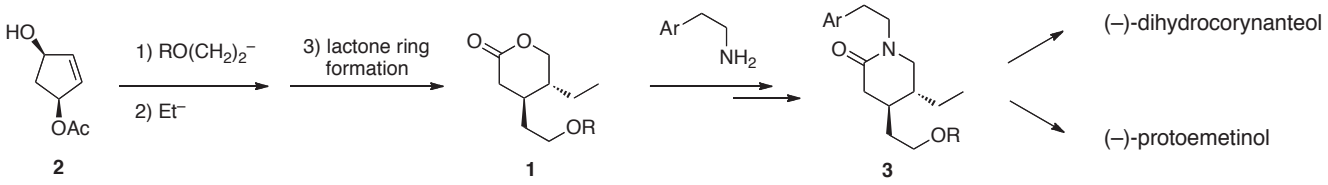


Figure 1. Target compounds and the key intermediate (TBDPS = *t*-BuPh_2Si)

installation of the two side chains and subsequent lactone ring formation as illustrated in Scheme 1. For installation of the $(CH_2)_2OR$ group, a reaction taking place with retention of the configuration requires the (*S*)-acetate as shown in Scheme 1, while that with inversion does the (*R*)-enantiomer. Since both of the enantiomers can be available easily by using the enzyme-assisted asymmetric hydrolysis of the corresponding diacetate,[3,4] both approaches are feasible. Consequently, we investigated the synthesis using palladium-catalyzed allylation with malonate anion, which proceeds with retention of the configuration. Herein, we report preliminary results along this line using racemic monoacetate **2**, which furnished lactone **1b** (R = TBDPS). Furthermore, **1b** was transformed to dihydrocorynantheol[2a,b,5] and protoemetinol[2c,6] with modification.

