Synthesis of Enantiomerically Pure (−)-(*S*)-Brevicolline

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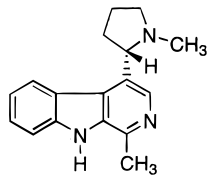
Received November 2, 1998

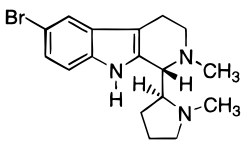
(−)-(*S*)-Brevicolline (**1**) and related *β*-carbolines were synthesized using an enantiomerically pure Michael-acceptor synthon (**3**). Subsequent Pictet−Spengler reaction afforded the tetrahydro-*β*-carboline skeleton, which, in turn, was transformed to the *β*-carboline by catalytic dehydrogenation.

β-Carboline derivatives are commonly found in plants.[1] Members of the structurally diverse family of *β*-carbolines exhibit a wide range of biological activities. The reported effects of these compounds include antineoplastic (tubuline binding),[2−4] anticonvulsive, hypnotic and anxiolytic (benzodiazepine receptor inhibitoric),[2,5−8] antiviral,[9] antimicrobial,[3] and topoisomerase II inhibition[10] and inhibition of *c*GMP-dependent processes.[11]

The *β*-carboline alkaloid brevicolline (**1**), the major alkaloid of the plant *Carex brevicollis* DC (Cyperacee), belongs to a group of pharmacologically interesting compounds[12] and was isolated,[13,14] determined,[15] and chemically modified[16] 30 years ago. Since that time, syntheses of racemic **1** were carried out, for example, by Winterfeldt[17] or Leete,[18] both using tryptamine as starting compound. A synthesis of the brevicolline enantiomers has yet not been described. This is remarkable because of the known various biological effects of **1**, such as a phototoxic effect against bacteria and fungi, a photosensitizing effect,[19] and its application against uterine inertia of pregnant women because of its oxytocic effect.[20] The *β*-carbolines and tetrahydro-*β*-carbolines of the "eudistomine family", such as woodinine (**2**),[21] also have interesting biological activities[22,23] and differ from **1** mainly in the position of the pyrrolidine ring.



(-)-(*S*)-Brevicolline (**1**)

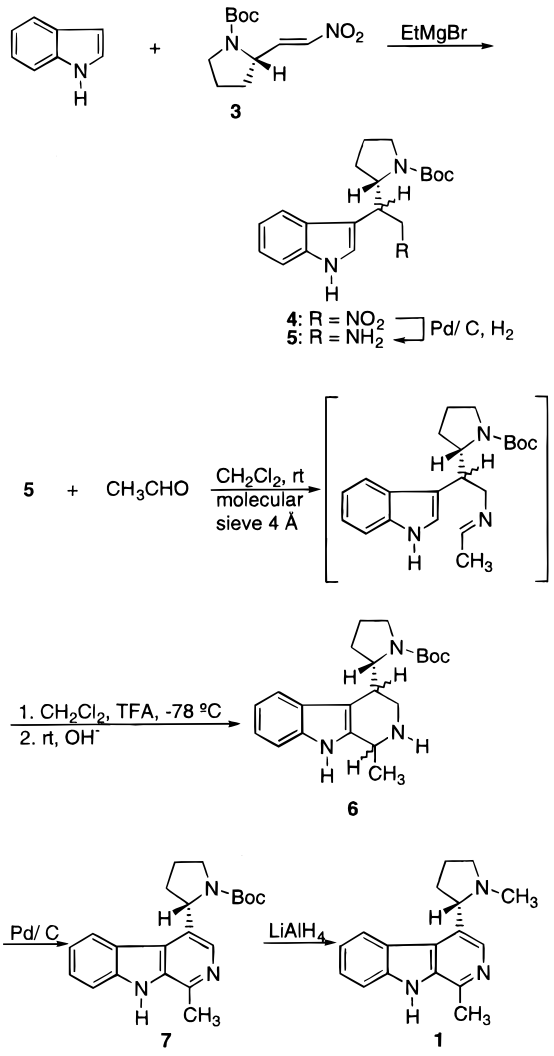


Woodinine (**2**)

