A Concise Total Synthesis of (+)-Heliotridine

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A practical synthesis of the necine base (+)-heliotridine (**1**) is reported here. The present total synthesis is based on the highly selective 1,3-dipolar cycloaddition of (*S*)-3-*tert*-butoxypyrroline *N*-oxide (**2**) to the commercially available ethyl 4-bromocrotonate, followed by a suitable elaboration of the adduct. The synthesis gives a 17% overall yield from nitrone **2**.

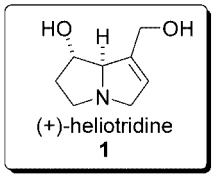
Introduction

(+)-Heliotridine (**1**) is a 1,2-unsaturated pyrrolizidine compound present as the necine base of many pyrrolizidine alkaloids (PAs). Heliotridine **1** and the most common retronecine (the 7-epimer of heliotridine) possess, besides the double bond between carbon atoms 1 and 2, a hydroxymethyl group on C-1 and a hydroxyl group on C-7. Necine bases are distributed across numerous plant families and genera, and their broad structural diversity depends on the various combinations with the necic acids.

The presence of PAs in food is a threat to human health and safety,[1] because they are converted by liver enzymes into pyrrolic metabolites that are able to bind strongly nucleophilic centers in tissues or crosslink DNA, leading to hepatotoxicity and carcinogenicity.

Several syntheses of **1** were reported in the literature and most of them have L-malic acid as the starting material. One efficient synthesis was reported by Chamberlin and Chung.[2] They started from the L-malic acid derived acetoxysuccinimide and exploited an acyliminium ion-ketene dithioacetal cyclization in the formation of the second pyrrolidine ring. They obtained enantiopure **1** in 7 steps and a 10.8% overall yield from L-malic acid.

Other total syntheses of **1** were described,[3,4,5] but they proved less efficient than the Chamberlin one.



(+)-heliotridine
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In the present paper, we report a concise total synthesis of (+)-heliotridine. The synthetic approach is based on the completely regio- and diastereoselective 1,3-dipolar cycloaddition of the L-malic derived (*S*)-3-*tert*-butoxypyrroline *N*-oxide (**2**) with the commercially available crotonate derivative **3**.

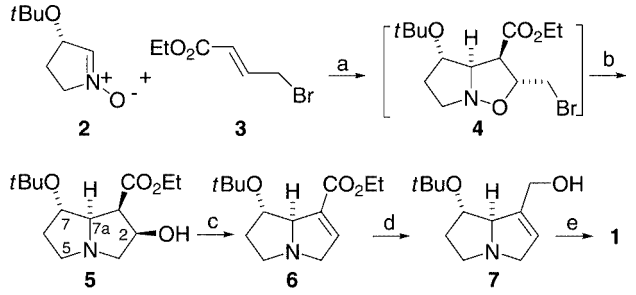
Results and Discussion

Recently, we have demonstrated the efficiency of the cycloaddition strategy in the total synthesis of (−)-rosmarinecine[6] and other pyrrolizidines, analogues of natural occurring necine bases.[7,8]

The first step in the synthesis of **1** consisted in the 1,3-dipolar cycloaddition of nitrone **2**[9] to ethyl 4-bromocrotonate (**3**) in toluene at room temperature, which ran in a complete regio- and diastereoselective manner to afford the sole isoxazolidine derivative **4**. Adduct **4** derived from the *anti-(CO$_2$Et)endo* transition state is the most favored, either for steric and electronic factors. Moreover, the carbethoxy and the alkyl groups drive the orbital interactions which lead to the complete regioselectivity. Compound **4** was very unstable, it could not be isolated, and it was directly treated with Raney Nickel and H_2 to give the enantiomerically pure pyrrolizidine derivative **5** in a 46% overall yield from **2** (Scheme 1).[10,11]

The relative and absolute configurations of the four contiguous stereogenic centers, achieved in a single step by the cycloaddition reaction, were particularly suited for the transformation of **5** in (+)-heliotridine (**1**). C-7 and C-7a showed the absolute configuration of **1**, and 1-H and 2-OH possessed the *trans* relationship suitable to set up the double bond between C-1 and C-2 through an elimination reaction. The elimination was carried out by treating **5** with nosyl chloride (NsCl), dimethylaminopyridine (DMAP), and triethylamine (TEA) (Scheme 1).

