A Short Synthesis of (±)-Eburnamonine

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We recently reported a novel three-component coupling reaction where a range of 2-substituted ethyl α-(tetrahydro-3-pyrilidene)acetates were prepared conveniently.[1] As illustrated in Figure 1, $TiCl_4$-promoted condensation of ethyl glyoxylate and 3,4-dihydro-2*H*-pyran presumably provided an oxonium ion **3**, which was trapped with various carbon, oxygen, or sulfur nucleophiles to provide the respective heterocycle **4**. We subsequently considered trapping of the oxonium cation intermediate by primary amine nucleophile to deliver the corresponding imine functionality for further synthetic applications. Of particular relevance, reaction of the presumed oxonium ion with tryptamine followed by opening of the resulting tetrahydropyran ring may lead to the imine derivative **5** in a single operation. Imine **5** was previously synthesized in six steps from dihydropyran by Martel and co-workers.[2] This imine derivative would be an advanced intermediate for the synthesis of the pentacyclic indole alkaloid eburnamonine (**1**), which has been the subject of continuing synthetic interest over the years.[3] Herein we report the synthesis of eburnamonine (**1**) in only four steps utilizing a $TiCl_4$-mediated three component coupling reaction as the key step.

The key coupling reaction was carried out as follows in a one-pot operation (Scheme 1). Reaction of ethyl glyoxylate (1 equiv) and dihydropyran (1.5 equiv) in the presence of $TiCl_4$ (1 equiv) in CH_2Cl_2 at −78 to 23 °C for 2 h provided the corresponding oxonium ion. Treatment of the resulting oxonium ion with diisopropylethylamine followed by a solution of tryptamine in CH_2Cl_2 at 23 °C for 1 h afforded the mixture (*E*/*Z* ratio 1.2:1) of imine derivatives **5** after a series of bond-making and bond-breaking events.[4] Identification of the *E*- and *Z*-isomers in **5** was made by NOE experiment.[5] Attempted chromatographic purification of the crude mixture, however, resulted in significant decomposition of these imines. The mixture of crude imines was then exposed to subsequent cyclization conditions without further purification. Thus, treatment of the crude mixture with aqueous 6 N HCl in ethanol at 0 to 23 °C for 1 h furnished the amino

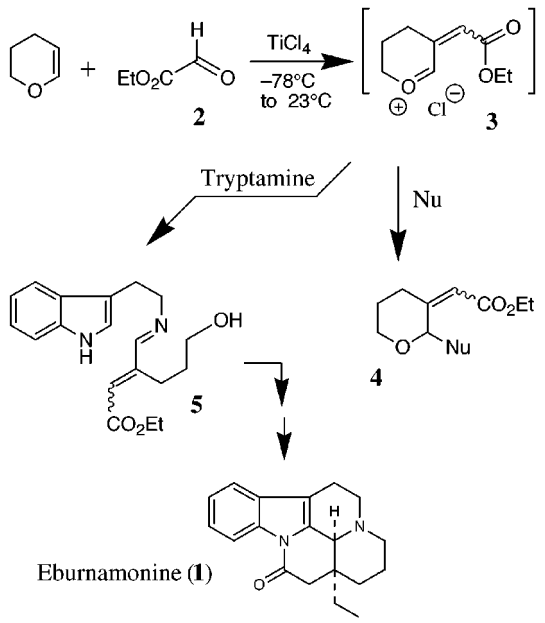

Figure 1.

alcohol **6** as a single diastereomer (by ^1H and ^{13}C NMR) in 25−34% yield (from **2**) after the silica gel column chromatography. The olefin geometry of **6** was established by comparison of ^1H NMR data with the reported values.[2] To improve the reaction yield, a number of other reaction conditions were surveyed. Reaction of the imines with *p*-toluenesulfonic acid or camphorsulfonic acid in CH_2Cl_2 at 23 °C and also $TiCl_4$ in CH_2Cl_2 at −78 °C also provided **6** exclusively. While only amino alcohol **6** was obtained under these conditions, the overall product yield was not improved.[6] Presumably, the cyclization occurred from the *E*-isomer only and the *Z*-isomer may have decomposed under the acidic reaction conditions.