Results and Discussion

Synthesis began using the chiral Michael-acceptor synthon (**3**) (Scheme 1).[24] Indole-anion, accessible from indole and ethylmagnesium bromide, reacted with the nitroethene derivative **3**, afforded the precursor **4**. The nitro indole **4** was converted to the amino indole **5** by catalytic hydrogenation over Pd/C. Subsequently, the *β*-carboline ring was closed by Pictet−Spengler reaction using acetaldehyde and trifluoroacetic acid. In our hands, imine formation proceeded very well at room temperature, using a molecular sieve (4 Å) to remove H_2O prior to addition of TFA at −78 °C. This modification makes isolation of the imine unnecessary. Aromatization of **6**, forming the *β*-carboline system **7**, was afforded by Pd in refluxing xylene.[25] Reduction of

Scheme 1



the Boc-protecting group with $LiAlH_4$ yielded the *N*-methyl group of title compound **1**. We deliberately did not reduce the Boc-protecting group at an earlier stage because it is known that (*N*-methylpyrrolidinyl)-*β*-carbolines and related compounds with a 3-(2-pyrrolidinyl)-1,2,3,4-tetrahydropyridine skeleton lose the pyrrolidine residue under dehydrogenating conditions.[26] To prevent this cleavage, the pyrrolidine nitrogen should be protected as an amide or carbamate (*N*-formyl, *N*-Boc).[26]

^{1}H NMR, IR, and MS data match exactly with those reported for natural **1**.[1,13] The melting point and optical rotation, however, differ slightly from literature values. A

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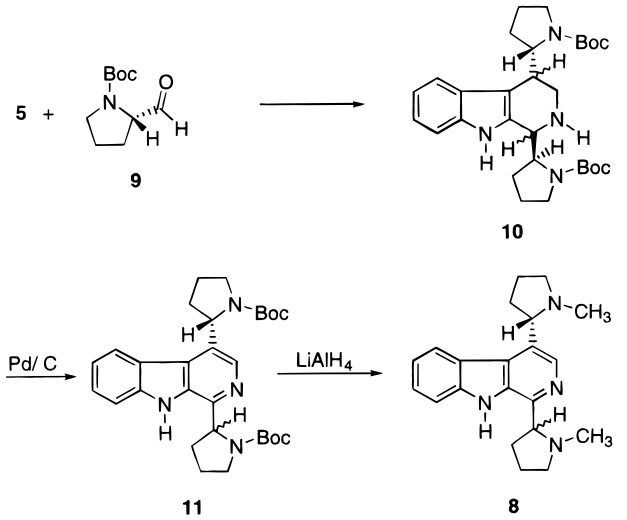
10.1021/np980492h CCC: $18.00
Published on Web 04/03/1999

Scheme 2



higher melting point (232−233 °C instead of 223−224 °C) and an increased $[\alpha]^{20}_D$ (−164.5 instead of −145.8) indicate higher purity.

The same reactions were used for synthesis of the eudistomine analogue **8**. By the enantiomeric pure aldehyde **9** a second stereogenic center was introduced into the molecule (Scheme 2). In accordance with McNulty et al.,[25] dehydrogenation of the tetrahydro-*β*-carboline **10** affects the stereogenic center in the pyrrolidine ring. High and low temperature ^{1}H NMR experiments (in order to suppress effects of *E*/*Z*-isomerism of the Boc-protecting groups) and HPLC analysis proved the existence of two diastereomeric *β*-carbolines **11**, which could not be preparatively separated. This holds true also for the diamine **8**.

