Synthesis of (±)-D-Homocephalotaxine, an Unnatural Analogue of Cephalotaxine

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(±)-D-Homocephalotaxine (2), an unnatural analogue of cephalotaxine, has been synthesized by a synthetic sequence involving an acid-catalyzed cyclization of the α -sulfinylacetamide 8 as a key step.

Keywords cationic cyclization; Pummerer reaction; sulfoxide; α -chlorosulfide; α -thiocarbocation; cephalotaxine analogue; D-homocephalotaxine

Cephalotaxine (1), the predominant alkaloid of *Cephalotaxus* species, has attracted much attention from synthetic chemists due to its unique structural features as well as the antileukemic activities of its ester derivatives, harringtonine and homoharringtonine.^{1–3)} So far, six total syntheses of 1, including ours, have been reported.^{4–9)} In addition, considerable efforts to synthesize a variety of structural analogues of cephalotaxine have been made.^{6,10–15)}

As a part of our studies on carbon–carbon bond-forming reactions by using α -thiocarbocations,¹⁶⁾ we have recently reported a new entry to 3-methyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-ones which involves the acid-catalyzed cyclization of *N*-(2-arylethyl)-*N*-methyl- α -sulfinylacetamides.¹⁷⁾ As an extension of this work, it appeared to be of interest to see if the method could be applied to more complex systems such as 8, because it has been reported that attempts to cyclize a variety of *N*-substituted derivatives of either the amine 3 or lactam 4 to the benzazepine ring system failed.^{10–12,18)} We describe here a successful application of our method to the synthesis of (±)-D-homocephalotaxine (2), an unnatural analogue of cephalotaxine (1).

The sulfoxide 8 required to test the feasibility of the cyclization was prepared by acylation of the readily available amine 3^{10–12)} with (methylthio)acetic acid in the presence of 1,3-dicyclohexylcarbodiimide (DCC) followed by oxidation of the resulting sulfide 7 with sodium metaperiodate (NaIO₄) in aqueous methanol.

Cyclization of the sulfoxide 8 to the benzazepinone 10

was conducted under the Pummerer reaction conditions described previously.¹⁷⁾ Thus, treatment of 8 with trifluoroacetic anhydride (TFAA) in dichloromethane at room temperature for 24 h (procedure A) gave the benzazepinone 10 as an inseparable mixture of two diastereomers (*ca.* 10:1) due to the methylthio group in 63% yield. The benzazepinone 10 was also obtained in 65% yield, when 8 was treated with 2 eq of anhydrous *p*-toluenesulfonic acid (*p*-TsOH) in boiling 1,2-dichloroethane for 15 min (procedure B). Evidence that cyclization had occurred was given by the ¹H-NMR spectrum of the major isomer, which showed signals due to only two aromatic protons at δ 6.63 (s) and 6.83 (s) as well as a methine proton (H-12) at δ 4.48 (s) (the corresponding signals for the minor product appeared at δ 6.91, 7.47, and 5.30). Desulfurization of 10 with zinc in acetic acid gave the benzazepinone 11 in quantitative yield.

For comparison, a Lewis acid-catalyzed cyclization of the α -chlorosulfide 9 was also examined. Thus, treatment of 9, prepared by direct acylation of 3 with chloro(methylthio)acetyl chloride, with stannic chloride (SnCl₄) in dichloromethane at 0°C (procedure C) gave the same benzazepinone 10, but in lower yield (34%).