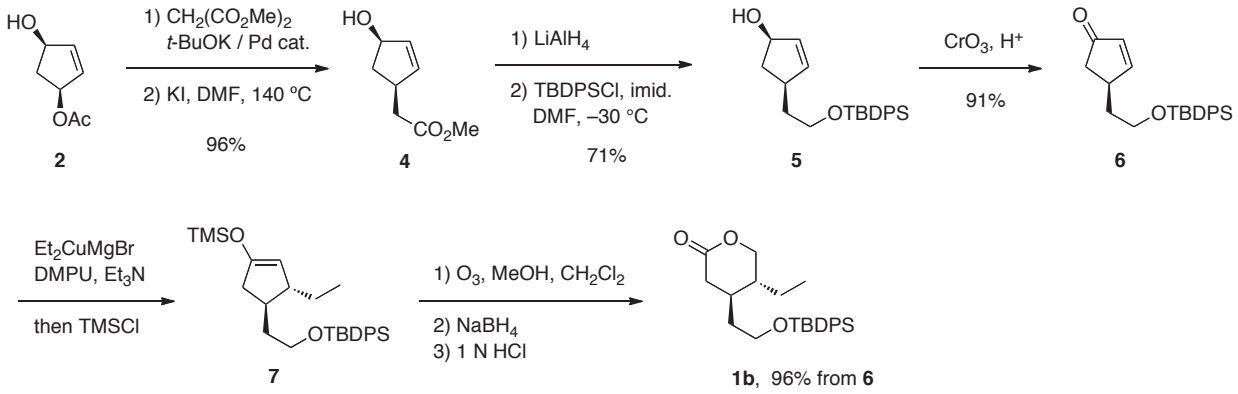


Scheme 1. Our approach to the target compounds

RESULTS AND DISCUSSION

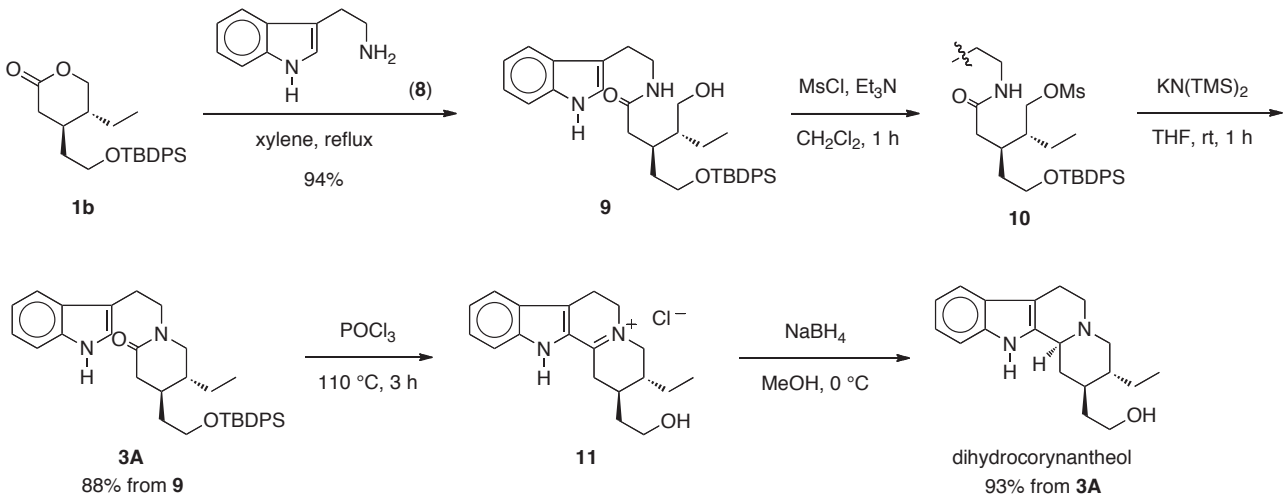
Palladium-catalyzed reaction of the racemic monoacetate **2** with malonate in the presence of *t*-BuOK at room temperature proceeded regioselectively with retention of stereochemsitry.[7] Next, decarboxylation of the product under the standard conditions afforded **4** in 96% yield (Scheme 2). Hydride reduction produced the corresponding diol, and the primary hydroxyl group was protected with TBDPSCl under carefully controlled conditions to prevent participation of the secondary hydroxyl group in the protection reaction (slow addition of TBDPSCl in DMF, –30 °C). Jones oxidation of the remaining hydroxyl group in the mono-TBDPS ether **5** afforded enone **6** in 91% yield. To install the Et group, EtMgBr and CuI was mixed to prepare $Et_2CuMgBr$, which was subjected to conjugate addition to enone **6** in the presence of DMPU and Et_3N at –78 to –40 °C. The enolate thus generated was quenched with TMSCl to afford TMS

ether **7**. Without purification by chromatography, enol ether **7** was subjected to ozonolysis and the resulting peroxide was reduced with $NaBH_4$ in one-pot. Finally, the product was treated with 1 N HCl at room temperature to afford lactone **1b** in high yield. Total yield was 60% from the monoacetate **2**.