Thus, a facile synthesis was established, stereospecific for (−)-(*S*)-brevicolline (**1**) and diastereoselective for related alkaloids, for example, **8** in good overall yields. The functionality of the starting materials, which, in addition, are easily accessible, allows the synthesis of a wide spectrum of optically active derivatives.

Experimental Section

General Experimental Procedures. Melting points were measured with a Reichert Thermovar 300419 microscope heating stage, standardized with gauge substances, and are not corrected. ^{1}H NMR data were obtained on a Bruker AC250 (250 MHz) spectrometer. All chemical shifts are quoted on the *δ*-scale. FT-IR spectroscopy was performed on a Nicolet 510 FT-IR spectrometer. MS were recorded on a Varian MAT 311 A, 70 eV for electron impact ionization (EI), or on a Finnigan MAT 95 for fast atomic bombardment (FAB) and for field desorption (FD) as stated. Optical rotations were measured on a Perkin−Elmer 241 MC polarimeter. Microanalyses were performed by Analytisches Lab., University Regensburg. TLC was carried out on Al sheets coated with $60F_{245}$ silica. Compounds were detected using sprays of 3% w/v vanillin in 96% EtOH followed by 5% w/v H_2SO_4 in 96% EtOH. Column chromatography was carried out using Merck 60 (70−230 mesh ASTM) silica. Solvents and commercially available reagents were dried and purified before use according to standard procedures. All reactions were carried out under dried N_2 in flame- or oven-dried vessels.

3-{2-Nitro-1-[(2*S*)-*N*-(*tert*-butyloxycarbonyl)pyrrolidin-2-yl]ethyl}-1*H*-indole (4). Magnesium shavings (0.66 mg, 25.0 mmol) and ethyl bromide (0.96 mL, 12.5 mmol) were added to dry THF (13 mL). When the reaction began, further ethyl bromide (0.96 mL, 12.5 mmol) was added drop by drop so that the solution was refluxing slightly. The solution was refluxed until all Mg was dissolved (ca. 30 min). After cooling to room temperature, indole (2.88 g, 24.6 mmol), dissolved in THF (13 mL), was added slowly, and the mixture was stirred for 45 min at 45 °C. When the mixture cooled to room temperature, a solution of **3**[24] (5.70 g, 23.5 mmol) in dry THF (25 mL) was added drop by drop over 1 h, and the resulting solution was heated to reflux overnight. Ice and 20% citric acid (50 mL) were then added, the organic layer was separated, and the aqueous phase was extracted with Et_2O (4 × 40 mL). The combined organic phases were washed with H_2O, dried over Na_2SO_4, and evaporated in vacuo. The crude product was separated from remaining starting material and byproducts by column chromatography (CH_2Cl_2−EtOAc 20:0.5) affording product **4** (mixture of diastereomers) as a yellowish powder (3.94 g, 11.0 mmol, 47%): melting range 104−111 °C; UV (EtOH) λ_{max} (log ϵ) 288 (3.80), 279 (3.88), 217 (4.65) nm; IR (KBr) ν 3419, 3321 (NH), 3060, 2977 (CH), 1673 (C═O), 1553 (NO) cm^{-1}; ^{1}H NMR (DMSO-d_2, 250 MHz) δ 1.40−1.99 (13H, m), 2.88−3.70 (2H, m), 4.22−4.62 (2H, m), 4.67−5.06 (2H, m), 7.02−7.25 (3H, m), 7.31−7.43 (1H, m), 7.63−7.82 (1H, m), 8.18 (1H, s); FABMS *m*/*z* 360 [M + H]$^+$, 719 [2M + H]$^+$; *anal.* C 63.40%, H 6.89%, N 11.52%, calcd for $C_{19}H_{25}N_3O_4$ (359.43), C 63.49%, H 7.01%, N 11.69%.