Introduction of the oxygen functionalities into the D-ring essentially followed the method of Kuehne and coworkers.⁸⁾ The benzazepinone 11 was oxidized with a catalytic amount of osmium tetroxide (OsO₄) in the presence of *N*-methylmorpholine *N*-oxide to give the diol 12 as a diastereomeric mixture (*ca.* 7:3). Oxidation of the crude diol 12 with Corey–Kim reagent¹⁹⁾ [*N*-chlorosuccinimide (NCS) and dimethyl sulfide] gave the α -diketone 13 in 77% overall yield (from 11). The ¹H-NMR spectrum of 13 showed a singlet at δ 5.96 due to the olefinic proton at C₁, indicating that the α -diketone exists in the enolic form, as shown in Chart 2. The α -diketone 13 was then methylated by using Ponaras' procedure²⁰⁾ [methoxytrimethylsilane (TMSOMe) in the presence of trifluoromethanesulfonic acid in dichloromethane] to give two isomeric methyl ethers 14a (63%) and 14b (16%), along with a small amount of the starting material 13. The structures of 14a, b were apparent from an examination of the ¹H-NMR spectra: the olefinic proton (H-1) signal of 14a appeared at δ 5.68 as a singlet, whereas the olefinic proton (H-4) signal of 14b appeared at δ 5.72 as a doublet ($J=4.0$ Hz) due to coupling with the C₅ proton at δ 4.27 (d, $J=4.0$ Hz).

Reduction of the resultant enone 14a with sodium borohydride in methanol at 0°C resulted in the formation of a mixture of two alcohols, 15a (63%) and 15b (36%). The stereochemical assignments of 15a, b were made by

Chart 1

Chart 2

examining the ^1H -NMR spectra. The distinguishing feature of the ^1H -NMR spectrum of **15a** is the C_3 proton signal which displays relatively small couplings of 4.6 and 2.7 Hz. In contrast, the same proton of **15b** exhibits greater splittings ($J=10.4$ and 5.1 Hz). These coupling patterns, along with the fact that the C_5 proton signal in both compounds appears as a triplet with $J=3.9$ Hz, are consistent with the assigned conformations in which the hydroxyl group is axial in **15a** and equatorial in **15b**. The preferential formation of **15a** from **14a** can be rationalized by assuming the conformation of **14a** to be as shown in Chart 3, in which hydride attacks the convex face of the carbonyl group. In fact, when **14a** was reduced with bulkier lithium tri-*sec*-butylborohydride (L-Selectride), **15a** was obtained exclusively.

Finally, reduction of **15a** with sodium bis(2-methoxy-

ethoxy)aluminum hydride (Red-Al) gave the desired ($\pm$)-D-homocephalotaxine (**2**) in 60% yield. The structure of **2** was fully supported by the spectroscopic data (see Experimental).

In summary, the acid-catalyzed aromatic cyclization of the α -sulfinylacetamides opens up a new route to cephalotaxine and its analogues.

Experimental

Melting points are uncorrected. Infrared (IR) spectra were recorded with a JASCO IRA-1 spectrophotometer. ^1H -NMR spectra were determined with a JEOL JNM-PMX 60 (60 MHz) or a Varian XL-300 (300 MHz) spectrometer and C-13 nuclear magnetic resonance (^{13}C -NMR) spectra with a Varian XL-300 (75 MHz) spectrometer, using tetramethylsilane as an internal standard. High resolution mass spectra (MS) were obtained with a Hitachi M-80 instrument at 20 eV. Column chromatography was performed on Silica gel 60 PF₂₅₄ (Merck) under

Chart 3

pressure.

(5S*,10S*)-10-(1,3-Benzodioxol-5-yl)-1-[(methylthio)acetyl]-1-azaspiro[4.5]dec-7-ene (7) The Red-Al reduction was done essentially according to the procedure of Bryce *et al.*¹⁰ Red-Al (70% in toluene, 9 ml, 30 mmol) was added dropwise to a solution of **4** (1.36 g, 5.00 mmol) in dry benzene (50 ml) and the mixture was heated under reflux overnight. Water (30 ml) was then added under ice-cooling to the mixture to destroy the excess reagent and the whole was made alkaline with saturated NaHCO₃ solution. The precipitates were filtered off and the organic layer was separated. The aqueous layer was further extracted with dichloromethane. The combined extracts were dried (Na₂SO₄) and concentrated to give the amine **3** (1.19 g) as an oil, which was used in the next stage without further purification.

