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Synthetic Studies on *Cephalotaxus* Alkaloids. A Synthesis of (±)-Cephalotaxine

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A stereoselective total synthesis of (±)-cephalotaxine (1) has been achieved. Palladium-catalyzed [3+2] cycloaddition of 2-(trimethylsilylmethyl)-2-propenyl acetate to the nitrostyrene 7 gave the methylenecyclopentane 6, which was converted into the α-sulfinylacetamide 19. Treatment of 19 either with trifluoroacetic anhydride in dichloromethane at room temperature or with *p*-toluenesulfonic acid in boiling 1,2-dichloroethane gave the benzazepinone 20 in good yield, and this was transformed to (±)-1 *via* Hanaoka's key intermediate 4.

Keywords cephalotaxine; Pummerer reaction; [3+2] cycloaddition; 2-(trimethylsilylmethyl)-2-propenyl acetate; sulfoxide; iodobenzene diacetate

Cephalotaxine (**1**) is the major alkaloid isolated from the *Cephalotaxus* species in 1963 by Paudler[1] and its structure was determined by other workers using a combination of nuclear magnetic resonance (NMR)[2] spectroscopy and an X-ray crystallographic technique.[3] Over 20 alkaloids have thus far been isolated and identified.[4] Although cephalotaxine itself is biologically inactive, it was found that its ester derivatives, harringtonine (**2**) and homoharringtonine (**3**) showed potent antileukemic activity.[5] Because of this, as well as its unique structural features, cephalotaxine has received much attention from synthetic chemists and so far five total syntheses of (±)-**1** have been reported.[6] In addition to the work along this line, considerable efforts have been made to synthesize a variety of structural analogues of **1**.[6c,7]

A particularly attractive approach occurred to us during our investigation in this area. As shown in Chart 1, we envisioned that the ketolactam **4**, an important intermediate in Hanaoka's synthesis,[6c] would be obtainable from the azaspiro[4.4]nonanone or its equivalent **5** by sulfur-assisted aromatic cyclization (Pummerer reaction)[8] followed by desulfurization. Compound **5** in turn would be readily accessible from the nitrostyrene **7** by using Trost's methylenecyclopentane annelation ([3+2] cycloaddition)[9] followed by standard chemical transformations of the resulting cyclopentane **6**. We present here full details of our new total synthesis of (±)-**1**.[10]

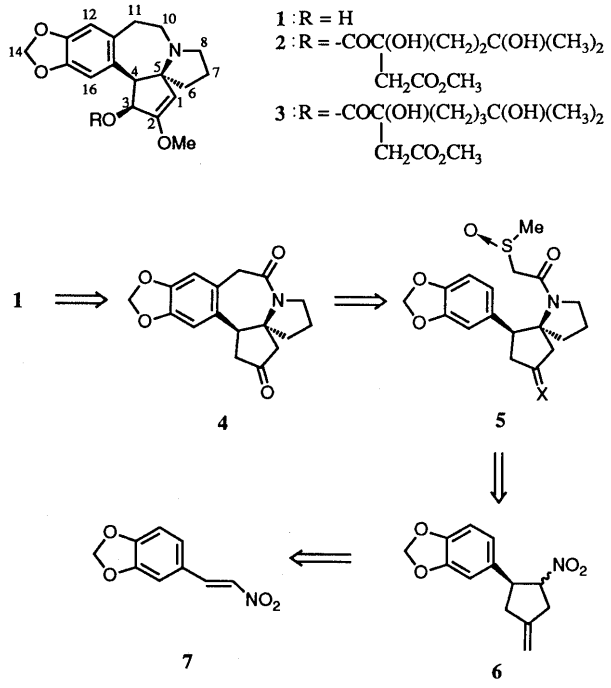
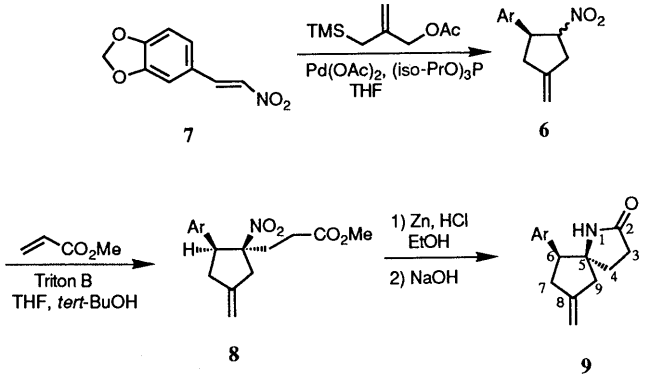