3-{2-Amino-1-[(2*S*)-*N*-(*tert*-butyloxycarbonyl)pyrrolidin-2-yl]ethyl}-1*H*-indole (5). A solution of compound **4** (3.24 g, 9.01 mmol) and 10% Pd/C (1.60 g) in dry EtOH (100 mL) was stirred for 24 h at a H_2 pressure of 10 bar. When the reaction ceased (TLC control) the catalyst was filtered off through Celite, the filter was washed with warm EtOH (200 mL), and the solvent was evaporated. The residue was purified by column chromatography (CH_2Cl_2−MeOH 9:2) yielding **5** (mixture of diastereomers) as a white foam (1.84 g, 5.59 mmol, 62%): mp 160 °C (dec); IR (KBr) 3298 (NH), 3060, 2975 (CH), 1684 (C═O) cm^{-1}; UV (EtOH) λ_{max} (log ϵ) 288 (4.00), 280 (4.07), 218 (4.80) nm; ^{1}H NMR (DMSO-d_6) (250 MHz) δ 1.19−1.88 (16H, m), 2.72−3.15 (3H, m), 3.37−3.51 (1H, m), 4.00−4.26 (1H, m), 6.87−7.08 (2H, m), 7.09−7.18 (1H, m), 7.26−7.40 (1H, m), 7.54−7.75 (1H, m), 10.89 (1H, s, indole-NH); FABMS *m*/*z* 330 [M + H]$^+$, 659 [2M + H]$^+$; *anal.* C 69.63%, H 8.65%, N 12.13%, calcd for $C_{19}H_{27}N_3O_2$ (329.45), C 69.27%, H 8.26%, N 12.75%.

1-Methyl-4-[(2*S*)-*N*-(*tert*-butyloxycarbonyl)pyrrolidin-2-yl]-1,2,3,4-tetrahydro-*β*-carboline (6). The solution of **5** (1.00 g, 3.04 mmol) and acetaldehyde (0.17 mL, 3.02 mmol) in dry CH_2Cl_2 (60 mL) was stirred with molecular sieve (4 Å) (500 mg) under N_2 for 1 h at room temperature. After filtration and washing with dry CH_2Cl_2, the solution of the intermediate imine was cooled to −78 °C. TFA (0.73 mL, 9.48 mmol) was added drop by drop over 2.5 h at −78 °C, the solution was allowed to warm to room temperature overnight, poured into ice water, basified with 2N Na_2CO_3 at 0 °C, washed with H_2O (2 × 20 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2−MeOH 9:2) yielding the tetrahydro-*β*-carboline **6** (0.51 g, 1.43 mmol, 47%) as an off-white foam (mixture of diastereomers): melting range 113−120 °C; IR (KBr) 3299 (NH), 3058, 2973 (CH), 1669 (C═O) cm^{-1}; UV (EtOH) λ_{max} (log ϵ) 281 (3.88), 222 (4.46) nm; ^{1}H NMR (DMSO-d_6) (250 MHz) δ 1.42 (3H, d, J = 6.4 Hz), 1.48 (9H, s), 1.53−1.81 (4H, m), 2.06−2.22 (1H, m), 2.71−2.89 (1H, m), 2.94−3.14 (3H, m), 3.18−3.28 (1H, m), 3.87−3.99 (1H, m), 4.02 (1H, q, J = 6.4 Hz), 6.87−7.05 (2H, m), 7.21−7.34 (2H, m), 10.83 (1H, s); FABMS *m*/*z* 356 [M + H]$^+$, 711 [2M + H]$^+$; *anal.* C 70.50%, H 8.25%, N 11.45%, calcd for $C_{21}H_{29}N_3O_2$ (355.48), C 70.96%, H 8.22%, N 11.82%.