(Methylthio)acetic acid (542 mg, 4.92 mmol) and DCC (1.04 g, 4.92 mmol) were added to a solution of **3** (1.15 g, 4.45 mmol) in dry dichloromethane (35 ml) at 0°C and the mixture was stirred at room temperature for 48 h. Precipitated dicyclohexylurea was filtered off and the filtrate was concentrated. The residual oil was chromatographed on silica gel (hexane-AcOEt, 1:1) to give **7** (1.47 g, 90% from **3**) as an oil. IR $\nu_{\text{max}}^{\text{CHCl}_3}$: 1645. ¹H-NMR (CDCl₃, 60 MHz) δ : 1.5–3.8 (13H, m), 2.10 (3H, s, SMe), 5.7–5.9 (2H, m, CH=CH), 5.84 (2H, s, OCH₂O), 6.6–6.8 (3H, m, aromatic protons). Exact MS m/z : Calcd for C₁₉H₂₁NO₃S: 345.1396. Found: 345.1367.

(5S*,10S*)-10-(1,3-Benzodioxol-5-yl)-1-[(methylsulfinyl)acetyl]-1-azaspiro[4.5]dec-7-ene (8) A solution of NaIO₄ (451 mg, 2.11 mmol) in water (12 ml) was added dropwise to an ice-cooled solution of **7** (665 mg, 1.92 mmol) in methanol (6.0 ml) and the mixture was stirred at room temperature overnight. The precipitated inorganic material was removed by filtration and water (10 ml) was added. The aqueous layer was extracted with dichloromethane and the extract was washed with brine, dried (MgSO₄), and concentrated. The residue was chromatographed on silica gel (CH₂Cl₂-MeOH, 10:1) to give the sulfoxide **8** (607 mg, 87%), which solidified on standing. IR $\nu_{\text{max}}^{\text{CHCl}_3}$: 1650. ¹H-NMR (CDCl₃, 60 MHz) δ : 1.6–4.0 (13H, m), 2.60 (3H, brs, SMe), 5.7–6.0 (2H, m, CH=CH), 5.82 (2H, s, OCH₂O), 6.5–6.8 (3H, m, aromatic protons). The sulfoxide **8** was used in the next stage without further purification.

(5S*,6S*)-12-Methylthio-4,5,8,9,11,12-hexahydro-1H,7H-[1,3]benzodioxolo[5,6-*d*]pyrrolo[2,1-*k*][1]benzazepine-11-one (10) Procedure A: Trifluoroacetic anhydride (0.064 ml, 0.28 mmol) was added dropwise to a solution of the sulfoxide **8** (100 mg, 0.28 mmol) in dry dichloromethane (1.5 ml) at 0°C under nitrogen and the mixture was stirred at room temperature for 24 h. Dichloromethane (10 ml) was added and the whole mixture was washed with saturated NaHCO₃ solution and brine, dried (MgSO₄), and concentrated. The residue was chromatographed on silica gel (hexane-AcOEt, 2:1) to give **10** (60 mg, 63%) as an inseparable mixture of two diastereomers (*ca.* 10:1) due to the methylthio group: mp 192–194°C (from MeOH). IR $\nu_{\text{max}}^{\text{CHCl}_3}$: 1610. ¹H-NMR (CDCl₃, 300 MHz) δ (only the signals for the major isomer are recorded): 1.45–2.08

(6H, m), 2.27 (3H, s, SMe), 2.58 (2H, br), 3.31–3.41 (1H, m), 4.08–4.25 (2H, m), 4.48 (1H, s, H-12), 5.53–5.62, 5.84–5.92 (1H each, 2×m, CH=CH), 5.94 (2H, s, OCH₂O), 6.63, 6.83 (1H each, 2×s, aromatic protons). ¹³C-NMR (CDCl₃, 75 MHz) δ (only the signals for the major isomer are recorded): 17.58 (SMe), 18.69, 30.10, 30.99, 36.35, 40.11 (C-5), 46.41, 57.61 (C-12), 66.94 (C-6), 101.23 (OCH₂O), 103.37, 110.31, 125.54, 127.11, 128.24, 132.83, 145.99, 147.36, 166.41 (C-11). Anal. Calcd for C₁₉H₂₁NO₃S: C, 66.45; H, 6.16; N, 4.08. Found: C, 66.56; H, 6.12; N, 4.18.