Treatment of the amino alcohol **6** with triflic anhydride (2 equiv) and Et_3N (3 equiv) in CH_2Cl_2 at −78 °C for 1 h furnished the indoloquinolizidine **7** in 70% yield after silica gel chromatography. Attempted cyclization with thionyl chloride (1.4 equiv) and pyridine (2.2 equiv) in benzene at 23 °C as described by Martel and co-workers provided **7** in significantly lower yield (30−40%).[2] The identity of *cis*-stereochemistry in the tetracyclic indoloquinolizidine **7** was established on the basis of comparison of spectroscopic data reported by Santamaria et al.[7] The indoloquinolizidine derivative **7**, with its assumed folded conformation, has been shown to undergo 1,4-addition by ethyl Grignard selectively from the α-face.[2,7] Thus, reaction of **7** with EtMgBr in the presence of CuCl in ether at −20 to 0 °C for 2 h furnished (±)-eburnamonine (**1**). Spectral data (^1H and ^{13}C NMR) for the synthetic (±)-**1** is identical to that reported in the literature.[3b]

In summary, a four-step synthesis of (±)-eburnamonine has been described. The key step involved a $TiCl_4$-promoted three-component coupling of dihydropyran,

(1) Ghosh, A. K.; Kawahama, R. *Tetrahedron Lett.* **1999**, *40*, 4751.

(2) Costerousse, G.; Buendia, J.; Toromanoff, E.; Martel, J. *Bull. Chem. Soc. Fr.* **1978**, II-355.

(3) For recent work on the synthesis of (−)- and (±)-eburnamonine, see: (a) Wee, A. G. H.; Yu, Q. *Tetrahedron Lett.* **2000**, *41*, 587. (b) Grieco, P. A.; Kaufman, M. D. *J. Org. Chem.* **1999**, *64*, 7586. (c) Schultz, A. G.; Pettus, L. *J. Org. Chem.* **1997**, *62*, 6855. (d) Kaufman, M. D.; Grieco, P. A. *J. Org. Chem.* **1994**, *59*, 7197. (e) Palmisano, G.; D'Anniballa, P.; Santagostino, M. *Tetrahedron* **1994**, *50*, 9487 and references therein.

(4) Using a bulky glyoxylate, such as cyclohexylglyoxylate, did not improve the *E*/*Z* ratio.

(5) For the major *E*-isomer, an NOE (13%) was observed between the olefinic proton (6.99 ppm) and the imine proton (7.70 ppm). However, no NOE was observed between the olefinic proton (7.02 ppm) and the imine proton (9.10 ppm) of the *Z*-isomer.

(6) As per suggestion of one referee, we have attempted cyclization of **5** to **7** with 48% HBr at 0−90 °C for 6 h. This condition provided only **6** in 13% yield after silica gel chromatography.

(7) Da Silva Goes, A.; Ferroud, C.; Santamaria, J. *Tetrahedron Lett.* **1995**, *36*, 2235.

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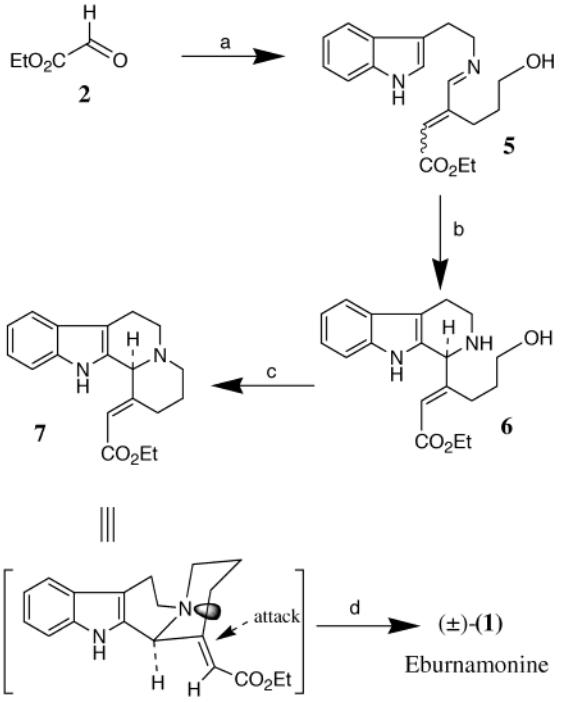
Scheme 1[a]



[a](a) 3,4-Dihydro-2*H*-pyran, $TiCl_4$, CH_2Cl_2; then *i*Pr_2NEt, tryptamine; (b) 6 N HCl (aq), EtOH, 23 °C (25%, two steps); (c) Tf_2O, Et_3N, CH_2Cl_2, −78 °C (70%); (d) EtMgBr, CuCl (cat.), Et_2O, THF, −20 to 0 °C (65%).

ethyl glyoxylate, and tryptamine to form the intermediate imine derivative. While the overall reaction yield is somewhat modest (25−34% two steps), the formation of the key imine after a series of bond-making and bond-breaking processes is particularly noteworthy.

Experimental Section

Melting points were recorded and are uncorrected. Anhydrous solvents and reagents were obtained as follows: tetrahydrofuran and diethyl ether, distillation from sodium/benzophenone; methylene chloride, distillation from CaH_2; diisopropylethylamine and triethylamine, distillation from CaH_2. All other solvents were HPLC grade. Column chromatography was performed with Whatman 240−400 mesh silica gel under low pressure of 5−10 psi. Thin-layer chromatography (TLC) was carried out with E. Merck silica gel 60 F-254 plates.

