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Preparation of the (R) and (S) Enantiomers of 10-Hydroxymethylfuro[3,4-c]-β-carboline-2(10H)one, the First Example of a Benzodiazepine Receptor Ligand of the β-Carboline Family Having a Stereogenic Center

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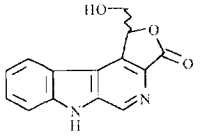
Abstract : The preparation of both enantiomers of (R,S)-1, a novel, chiral benzodiazepine receptor ligand of the β-carboline family, using (R)- and (S)-D-glyceraldehyde as sources of chirality, is described. Racemic (R,S)-1 was also resolved by chromatographic separation of their diastereomeric 5-N-(-)-menthylcarbamates. (S)-1 had a higher affinity for the benzodiazepine receptor in vitro than (R)-1, demonstrating for the first time that β-carbolines, like benzodiazepines, can also be recognized stereospecifically by this receptor.

Introduction

The novel (*R,S*)-10-hydroxymethylfuro[3,4-c]-β-carboline-2(10H)one, (*R,S*)-1, has recently been described as a high-affinity antagonist of the benzodiazepine receptor (BZR) of the central nervous system.[1] The structural characteristics which distinguish (*R,S*)-1 from the typical β-carboline-3-carboxylate class of BZR ligands[2] are the rigid, receptor preferred conformation of the carbonyl group conferred by the lactone ring[3] and the presence of a chiral center. Because the BZR recognizes optically active benzodiazepines stereospecifically,[4] it may be assumed that the same holds true for optically active β-carbolines such as 1. In order to verify this, the preparation of the enantiomerically pure



(*R,S*)- **1**

enantiomers of **1** was required. As described in this report, the synthesis of (*R*)-1 and (*S*)-**1** has been achieved by two independent methods, the first relying on the use of (*R*)- or (*S*)-D-glyceraldehyde as source of chirality[5] and the second based on resolution of racemic (*R,S*)-**1** via formation of the 5-N-(-)-menthylcarbamate diastereomeric derivatives.

Results and Discussion

The general procedure described by Neef and coworkers[6] for the synthesis of 4-substituted β-carboline-3-carboxylic esters was adapted to the use of (*R*)-2,3-O-isopropylidene-D-glyceraldehyde[7] ((*R*)-**2**) as starting aldehyde (Scheme 1). Thus, condensation of (*R*)-**2** with isopropylamine at 0°C in

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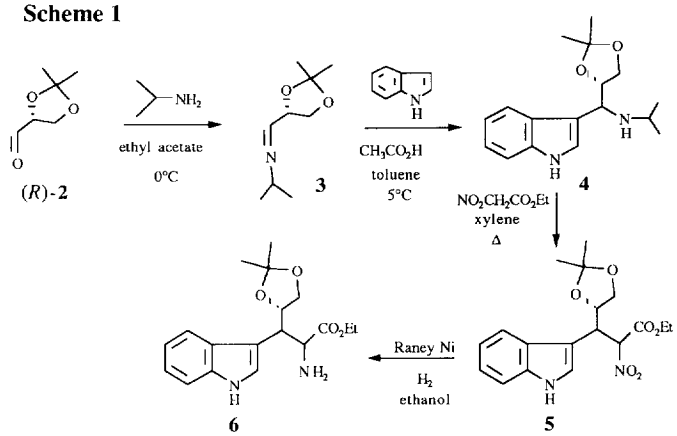
This paper is dedicated to Professor Charles W. Jefford on the occasion of his 65th birthday.

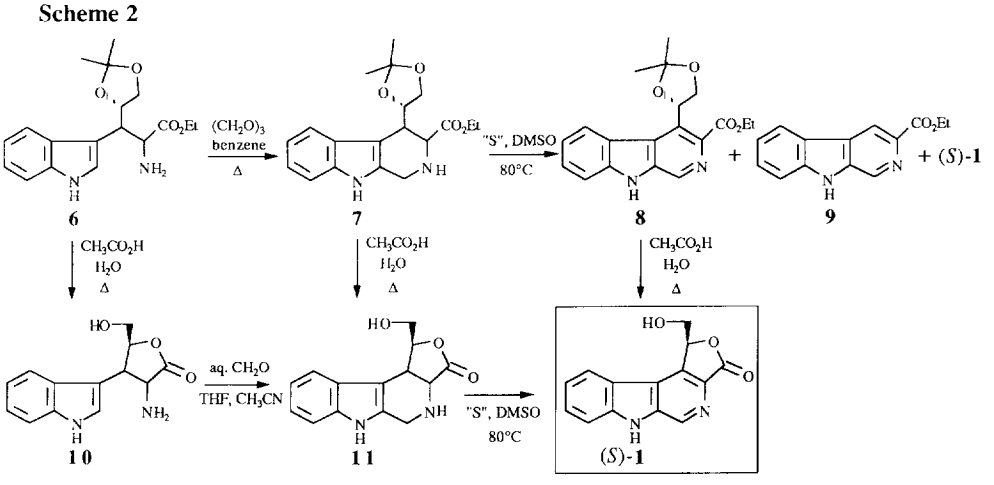
ethyl acetate gave imine **3** which in turn reacted with indole in a mixture of toluene and acetic acid to afford the gramine-type derivative **4** in 42% yield. Displacement of the isopropylamine group of **4** by