Procedure B: A solution of *p*-toluenesulfonic acid monohydrate (700 mg, 3.68 mmol) in 1,2-dichloroethane (10 ml) was heated under reflux with azeotropic removal of water for 2 h, then cooled under a nitrogen atmosphere. A solution of the sulfoxide **8** (664 mg, 1.84 mmol) in 1,2-dichloroethane (4 ml) was added to the above solution containing anhydrous *p*-toluenesulfonic acid, and the mixture was heated again under reflux with azeotropic removal of water for 15 min. The reaction mixture was washed with saturated NaHCO₃ solution and brine, dried (MgSO₄), and concentrated. The residue was chromatographed on silica gel (hexane-AcOEt, 2:1) to give **10** (407 mg, 65%).

Preparation and Cyclization of 10-(1,3-Benzodioxol-5-yl)-1-[chloro(methylthio)acetyl]-1-azaspiro[4.5]dec-7-ene (9) Procedure C: A solution of chloro(methylthio)acetyl chloride (610 mg, 3.84 mmol) in dry ether (7.5 ml) was added to a solution of the crude amine **3** (758 mg, 2.95 mmol) and triethylamine (0.63 ml, 4.43 mmol) in dry ether (10 ml) at 0°C and the mixture was stirred for 30 min. The precipitates were filtered off and the filtrate was concentrated to give crude **9** as an oil, which was dissolved in dry dichloromethane (10 ml). SnCl₄ (0.52 ml, 4.43 mmol) was added to the above solution at 0°C and the mixture was stirred at the same temperature for 2 h. The reaction was quenched with water and the organic layer was separated, washed with brine, dried (MgSO₄), and concentrated. The residue was chromatographed on silica gel (hexane-AcOEt, 2:1) to give **10** (345 mg, 34% based on **3**).

(5S*,6S*)-4,5,8,9,11,12-Hexahydro-1H,7H-[1,3]benzodioxolo[5,6-*d*]pyrrolo[2,1-*k*][1]benzazepine-11-one (11) Zinc dust (458 mg, 7.00 mmol) was added to a solution of **10** (240 mg, 0.700 mmol) in acetic acid (1 ml) and the mixture was heated with vigorous stirring at 100–110°C overnight, then cooled. Dichloromethane (10 ml) was added and the inorganic material was filtered off. The mother liquor was concentrated *in vacuo* and the residue was chromatographed on silica gel (hexane-AcOEt, 1:1) to give **11** (208 mg, quant.), mp 223–224°C (from MeOH). IR $\nu_{\text{max}}^{\text{CHCl}_3}$: 1600. ¹H-NMR (CDCl₃, 60 MHz) δ : 1.4–2.7 (8H, m), 2.8–3.6 (2H, m), 3.49, 4.00 (1H each, ABq, *J* = 16 Hz, H-12), 3.8–4.5 (1H, m), 5.3–6.1 (2H, m, CH=CH), 5.88 (2H, s, OCH₂O), 6.64, 6.82 (1H each, 2×s, aromatic protons). Anal. Calcd for C₁₈H₁₉NO₃: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.72; H, 6.30; N, 4.78.