1-Methyl-4-[(2*S*)-*N*-(*tert*-butyloxycarbonyl)pyrrolidin-2-yl]-*β*-carboline (7). A suspension of **6** (0.10 g, 0.28 mmol) and 10% Pd/C (60.0 mg) in dry xylene (10 mL) was refluxed for 2 h. When the reaction ceased the catalyst was filtered off through Celite, the filter was washed with warm EtOH (50 mL), and the solvent was evaporated. The residue was purified by column chromatography (CH_2Cl_2−MeOH 9:1) yielding the *β*-carboline **7** as colorless prisms (77.6 mg, 0.22 mmol, 79%): mp 243−244 °C (dec) (EtOH); $[\alpha]^{20}_D$ = −85.6° (*c* 2.4, EtOH); IR (KBr) 3298 (NH), 3060, 2975 (CH), 1684 (C═O) cm^{-1}; UV

(EtOH) λ_{max} (log ϵ) 349 (4.15), 336 (4.12), 286 (4.44), 278 (4.25), 234 (4.66) nm; ^{1}H NMR (DMSO-d_6) (250 MHz) δ 1.04 (4H, s), 1.43 (5H, s), 1.69−2.00 (3H, m), 2.53−2.65 (1H, m), 2.73 (3H, s, CH_3), 3.41−3.58 (1H, m), 3.61−3.78 (1H, m), 5.62−5.74 (1H, m), 7.25 (1H, t, J = 8.0 Hz), 7.53 (1H, t, J = 8.0 Hz), 7.62 (1H, d, J = 8.0 Hz), 7.85 (1H, s), 8.15 (1H, d, J = 8.0 Hz), 11.63 (1H, s); FABMS m/z 352 $[M + H]^+$, 703 $[2M + H]^+$, 1054 $[3M + H]^+$; *anal.* C 70.92%, H 7.44%, N 11.54%, calcd. for $C_{21}H_{25}N_3O_2$ (351.45), C 70.77%, H 7.17%, N 11.96%.

1-Methyl-4-[(2*S*)-*N*-methylpyrrolidin-2-yl]-β-carboline (1). A solution of compound **7** (0.15 g, 0.43 mmol) in THF (2.5 mL) was added drop by drop to a suspension of $LiAlH_4$ (0.18 g, 4.74 mmol) in THF (10 mL) with ice cooling. The resulting mixture was refluxed for 12 h. When the reaction was finished (TLC), the mixture was allowed to cool to room temperature. Ice water was then carefully added, and the resulting suspension was basified with 10% NaOH. The resulting mixture was extracted with Et_2O (4 × 15 mL), the EtOH extract was dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2−MeOH 9:1) and recrystallized from MeOH yielding (−)-(*S*)-brevicolline as colorless prisms (91.0 mg, 0.34 mmol, 79%): mp 232−233 °C;[1,13] $[\alpha]^{20}_D$ = −164.5° (*c* 1.8, EtOH); IR (KBr) 3422 (NH), 3147, 2089, 2873 (CH), 1684 (C=O) cm^{-1}; UV (EtOH) λ_{max} (log ϵ) 351 (4.12), 337 (4.09), 287 (4.39), 279 (4.19), 232 (4.68), 213 (4.54) nm; ^{1}H NMR ($CDCl_3$) (250 MHz) δ 1.87−2.11 (3H, m), 2.30 (3H, s), 2.38−2.51 (2H, m), 2.83 (3H, s), 3.34−3.44 (1H, m), 3.87−3.97 (1H, m), 7.26−7.33 (1H, m), 7.50−7.56 (2H, m), 8.45 (1H, d, J = 8.3 Hz), 8.50 (1H, s), 9.07 (1H, s); EIMS m/z 265 $[M]^{\bullet+}$ (6), 84 (100), 42 (90).