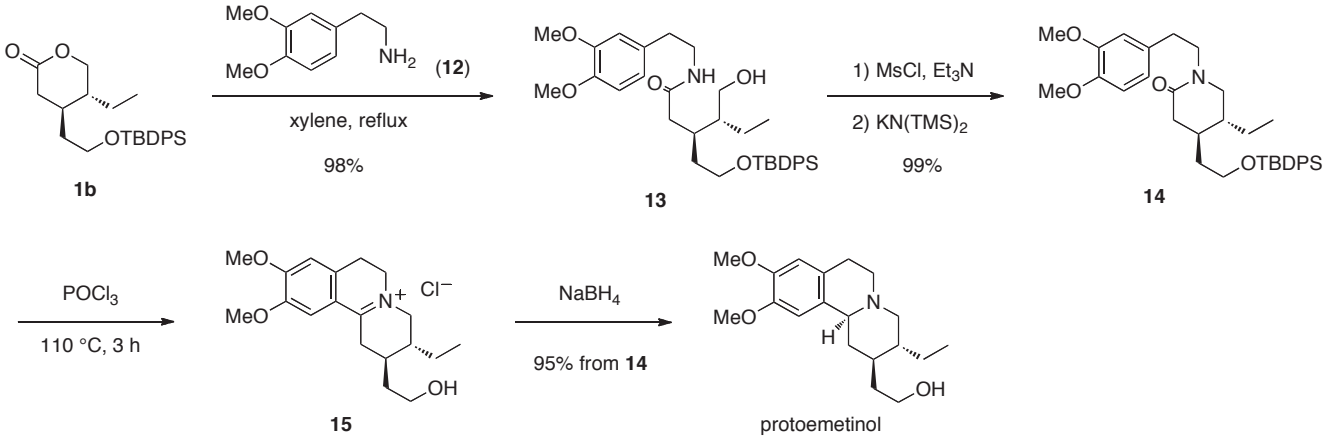
Scheme 2. Synthesis of the key intermediate **3**

Transformation of **1b** to dihydrocorynatheol is summarized in Scheme 3, in which reactions being different from the original method[2a,b] are involved. First, a mixture of **1b** and tryptamine (**8**) in xylene was heated under reflux to give amide alcohol **9** in 94% yield, which was converted to mesylate **10**. For construction of the lactam ring, $KN(TMS)_2$ in THF was selected due to operational convenience (*cf*. KH with 18-crown-6 by Ihara and Fukumoto[2a,b]). The reaction proceeded at room temperature smoothly to afford lactam **3A** in 88% yield, which was treated with $POCl_3$ at 110 °C to produce iminium salt **11**. During the conversion, the TBDPS group was removed. Finally, reduction of **11** with $NaBH_4$[2a,b,5h] furnished dihydrocorynantheol stereoselectively in 93% yield from the lactam **3A**. The ^1H NMR spectrum of the product was identical with that reported.[5b,e–g]



Scheme 3. Synthesis of dihydrocorynantheol

In a similar manner, reaction of lactone **1b** with homoveratrylamine (**12**) in xylene under reflux afforded hydroxyamide **13**, which upon reaction with MsCl followed by cyclization with $KN(TMS)_2$ produced lactam **14** quantitatively as shown in Scheme 4. Finally, reaction with $POCl_3$ followed by hydride reduction of the iminium salt **15** with $NaBH_4$[8] produced protoemetinol stereoselectively. The product was identified by ^1H NMR spectroscopy.[6a]



Scheme 4. Synthesis of protoemetinol

CONCLUSION

The key lactone **1b** was synthesized from the easily available monoacetate **2** by using the stereoselective installation of the two side chains (Scheme 2), and transformed to dihydrocorynantheol (Scheme 3) and protoemetinol (Scheme 4) with modification of reaction conditions. Since the present method has no restriction on using oxygenated indol and aryl groups, the method would be applicable to a wide variety of alkaloids possessing the indoloquinolizidine and benzo[*a*]quinolizine structures.

EXPERIMENTAL

General. Infrared (IR) spectra are reported in wave numbers (cm^{-1}). The ^1H NMR (300 and 500 MHz) and ^{13}C NMR (75 MHz) spectra were measured in $CDCl_3$ using $SiMe_4$ (δ = 0 ppm) and the center line of $CDCl_3$ triplet (δ = 77.1 ppm) as internal standards, respectively. The following solvents were distilled before use: THF (from Na/benzophenone), Et_2O (from Na/benzophenone), and CH_2Cl_2 (from CaH_2).