(5S*,6R*)-2-Hydroxy-4,5,8,9,11,12-hexahydro-3H,7H-[1,3]benzodioxolo[5,6-*d*]pyrrolo[2,1-*k*][1]benzazepine-3,11-dione (13) *N*-Methyl-

morpholine *N*-oxide (1.38 g, 11.8 mmol) and a catalytic amount of OsO₄ was added to a solution of **11** (700 mg, 2.35 mmol) in *tert*-butanol (32 ml), tetrahydrofuran (THF) (36 ml), and water (4 ml) and the mixture was stirred overnight. Saturated NaHSO₃ solution (15 ml) was added, and the whole was stirred for 20 min. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were concentrated *in vacuo* and the residue was chromatographed on silica gel (CH₂Cl₂–MeOH, 15:1) to give the crude diol **12** (723 mg, 93%) as a mixture of two diastereomers (*ca.* 7:3 from the ¹H-NMR spectrum), which was used in the next step without further purification.

A solution of the crude diol **12** (375 mg, 1.13 mmol) in dry dichloromethane (30 ml) was added dropwise to a solution of Corey–Kim reagent¹⁹ [prepared from *N*-chlorosuccinimide (754 mg, 5.65 mmol) and dimethyl sulfide (0.414 ml, 5.65 mmol) in dichloromethane (14 ml)] at –42 °C and the mixture was stirred for 2 h. Triethylamine (1.26 ml, 9.04 mmol) was added and the whole was stirred at room temperature overnight. The reaction mixture was poured into brine (50 ml) and extracted with dichloromethane. The extract was dried (MgSO₄) and concentrated, and the residue was chromatographed on silica gel (AcOEt) to give **13** (306 mg, 83%), mp 239–240 °C (from MeOH). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{–1}: 3450, 1680, 1640, 1610. ¹H-NMR (DMSO-*d*₆, 300 MHz) δ : 1.75–1.93 (2H, m, H-8), 2.12 (1H, ddd, *J* = 12.9, 11.0, 6.7 Hz, one of H-7), 2.61 (1H, ddd, *J* = 12.9, 5.2, 3.4 Hz, one of H-7), 2.82 (1H, dd, *J* = 16.7, 2.3 Hz, one of H-4), 3.11 (1H, d, *J* = 14.7 Hz, one of H-12), 3.24 (1H, dd, *J* = 16.6, 5.2 Hz, one of H-4), 3.47 (1H, dt, *J* = 10.5, 4.0 Hz, one of H-9), 3.50–3.56 (1H, m, H-5), 4.12 (1H, dd, *J* = 10.5, 5.2 Hz, one of H-9), 4.28 (1H, d, *J* = 14.7 Hz, one of H-12), 5.96 (3H, s, OCH₃O, H-1), 6.68, 6.90 (1H each, 2 × s, aromatic protons), 8.83 (1H, s, OH). ¹³C-NMR (DMSO-*d*₆, 75 MHz) δ : 21.44, 39.27, 41.96, 45.16, 46.87 (C-5), 47.05, 62.57 (C-6), 100.92 (OCH₃O), 110.07, 110.90, 123.52 (C-1), 123.60, 131.62, 145.64, 146.69, 146.81, 169.37 (C-11), 193.69 (C-4). Exact MS *m/z*: Calcd for C₁₈H₁₇NO₅: 327.1105. Found: 327.1107. Anal. Calcd for C₁₈H₁₇NO₅·CH₃OH: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.35; H, 5.95; N, 3.98.