Scheme 1



ethyl nitroacetate in refluxing xylene then furnished compound **5**, the nitro group of which was efficiently reduced by hydrogenation in the presence of Raney nickel to give the β-substituted tryptophan derivative **6**. Conversion of **6** into the 4-substituted 1,2,3,4-tetrahydro-β-carboline **7** under Pictet-Spengler conditions then proceeded uneventfully, though in modest yield (Scheme 2). Dehydrogenation of **7** to form the fully aromatic β-carboline **8** was complicated by formation of ethyl β-carboline-3-carboxylate **9** as the major product, regardless of the dehydrogenating agent utilized (DDQ, activated MnO_2, palladium on carbon).[8] Finally, it was found that formation of **9** from **7** could be minimized by conducting the dehydrogenation in DMSO at 80°C in the presence of 2 eq of sulfur and carefully monitoring the reaction by TLC. However, even under these conditions, yields of the desired 4-substituted β-carboline **8** never surpassed 13%. A small percentage (5%) of the desired lactone derivative (*S*)-**1** was also formed in this reaction, probably as a result of traces of water in the mixture. Compound (*S*)-**1** was, however, the unique product formed when the acetonide protecting group of **8** was removed by hydrolysis in aqueous, refluxing acetic acid. No trace of δ-lactone, which would have resulted from intramolecular attack of the ester by the free primary hydroxyl group, could be observed in the reaction mixture.

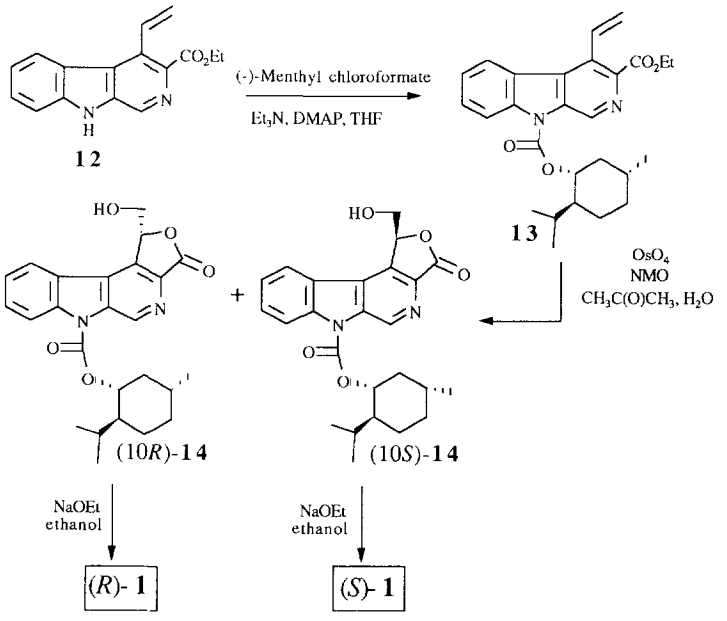
Scheme 2



In an effort to by-pass the problems associated with dehydrogenation of **7**, an alternative route was studied in which the γ-lactone ring was generated before dehydrogenation was attempted. Thus, treatment of the tryptophan intermediate **6** with acetic acid gave γ-lactone **10**. Condensation of the latter with formaldehyde then afforded the tetrahydro derivative **11**. This compound could also be prepared by hydrolysis of the acetonide **7** in aqueous acetic acid, though in lower overall yield. Dehydrogenation of **11** using sulfur in DMSO as before furnished β-carboline (*S*)-**1**. The low yield (11%) observed in this case can be attributed to mechanical losses during the course of purification of the product due to its highly insoluble nature in organic solvents and to the difficulty in separating this compound from unreacted sulfur. Nevertheless, the relative cleanness of these reactions encouraged us to prepare the enantiomer, (*R*)-**1**, by this route starting from (*S*)-2,3-O-isopropylidene-D-glyceraldehyde[9] ((*S*)-**2**). The optical purities of (*S*)-**1** and (*R*)-**1** so obtained were observed to be in both cases in excess of 98% by chiral HPLC using a Chiracel OD column.