The unsaturated ester **6** was obtained in a very high yield and in a spectroscopically pure form from the aqueous



Scheme 1. Reagents and conditions: a) toluene, 0 °C→room temp., 7d; b) *i*. H_2, Raney Ni, EtOH. *ii*. Ambersep 900 OH (46%); c) NsCl, DMAP, TEA, 0 °C→room temp., overnight; d) DIBAL, 0 °C, CH_2Cl_2; e) *i*. TFA, H_2O; *ii*. DOWEX 50WX8−200 ionic exchange resin (37%)

workup of the reaction, but it proved to be rather unstable. Therefore, **6** was immediately used in the next step without further purification.

Reduction of **6** with diisobutylaluminum hydride (DIBAL) in CH_2Cl_2 at 0 °C gave the alcohol **7**, which was recovered spectroscopically pure after the common aqueous workup of the reduction, but in a very low yield (29%). To increase the yield of this step, the crude reduction mixture was concentrated and directly filtered through silica gel by eluting with MeOH/NH_4OH, 100:1. Next, compound **7** was directly treated with trifluoroacetic acid (TFA) at 0 °C for 2 h to remove the *tert*-butyl protecting group (Scheme 1). The ammonium salt, as yielded after simple evaporation of TFA, was deprotonated and purified by ion-exchange chromatography (DOWEX 50WX8−200) to give **1** in a 37% yield from **5** and a 17% yield from **2** as a spectroscopically pure colorless oil ($[\alpha]_D^{20}$= +26.5), which tended to crystallize. A further purification of **1** by chromatography on silica gel (eluent: $CHCl_3$/MeOH/NH_4OH, 10:4:1) gave the expected, analytically pure white solid, whose physical and spectroscopic data were consistent with those reported in the literature.[2,3]

Conclusion

We have described an efficient application of the cycloaddition/cyclization strategy for the synthesis of the intermediate pyrrolizidine **5**. Compound **5** was successfully transformed in (+)-heliotridine (**1**) in three steps and satisfactory yields. To the best of our knowledge, this is the first total synthesis of **1** based on a 1,3-dipolar cycloaddition as the key step for the construction of the pyrrolizidine skeleton and among the shortest syntheses reported in the literature. The methodology can be applied to the synthesis of other necine bases, simply by changing the configuration of the starting nitrone **2** and by selecting an inter- or intramolecular approach between the cycloaddition partners.[12]

Experimental Section

General Remarks: All the reactions requiring anhydrous conditions were carried out under nitrogen and the solvents were appropriately dried before use. R_f values refer to TLC on 0.25 mm silica gel plates (Merck F254). Melting points (m.p.) were determined on a RCH Kofler apparatus. Polarimetric measures were performed on a JASCO DIP-370 or a Perkin−Elmer 343 polarimeter. NMR spectra were recorded on Varian Gemini (^{1}H, 200 MHz) or Bruker ADVANCE 400 (^{1}H, 400 MHz) instrument, the NMR spectroscopic data are reported in δ (ppm) from TMS at 25 °C. IR spectra were recorded with a Perkin−Elmer Spectrum BX FT-IR System spectrophotometer. Mass spectra were recorded on a QMD 1000 Carlo Erba instrument by GC or direct inlet; relative percentages are shown in brackets. Elemental analyses were performed with a Perkin−Elmer 2400 analyzer.

