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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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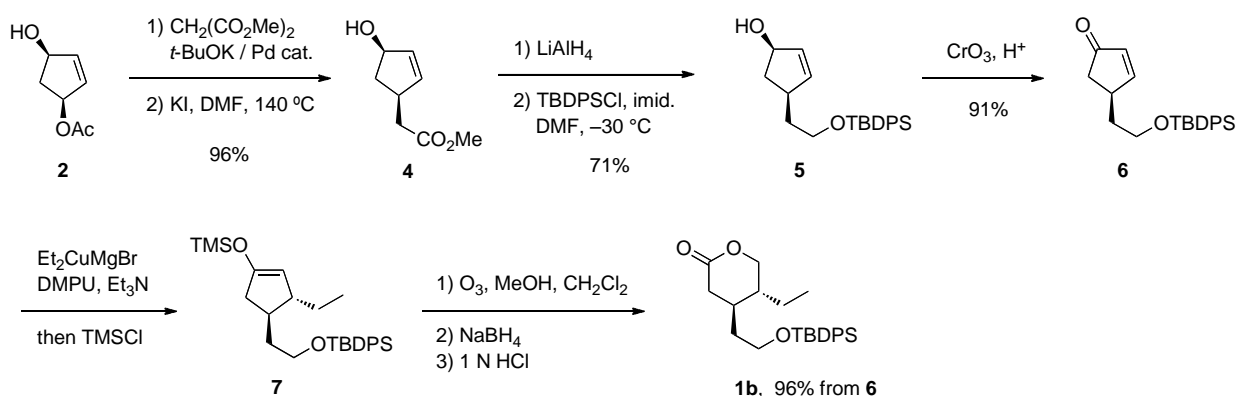
Abstract – We invented an efficient method to obtain the key δ -lactone possessing the $(\text{CH}_2)_2\text{OTBDPS}$ and Et groups at C3 and C4, respectively, starting with the acetate of 4-cyclopentene-1,3-diol, which was subjected to Pd-catalyzed allylation with malonate anion to attach the $(\text{CH}_2)_2\text{OTBDPS}$ 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 Fukumoto² 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

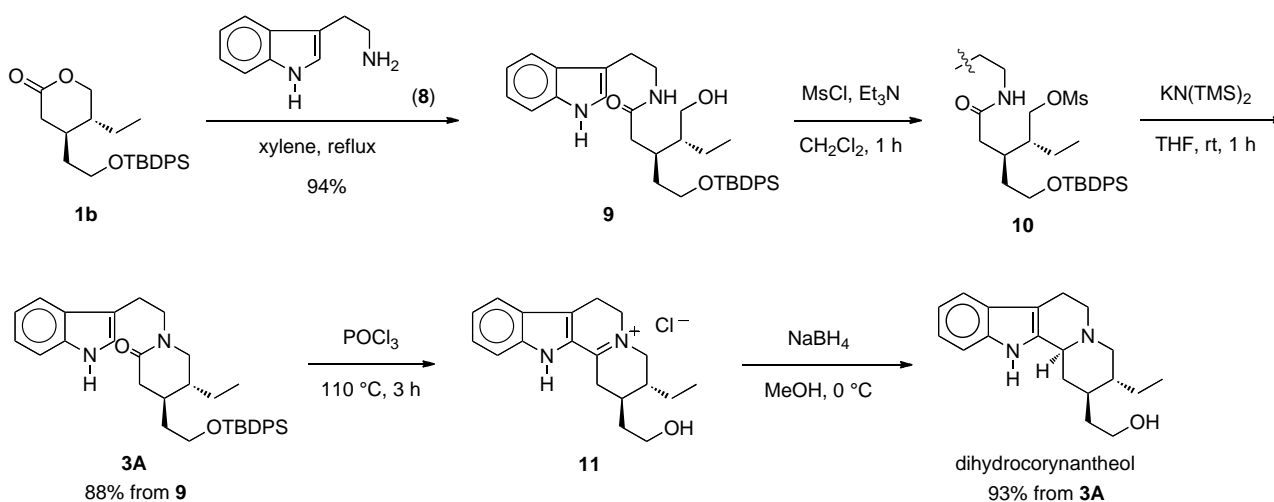
[†] This paper is dedicated to Professor Albert Eschenmoser on the occasion of his 85th birthday.