(5*S**,6*R**)-2-Methoxy-4,5,8,9,11,12-hexahydro-3*H*,7*H*-[1,3]benzodioxolo[5,6-*d*]pyrrolo[2,1-*k*][1]benzazepine-3,11-dione (**14a**) and (5*S**,6*R**)-3-Methoxy-1,2,8,9,11,12-hexahydro-5*H*,7*H*-[1,3]benzodioxolo[5,6-*d*]pyrrolo[2,1-*k*][1]benzazepine-2,11-dione (**14b**) Methylation of **13** was conducted essentially according to the procedure of Ponaras and Meah.²⁰ Methoxytrimethylsilane (0.051 ml, 0.376 mmol) and trifluoromethanesulfonic acid (0.132 ml, 1.50 mmol) were added dropwise to a solution of **13** (123 mg, 0.376 mmol) in dry dichloromethane (20 ml) at 0 °C, and the mixture was stirred at room temperature for 72 h. The reaction mixture was washed with saturated NaHCO₃ solution and brine, dried (MgSO₄), and concentrated. The residue was submitted to preparative thin layer chromatography (silica gel, AcOEt) to give **14b** (20 mg, 16%), **14a** (80 mg, 63%), and the unreacted starting material **13** (25 mg).

Compound **14a** had mp 249–251 °C (from MeOH). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{–1}: 1685, 1635, 1620. ¹H-NMR (CDCl₃, 300 MHz) δ : 1.85–2.10 (2H, m, H-8), 2.25 (1H, ddd, *J* = 13.0, 11.3, 6.6 Hz, one of H-7), 2.61 (1H, ddd, *J* = 13.0, 5.8, 3.0 Hz, one of H-7), 3.01 (1H, dd, *J* = 16.4, 2.7 Hz, one of H-4), 3.13 (1H, dd, *J* = 16.4, 5.4 Hz, one of H-4), 3.19 (1H, d, *J* = 15.0 Hz, one of H-12), 3.51–3.56 (1H, br, H-5), 3.61 (1H, ddd, *J* = 11.8, 9.8, 6.8 Hz, one of H-9), 3.66 (3H, s, OMe), 3.77 (1H, ddd, *J* = 11.2, 8.0, 3.0 Hz, one of H-9), 4.42 (1H, d, *J* = 15.0 Hz, one of H-12), 5.68 (1H, s, H-1), 5.90, 5.91 (1H each, ABq, *J* = 1.4 Hz, OCH₃O), 6.51, 6.62 (1H each, 2 × s, aromatic protons). ¹³C-NMR (CDCl₃, 75 MHz) δ : 22.06, 41.19, 43.19, 46.02, 47.62 (C-5), 47.67, 55.16 (OMe), 63.25 (C-6), 101.27 (OCH₃O), 110.54, 110.74, 120.73 (C-1), 123.47, 130.25, 146.64, 147.57, 150.12 (C-2), 170.83 (C-11), 191.61 (C-3). Exact MS *m/z*: Calcd for C₁₅H₁₉NO₅: 341.1262. Found: 341.1266.

Compound **14b** had mp 212–213 °C (from CH₂Cl₂–AcOEt). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{–1}: 1700, 1625. ¹H-NMR (CDCl₃, 300 MHz) δ : 1.75–1.96 (4H, m, H-7, H-8), 2.61, 2.92 (1H each, ABq, *J* = 16.1 Hz, H-1), 3.28 (1H, ddd, *J* = 12.0, 8.4, 6.5 Hz, one of H-9), 3.45 (1H, d, *J* = 15.3 Hz, one of H-12), 3.68 (3H, s, OMe), 4.06 (1H, ddd, *J* = 12.0, 8.3, 7.6 Hz, one of H-9), 4.17 (1H, d, *J* = 15.3 Hz, one of H-12), 4.27 (1H, d, *J* = 4.0 Hz, H-5), 5.72 (1H, d, *J* = 4.0 Hz, H-4), 5.97, 5.98 (1H each, ABq, *J* = 1.4 Hz, OCH₃O), 6.72, 6.76 (1H each, 2 × s, aromatic protons). ¹³C-NMR (CDCl₃, 75 MHz) δ : 18.65, 38.35, 41.92, 44.87, 46.54 (C-5), 46.67, 55.35 (OMe), 67.86 (C-6), 101.40 (OCH₃O), 110.10, 110.60, 115.83, 128.64, 128.78, 146.97, 147.44, 151.94, 167.67 (C-11), 191.07 (C-2). Exact MS *m/z*: Calcd for C₁₅H₁₉NO₅: 341.1261. Found: 341.1247.