Having established the absolute configuration at C-10 of both enantiomers of **1**, a more efficient method of obtaining each optical isomer, based on the chromatographic separation of the diastereomers resulting from formation of their 5-N-menthylcarbamates,[10] was investigated. Thus, treatment of the known 4-vinyl-β-carboline-3-carboxylic ester **12**[6] with (-)-menthylchloroformate in THF in the presence of triethylamine and DMAP gave the (-)-menthylcarbamate **13** in 83% yield (Scheme 3). Dihydroxylation of the vinyl bond of **13** was next effected using catalytic osmium tetroxide and NMO as co-oxidant.[1,11] The resulting diol spontaneously cyclized to afford a mixture of the diastereomers (10*R*)-**14** and (10*S*)-**14**. These were easily separated by HPLC. The menthylcarbamate group was then removed from each diastereomer by the action of catalytic sodium in ethanol, giving (*R*)-**1** and (*S*)-**1**, respectively, identical in all respects to the enantiomers prepared from (*S*)- and (*R*)-glyceraldehydes **2**. The enantiomeric excesses of (*R*)-**1** and (*S*)-**1** prepared in this fashion were also observed in each case to be greater than 98% by chiral HPLC.

Scheme 3



Biological Evaluation

The affinities of (*R*)-1 and (*S*)-1 for the BZR were determined *in vitro* following previously described procedures.[1,3] The (*S*) enantiomer was found to have a higher affinity (IC_{50} = 0.20 nM) for this receptor than the (*R*) enantiomer (IC_{50} = 0.54 nM). Though the differences in affinity for each enantiomer of **1** are modest, this represents the first example of chiral discrimination in the β-carboline family of ligands by the BZR.

Experimental

General. Melting points were obtained on a Büchi apparatus using an open capillary and are uncorrected. IR spectra of samples were obtained either as KBr pellets (for solids) or in chloroform solution (for oils) with a Nicolet 205 FT-IR spectrometer. ^1H NMR and ^{13}C NMR spectra were determined on Bruker WP200, WP250 or AM400 MHz instruments. Chemical shifts are given as δ values with reference to Me_4Si as internal standard. Electron impact (EI) and chemical ionization (CI) mass spectra were recorded on an AEI MS-50 and AEI MS-9 spectrometer, respectively. High resolution (HR) mass spectra were recorded on a Kratos MS 80 RF instrument. Optical rotations were determined with a Perkin-Elmer 241 polarimeter. Thin-layer chromatography (TLC) and preparative chromatography were performed on Merck silica gel 60 plates or neutral type E alumina 60 plates with fluorescent indicator. The plates were visualized with UV light (254 nm) and, for TLC, with a 3.5% solution of phosphomolybdic acid in ethanol. All column chromatography was conducted on Merck 60 silica gel (230-240 mesh) at medium pressure (200 mbar). High-performance liquid chromatography (HPLC) was performed on a Waters 6000 A instrument equipped with a UV440 detector. All solvents were distilled and stored over 4 Å molecular sieves before use. Indole, ethyl nitroacetate, (-)-menthylchloroformate, osmium tetroxide solution and 4-methylmorpholine N-oxide were purchased from Aldrich Chemical Co. and were used without further purification. Elemental analyses were performed at the ICSN,CNRS, Gif-sur-Yvette.

*(S)-N-Isopropyl-2,3-O-isopropylidene-D-glyceraldimine (**3**).* To freshly distilled isopropylamine (23 mL, 0.27 mol) held at 0 °C was added dropwise over 2 h with stirring a solution of (R)-2[7] (35.6 g, 0.27 mol) in ethyl acetate (500 mL). After completion of the addition, the reaction mixture was stirred for an additional 15 min before powdered potassium hydroxide (130 g, 2.32 mol) was added. The mixture was allowed to stand at 0 °C for 10 min, the supernatant organic phase was carefully decanted and dried over potassium hydroxide pellets for 15 h at 4 °C. The supernatant was again collected by decantation and concentrated under reduced pressure to give aldimine **3** (30.9 g, 66%) as a colorless oil which was used without further purification in the following step ; ^1H NMR (200 MHz, $CDCl_3$) δ 1.17 (t, 6H, J = 6.0 Hz, $CH(C\underline{H}_3)_2$), 1.40 (s, 3H, $OCC\underline{H}_3$), 1.43 (s, 3H, $OCC\underline{H}_3$), 3.35 (m, 1H, $C\underline{H}(CH_3)_2$), 3.85-4.25 (m, 2H, J = 7.0 Hz and 9.0 Hz, CH_2O), 4.56 (q, 1H, J = 9.0 Hz and 6.0 Hz, CHO), 7.66 (d, 1H, J = 6.0 Hz, CH=N) ; IR (film) 1670 cm^{-1} (C=N) ; mass spectrum (CI), m/z 172 $(MH)^+$.