(4*S,5*R**)-4-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-5-ethyltetrahydro-2*H*-pyran-2-one (1b).** To a slurry of CuI (302 mg, 1.59 mmol) in THF (0.6 mL) was added EtMgBr (3.90 mL, 0.75 M in THF, 2.93 mmol) slowly at –78 °C. After 1 h of stirring at –30 °C, a solution of cyclopentenone **6** (463 mg, 1.32 mmol), DMPU (0.33 mL, 2.73 mmol), and Et_3N (0.33 mL, 2.37 mmol) in THF (6 mL) was added dropwise at –78 °C. The mixture was stirred at –78 °C for 45 min and then at –40 °C for 5 min. TMSCl

(0.50 mL, 3.96 mmol) was added at –40 °C. The mixture was gradually warmed to 0 °C over 1 h, and diluted with saturated $NaHCO_3$. The resulting mixture was extracted with hexane five times. The combined extracts were dried over Na_2SO_4 and concentrated to leave the enol ether **7**. A steam of O_3 in O_2 was gently bubbled into a solution of the enol ether **7** in MeOH (6.6 mL) and CH_2Cl_2 (0.66 mL) at –78 °C for 5 min. Excess O_3 remaining in the solution was purged by bubbling argon at –78 °C. The solution was warmed to 0 °C and $NaBH_4$ (250 mg, 6.61 mmol) was added. The solution was stirred at 0 °C for 1 h and diluted with EtOAc and 1 N HCl (6 mL). The mixture was stirred at room temperature for 2 h and extracted with EtOAc three times. The combined extracts were dried over $MgSO_4$ and concentrated to leave a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to provide lactone **1b** (522 mg, 96%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.5 Hz, 3 H), 1.05 (s, 9 H), 1.20–1.56 (m, 4 H), 1.68–1.82 (m, 1 H), 1.89–2.03 (m, 1 H), 2.19 (dd, *J* = 16, 7.5 Hz, 1 H), 2.56 (dd, *J* = 16, 6.5 Hz, 1 H), 3.60–3.76 (m, 2 H), 3.99 (dd, *J* = 11, 7 Hz, 1 H), 4.27 (dd, *J* = 11, 4 Hz, 1 H), 7.34–7.46 (m, 6H), 7.61–7.67 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.2, 19.2, 24.2, 26.9, 32.5, 34.0, 38.0, 39.9, 60.8, 70.4, 127.7, 127.8, 129.77, 129.80, 133.5, 135.5, 172.7. HRMS (FAB) calcd for $C_{25}H_{35}O_3Si$ [$(M+H)^+$] 411.2355, found 411.2558.

(3*S,4*R**)-*N*-(2-(1*H*-Indol-3-yl)ethyl)-3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-4-(hydroxymethyl)-hexanamide (9).** A mixture of lactone **1b** (312 mg, 0.760 mmol) and tryptamine **8** (304 mg, 1.90 mmol) in *p*-xylene (3.5 mL) was heated under reflux overnight. Most of the volatile materials were removed under reduced pressure to afford an oil, which was purified by chromatography on silica gel (CH_2Cl_2/MeOH) to furnish **9** (408 mg, 94%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7 Hz, 3 H), 1.05 (s, 9 H), 1.15–1.49 (m, 5 H), 1.60–1.79 (m, 2 H), 1.94–2.21 (m, 2 H), 2.71 (br s, 1 H), 2.91 (t, *J* = 7 Hz, 2 H), 3.35–3.74 (m, 6 H), 5.56 (t, *J* = 5.5 Hz, 1 H), 6.94 (d, *J* = 2 Hz, 1 H), 7.11 (t, *J* = 7 Hz, 1 H), 7.19 (t, *J* = 7.5 Hz, 1 H), 7.23–7.50 (m, 7 H), 7.50–7.72 (m, 5 H), 7.98 (br s, 1 H).