Reduction of Compound 14a With NaBH₄: NaBH₄ (44 mg, 1.17 mmol) was added to a solution of **14a** (40 mg, 0.117 mmol) in MeOH (5 ml) and dichloromethane (2.5 ml) at 0 °C and the mixture was stirred at room temperature for 2 h. The mixture was diluted with water (5 ml) and extract-

ed with dichloromethane, then the extract was dried (MgSO₄) and concentrated. The residue was chromatographed on silica gel. The first eluate gave (3*S**,5*S**,6*R**)-3-hydroxy-2-methoxy-4,5,8,9,11,12-hexahydro-3*H*,7*H*-[1,3]benzodioxolo[5,6-*d*]pyrrolo[2,1-*k*][1]benzazepin-11-one (**15a**) (25 mg, 63%) and the second eluate gave the isomeric alcohol **15b** (15 mg, 36%).

Compound **15a** had mp 217–218 °C (from CH₂Cl₂–AcOEt). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{–1}: 3570, 1660, 1625. ¹H-NMR (CDCl₃, 300 MHz) δ : 1.26 (1H, d, *J* = 8.3 Hz, OH), 1.70–1.96 (2H, m, H-8), 2.04 (1H, ddd, *J* = 12.8, 11.1, 6.2 Hz, one of H-7), 2.25 (1H, ddd, *J* = 12.8, 5.8, 3.5 Hz, one of H-7), 2.35 (1H, dt, *J* = 14.8, 4.7 Hz, one of H-4), 2.50 (1H, ddd, *J* = 14.8, 3.5, 2.7 Hz, one of H-4), 3.15 (1H, d, *J* = 14.4 Hz, one of H-12), 3.16 (1H, t, *J* = 3.9 Hz, H-5), 3.52 (1H, ddd, *J* = 11.7, 9.8, 6.6 Hz, one of H-9), 3.63 (3H, s, OMe), 3.65–3.75 (1H, m, one of H-9), 4.05 (1H, ddd, *J* = 8.3, 4.6, 2.7 Hz, H-3), 4.64 (1H, d, *J* = 14.4 Hz, one of H-12), 4.69 (1H, s, H-1), 5.91, 5.92 (1H each, ABq, *J* = 1.4 Hz, OCH₃O), 6.58, 6.74 (1H each, 2 × s, aromatic protons). ¹³C-NMR (CDCl₃, 75 MHz) δ : 21.63, 37.95, 42.95, 43.49, 43.68 (C-5), 47.52, 54.78 (OMe), 63.87 (C-6), 65.52 (C-3), 101.23 (OCH₃O), 103.85 (C-1), 110.88, 110.95, 124.40, 132.72, 146.48, 147.34, 157.29 (C-2), 171.41 (C-11). Exact MS *m/z*: Calcd for C₁₉H₂₁NO₅: 343.1419. Found: 343.1424. Anal. Calcd for C₁₉H₂₁NO₅·1/2H₂O: C, 64.76; H, 6.29; N, 3.98. Found: C, 65.18; H, 6.20; N, 4.11.