Synthesis of Imine 5. To a mixture of ethyl glyoxylate (204 mg, 2 mmol) and 3,4-dihydro-2*H*-pyran (252 mg, 3 mmol) in dry CH_2Cl_2 (7 mL) was added $TiCl_4$ (0.22 mL, 2 mmol) at −78 °C, and the resulting yellow solution was stirred for 1 h at −78 °C. The cooling bath was removed, and the mixture was stirred for an another 1 h at 23 °C. Dry CH_2Cl_2 (6 mL) was added to the resulting suspension, and the mixture was stirred vigorously for 2 min. The clear supernatant was taken up by syringe and transferred to another flask. To this solution at 23 °C was added *i*Pr_2NEt (0.70 mL, 4 mmol), and the mixture was stirred for 5 min. The resulting mixture was added into a CH_2Cl_2 (10 mL) solution of tryptamine (320 mg, 2 mmol), and the mixture was stirred for 1 h at 23 °C. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2. The organic extracts were dried over anhydrous Na_2SO_4 and evaporated. The residue was used for the next reaction without further purification. An analytical sample was prepared by purification over silica gel column: $R_f = 0.30$ (5% MeOH in $CHCl_3$); IR (film) 3406, 3291, 1712, 1622, 1455 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) *E*-isomer δ 1.33 (3H, t, $J = 7.1$ Hz), 1.82−1.87 (2H, m), 2.99 (2H, t, $J = 6.6$ Hz), 3.17 (2H, t, $J = 7.0$ Hz), 3.46 (2H, t, $J = 5.5$ Hz), 3.93 (2H, t, $J = 7.1$ Hz), 4.23 (2H, q, $J = 7.1$ Hz), 6.02 (1H, s), 6.99 (1H, d, $J = 2.2$ Hz), 7.12 (1H, m), 7.20 (1H, td, $J = 8.1$ and 1.2 Hz), 7.35 (1H, d, $J = 8.1$ Hz), 7.61 (1H, d, $J = 7.8$ Hz), 7.70 (1H, s), 8.04 (1H, br s); *Z*-isomer δ 1.30 (3H, t, $J = 7.1$ Hz), 1.73−1.79 (2H, m), 2.60 (2H, t, $J = 6.7$ Hz), 3.16 (2H, t, $J = 7.4$ Hz), 3.52 (2H, t, $J = 5.7$ Hz), 3.96 (2H, t, $J = 7.3$ Hz), 4.19 (2H, q, $J = 7.1$ Hz), 6.18 (1H, s), 7.02 (1H, d, $J = 2.2$ Hz), 7.11 (1H, m), 7.19 (1H, td, $J = 8.1$ and 1.2 Hz), 7.34 (1H, d, $J = 8.1$ Hz), 7.62 (1H, d, $J = 7.8$ Hz), 8.04 (1H, br s), 9.10 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) *E*-isomer δ 13.9, 22.1, 26.3, 31.7, 59.8, 60.3, 61.2, 111.0, 112.5, 118.4, 118.6, 121.4, 122.0, 127.5, 128.0, 136.3, 154.9, 165.1, 165.9; *Z*-isomer δ 13.9, 21.2, 28.3, 32.6, 59.8, 60.3, 61.6; 110.6, 112.8, 118.4, 118.6, 121.4, 122.3, 127.1, 128.8, 136.1, 153.9, 161.2, 165.3; HRMS (EI) *m*/*z* calcd for $C_{19}H_{24}O_3N_2$ (M^+) 328.1788, found 328.1786.

Amino Alcohol 6. To a stirred solution of the above crude imine **5** in EtOH (40 mL) at 0 °C was added 6 N aqueous HCl solution (2 mL). The resulting reaction mixture was stirred at 23 °C for 1 h. The reaction mixture was poured into ice-cooled saturated aqueous $NaHCO_3$ solution (10 mL) and thoroughly extracted with CH_2Cl_2. The organic extracts were dried over anhydrous Na_2SO_4 and evaporated. Flash column chromatography (EtOAc) of the residue afforded the title amino alcohol **6** (164 mg) in 25% yield (2 steps) as a pale brown foam: $R_f = 0.20$ (10% MeOH in $CHCl_3$); IR (film) 3390, 3296, 1704, 1643, 1450 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.29 (3H, t, $J = 7.1$ Hz), 1.84−1.96 (2H, m), 2.60 (1H, quint, $J = 6.6$ Hz), 2.81 (1H, m), 2.86−2.97 (2H, m), 3.15 (1H, ddd, $J = 12.7$, 7.1, and 4.9 Hz), 3.31 (1H, dt, $J = 12.7$ and 5.5 Hz), 3.61−3.70 (2H, m), 4.19 (2H, q, $J = 7.1$ Hz), 4.77 (1H, s), 5.82 (1H, s), 7.15 (1H, t, $J = 7.8$ Hz), 7.21 (1H, t, $J = 7.8$ Hz), 7.34 (1H, dd, $J = 8.1$, 0.5 Hz), 7.54 (1H, d, $J = 7.8$ Hz), 7.93 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.2, 26.7, 31.5, 41.3, 59.7, 60.3, 61.1, 110.8, 110.9, 118.2, 119.4, 120.3, 122.0, 127.1, 131.6, 135.9, 161.5, 166.5; HRMS (EI) *m*/*z* calcd for $C_{19}H_{24}O_3N_2$ (M^+) 328.1788, found 328.1785.