*(1RS,2S)-1-(3-Indolyl)-2,3-O-isopropylidene-1-N-isopropylamino-2,3-propanediol (**4**).* To a cooled solution of indole (25.0 g, 0.22 mol) in anhydrous toluene (300 mL) and acetic acid (172 mL) was added dropwise aldimine **3** (36.6 g, 0.22 mol) such that the temperature of the reaction mixture was maintained between 5 and 10 °C. After completion of the addition, the reaction mixture was left to stir at 4 °C for 48 h. Ice-water (800 mL) and ether (80 mL) were then added, the aqueous phase was separated and extracted with ether (100 mL). The combined organic extracts were in turn extracted with 1 M aqueous potassium hydrogen sulfate solution (2 x 160 mL). These aqueous extracts were combined with the previous aqueous fraction, washed with ether (2 x 80 mL) and made basic (pH 9-10) by addition of 5N sodium hydroxide solution. A second oily phase consisting of compound **4** gradually separated from the aqueous phase and was collected by decantation (27.1 g, 42%) : ^1H NMR (200 MHz, $CDCl_3$) δ 1.02 (pseudo t, 6H, J = 6.0 Hz, $CH(C\underline{H}_3)_2$), 1.33 (s, 3H, $OCCH_3$), 1.40 (s, 3H, $OCCH_3$), 2.77 (m, 1H, J = 7.0 Hz, $C\underline{H}(CH_3)_2$), 3.80 (m, 2H, J = 6.6 Hz and 12 Hz, H-3), 4.30 (m, 1H, J = 5.0 Hz and 4.5 Hz, H-1), 4.51 (m, 1H, J = 6.6 Hz and 5.0 Hz, H-2), 7.10-7.70 (m, 5H, H_{arom}, H-2'), 8.43 (br s, 1H, exchangeable

with D_2O, NH), 9.66 (br s, 1H, exchangeable with D_2O, NH) ; ^{13}C NMR (65.5 MHz, $CDCl_3$) δ 22.05, 22.22, 24.36, 24.38, 25.25, 25.37, 26.59, 27.23, 45.32, 45.48, 54.00, 57.52, 65.86, 66.22, 79.20, 80.29, 109.03, 111.64, 111.70, 114.60, 119.30, 119.37, 119.39, 119.83, 122.04, 122.28, 122.86, 122.88, 126.44, 136.57 ; IR (film) 1610, 3360 cm^{-1} ; mass spectrum (CI), m/z 289 $(MH)^+$, 230 $(MH\text{-}NHCH(CH_3)_2)^+$.

Ethyl (2RS,3RS,4S)-4,5-dihydroxy-3-(3-indolyl)-4,5-O-isopropylidene-2-nitropentanoate (**5**). A solution of compound **4** (21.6 g, 75 mmol) and ethyl nitroacetate (9.97 g, 75 mmol) in anhydrous xylene (50 mL) was refluxed for 6 h, a steady stream of nitrogen being maintained through the vessel during the course of the reaction. The solvent was then removed under reduced pressure and the crude product was purified by column chromatography on silica gel (dichloromethane) affording compound **5** as a pale yellow oil (19.2 g, 71%) : ^1H NMR (400 MHz, $CDCl_3$) δ 0.62 (t, 0.75H, $CH_2C\underline{H}_3$), 0.80 (t, 0.75H, $CH_2C\underline{H}_3$), 1.20 (t, 0.75H, $CH_2C\underline{H}_3$), 1.42 (m, 6.75H, $CH_2C\underline{H}_3$, $C(CH_3)_2$), 3.64 (m, 1H, H-5a), 3.82 (m, 1H, H-5b), 3.90 (m, 1H, $C\underline{H}_2CH_3$), 4.10 (m, 1H, $C\underline{H}_2CH_3$), ~ 4.20 (m, 1H, H-3), ~ 4.50 (m, 0.5H, H-4), ~ 4.70 (m, 0.5H, H-4), 5.85 (m, 1H, H-2), 7.05-7.40 (m, 4H, H_{arom}), 7.68 (m, 1H, H-2'), 8.30 (br s, 1H, exchangeable with D_2O, NH) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 13.30, 14.45, 25.25, 27.14, 40.76, 41.22, 43.52, 43.82, 63.28, 63.89, 66.73, 68.93, 74.71, 77.13, 89.54, 91.02, 107.05, 108.22, 110.92, 112.04, 118.74, 120.24, 124.58, 127.93, 128.00, 136.05, 164.19 ; IR (film) 1563, 1740 cm^{-1} ; mass spectrum (HREI), calcd for $C_{18}H_{22}N_2O_6$: m/z 362.1477. Found : m/z 362.1488. Anal. Calcd for $C_{18}H_{22}N_2O_6$: C, 59.66 ; H, 6.07; N, 7.73. Found : C, 59.72 ; H, 5.95 ; N, 7.57.