Chart 1

Results and Discussion

Treatment of the nitrostyrene **7** with 2-(trimethylsilylmethyl)-2-propenyl acetate (TMM) in the presence of $Pd(OAc)_2$ and $(iso\text{-}PrO)_3P$ in tetrahydrofuran (THF) gave the methylenecyclopentane derivative **6** as a diastereomeric mixture [*cis*/*trans* ratio = 2:8, determined by high-performance liquid chromatography (HPLC)] in 90% yield. Michael addition of methyl acrylate to the isomeric mixture of **6** gave the nitroester **8** as a single stereoisomer in quantitative yield. The stereochemistry of **8** was tentatively assigned as having the desired orientation on the basis of the sterically favored approach of the acrylate from the less hindered side of **6**, and this stereochemical assignment was later confirmed by its conversion to **4**. The nitroester **8** was then reduced with zinc in boiling ethanolic hydrochloric acid to afford the lactam **9** in 81% overall yield from **8**. It is of interest to note that the *exo* double bond of **8** remained intact under these acidic conditions. The lactam **9** was then converted into the sulfoxide **11** in three steps: (i) reduction of **9** with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al), (ii) acylation of the resulting amine with (methylthio)acetic acid and 1,3-dicyclohexylcarbodiimide (DCC), and (iii) oxidation of the sulfide **10** with sodium metaperiodate ($NaIO_4$). The sulfoxide **11** was then subjected to the cyclization conditions[8] to give a complex mixture. Since the signal of the *exo* methylene protons disappeared in the ^{1}H-NMR spectrum of the crude reaction mixture, this reaction was not further examined.

We next examined the cyclization of the ketosulfoxide **16**, which was prepared by the following sequential treatments of **9**. Oxidative cleavage of **9** with osmium tetroxide (OsO_4)–$NaIO_4$ quantitatively gave the cyclopentanone **12**,



