An Efficient Synthesis of Racemic Necine Bases from a Common Intermediate

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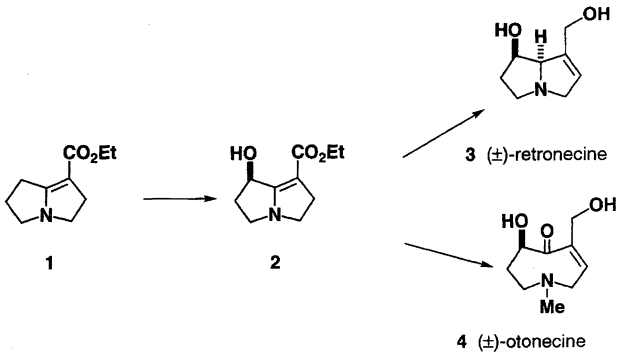
Necine bases of pyrrolizidine alkaloids, turneforcidine, hastanecine, and platynecine are synthesized from ethyl 1-hydroxy-2,3,5,6-tetrahydro-1*H*-pyrrolizine-7-carboxylate in racemic form.

Pyrrolizidine alkaloids are known to possess remarkable hepatotoxicity and, in certain cases, carcinogenicity and antitumor activity.[1] The characteristic structures coupled with diverse biological activities have made these alkaloids attractive synthetic targets. During the past decade we have engaged in synthetic studies on macrocyclic pyrrolizidine alkaloids.[2] In connection with continuous synthetic studies, we wish to describe an efficient synthesis of racemic necine bases ((±)-turneforcidine (**7**), (±)-hastanecine (**8**), and (±)-platynecine (**10**)) from a common intermediate, ethyl (±)-1-hydroxy-2,3,5,6-tetrahydro-1*H*-pyrrolizine-7-carboxylate (**2**).

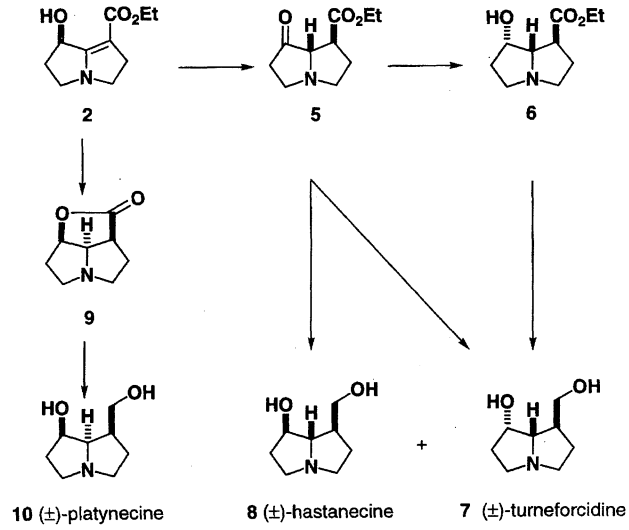
Results and Discussion

Previously, we reported on the syntheses of (±)-retronecine (**3**)[3] and (±)-otonecine (**4**)[4] from a common intermediate, hydroxy unsaturated ester **2** prepared by the γ-hydroxylation of the β-amino-α,β-unsaturated ester system

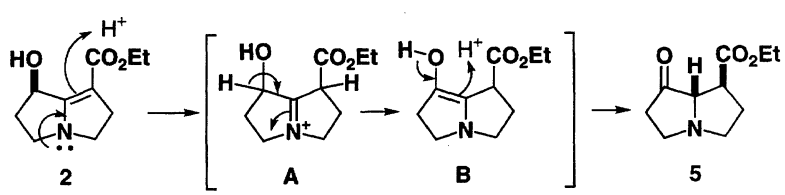


Scheme 1.

in ethyl 2,3,5,6-tetrahydro-1*H*-pyrrolizine-7-carboxylate (**1**) (Scheme 1). We have found that hydroxy unsaturated ester **2** was isomerized smoothly into bicyclic keto ester **5** in 54% yield upon an AcOH treatment (Scheme 2). This isomerization of **2** into **5** may proceed through intermediates **A** and **B**, as shown in Scheme 3. Thus, the initial protonation of **2** provides iminium salt **A**, which in turn is deprotonated to give enol **B**. Tautomerization of **B** gives **5**. The stereochemistry of **5** was tentatively assigned, which was confirmed by successive transformations of **5** into (±)-turneforcidine (**7**). Thus, the hydrogenation of keto ester **5** over PtO_2 gave hydroxy ester **6** (40%), from which (±)-turneforcidine (**7**) was synthe-



Scheme 2.