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**

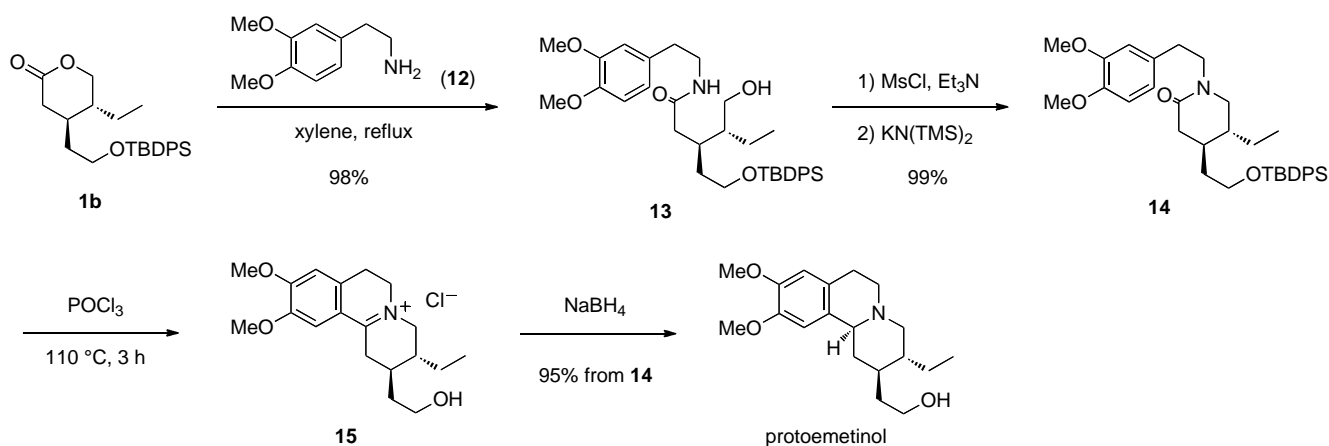
Transformation of **1b** to dihydrocorynantheol is summarized in Scheme 3, in which reactions being different from the original method^{2a,b} are involved. First, a mixture of **1b** and tryptamine (**8**) in xylene was heated under reflux to give amide alcohol **9** in 94% yield, which was converted to mesylate **10**. For construction of the lactam ring, $\text{KN}(\text{TMS})_2$ 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 POCl₃ followed by hydride reduction of the iminium salt **15** with NaBH₄⁸ 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*]quinolizidine structures.

EXPERIMENTAL

General. Infrared (IR) spectra are reported in wave numbers (cm⁻¹). The ¹H NMR (300 and 500 MHz) and ¹³C NMR (75 MHz) spectra were measured in CDCl₃ using SiMe₄ (δ = 0 ppm) and the center line of CDCl₃ triplet (δ = 77.1 ppm) as internal standards, respectively. The following solvents were distilled before use: THF (from Na/benzophenone), Et₂O (from Na/benzophenone), and CH₂Cl₂ (from CaH₂).

(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 Et₃N (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 NaHCO₃. The resulting mixture was extracted with hexane five times. The combined extracts were dried over Na₂SO₄ and concentrated to leave the enol ether **7**. A stream of O₃ in O₂ was gently bubbled into a solution of the enol ether **7** in MeOH (6.6 mL) and CH₂Cl₂ (0.66 mL) at -78 °C for 5 min. Excess O₃ remaining in the solution was purged by bubbling argon at -78 °C. The solution was warmed to 0 °C and NaBH₄ (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 MgSO₄ and concentrated to leave a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to provide lactone **1b** (522 mg, 96%): ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₂₅H₃₅O₃Si [(M+H)⁺] 411.2355, found 411.2558.

(3S*,4R*)-N-(2-(1H-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 (CH₂Cl₂/MeOH) to furnish **9** (408 mg, 94%): ¹H NMR (300 MHz, CDCl₃) 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).

(4S*,5R*)-1-(2-(1H-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 Et₃N (0.020 mL, 0.14 mmol) in CH₂Cl₂ (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 CH₂Cl₂ and washed successively with saturated NaHCO₃ and H₂O. The organic layer was dried over Na₂SO₄ 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 NH₄Cl. The resulting mixture was extracted with EtOAc three times. The combined extracts were dried over Na₂SO₄ and concentrated to leave a residue, which was purified by chromatography on silica gel (CH₂Cl₂/MeOH) to provide **3A** (27 mg, 88%): ¹H NMR (300 MHz, CDCl₃) 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 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$) to afford (–)-dihydrocorynanteol (10 mg, 93%): ^1H 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 (–)-dihydrocorynanteol in the literature.^{5b,e-g}

(3S*,4R*)-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-dimethoxyphenethylamine **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 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$) to furnish **13** (232 mg, 98%): ^1H 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).

(4S*,5R*)-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 $\text{KN}(\text{TMS})_2$ (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 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$) to provide **14** (28 mg, 99%): ^1H 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 POCl₃ (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 NaBH₄ (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 CH₂Cl₂ three times. The combined extracts were dried (K₂CO₃) and concentrated. The residue was purified by chromatography on silica gel (CH₂Cl₂/MeOH) to afford (-)-protoemetinol (9 mg, 95%): ¹H NMR (300 MHz, CDCl₃) 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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