Indoloquinolizidine 7. To a stirred solution of amino alcohol **6** (75 mg, 0.23 mmol) and Et_3N (0.1 mL, 0.69 mmol) in CH_2Cl_2 (2.3 mL) was added triflic anhydride (0.08 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h. After this period, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (1 mL) at −78 °C and extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and evaporated. Flash column chromatography (70% EtOAc in hexane) of the residue afforded the indoloquinolizidine **7** (50 mg) in 70% yield as a pale yellow foam: $R_f = 0.37$ (5% MeOH in $CHCl_3$); IR (film) 3356, 1704, 1649, 1450 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (3H, t, $J = 7.1$ Hz), 1.75−1.91 (2H, m), 2.73 (1H, m), 2.82−2.90 (2H, m), 2.93−3.08 (4H, m), 3.27 (1H, m), 4.18 (2H, qd, $J = 7.1$ and 1.4 Hz), 4.51 (1H, s), 5.85 (1H, s), 7.12 (1H, td, $J = 7.9$ and 1.1 Hz), 7.18 (1H, td, $J = 7.9$ and 1.1 Hz), 7.33 (1H, d, $J = 8.0$ Hz), 7.51 (1H, d, $J = 7.7$ Hz), 7.82 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 19.0, 25.9, 26.9, 50.5, 50.6, 60.1, 63.4, 109.1, 111.0, 116.7, 118.3, 119.5, 121.9, 127.2, 129.9, 135.9, 156.8, 166.4; HRMS (EI) *m*/*z* calcd for $C_{19}H_{22}O_2N_2$ (M^+) 310.1682, found 310.1685.

Synthesis of (±)-Eburnamonine. Ethylmagnesium bromide (0.4 mL, 0.4 mmol; 1.0 M solution in Et_2O) was added to anhydrous cuprous chloride (5 mg) at 23 °C, and the resulting mixture was stirred for 10 min. A solution of indoloquinolizidine **7** (10 mg, 0.032 mmol) in THF (1.0 mL) was added to the above reaction mixture at −10 °C, and the mixture was stirred for 1 h. After this period, the mixture was warmed to 0 °C and stirred for 30 min. The reaction mixture was then quenched with saturated aqueous NH_4Cl solution (0.5 mL) and extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and evaporated. Flash column chromatography (70% EtOAc in hexane) of the residue afforded (±)-eburnamonine (6.2 mg) in 65% yield as a white solid. The colorless crystalline (±)-eburnamonine was obtained after recrystallization from ethanol (mp 199.5−200 °C, lit.[2] 200 °C): $R_f = 0.45$ (5% MeOH in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, t, $J = 7.6$ Hz), 1.05 (1H, td, $J = 13.4$ and 3.9 Hz), 1.40 (1H, dm, $J = 13.4$ Hz), 1.50 (1H, d, $J = 13.4$ Hz), 1.68 (1H, dq, $J = 14.5$ and 7.3 Hz), 1.76 (1H, m), 2.06 (1H, dq, $J = 14.5$ and 7.6 Hz), 2.43 (1H, br t, $J = 11.0$ Hz), 2.51 (1H, ddd, $J = 16.9$, 5.7 and 1.2 Hz), 2.60 (1H, d, $J = 16.7$ Hz), 2.61 (1H, m), 2.68 (1H, d, $J = 16.7$ Hz), 2.91 (1H, m), 3.28 (1H, ddd, $J = 13.8$, 11.2 and 5.7 Hz), 3.36

(1H, dd, J = 13.8 and 6.6 Hz), 4.01 (1H, br s), 7.24−7.33 (2H, m), 7.44 (1H, dd, J = 7.7 and 1.4 Hz), 8.37 (1H, dd, J = 7.7 and 1.4 Hz); HRMS (EI) m/z calcd for $C_{19}H_{22}ON_2$ (M^+) 294.1733, found 294.1724.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds **1**, **6** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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