(4*S,5*R**)-1-(2-(1*H*-Indol-3-yl)ethyl)-4-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-5-ethylpiperidin-2-one (3A).** To an ice-cold solution of alcohol **9** (32 mg, 0.056 mmol) and Et_3N (0.020 mL, 0.14 mmol) in CH_2Cl_2 (0.6 mL) was added MsCl (0.009 mL, 0.12 mmol). After being stirred at room temperature for 1 h, the solution was diluted with CH_2Cl_2 and washed successively with saturated $NaHCO_3$ and H_2O. The organic layer was dried over Na_2SO_4 and concentrated to give mesylate **10**, which was subjected to the next reaction without further purification. To an ice-cold solution of the above mesylate **10** in THF (0.6 mL) was added $KN(TMS)_2$ (0.13 mL, 0.50 M in toluene, 0.065 mmol). After being stirred at room temperature for 1 h, the reaction was quenched by addition of saturated NH_4Cl. The resulting mixture was extracted with EtOAc three times. The combined extracts were dried over Na_2SO_4 and concentrated to leave a residue, which was purified by chromatography on silica gel (CH_2Cl_2/MeOH) to provide **3A** (27 mg, 88%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.74 (t, *J* = 7.5 Hz, 3 H), 1.04 (s, 9 H), 1.05–1.53 (m, 4 H),

1.63–1.84 (m, 2 H), 2.00 (dd, *J* = 17, 8 Hz, 1 H), 2.47 (dd, *J* = 17, 5.5 Hz, 1 H), 2.85 (dd, *J* = 13, 7 Hz, 1 H), 3.02 (t, *J* = 7.5 Hz, 2 H), 3.12 (dd, *J* = 13, 5 Hz, 1 H), 3.50–3.75 (m, 4 H), 7.03 (d, *J* = 2 Hz, 1 H), 7.11 (t, *J* = 7.5 Hz, 1 H), 7.17 (t, *J* = 7 Hz, 1 H), 7.29–7.47 (m, 7 H), 7.58–7.69 (m, 5 H), 7.96 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.0, 19.3, 23.2, 23.8, 27.0, 33.0, 36.1, 36.5, 39.3, 48.1, 51.4, 61.3, 111.2, 113.5, 118.9, 119.5, 122.0, 122.1, 127.77, 127.79, 129.75, 129.78, 133.9, 135.6, 169.6.

(–)-Dihydrocorynanteol. A mixture of lactam **3A** (20 mg, 0.036 mmol) and $POCl_3$ (0.2 mL) was refluxed for 3 h. Most of the volatile materials were removed, and the resulting residue was dried up by azeotropic distillation with THF three times for the next reaction. To an ice-cold solution of the crude iminium salt **11** in MeOH (0.4 mL) was added $NaBH_4$ (7 mg, 0.18 mmol). The solution was stirred at 0 °C for 1 h and diluted with 1 N NaOH, brine, and EtOAc. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 three times. The combined extracts were dried over K_2CO_3 and concentrated to leave a residue, which was purified by chromatography (CH_2Cl_2/MeOH) to afford (–)-dihydorocorynanteol (10 mg, 93%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, *J* = 7.5 Hz, 3 H), 1.1–1.8 (m, 8 H), 2.08–2.24 (m, 2 H), 2.55–2.80 (m, 2 H), 2.93–3.17 (m, 3H), 3.23 (d, *J* = 11 Hz, 1 H), 3.54–3.76 (m, 2 H), 7.04–7.19 (m, 2 H), 7.33 (d, *J* = 7.5 Hz, 1 H), 7.47 (d, *J* = 7.5 Hz, 1 H), 7.88 (br s, 1 H). The spectrum was identical with the data reported for (–)-dihydorocorynanteol in the literature.[5b,e–g]