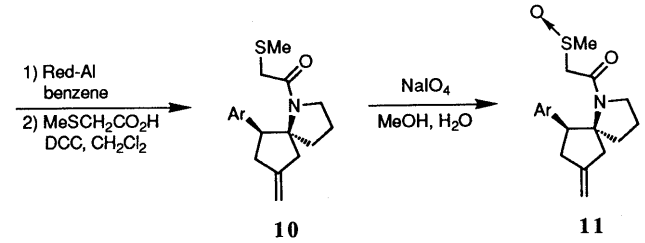


Chart 2

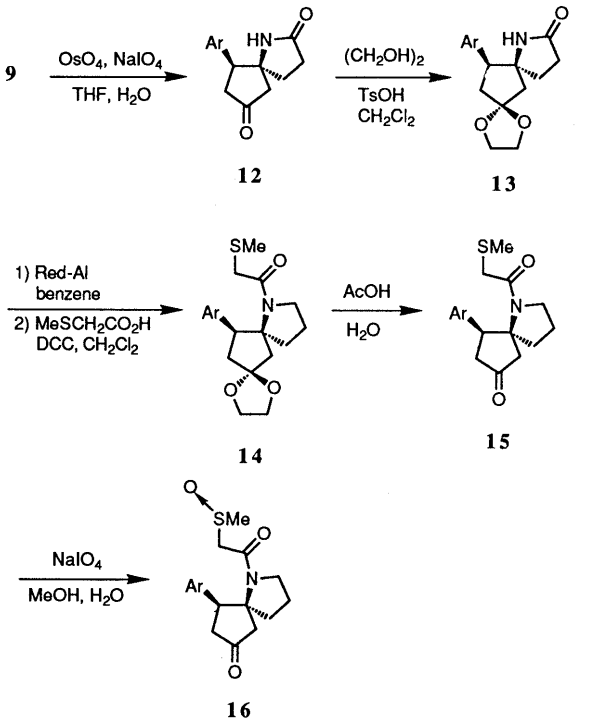


Chart 3

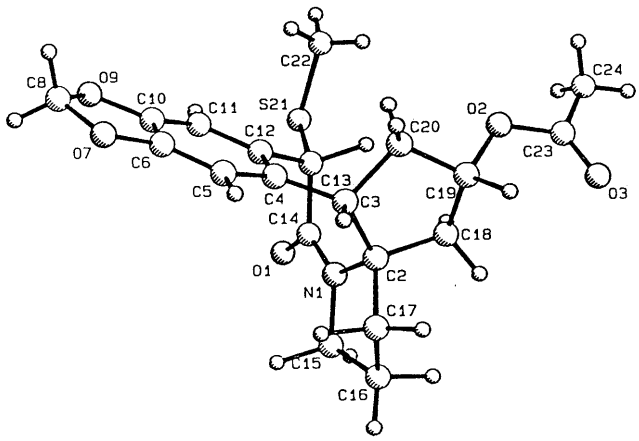


Fig. 1. Perspective ORTEP Drawing of Compound **20**

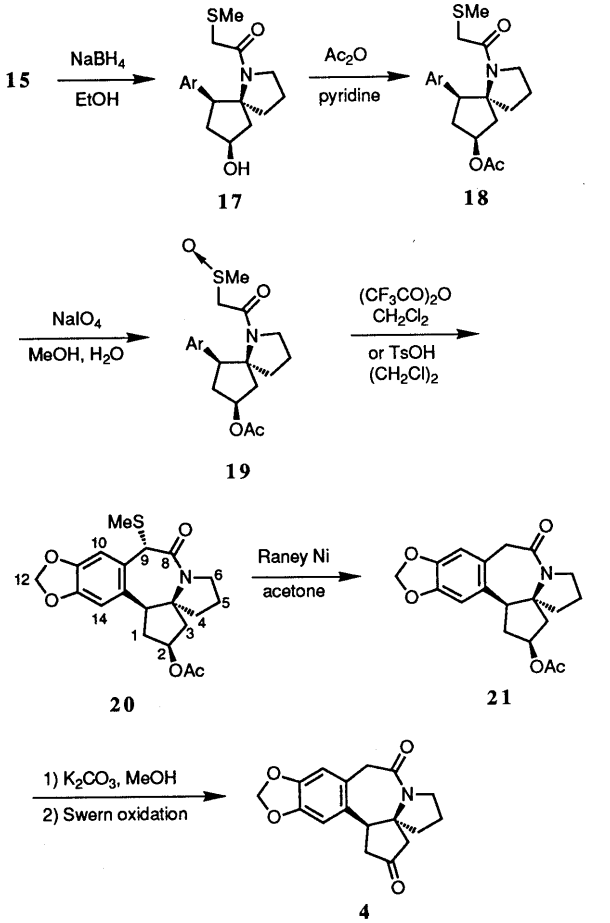


Chart 4

which was characterized by the carbonyl bands (1750 and 1695 cm^{-1}) in the infrared (IR) spectrum. Acetalization of **12**, followed by reduction of the acetal **13** with Red-Al in benzene, acylation of the resulting amine, deprotection of **14**, and then $NaIO_4$ oxidation of the sulfide **15** gave the sulfoxide **16** in 84% overall yield from **9**. Disappointingly, all attempts to cyclize **16** under various acidic conditions[8] were again unsuccessful: only a complex mixture was obtained.

Therefore, we examined acid-catalyzed cyclization of the acetoxysulfoxide **19**, which was prepared in a straightforward manner from **15** in three steps in 93% overall yield. Thus, sodium borohydride ($NaBH_4$) reduction of **15** gave the alcohol **17** as a single isomer, whose stereochemistry was assigned as shown in Chart 4 on the basis of the assumption that hydride would attack from the less hindered side of the ketone **15**. This assignment was later confirmed by transformation of **17** to **20**. Acetylation of **17** with acetic anhydride in pyridine followed by oxidation of the sulfide **18** with $NaIO_4$ gave the desired sulfoxide **19**.[11]

Cyclization of the sulfoxide **19** was effected either by treatment with 2 eq of trifluoroacetic anhydride (TFAA) in dichloromethane at room temperature (procedure A) or with 5 eq of anhydrous *p*-toluenesulfonic acid (PTSA) in