Ethyl (1*R*,2*R*,7*S*,7a*R*)-7-*tert*-Butoxy-2-hydroxyhexahydro-1*H*-pyrrolizine-1-carboxylate (5): A solution of ethyl 4-bromocrotonate (**3**; 750 μL, 5.5 mmol) in dry toluene (30 mL) was cooled to 0 °C, treated with a solution of nitrone **2**[9] (947 mg, 6.0 mmol) in toluene (25 mL), and then stirred at room temp. for 7 days. EtOH (100 mL) and a catalytic amount of Raney Ni were added to the reaction solution, and the mixture was hydrogenated at room temp. and atmospheric pressure overnight. Raney Ni was removed by filtration, and Ambersep 900 OH was added to the solution, which was stirred at room temp. overnight. Filtration of the mixture, evaporation of the solvents, and chromatography on silica gel (eluent: $CHCl_3$/EtOH/TEA, 100:10:0.01) of the crude product afforded pure **5** (508 mg, 46% yield) as a yellow solid. R_f = 0.21 ($CHCl_3$/EtOH, 10:1); m.p. 79−81 °C. $[\alpha]_D^{22}$ = +12.1 (*c* = 0.6 in $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.17 (s, 9 H, C*Me*$_3$), 1.28 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.59−1.79 (m, 1 H, 6-H_a), 1.93−2.16 (m, 1 H, 6-H_b), 2.52 (dd, *J* = 7.8, 4.1 Hz, 1 H, 3-H_a), 2.57 (dd, *J* = 7.9, 2.2 Hz, 1 H, 1-H), 2.73 (ddd, *J* = 11.7, 6.1, 4.8 Hz, 1 H, 5-H_a), 3.11−3.24 (m, 1 H, 5-H_b), 3.35 (dd, *J* = 10.0, 6.1 Hz, 1 H, 3-H_b), 3.42 (dd, *J* = 8.5, 3.2 Hz, 1 H, 7a-H), 4.04−4.14 (m, 1 H, 7-H), 4.18 (q, *J* = 7.1 Hz, 1 H, C*H*HCH$_3$), 4.19 (q, *J* = 7.1 Hz, 1 H, C*H*HCH$_3$), 4.60 (dt, *J* = 6.1, 7.7 Hz, 1 H, 2-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.2 (q; CH_2CH_3), 28.4 (q, 3 C; C*Me*$_3$), 33.1 (t; C-6), 53.2 (t; C-5), 56.2 (d; C-1), 60.8, 60.9 (t; C-3, CH_2CH_3), 73.3 (d; C-7a), 73.6 (s; *C*Me$_3$), 75.1, 76.8 (d; C-2, C-7), 172.8 (s; CO) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3611, 2978, 2932, 1724, 1366, 1190 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 226 (0.3) [M$^+$ − OEt], 214 (100) [M$^+$ − CMe$_3$], 186 (28), 154 (8), 57 (73). $C_{14}H_{25}NO_4$ (271.35): calcd. C 61.97, H 9.29, N 5.16; found C 62.24, H 9.32, N 4.89.

Ethyl (7*S*,7a*S*)-7-*tert*-Butoxy-5,6,7,7a-tetrahydro-3*H*-pyrrolizine-1-carboxylate (6): TEA (55 μL, 0.42 mmol) was added dropwise to a solution of pyrrolizidine **5** (103.1 mg, 0.38 mmol), NsCl (93.0 mg, 0.42 mmol), and DMAP (23.2 mg, 0.19 mmol) in dry CH_2Cl_2 (4 mL) cooled to 0 °C. The mixture was stirred overnight at room temp. before CH_2Cl_2 (1 mL) and H_2O (1 mL) were added. The two phases were separated, and the organic layer was washed successively with a saturated solution of $NaHCO_3$ and brine, and then dried with Na_2SO_4. Evaporation of the solvent under reduced pressure afforded **6** (87.4 mg, 91%) as a colorless oil, which was used in the next step without further purification. R_f = 0.15 ($CHCl_3$/EtOH, 10:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.22 (s, 9 H, C*Me*$_3$), 1.30 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.58−1.70 (m, 2 H, 6-H), 2.60−2.72 (m, 1 H, 5-H_a), 3.24 (dt, *J* = 9.7, 7.7 Hz, 1 H, 5-H_b), 3.45 (ddd, *J* = 18.5, 5.5, 2.4 Hz, 1 H, 3-H_a), 4.04 (dt, *J* = 18.5, 2.7 Hz, 1 H, 3-H_b), 4.12−4.29 (m, 4 H, 7-H, 7a-H, CH_2CH$_3$), 6.75 (q, *J* = 2.0 Hz, 1 H, 2-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.2 (q; CH_2CH_3), 28.5 (q, 3 C; C*Me*$_3$), 33.1 (d; C-2), 55.3, 60.4, 63.0 (t; C-3, C-5, CH_2CH_3), 73.8 (s; *C*Me$_3$), 74.7 (d; C-7a), 78.8 (d; C-1), 134.2 (d; C-7), 141.5 (d; C-6), 163.6 (s; CO) ppm. IR

($CDCl_3$): $\tilde{\nu}$ = 2978, 1722, 1604, 1526, 1349, 1243, 1190, 1120 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 253 (8) [M^+], 196 (41), 177 (14), 124 (45), 80 (100), 57 (34).