(3*S,4*R**)-3-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-*N*-(3,4-dimethoxyphenethyl)-4-(hydroxymethyl)-hexanamide (13).** A mixture of the lactone **1b** (165 mg, 0.402 mmol) and 3,4-dimethoxyphenyethyl-amine **12** (0.47 mL, 2.82 mmol) was heated under reflux overnight. Most of the volatile materials were removed under reduced pressure to afford an oil, which was purified by chromatography on silica gel (CH_2Cl_2/MeOH) to furnish **13** (232 mg, 98%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.5 Hz, 3 H), 1.05 (s, 9 H), 1.14–1.80 (m, 6 H), 2.15 (s, 2 H), 2.55 (br s, 1 H), 2.69 (t, *J* = 7 Hz, 2 H), 3.35–3.75 (m, 6 H), 3.84 (s, 3 H), 3.85 (s, 3 H), 5.56–5.66 (m, 1 H), 6.65–6.72 (m, 2 H), 6.77 (d, *J* = 9 Hz, 1 H), 7.33–7.46 (m, 6 H), 7.62–7.68 (m, 4 H).

(4*S,5*R**)-4-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-1-(3,4-dimethoxyphenethyl)-5-ethylpiperidin-2-one (14).** To an ice-cold solution of alcohol **13** (30 mg, 0.0507 mmol) and Et_3N (0.036 mL, 0.256 mmol) in THF (0.5 mL) was added MsCl (0.020 mL, 0.26 mmol). The solution was stirred at room temperature for 10 min and cooled to 0 °C. To this solutions was added $KN(TMS)_2$ (0.72 mL, 0.70 M in toluene, 0.504 mmol). The solution was stirred at room temperature overnight and diluted with brine. The resulting mixture was extracted with CH_2Cl_2 three times. The combined extracts were dried over Na_2SO_4 and concentrated to leave a residue, which was purified by chromatography on silica gel (CH_2Cl_2/MeOH) to provide **14** (28 mg, 99%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (t, *J* = 7.5 Hz, 3 H), 1.04 (s, 9 H), 1.1–1.9 (m, 6 H), 1.99 (dd, *J* = 17, 8 Hz, 1H), 2.47 (dd, *J* = 17, 5 Hz, 1 H), 2.80 (t, *J* = 7.5 Hz, 2 H), 2.75–2.90 (m, 1 H), 3.12 (dd, *J* = 12, 5 Hz, 1 H), 3.34–3.76 (m, 4 H), 3.84 (s, 3 H), 3.86 (s, 3 H),

6.71–6.81 (m, 3 H), 7.34–7.45 (m, 6 H), 7.64 (ddm, J = 7.5, 1.5 Hz, 4 H).

(–)-Protoemetiol. A mixture of lactam **14** (17 mg, 0.0296 mmol) and $POCl_3$ (0.14 mL) was refluxed at 110 °C for 3 h. Most of the volatile materials were removed and the resulting residue was dried up by azeotropic distillation with THF three times to give the iminium salt **15**, which was used for the next reaction without further purification. To an ice-cold solution of the above salt **15** in MeOH (0.3 mL) was added $NaBH_4$ (6 mg, 0.16 mmol). The solution was stirred at 0 °C for 1 h, and diluted with 1 N NaOH, brine, and EtOAc. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 three times. The combined extracts were dried (K_2CO_3) and concentrated. The residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH) to afford (–)-protoemetinol (9 mg, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, J = 7.5 Hz, 3 H), 1.06–1.31 (m, 3 H), 1.35–1.77 (m, 5 H), 2.05 (t, J = 11 Hz, 1 H), 1.95–2.23 (m, 1 H), 2.32 (dt, J = 13, 3 Hz, 1 H), 2.48 (dt, J = 4, 11 Hz, 1 H), 2.62 (dm, J = 16 Hz, 1 H), 2.96 (dd, J = 11, 6 Hz, 1 H), 3.06 (dd, J = 11, 4 Hz, 2 H), 3.52–3.76 (m, 2 H), 3.85 (s, 3 H), 3.87 (s, 3 H), 6.58 (s, 1 H), 6.68 (s, 1 H). The spectrum was identical with the data reported for (–)-protoemetinol in the literature.[6a]

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