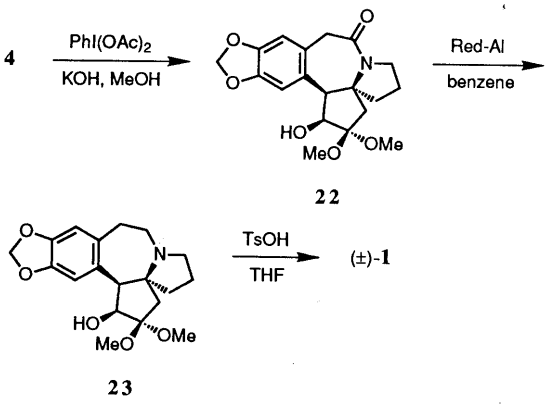


Chart 5

boiling 1,2-dichloroethane (procedure B) to give the desired benzazepinone derivative **20** in 85 and 77% yields, respectively. Evidence that cyclization had occurred came from the NMR spectrum which showed the signals of only two aromatic protons at δ 6.60 and 7.52 as singlets as well as a methine proton (C_9–H) at δ 4.99. Final confirmation of the structure and stereochemistry of **20** was given by an X-ray analysis (Fig. 1).

Desulfurization of **20** with Raney nickel, followed by hydrolysis of the acetate **21** with potassium carbonate in methanol and Swern oxidation of the resulting alcohol furnished the ketolactam **4** in 83% overall yield from **19**. The spectra of this material were identical with those of an authentic sample kindly provided by Professor Hanaoka.

Conversion of the ketolactam **4** into (±)-**1** essentially followed the procedure of Hanaoka *et al.*[6] The ketolactam **4** was oxidized with iodobenzene diacetate [$PhI(OAc)_2$][12] followed by Red-Al reduction of the resulting hydroxyacetal **22** and treatment of **23** with PTSA in THF to give (±)-**1** in 55% overall yield from **4**. We have accomplished the synthesis of (±)-**1** in 17 steps and in 21% overall yield from the nitrostyrene **7**.

Experimental

Melting points are uncorrected. IR spectra were recorded with a JASCO IRA-1 spectrophotometer. ^{1}H-NMR spectra were determined with a JEOL JNM-PMX 60 (60 MHz) or a Varian XL-300 (300 MHz) spectrometer, using tetramethylsilane as an internal standard. High-resolution mass spectra were obtained with a Hitachi M-80 instrument at 20 eV. Column chromatography was performed on Silica gel 60 PF_{254} (Merck) under pressure.

***trans*-4-Methylene-1-(3,4-methylenedioxyphenyl)-2-nitrocyclopentane (6)** (iso-PrO)$_3$P (727 mg, 30 mol%), TMM (2.17 g, 11.7 mmol), and the nitrostyrene **7** (1.50 g, 7.77 mmol) were added to a solution of $Pd(OAc)_2$ (184 mg, 7 mol%) in dry THF (80 ml) and the mixture was refluxed under a nitrogen atmosphere for 2 h. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane–benzene, 3 : 1) to give **6** (1.73 g, 90%) as an oily diastereomeric mixture. Analysis of the crude mixture by HPLC showed that the ratio of the *cis* and *trans* isomers was 2 : 8. Preparative thin layer chromatography on silica gel (hexane–benzene, 1 : 3) gave a pure sample of the *trans* isomer of **6** as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1550, 1370. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.4—3.3 (4H, m), 3.70 (1H, dt, J=10, 8 Hz), 4.85 (1H, q, J=8 Hz), 4.9—5.15 (2H, m), 5.89 (2H, s), 6.66 (3H, s). Exact MS m/z: Calcd for $C_{13}H_{13}NO_4$: 247.0843. Found: 247.0845.

An attempt to obtain a pure sample of the *cis* isomer of **6** was unsuccessful because of partial isomerization of the *cis* isomer to the *trans* isomer on a silica gel plate. For the next reaction the isomeric mixture was used.

Methyl (1*S,2*S**)-3-[4-Methylene-2-(3,4-methylenedioxyphenyl)-1-nitrocyclopent-1-yl]propionate (8)** Methyl acrylate (0.52 ml, 5.76 mmol) and Triton B (0.29 ml) were added to a solution of **6** (1.42 g, 5.76 mmol) in dry THF (15 ml) and *tert*-butyl alcohol (30 ml), and the mixture was stirred under a nitrogen atmosphere at room temperature for 48 h. The solvent was evaporated off, and dichloromethane was added. The solution was washed successively with 0.2% HCl, saturated $NaHCO_3$ solution, and brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel (hexane–benzene, 1 : 5) to give **8** (1.92 g, quant.), mp 107—108 °C (from ethanol). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1735, 1535, 1305. ^{1}H-NMR (60 MHz, $CDCl_3$) δ:2.1—2.6 (4H, m), 2.7—3.7 (5H, m), 3.66 (3H, s), 4.9—5.2 (2H, m), 5.89 (2H, s), 6.5—6.8 (3H, m). *Anal.* Calcd for $C_{17}H_{19}NO_6$: C, 61.25; H, 5.74; N, 4.20. Found: C, 61.35; H, 5.90; N, 4.28.