Ethyl (2RS,3RS,4S)-2-amino-4,5-dihydroxy-3-(3-indolyl)-4,5-O-isopropylidenepentanoate (**6**). A vigorously stirred mixture of compound **5** (9.66 g, 26.7 mmol) and Raney nickel (20 g) in ethanol (100 mL) was hydrogenated at atmospheric pressure for 3 h. The reaction mixture was filtered through a pad of Celite and the catalyst was thoroughly washed with warm ethanol followed by n-butylamine. The combined filtrate and washings were concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (dichloromethane-ethanol, 95:5), yielding amine **6** as a pale yellow oil (7.71 g, 87%) : ^1H NMR (400 MHz, $CDCl_3$) δ 1.08-1.15 (m, 2.3H, $CH_2C\underline{H}_3$), 1.30 (m, 6.7H, $CH_2C\underline{H}_3$, $C(CH_3)_2$), 1.90 (s, 2H, exchangeable with D_2O, NH_2), 3.65-3.70 (m, 2H, H-5), ~3.80 (2 x q, 2H, J = 5.0 Hz, $C\underline{H}_2CH_3$), ~ 3.90 (m, 1H, J = 4.2 Hz and 3.0 Hz, H-3), 4.10 (m, 1H, J = 3.0 Hz and 5.0 Hz, H-4), 4.65-4.80 (m, 1H, J = 7.0 Hz, 4.2 Hz and 3.0 Hz, H-2), 7.10 (m, 3H, H_{arom}), 7.25 (m, 1H, H_{arom}), 7.61 (d, 0.5H, J = 5.0 Hz, H-2'), 7.66 (d, 0.5H, H-2'), 8.60 (br s, 1H, exchangeable with D_2O, NH) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 13.73, 14.21, 25.52, 27.31, 41.90, 41.93, 44.45, 45.29, 54.91, 54.96, 57.85, 58.36, 60.31, 60.67, 60.86, 60.98, 67.46, 67.83, 68.83, 69.24, 75.11, 75.95, 76.37, 77.66, 109.71, 111.14, 111.25, 118.59, 119.58, 121.77, 122.61, 127.05, 135.91, 165.02 ; IR (film) 1729, 3365 cm^{-1} ; mass spectrum (HREI), calcd for $C_{18}H_{24}N_2O_4$: m/z 332.1752. Found : m/z 332.1744. Anal. Calcd for $C_{18}H_{24}N_2O_4.C_2H_5OH$: C, 63.49 ; H, 7.93, N, 7.40. Found : C, 63.45 ; H, 7.93 ; N, 7.88.

Ethyl (3RS,4RS,1'S)-4-(1,2-dihydroxyethyl-1,2-O-isopropylidene)-1,2,3,4-tetrahydro-β-carboline-3-carboxylate (**7**). A mixture of amine **6** (14.8 g, 44,5 mmol) and paraformaldehyde (1.33 g, 44.5 mmol) in benzene (300 mL) was refluxed for 2.5 h using a Dean-Stark apparatus for the removal of water. At the end of the reaction period, the solution was cooled, concentrated under reduced pressure and the residue was partitioned between ethyl acetate (150 mL) and water (150 mL). The organic phase was separated, washed with water (3 x 30 mL) and dried over sodium sulfate. The crude product left after removal of the solvents *in vacuo* was purified by column chromatography on silica gel (toluene-ethanol 80:2.5 followed by 80:10) to give compound **7** as an oil (6.2 g, 41%) : ^1H NMR (200 MHz, $CDCl_3$) δ 1.10-1.40 (m, 9H, $CH_2C\underline{H}_3$, $C(CH_3)_2$), 3.40 (s, 1H, exchangeable with D_2O, $CH_2N\underline{H}$), 3.60-4.10 (m, 5H, H-1, H-4, H-2'), 4.20 (m, 2H, $C\underline{H}_2CH_3$), 4.20-4.40 (m, 2H, H-3, H-1'), 7.10 (m, 2H, H-6, H-7), 7.30 (m, 1H, H-5), 7.55 (m, 1H, H-8), 8.40 (br s, 1H, exchangeable with D_2O, NH indole) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.19, 14.31, 26.02, 35.87, 42.62, 59.88, 60.49, 61.48, 67.86, 77.13, 109.05, 111.03, 111.25, 115.04, 118.29, 121.79, 128.92, 136.32, 163.04 ; IR (film) 1733, 3349 cm^{-1} ; mass spectrum (HREI), calcd for $C_{19}H_{24}N_2O_4$: m/z 344.1727. Found : m/z 344.1735.