Scheme 3.

sized by $LiAlH_4$ reduction in 86% yield. On the other hand, the direct reduction of keto ester **5** with $LiAl_4$ gave (±)-hastanecine (**8**) along with the (±)-turneforcidine (**7**) in 40% and 26% yield, respectively. Finally, (±)-platynecine (**10**) was synthesized by the $LiAlH_4$ reduction of lactone **9**, which was previously employed in our synthesis of (±)-retronecine (**3**).[3]

In the present and previous synthesis we achieved efficient syntheses of necine bases, turneforcidine (**7**), hastanecine (**8**), platynecine (**10**), retronecine (**3**), and otonecine (**4**) from the common intermediate hydroxy unsaturated ester **2** in racemic form.

Experimental

The melting points are uncorrected. IR spectra were taken on a JASCO IR-810 spectrophotometer. ^{1}H NMR spectra were recorded on a JEOL JNM EX-270 (270 MHz) spectrometer. The chemical shifts (δ) are reported in ppm downfield from internal tetramethylsilane, and the coupling constants in Hz. Low-resolution (EIMS) and high-resolution mass spectra (HREIMS) were measured on a JEOL JMS-LG2000 instrument. Fuji-Davison silica gel BW-820MH and Merck aluminum oxide 90 (activity II-III, Art. 1097) (alumina) were used for column chromatography. Merck precoated silica gel 60 F_{254} plates, 0.25 mm thickness and Merck precoated alumina 150 F_{254} (Type T) plates, 0.25 mm thickness were used for analytical thin-layer chromatography (TLC) and for preparative TLC. Dichloromethane (CH_2Cl_2) and diisopropylamine were distilled from calcium hydride (CaH_2) under nitrogen. Benzene and toluene were distilled from sodium (Na) under nitrogen. Tetrahydrofuran (THF) was distilled from sodiumbenzophenone ketyl. Methanol (MeOH) and ethanol (EtOH) were distilled from $Mg(OMe)_2$ and $Mg(OEt)_2$ under nitrogen, respectively. Chloroform ($CHCl_3$) was distilled from phosphorus pentaoxide.

Ethyl (±)-1-Hydroxy-2,3,5,6-tetrahydro-1*H*-pyrrolizine-7-carboxylate (2). (A) Hydroxylation with (±)-3-Phenyl-2-phenylsulfonyloxaziridine. To a cooled (−78 °C), stirred solution of ethyl 2,3,5,6-tetrahydro-1*H*-pyrrolizine-7-carboxylate (**1**)[5] (29.2 mg, 0.161 mmol) in THF (1.5 ml) under nitrogen was added dropwise a 0.5 M (1 M = 1 mol dm^{-3}) toluene solution of potassium bis(trimethylsilyl)amide (1.13 ml, 0.565 mmol). After the mixture was stirred at −78 °C for 1 h, a solution of (±)-3-phenyl-2-phenylsulfonyloxaziridine[6] (88.5 mg, 0.339 mmol) in THF (3.0 ml) was added to the cooled solution. The mixture was stirred at −78 °C for 30 min, and the reaction was quenched by the addition of saturated $Na_2S_2O_3$ solution (1 ml). The mixture was diluted with H_2O (3 ml) and extracted with EtOAc (2 ml×5). The combined extracts were washed, dried, and concentrated under reduced pressure. The residue was purified by repeated column chromatography [(1) silica gel 3 g, $CHCl_3$ containing 1% Et_3N; (2) silica gel 2.0 g, benzene containing 1% Et_3N], affording **2** (19.7 mg, 62%) as a colorless oil: IR ($CHCl_3$) 3340, 1595 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 1.27 (3 H, t, J = 7.3 Hz), 2.31 (1 H, m), 2.96—3.10 (3 H, m), 3.20 (1 H, dt, J = 3.6, 8.7 Hz), 3.28—3.48 (2 H, m), 4.16 (2 H, q, J = 7.3 Hz), 4.92 (1 H, t, J = 7.9 Hz); EIMS *m/z* (rel intensity) 197 (M^+; 30), 179 (56), 169 (38), 152 (16), 135 (96), 96 (100). HREIMS. Found: *m/z* 197.1053. Calcd for $C_{10}H_{15}NO_3$: M, 197.1052.