(5*S,6*S**)-8-Methylene-6-(3,4-methylenedioxyphenyl)-1-azaspiro[4.4]-nonan-2-one (9)** Zinc dust (4.16 g) was added to a solution of **8** (1.30 g, 3.90 mmol) in ethanol (30 ml) and concentrated HCl (5.2 ml), and the mixture was refluxed for 15 h. The inorganic material was filtered off, and the mother liquor was made alkaline with 20% NaOH solution, then refluxed for 3 h. After cooling, the mixture was neutralized with 10% HCl, and the precipitated inorganic material was filtered off. The mother liquor was extracted with chloroform and the extract was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 1 : 1) to give **9** (0.86 g, 81%) as colorless crystals, mp 148—149 °C (from EtOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1690. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.8—2.3 (4H, m), 2.5—3.2 (5H, m), 5.00 (2H, br s), 5.87 (2H, s), 6.49 (1H, br s), 6.66 (3H, s). *Anal.* Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.45; H, 6.47; N, 5.28.

(5*S,6*S**)-8-Methylene-6-(3,4-methylenedioxyphenyl)-1-[(methylthio)-acetyl]-1-azaspiro[4.4]nonane (10)** Red-Al (70% in toluene, 3.3 ml, 11 mmol) was added dropwise to a solution of **9** (500 mg. 1.84 mmol) in dry benzene (20 ml) and the mixture was heated under reflux overnight. Water (10 ml) was then added under ice-cooling to the mixture to destroy the excess reagent and the whole was made alkaline with saturated $NaHCO_3$ 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 ($MgSO_4$) and concentrated to give 8-methylene-6-(3,4-methylenedioxyphenyl)-1-azaspiro-[4.4]nonane (475 mg) as an oil, which was used immediately for the next stage.

(Methylthio)acetic acid (71 mg, 0.64 mmol) and DCC (136 mg, 0.64 mmol) were added to a solution of the above pyrrolidine derivative (150 mg, 0.58 mmol) in dry dichloromethane (6 ml) and the mixture was stirred at room temperature for 2 d. Precipitated dicyclohexylurea was filtered off, and the filtrate was concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 3 : 1) to give **10** (185 mg, 94%) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1635. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.4—1.9 (2H, m), 1.9—3.7 (9H, m), 2.16 (3H, s), 3.02 (2H, s), 4.7—5.0 (2H, m), 5.84 (2H, s), 6.6—6.8 (3H, m). Exact MS m/z: Calcd for $C_{19}H_{23}NO_3S$: 345.1396. Found: 345.1369.

Preparation and an Attempted Cyclization of 8-Methylene-6-(3,4-methylenedioxyphenyl)-1-[(methylsulfinyl)acetyl]-1-azaspiro[4.4]nonane (11) A solution of $NaIO_4$ (68 mg, 0.32 mmol) in water (3 ml) was added dropwise to an ice-cooled solution of the sulfide **10** (100 mg, 0.29 mmol) in methanol (1.0 ml) and the mixture was stirred at room temperature overnight. The precipitated inorganic material was filtered off and water (2 ml) was added. The aqueous layer was extracted with dichloromethane and the extract was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (CH_2Cl_2–MeOH, 10 : 1) to give **11** (111 mg, quant.) as an oil. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.5—4.0 (11H, m), 2.63 (3H, s), 2.70 (2H, s), 4.7—5.0 (2H, m), 5.88 (2H, s), 6.6—6.8 (3H, m). The crude sulfoxide **11** was treated with PTSA[8] to give a complex mixture.