Compound **15b** had mp 179–180 °C (from AcOEt–hexane). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{–1}: 3600, 1660, 1625. ¹H-NMR (CDCl₃, 300 MHz) δ : 1.70–1.96 (2H, m, H-8), 2.09–2.20 (1H, m, one of H-7), 2.14 (1H, ddd, *J* = 13.0, 10.4, 3.9 Hz, one of H-4), 2.30–2.39 (1H, m, one of H-7), 2.46 (1H, ddd, *J* = 13.0, 5.1, 3.9 Hz, one of H-4), 2.57 (1H, d, *J* = 1.9 Hz, OH), 3.08 (1H, d, *J* = 14.4 Hz, one of H-12), 3.24 (1H, t, *J* = 3.9 Hz, H-5), 3.48 (1H, ddd, *J* = 11.5, 10.3, 6.6 Hz, one of H-9), 3.62 (3H, s, OMe), 3.67–3.76 (1H, m, one of H-9), 4.06 (1H, br dd, *J* = 10.4, 5.1 Hz, H-3), 4.57 (1H, d, *J* = 14.4 Hz, one of H-12), 4.57 (1H, s, H-1), 5.90, 5.92 (1H each, ABq, *J* = 1.4 Hz, OCH₃O), 6.54, 6.70 (1H each, 2 × s, aromatic protons). ¹³C-NMR (CDCl₃, 75 MHz) δ : 21.92, 39.17, 42.85, 44.72, 46.39 (C-5), 47.64, 54.89 (OMe), 63.01 (C-3), 63.89 (C-6), 101.08 (OCH₃O), 103.10 (C-1), 110.35, 110.42, 125.07, 132.03, 146.07, 147.08, 157.60 (C-2), 171.43 (C-11). Exact MS *m/z*: Calcd for C₁₉H₂₁NO₅: 343.1418. Found: 343.1401.

With L-Selectride: L-Selectride (1.0 M solution in THF, 0.112 ml, 0.528 mmol) was added to a solution of **14a** (60 mg, 0.176 mmol) in dry THF (20 ml) and dry dichloromethane (4 ml) at –78 °C and the mixture was stirred at the same temperature for 3 h. The solvent was evaporated off and the residue was diluted with dichloromethane (20 ml) and 5% HCl (10 ml). The organic layer was separated, washed with brine, dried (MgSO₄), and concentrated. The residue was chromatographed on silica gel (AcOEt) to give **15a** (60 mg, quant.).

(3*S**,5*S**,6*R**)-3-Hydroxy-2-methoxy-4,5,8,9,11,12-hexahydro-3*H*,7*H*-[1,3]benzodioxolo[5,6-*d*]pyrrolo[2,1-*k*][1]benzazepine [(±)-D-Homoccephalotaxine (**2**)] The procedure was essentially the same as that employed for the preparation of the amine **3**. A solution of **15a** (60 mg, 0.175 mmol) in dry benzene (15 ml) and dry dichloromethane (2 ml) was treated with Red-Al (70% in toluene, 2.02 ml, 7.00 mmol) to afford, after work-up, **2** (35 mg, 60%), mp 214–216 °C (from CH₂Cl₂–AcOEt). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{–1}: 3350, 1650. ¹H-NMR (CDCl₃, 300 MHz) δ : 1.80–2.10 (3H, m), 2.10–2.25 (1H, m), 2.31 (1H, ddd, *J* = 13.5, 8.0, 3.4 Hz, one of H-4), 2.70 (1H, ddd, *J* = 16.6, 6.0, 2.7 Hz, one of H-12), 2.80–2.95 (2H, m), 2.98–3.09 (2H, m), 3.52 (1H, ddd, *J* = 13.4, 6.0, 3.1 Hz, one of H-11), 3.59–3.79 (2H, m), 3.68 (3H, s, OMe), 4.32 (1H, t, *J* = 8.1 Hz, H-3), 4.76 (1H, s, H-1), 5.95 (2H, s, OCH₃O), 6.58, 6.59 (1H each, 2 × s, aromatic protons). ¹³C-NMR (CDCl₃, 75 MHz) δ : 19.08, 31.31, 34.31, 34.87, 48.07 (C-5), 50.32, 53.29, 53.41 (C-6), 55.19 (OMe), 66.87 (C-3), 97.09 (C-1), 101.22 (OCH₃O), 110.60, 111.34, 130.83, 131.63, 146.60, 146.87, 161.23 (C-2). Exact MS *m/z*: Calcd for C₁₉H₂₃NO₄: 329.1625. Found: 329.1613.

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