(B) Hydroxylation with MoO_5·HMPA·Py. To a cooled (−78 °C), stirred solution of **1**[5] (250.8 mg, 1.836 mmol) in THF (6.3 ml) under nitrogen was added dropwise a 0.215 M THF solution of lithium diisopropylamide (19 ml, 4.08 mmol). After the mixture was stirred at −78 °C for 1 h, MoO_5·HMPA·Py[7] (1.2 g, 2.8 mmol) was added to the cooled solution. The mixture was stirred at −78 °C for 20 min, and the reaction was quenched by the addition of saturated Na_2SO_3 solution (4.4 ml). The mixture was diluted with H_2O (1.5 ml) and extracted with EtOAc (60 ml×2). The combined extracts were washed, dried, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (5.2 g, CH_2Cl_2–EtOAc (5 : 1) → EtOAc → MeOH), affording **2** (193.3 mg, 71%).

Ethyl (1*R,7a*R**)-(±)-7-Oxo-2,3,5,6,7,7a-hexahydro-1*H*-pyrrolizine-1-carboxylate (±)-(5).** A mixture of **2** (47.6 mg, 0.426 mmol) and AcOH (1 ml) was stirred at room temperature for 2 d. The reaction mixture was concentrated in vacuo. The residue was dissolved in saturated $NaHCO_3$ (1 ml) and the mixture was extracted with EtOAc (4 ml×3). The combined extracts were washed, dried, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel [3 g, $CHCl_3$–MeOH (50/1) → (20/1)], affording **5** (25.5 mg, 54%) as a colorless oil: IR ($CHCl_3$) 1750, 1725 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 1.28 (3 H, t, J = 7.3 Hz), 2.08—2.17 (2 H, m), 2.44 (2 H, t, J = 7.3 Hz), 2.71 (1 H, tt, J = 10.6, 7.3 Hz), 2.94—3.03 (2H, m), 3.20 (1 H, ddd, J = 12.5, 6.9, 5.6 Hz), 3.40 (1 H, dt, J = 11.5, 7.3 Hz), 3.75 (1 H, d, J = 4.9 Hz), 4.18 (2 H, q, J = 7.3 Hz); EIMS *m/z* (rel intensity) 197 (M^+; 34), 169 (47), 152 (30), 96 (100), 68 (40). HREIMS. Found: *m/z* 197.1051. Calcd for $C_{10}H_{15}NO_3$: M, 197.1052.

Ethyl (1*R,7*R**,7a*R**)-(±)-7-Hydroxy-2,3,5,6,7,7a-hexahydro-1*H*-pyrrolizine-1-carboxylate (±)-(6).** A mixture of **5** (31.1 mg, 0.158 mmol) and PtO_2 (22.1 mg) in EtOH (1.2 ml) was stirred at room temperature for 2.5 h under a hydrogen atmosphere and then filtrated through a pad of Celite. The combined filtrate and washings were concentrated under reduced pressure. The residue was purified by column chromatography on alumina [1 g, EtOAc–MeOH (3/1)], providing **6** (12.7 mg, 40%) as a colorless oil: IR ($CHCl_3$) 3420, 1720 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 1.27 (3 H, t, J = 7.3 Hz), 1.93—2.02 (1 H, m), 2.05—2.18 (1 H, m), 2.20—2.28 (3 H, m), 2.56—2.72 (2 H, m), 3.06—3.23 (2 H, m), 3.72 (1 H, dd, J = 5.6, 4.6 Hz), 3.40 (1 H, dt, J = 11.5, 7.3 Hz), 3.75 (1 H, d, J = 4.9 Hz), 4.18 (2 H, q, J = 7.3 Hz), 4.38 (1 H, m); EIMS *m/z* (rel intensity) 199 (M^+; 8), 181 (25), 167 (8), 155 (42), 82 (52), 58 (100). Found: *m/z* 199.1215. Calcd for $C_{10}H_{17}NO_3$: M, 199.1208.