(+)-Heliotridine (1): Pyrrolizidine **6** (84 mg, 0.33 mmol) was dissolved in dry CH_2Cl_2 (3.3 mL) and cooled to 0 °C. DIBAL (1 M solution in CH_2Cl_2; 1.1 mL, 1.09 mmol) was added dropwise, and the mixture was stirred at 0 °C for 30 min. The excess of DIBAL was quenched with MeOH, and a small amount of saturated solution of potassium sodium tartrate (Rochelle salt) was added. The mixture was stirred overnight, before the solution was decanted and filtered through silica gel. Crude **7** (61 mg) was recovered eluting with MeOH (1% NH_4OH) and used in the next step without further purification.

7-*O*-*tert*-Butylheliotridine (7): ^1H NMR (200 MHz, $CDCl_3$): δ = 1.23 (s, 9 H, C*Me*$_3$), 1.73−1.86 (m, 1 H, 6-H_a), 1.94−2.06 (m, 1 H, 6-H_b), 2.60 (ddd, *J* = 10.1, 8.8, 5.7 Hz, 1 H, 5-H_a), 3.25−3.33 (m, 2 H, 3-H_a, 5-H_b), 3.80−4.00 (m, 3 H, 3-H_b, 7-H, 7a-H), 4.28 (s, 2 H, C*H*$_2$OH), 5.52 (s; 1 H, 2-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.8 (q, 3 C; C*Me*$_3$), 34.8 (t; C-6), 54.6, 60.1, 62.4 (t; C-3, C-5, *C*H_2OH), 76.0 (s; *C*Me$_3$), 74.2, 78.5 (d; C-7, C-7a), 121.7 (d; C-2), 142.1 (s; C-1) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3405, 2977, 1601, 1462, 1392, 1366, 1193, 1103 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 211 (11) [M^+], 154 (27), 136 (32), 124 (43), 111 (51), 80 (100).

Crude **7** (61 mg, 0.29 mmol) was cooled to 0 °C, and dissolved in TFA (2 mL) and water (0.2 mL). The mixture was stirred for 3 h at 0 °C and then concentrated. The crude trifluoroacetate salt of **1** (92 mg) was treated with ion-exchange resin (DOWEX 50 W8−200) and sequentially washed with MeOH H_2O and 5% NH_4OH to recover **1** (21.6 mg, 37% from **5**) as a spectroscopically pure colorless oil ($[\alpha]_D^{20}$ = +26.5, *c* = 0.8 in MeOH), which tended to crystallize. A small portion of **1** was purified by flash chromatography on silica gel ($CHCl_3$/MeOH/NH_4OH, 10:4:1) to yield the expected white solid (15.1 mg, 11.9% from **2**).

Compound 1: m.p. 114−115 °C. $[\alpha]_D^{20}$ = +30.2 (*c* = 0.5 in MeOH);.^1H NMR (400 MHz, $CDCl_3$): δ = 1.83−1.92 (m, 1 H, 6-H_a), 1.94−2.03 (m, 1 H, 6-H_b), 2.69 (dt, *J* = 12.6, 6.7 Hz, 1 H, 5-H_a), 3.11 (bs s, 2 H, OH), 3.29−3.38 (m, 2 H, 3-H_a, 5-H_b), 3.92 (dm, *J* = 15.6 Hz, 1 H, 3-H_b), 4.03−4.08 (m, 1 H, 7a-H), 4.08−4.14 (m, 1 H, 7-H), 4.28 (part A of an AB system, 1 H, C*H*HOH), 4.33 (part B of an AB system, 1 H, C*H*HOH), 5.53 (s, 1 H, 2-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 33.3 (t; C-6), 53.9, 59.1, 61.9 (t; C-3, C-5, CH_2OH), 74.4, 79.9 (d; C-7, C-7a), 122.6 (d; C-2), 141.4 (s; C-1) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3350, 2851, 1602, 1436, 1337, 1106 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 155 (12) [M^+], 111 (46), 110 (49), 94 (36), 79 (100). $C_8H_{13}NO_2$ (155.19): calcd. C 61.91, H 8.44, N 9.03; found C 61.60, H 8.38, N 8.84.

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