1,4-Bis[(2*S*)-*N*-(*tert*-butyloxycarbonyl)pyrrolidin-2-yl]-1,2,3,4-tetrahydro-β-carboline (10). The reaction of **5** (1.10 g, 3.34 mmol) with **9** (0.67 g, 3.36 mmol) was performed as described for compound **6**, yielding products **10** as a white foam (1.08 g, 2.11 mmol, 63%): melting range 128−135 °C; IR (KBr) 3332 (NH), 2975 (CH), 1690 (C=O) cm^{-1}; UV (EtOH) λ_{max} (log ϵ) 281 (4.07), 224 (4.60), 203 (4.47) nm; ^{1}H NMR ($CDCl_3$) (250 MHz) δ 1.21−1.86 (22H, m), 1.91−2.36 (4H, m), 2.91−3.05 (1H, m), 3.13−3.86 (7H, m), 3.95−4.13 (1H, m), 4.44−4.57 (1H, m), 4.66−4.78 (1H, m), 7.01−7.21 (2H, m), 7.29−7.42 (1H, m), 7.58−7.70 (1H, m), 7.89−7.14 (1H, m); FABMS m/z 511 $[M + H]^+$, 411, 1021 $[2M + H]^+$; *anal.* C 67.99%, H 8.31%, N 10.72%, calcd for $C_{29}H_{42}N_4O_4$ (510.68), C 68.21%, H 8.29%, N 10.97%.

1,4-Bis[(2*S*)-*N*-(*tert*-butyloxycarbonyl)pyrrolidin-2-yl]-β-carboline (11). The dehydrogenation of **10** (0.24 g, 0.50 mmol) with Pd/C (600 mg) was effected as described for compound **6**, yielding products **11** as a white powder (0.15 g, 0.30 mmol, 59%): mp 225−228 °C; IR (KBr) 3267 (NH), 2970 (CH), 1700 (C=O) cm^{-1}; UV (EtOH) λ_{max} (log ϵ) 350 (4.01), 339 (4.00), 288 (4.33), 235 (4.68), 213 (4.45), 203 (4.45) nm; ^{1}H NMR ($CDCl_3$) (250 MHz) δ 1.37−1.69 (18H, m), 1.65−2.19 (6H, m), 2.38−2.64 (2H, m), 2.94−3.14 (1H, m), 3.24−3.44 (1H, s), 3.48−3.71 (2H, m), 3.71−3.81 (1H, m), 5.73−5.97 (1H, m), 7.17−7.33 (1H, m), 7.44−7.63 (2H, m), 8.03−8.15 (2H, m), 11.09−11.36 (1H, m); FDMS m/z 506 $[M^+]$; *anal.* C 68.60%, H 7.66%, N 11.13%, calcd for $C_{29}H_{38}N_4O_4$ (506.65), C 68.75%, H 7.56%, N 11.06%.

1,4-Di[(2*S*)-*N*-methylpyrrolidin-2-yl]-β-carboline (8). The reduction of **11** (85.0 mg, 0.17 mmol) with $LiAlH_4$ (0.15 g, 3.95 mmol) was executed as described for compound **7**, yielding product **8** as a off-white powder (40.0 mg, 0.12 mmol, 70%): melting range 87−93 °C; IR (KBr) 3359 (NH), 2966, 2779 (CH) cm^{-1}; UV (EtOH) λ_{max} (log ϵ) 352 (4.59), 339 (4.57), 288 (4.79), 243 (5.14), 212 (5.01) nm; ^{1}H NMR ($CDCl_3$) (250 MHz) δ 1.81−2.14 (m, 6H), 2.30, 2.31 (2 s, 3H), 2.32, 2.33 (2 s, 3H), 2.37−2.56 (m, 4H), 3.34−3.46 (m, 2H), 3.72−3.86 (m, 1H), 3.87−3.99 (m, 1H), 7.21−7.31 (m, 1H), 7.48−7.61 (m, 2H), 8.40−8.50 (m, 2H), 10.37 (br s, 1H); EIMS m/z 334 $[M]^{\bullet+}$ (88), 278 (100); *anal.* C 75.22%, H 7.64%, N 17.00%, calcd for $C_{21}H_{26}N_4$ (334.47), C 75.41%, H 7.84%, N 16.75%.

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NP980492H