(5*S,6*S**)-6-(3,4-Methylenedioxyphenyl)-1-azaspiro[4.4]nonane-2,8-dione (12)** A small amount of OsO_4 was added to a solution of **9** (435 mg, 1.60 mmol) in THF–H_2O (4 : 1) (12 ml) at 0 °C, and the mixture was stirred for 5 min. $NaIO_4$ (681 mg, 3.20 mmol) was added portionwise to the above mixture at room temperature over 30 min, and the whole was stirred for 1.5 h. The mixture was diluted with water (10 ml) and extracted with chloroform. The extract was dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 1 : 2) to give **12** (438 mg, quant.), mp 195—196 °C (from AcOEt). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750, 1695. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.8—2.4 (4H, m), 2.5—2.9 (4H, m), 3.33 (1H, t, J=9 Hz), 5.91 (2H, s), 6.72 (3H, s), 8.05 (1H, br s). *Anal.* Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.68; H, 5.54; N, 5.07.

(5*S,6*S**)-8,8-Ethylenedioxy-6-(3,4-methylenedioxyphenyl)-1-azaspiro[4.4]nonan-2-one (13)** A solution of **12** (402 mg, 1.47 mmol), eth-

ylene glycol (108 mg, 1.74 mmol), and PTSA (20 mg) in dichloromethane (60 ml) was refluxed with azeotropic removal of water for 3 h. The organic layer was washed with water, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 1 : 4) to give **13** (467 mg, quant.), mp 161—162 °C (from AcOEt). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1690. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.6—2.6 (8H, m), 3.14 (1H, dd, J= 10, 9 Hz), 3.92 (4H, s), 5.86 (2H, s), 6.6—6.8 (3H, m), 6.98 (1H, br s). *Anal.* Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.27; H, 6.18; N, 4.26.

(5*S,6*S**)-6-(3,4-Methylenedioxyphenyl)-1-[(methylthio)acetyl]-1-azaspiro[4.4]nonan-8-one Ethylene Acetal (14)** Using a procedure similar to that described for the preparation of **10**, compound **13** (234 mg, 0.74 mmol) was reduced with Red-Al (1.33 ml, 4.42 mmol), and the crude product was purified by chromatography on alumina (hexane–AcOEt, 5 : 1) to give 6-(3,4-methylenedioxyphenyl)-1-azaspiro[4.4]nonan-8-one ethylene acetal (208 mg, 90%) as an oil, which was used immediately in the next stage.

(Methylthio)acetic acid (120 mg, 1.09 mmol) and DCC (230 mg, 1.09 mmol) were added to a solution of the above pyrrolidine derivative (300 mg, 0.99 mmol) in dry dichloromethane (10 ml) and the mixture was stirred at room temperature for 2 d. Precipitated dicyclohexylurea was filtered off, the solvent was evaporated off, and the residue was chromatographed on silica gel (hexane–AcOEt, 1 : 1) to give **14** (380 mg, 98%) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1640. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.3—2.3 (6H, m), 2.04 (3H, s), 2.7—3.7 (5H, m), 2.94 (2H, s), 3.92 (4H, s), 5.85 (2H, s), 6.66 (2H, s), 6.80 (1H, s). Exact MS *m/z*: Calcd for $C_{20}H_{25}NO_5S$: 391.1452. Found: 391.1461.

(5*S,6*S**)-6-(3,4-Methylenedioxyphenyl)-1-[(methylthio)-acetyl]-1-azaspiro[4.4]nonan-8-one (15)** A solution of the acetal **14** (687 mg, 1.76 mmol) in AcOH (10 ml) and water (2 ml) was refluxed for 1 h. After the mixture had cooled, dichloromethane (10 ml) was added. The organic layer was separated, washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 1 : 3) to give **15** (560 mg, 92%), mp 94—96 °C (from AcOEt). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 1635. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.2—2.0 (2H, m), 2.0—2.5 (2H, m), 2.24 (3H, s), 2.5—3.8 (7H, m), 3.12 (2H, s), 5.88 (2H, s), 6.68 (3H, s). *Anal.* Calcd for $C_{18}H_{21}NO_4S$: C, 62.23; H, 6.09; N, 4.03. Found: C, 61.87; H, 6.34; N, 3.95.

Preparation and an Attempted Cyclization of 6-(3,4-Methylenedioxyphenyl)-1-[(methylsulfinyl)acetyl]-1-azaspiro[4.4]nonan-8-one (16) By means of a procedure similar to that described for the preparation of **11**, the sulfide **15** (400 mg, 1.15 mmol) was oxidized with $NaIO_4$ (272 mg, 1.27 mmol) and work-up gave the sulfoxide **16** (420 mg, quant.), mp 201—203 °C (from acetone). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1745, 1640. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.3—1.9 (2H, m), 2.0—4.0 (11H, m), 2.72 (3H, s), 5.91 (2H, s), 6.73 (3H, s). *Anal.* Calcd for $C_{18}H_{21}NO_5S \cdot 1/2H_2O$: C, 58.05; H, 5.95; N, 3.76. Found: C, 58.45; H, 6.02; N, 3.87.