(1*R,7*R**,7a*R**)-(±)-7-Hydroxy-7-hydroxymethyl-2,3,5,6,7,7a-hexahydro-1*H*-pyrrolizine-1-methanol (±)-(7) [(±)-Turneforcidine)].** To an ice-cooled, stirred solution of **6** (12.7 mg, 0.064 mmol) in THF (2 ml) was added a 1 M THF solution of $LiAlH_4$ (0.19 ml, 0.191 mmol). The mixture was stirred at 0 °C for 3 h, and the reaction was quenched by the addition of 5% aqueous THF (0.5 ml). The mixture was stirred for a while and filtered through a pad of Celite. The combined filtrate and washings were concentrated under reduced pressure. The residue was purified by TLC on alumina [20 cm×20 cm, 0.25 mm thickness, CH_2Cl_2–MeOH–aq NH_3 (5/1/0.05)], providing (±)-**7** (8.6 mg, 86%) as a colorless oil: IR ($CHCl_3$) 3370 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 1.55—1.71 (2 H, m), 1.88—2.11 (2 H, m), 2.43—2.74 (3 H, m), 3.06 (1 H, m), 3.21 (1 H, m), 3.32 (1 H, dd, J = 8.2, 5.6 Hz), 3.85 (1 H, dd, J = 9.9, 4.6 Hz), 4.34 (1 H, dd, J = 10.0, 5.6 Hz); EIMS *m/z* (rel intensity) 157 (M^+; 27), 133 (10), 113 (39), 89 (14), 82 (100). Found: *m/z* 157.1090. Calcd for $C_8H_{15}NO_2$: M, 157.1110. Spectral properties of synthetic (±)-**7** were identical with those of authentic **7**[8] in all respects.

(1*R,7*S**,7a*R**)-(±)-7-Hydroxy-2,3,5,6,7,7a-hexahydro-1*H*-pyrrolizine-1-methanol (±)-(8) [(±)-Hastanecine)].** To an ice-cooled, stirred solution of **5** (27.9 mg, 0.141 mmol) in THF (4 ml)

was added a 1 M THF solution of $LiAlH_4$ (0.43 ml, 0.43 mmol). The mixture was stirred at 0 °C for 2 h, and the reaction was quenched by the addition of 5 % aqueous THF (1 ml). The mixture was stirred for a while and filtered through a pad of Celite. The combined filtrated and washings were concentrated under reduced pressure. The residue was purified by TLC on alumina [20 cm×20 cm, 0.25 mm thickness, CH_2Cl_2–MeOH–aq NH_3 (3/1/0.05)], providing (±)-**8** (8.7 mg, 40%) as a colorless oil along with (±)-**7** (26%). (±)-**8**: IR ($CHCl_3$) 3350 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ = 1.63 (1 H, m), 1.86—2.03 (3 H, m), 2.10 (1 H, m), 2.52 (1 H, dt, J = 10.6, 5.6 Hz), 2.64 (1 H, dt, J = 10.6, 6.6 Hz), 3.11—3.26 (3 H, m), 3.53 (1 H, dd, J = 10.2, 8.3 Hz), 3.81 (1 H, dd, J = 10.2, 4.6 Hz), 4.07 (1 H, dt, J = 4.3, 5.9 Hz); EIMS *m/z* (rel intensity) 157 (M^+; 17), 113 (25), 82 (100). Found: *m/z* 157.1111. Calcd for $C_8H_{15}NO_2$: M, 157.1110. The spectral properties of synthetic (±)-**8** was identical with those of authentic **8**[9] in all respects.

(1*R,7*S**,7a*S**)-(±)-7-Hydroxy-2,3,5,6,7,7a-hexahydro-1*H*-pyrrolizine-1-methanol (±)-(10) [(±)-Platynecine].** To a stirred solution of **9**[3,10] (20.0 mg, 0.130 mmol) in THF (2 ml) was added a 1 M THF solution of $LiAlH_4$ (0.4 ml, 0.4 mmol). The mixture was heated under reflux with stirring for 2 h. After the reaction mixture was cooled, the reaction was quenched by the addition of 5% aqueous THF (1 ml). The mixture was stirred for a while and filtered through a pad of Celite. The combined filtrate and washings were concentrated under reduced pressure. The residue was purified by TLC on alumina [20 cm×20 cm, 0.25 mm thickness, CH_2Cl_2–MeOH–aq NH_3 (3/1/0.05)], providing (±)-**10** (12.0 mg, 60%) as colorless oil: IR ($CHCl_3$) 3370 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ = 1.60—1.70 (2 H, m), 1.90—2.01 (2 H, m), 2.40—2.70 (3 H, m), 3.00 (1 H, m), 3.20 (1 H, m), 3.30 (1 H, dd, J=8.2, 3.0 Hz), 3.90—4.00 (2 H, m), 4.18 (1 H, ddd, J = 4.2, 4.0, 3.5 Hz); EIMS *m/z* (rel intensity) 157 (M^+; 15), 113 (25), 82 (100). Found: *m/z* 157.1095. Calcd for $C_8H_{15}NO_2$: M, 157.1110. Spectral properties of synthetic (±)-**10** were identical with those of authentic **10**[9] in all respects.

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