Ethyl (S)-4-(1,2-dihydroxyethyl-1,2-O-isopropylidene)-β-carboline-3-carboxylate (**8**) *and ethyl-β-carboline-3-carboxylate* (**9**). A mixture of compound **7** (465 mg, 1.35 mmol) and sulfur (86 mg, 2.7 mmol) in anhydrous DMSO (2 mL) was heated at 80°C for 6 h under a nitrogen atmosphere. The reaction mixture was then concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (medium pressure) using dichloromethane-ethanol 95:5 as developer. Compound **8** was first eluted and was isolated as a white foam (60 mg, 13%) : $[\alpha]_D^{20}$ + 56 (c 0.41, $CHCl_3$) ; ^1H NMR (200 MHz, $CDCl_3$) δ 1.42 (t, 3H, $CH_2C\underline{H}_3$), 1.60 (s, 3H, $C(CH_3)$), 1.71 (s, 3H, $C(CH_3)$), 4.19 (pseudo t, 1H, J = 9.0 Hz, H-2'a), 4.44-4.54 (q, 2H, J = 7.0 Hz, $C\underline{H}_2CH_3$), 4.60 (pseudo t, 1H, J = 9.0 Hz, H-2'b), 6.15-6.22 (2 x d, 1H, J = 9.0 Hz, H-1'), 7.35 (t, 1H, J = 8.0 Hz, H-7), 7.60 (m, 2H, H-5, H-6), 8.36 (d, 1H, H-8), 8.87 (s, 1H, H-1), 9.25 (br s, 1H, exchangeable with D_2O, NH) ; IR (film) 1729, 3365 cm^{-1} ; mass spectrum (HREI), calcd for $C_{19}H_{20}N_2O_4$: m/z 340.1428. Found : m/z 340.1426.

Continued elution of the column gave compound **9** (16 mg, 5%), identical in all respects to a commercial sample, followed by (*S*)-**1** (17 mg, 5%), identical to that prepared from **8**, as described below.

(2RS,3RS,4S)-2-Amino-4-hydroxymethyl-3-(3-indolyl)-1,4-butanolide (***10***). A solution of amine **6** (3.85 g, 11.6 mmol) in acetic acid (40 mL) and water (40 mL) was refluxed for 2.5 h. The solvents were removed under reduced pressure and the crude product was purified by column chromatography on silice gel (dichloromethane-ethanol 95:5 followed by 80:20), affording compound **10** as a white foam (1.0 g, 35%) : ^1H NMR (200 MHz, DMSO-d_6) δ 3.49-3.72 (m, 6H, diminishes to 3H after exchange with D_2O, H-3, H-5, OH, NH_2), 4.10-4.20 (d, 1H, H-2), 4.65 (m, 1H, $J_{4,5}$ = 3.0 Hz, H-4), 7.11-7.30 (sext, 2H, H_{arom}), 7.42 (s + d, 2H, H-2 of indole, H_{arom}), 7.84 (d, 1H, J = 7.5 Hz, H_{arom}), 11.22 (br s, 1H, exchangeable with D_2O, NH of indole) ; ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 42.51, 57.52, 60.25, 82.45, 110.62, 111.59, 118.64, 118.77, 121.26, 122.93, 126.90, 136.33, 177.88 ; IR (film) 1768, 3450 cm^{-1} ; mass spectrum (HREI), calcd for $C_{13}H_{14}N_2O_3$: m/z 246.1009. Found : m/z 246.1001.

(3RS,11RS,12S)-12-Hydroxymethyl-3,4,5,11-tetrahydrofuro[3,4-c]-β-carboline-2(12H)one (***11***). *From compound **10*** : To a stirring solution of **10** (1.0 g, 4.1 mmol) in THF (15 mL) and acetonitrile (15 mL) was added at 0°C 37% aqueous formaldehyde solution (0.4 mL, 5.0 mmol). After 3 h, a mixture of dichloromethane-heptane 75:25 (20 mL) was added and the reaction mixture was stored at 4°C for 2 h. The precipitate which formed was collected by filtration, washed with dichloromethane and crystallized from ethanol-heptane, yielding **11** as a white powder (746 mg, 71%) ; mp 210-212°C ; ^1H NMR (200 MHz, DMSO-d_6) δ 3.35 (br s, 1H, exchangeable with D_2O, $CH_2N\underline{H}$), 3.90 (m, 3H, H-5, H-11), 3.97 (m, 2H, J = 4.2 Hz and 2.0 Hz, $C\underline{H}_2OH$), 4.48 (d, 1H, J = 7.0 Hz, H-3), 4.61 (m, 1H, J = 2.0 Hz, H-12), 5.48 (t, 1H, J = 4.2 Hz, exchangeable with D_2O, OH), 7.15 (m, 2H, H_{arom}), 7.45 (d, 1H, J = 8.0 Hz, H_{arom}), 7.50 (d, 1H, H_{arom}), 11.04 (br s, 1H, exchangeable with D_2O, NH of indole) ; ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 34.56, 38.18, 54.08, 62.37, 83.63, 105.27, 117.40, 118.73, 120.89, 125.71, 135.60, 142.15, 174.82 ; IR (KBr) 1790, 3580 cm^{-1} ; mass spectrum (HREI), calcd for $C_{14}H_{14}N_2O_3$: m/z 258.1004. Found : m/z 258.1011.