The sulfoxide **16** was treated with either TFAA or PTSA to give a complex mixture.

(5*S,6*S**,8*S**)-6-(3,4-Methylenedioxyphenyl)-1-[(methylthio)acetyl]-1-azaspiro[4.4]nonan-8-ol (17)** $NaBH_4$ (131 mg, 3.46 mmol) was added portionwise to a solution of the ketone **16** (400 mg, 1.15 mmol) in ethanol (25 ml) and the mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with water (10 ml) and extracted with dichloromethane. The extract was dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 1 : 3) to give **17** (401 mg, quant.), mp 102—103 °C (from AcOEt). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 1630. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.2—1.8 (2H, m), 1.9—3.3 (8H, m), 2.23 (3H, s), 3.14 (2H, s), 3.55 (1H, dd, J=10, 8 Hz), 4.0—4.6 (2H, br), 5.86 (2H, s), 6.6—6.8 (3H, m). *Anal.* Calcd for $C_{18}H_{23}NO_4S$: C, 61.87; H, 6.63; N, 4.01. Found: C, 61.57; H, 6.71; N, 3.93.

(5*S,6*S**,8*S**)-8-Acetoxy-6-(3,4-methylenedioxyphenyl)-1-[(methylthio)acetyl]-1-azaspiro[4.4]nonane (18)** Acetic anhydride (0.21 ml, 2.42 mmol) was added dropwise to a solution of the alcohol **17** (420 mg, 1.20 mmol) in pyridine (4 ml) at 0 °C and the mixture was stirred overnight at room temperature. Pyridine was removed *in vacuo* and the residue was dissolved in dichloromethane. The solution was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatoraphed on silica gel (hexane–AcOEt, 1 : 1) to give **18** (433 mg, 92%), mp 91—92 °C (from hexane–Et_2O). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730, 1640. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.5—2.5 (6H, m), 2.06 (6H, s), 2.5—3.8 (5H, m), 2.96 (2H, s), 4.8—5.3 (1H, m), 5.90 (2H, s), 6.75 (2H, s), 6.89 (1H, s). *Anal.* Calcd for $C_{20}H_{25}NO_5S$: C, 61.36; H, 6.44; N, 3.58. Found: C, 61.08; H, 6.73; N, 3.49.

(5*S,6*S**,8*S**)-8-Acetoxy-6-(3,4-methylenedioxyphenyl)-1-[(methylsulfinyl)acetyl]-1-azaspiro[4.4]nonane (19)** By means of a procedure similar to that described for the preparation of **11**, the sulfide **18** (370 mg, 0.95 mmol) was oxidized with $NaIO_4$ (222 mg, 1.04 mmol) and work-up gave **19** (380 mg, quant.), mp 172—174 °C (from AcOEt). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730, 1640. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.6—2.4 (6H, m), 2.04 (3H, s), 2.49 (3H, s), 2.63 (2H, s), 2.7—4.0 (7H, m), 4.7—5.3 (1H, m), 5.87 (2H, s), 6.6—6.8 (3H, m). *Anal.* Calcd for $C_{20}H_{25}NO_6S \cdot 1/2H_2O$: C, 57.68; C, 6.29; N, 3.36. Found: C, 57.71; H, 6.43; N, 3.20.