*From compound **7*** : A solution of **7** (100 mg, 0.29 mmol) in acetic acid (10 mL) and water (10 mL) was refluxed for 2 h, the solvents were removed *in vacuo* and the crude product was purified by column chromatography on silica gel (dichloromethane-ethanol 95:5), giving **11** (30 mg, 40%). This material, crystallized from ethanol-heptane, was identical in all respects to that prepared from compound **10**, as described above.

(S)-10-Hydroxymethylfuro[3,4-c]-β-carboline-2(10H)one (S)-1. *From compound 8* : A solution of **8** (30 mg, 0.08 mmol) in acetic acid (3 mL) and water (3 mL) was refluxed for 2 h. The solvents were then removed under reduced pressure and the residue was purified by column chromatography on silica gel (dichloromethane-ethanol 9:1), yielding compound **10** as a white solid (8 mg, 39%) ; mp 278-280°C (decomp) ; $[\alpha]_D^{25}$ + 45 (c 0.4, DMSO) ; ^{1}H NMR (200 MHz, DMSO-d_6) δ 4.13 (m, 2H, J = 3.0 Hz, 5.5 Hz and 14.5 Hz, C$\underline{H}_2$OH), 5.07 (t, 1H, exchangeable with D_2O, $CH_2O\underline{H}$), 6.10 (dd, 1H, $J_{H,Ha}$ = 3.0 Hz, $J_{H,Hb}$ = 5.5 Hz, C$\underline{H}CH_2$), 7.28 (t, 1H, J = 8.0 Hz, H_{arom}), 7.57 (m, 2H, H_{arom}), 8.11 (d, 1H, H_{arom}), 9.85 (s, 1H, CH=N), 12.18 (br s, 1H, exchangeable with D_2O, NH) ; IR (KBr) 1760, 3500 cm^{-1} ; mass spectrum (HREI), calcd for $C_{14}H_{10}N_2O_3$: m/z 254.0691. Found : m/z 254.0683.

From compound 11 : A mixture of **11** (70 mg, 0.27 mmol) and sulfur (20 mg, 0.62 mmol) in DMSO (5 mL) was heated at 80°C for 24 h. The solution was then concentrated under reduced pressure and the solid residue was partitioned between water (20 mL) and ethyl acetate (50 mL). The organic phase was separated, dried over sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (dichloromethane-ethanol 9:1), affording (*S*)-**1** as a white powder (7.5 mg, 11%), identical in all respects to that prepared from compound **8**, as described above.

Preparation of (R)-1. Following the same procedure as for the preparation of (*S*)-**1** via compounds **10** and **11**, the enantiomer (*R*)-**1** was synthesized from (*S*)-2,3-O-isopropylidene-D-glyceraldehyde[9] ((*S*)-**2**); $[\alpha]_D^{25}$ -40 (c 0.25, DMSO) ; the mp, ^{1}H NMR, IR and mass spectra of (*R*)-**1** were identical to those of (*S*)-**1**.

The optical purities of (*S*)-**1** and (*R*)-**1** were determined by HPLC using a 4.6 x 250 mm Chiracel OD column and heptane-isopropanol-water (78.3:21:0.7) as developer at a flow rate of 1 mL/min. Compounds (*S*)-**1** (retention time = 16.0 min) and (*R*)-**1** (retention time = 17.5 min) each had an e.e. > 98%.

Ethyl 9-N-(-)-menthyloxycarbonyl-4-vinyl-β-carboline-3-carboxylate (13). To a solution of β-carboline **12**[6] (274 mg, 0.81 mmol) in anhydrous THF (50 mL) were added at 0°C triethylamine (373 μL, 3.3 mmol) and 4-dimethylaminopyridine (36 mg, 0.3 mmol) followed by dropwise addition of (-)-menthylchloroformate (0.53 mL, 2.42 mmol). The reaction mixture was stirred for 3 h, ethyl acetate (50 mL) and saturated aqueous sodium chloride (50 mL) were added and the organic phase was separated. The latter was dried over sodium sulfate, the solvents were evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (heptane-ethyl acetate 7:3), affording compound **13** (301 mg) as a white foam in 83% yield : $[\alpha]_D^{20}$ - 70 (c 0.9, CH_3OH) ; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.80-1.21 (m, 9H, CHC$\underline{H}_3$, CH(C$\underline{H}_3$)$_2$), 1.49 (t, 3H, J = 7.0 Hz, $CH_2C\underline{H}_3$), 1.20-2.10 (m, 8H, menthyl), 2.31 (m, 1H, J = 7.0 Hz and 11.0 Hz, C$\underline{H}$(CH_3)$_2$), 4.50 (q, 2H, C$\underline{H}_2CH_3$), 5.12 (sext, 1H, J = 5.0 Hz and 11.0 Hz, CHOC(=O)N), 5.58 (d, 1H, J = 17.0 Hz, CH=C$\underline{H}_a$H$_2$), 5.80 (d, 1H, J = 11.0 Hz, CH=CH$_a\underline{H}_b$), 7.5 (m, 3H, C$\underline{H}$=CH$_2$, H_{arom}), 8.43 (d, 2H, H_{arom}), 9.60(s, 1H, H-1) ; ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.31, 16.32, 20.89, 21.87, 21.97, 23.44, 26.50, 34.14, 41.33, 47.47, 61.67, 78.84, 116.48, 121.29, 123.66, 123.98, 129.78, 130.24, 132.18, 135.39, 136.53, 139.60, 141.62, 151.25, 166.56; mass spectrum (HREI), calcd for $C_{27}H_{32}N_2O_4$: m/z 448.2328. Found : m/z 448.2345.

(10R)- and (10S)-10-Hydroxymethyl-5-N-(-)-menthyloxycarbonylfuro[3,4-c]-β-carboline-2(10H)one ((10R)-14 and (10S)-14). A solution of compound **13** (200 mg, 0.45 mmol) in acetone (50 mL) and water (50 mL) was treated with a 3% aqueous solution of osmium tetroxide (74 μL, 9 μmol). The solution was stirred for 30 min, 4-methylmorpholine N-oxide (54 mg, 0.49 mmol) was added and stirring was continued for 8 days. At the end of the reaction period, sodium metabisulfite (92.5 mg, 0.49 mmol) was added and, after 10 min of stirring, the mixture was filtered. The solid product **14** (101 mg, 52%) was washed with water and with ethyl acetate. Ethyl acetate (200 mL) was added to the combined filtrate and washings, the organic phase was separated, washed with saturated aqueous sodium chloride

and dried over sodium sulfate. Concentration of the solution under reduced pressure left crude **14** (27 mg, 14%) which was purified by preparative TLC on alumina (ethyl acetate-heptane 1:1) (total yield of **14** : 66%) ; ^{1}H NMR (200 MHz,$(CD_3)_2CO$) δ 0.77-0.98 (m, 9H, CHC$\underline{H}_3$, CH(C$\underline{H}_3)_2$), 1.15-2.12 (m, 8H, menthyl), 2.30 (m, 1H, J = 7.0 Hz and 11.0 Hz, C$\underline{H}(CH_3)_2$), 4.31 (m, 2H, C$\underline{H}_2$OH), 5.15 (m, 2H, partly exchangeable with D_2O, J = 4.2 Hz and 11.0 Hz, O$\underline{H}$, C$\underline{H}$OC(=O)N), 6.27 (t, 1H, J = 1.5 Hz, C$\underline{H}$CH$_2$OH), 7.56 (t, 1H, H_{arom}), 7.76 (t, 1H, H_{arom}), 8.29 (d, 1H, H_{arom}), 8.50 (d, 1H, H_{arom}), 9.75 (s, 1H, CH=N of 10R (or 10S) isomer), 9.77 (s, 1H, CH=N of 10S (or 10R) isomer ; mass spectrum (HREI), calcd for $C_{25}H_{28}N_2O_5$: m/z 436.1979. Found : m/z 436.2003. Anal. Calcd for $C_{25}H_{28}N_2O_5.3/4H_2O$: C, 66.74 ; H, 6.56 ; N, 6.22. Found : C, 66.43 ; H, 6.30 ; N, 6.43.

The two diastereomers of **14**, that is, (10*R*)-**14** and (10*S*)-**14**, were separated by HPLC using a 10 x 250 mm Ultrasphere 5 μ C-18 reverse phase column and methanol-water (70:30) as developer (flow rate = 4 mL/min). *Compound (10R)-14* : retention time = 30.8 min ; $[\alpha]_D^{25}$ - 116.6 (c 0.18, CH_3OH). *Compound (10S)-14* : retention time : 32.6 min ; $[\alpha]_D^{25}$ + 25.2 (c 0.30, CH_3OH).

Preparation of (S)-1 from (10S)-14. A solution of (10*S*)-**14** (20 mg, 0.078 mmol) in ethanol (10 mL) was treated at room temperature with a solution of sodium in ethanol (0.1 eq). After 10 min, the reaction mixture was neutralized by the addition of acetic acid. Concentration of the solution under reduced pressure led to formation of a white precipitate which was collected by filtration. The solid was washed with water and then with dichloromethane and dried, yielding (*S*)-**1** (9.8 mg, 93%), identical in all respects with that prepared from compounds **8** and **11**, as described above : $[\alpha]_D^{25}$ + 41 (c 0.10, DMSO).

Preparation of (R)-1 from (10R)-14. Following the same procedure as above, (10*R*)-**14** gave a 69% yield of (*R*)-**1**, identical in all respects with that prepared from (*S*)-**2** : $[\alpha]_D^{25}$ - 38 (c 0.09, DMSO).

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