(2*S,3a*S**,9*S**,14b*S**)-2-Acetoxy-1,2,3,5,6,8,9,14b-octahydro-9-methylthio-4*H*-cyclopenta[*a*]-1,3-dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]benzazepin-8-one (20)** Procedure A: TFAA (1.00 ml, 3.19 mmol) was added dropwise to a solution of the sulfoxide **19** (1.30 g, 3.19 mmol) in dry dichloromethane (30 ml) at 0 °C under a nitrogen atmosphere and the mixture was stirred at room temperature for 24 h. Dichloromethane (30 ml) was added and the whole mixture was washed with saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 2 : 1) to give **20** (1.08 g, 85%), whose ^{1}H-NMR (300 MHz) spectrum showed the presence of a small amount of the diastereoisomer. However, recrystallization from ethanol gave a pure sample of **20**, mp 217—220 °C. IR ν_{max}^{KBr} cm^{-1}: 1735, 1650. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.72—1.92 (3H, m), 1.95 (1H, dt, J=10.7, 12.7 Hz), 2.06 (3H, s, SMe or OCOMe), 2.08 (3H, s, OCOMe or SMe), 2.02—2.19 (2H, m), 2.38—2.58 (2H, m), 3.12—3.23 (1H, m, one of 6-H), 3.24 (1H, dd, J=12.9, 8.1 Hz, 14b-H), 3.62—3.72 (1H, m, one of 6-H), 4.92—5.05 (1H, m, 2-H), 4.99 (1H, s, 9-H), 5.94, 5.97 (1H each, ABq, J=1.3 Hz, 12-H), 6.60 (1H, s, arom. H), 7.52 (1H, s, arom. H). ^{13}C-NMR ($CDCl_3$) δ: 14.2 (SCH_3), 21.1 ($COCH_3$), 21.2, 39.2, 44.6, 44.7, 47.5, 50.4 (9-C), 53.5 (14b-C), 67.9 (3b-C), 69.9 (2-C), 101.3 (12-C), 107.5, 111.4, 127.9, 130.5, 147.0, 147.7, 167.7 (8-C), 170.8. *Anal.* Calcd for $C_{20}H_{23}NO_5S$: C, 61.68; H, 5.95; N, 3.60. Found: C, 61.72; H, 6.30; N, 3.50.

Procedure B: A solution of PTSA monohydrate (466 mg, 2.45 mmol) in 1,2-dichloroethane (100 ml) was heated under reflux with azeotropic removal of water for 2 h, then cooled under a nitrogen atmosphere. A solution of the sulfoxide **19** (200 mg, 0.49 mmol) was added to the above solution containing anhydrous PTSA, and the mixture was heated again under reflux with azeotropic removal of water for 10 min. The reaction mixture was washed with saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel to give **20** (147 mg, 77%), mp 217—220 °C (from EtOH).

X-Ray Analysis of 20 Crystal Data: $C_{20}H_{23}NO_5S$, triclinic, space group $P\bar{1}$; a=10.070(5) Å, b=10.478(6) Å, c=9.713(5) Å, α=111.49(4)°, β=96.93(4)°, γ=92.61(5), V=942.2 Å^3, Z=2, D_C=1.373 g/cm^3 and $\mu(CuK_\alpha)$=17.52 cm^{-1}.

Data Collection: A crystal was mounted on a Rigaku AFC5S diffractometer with graphite-monochromated CuK_α radiation. The cell dimensions were refined by the least-squares method using 25 reflections. Intensity data were collected using the ω–2θ scan technique to a maximum 2θ value of 50°. Of 1827 independent reflections collected, 1681 reflections with $I > 3\sigma(I)$ were used for the structure determination and refinement. Data were corrected for Lorenz and polarization factors.

Structure Determination and Refinement: The structure was solved by the direct method using the TEXSAN program.[13] The positional co-

TABLE I. Bond Lengths of Non-H Atoms with e.s.d.'s in Parentheses

Atom	Atom	Distance (Å)	Atom	Atom	Distance (Å)
S21	C13	1.816 (6)	C3	C4	1.500 (7)
S21	C22	1.805 (8)	C3	C20	1.534 (8)
O1	C14	1.240 (6)	C4	C5	1.399 (7)
O2	C19	1.452 (7)	C4	C12	1.405 (7)
O2	C23	1.328 (7)	C5	C6	1.363 (7)
O3	C23	1.184 (7)	C6	C10	1.373 (7)
O7	C6	1.368 (6)	C10	C11	1.350 (7)
O7	C8	1.445 (8)	C11	C12	1.398 (7)
O9	C8	1.407 (8)	C12	C13	1.514 (8)
O9	C10	1.371 (6)	C13	C14	1.519 (8)
N1	C2	1.498 (6)	C15	C16	1.515 (8)
N1	C14	1.331 (7)	C16	C17	1.509 (8)
N1	C15	1.477 (7)	C18	C19	1.526 (8)
C2	C3	1.576 (7)	C19	C20	1.504 (8)
C2	C17	1.541 (8)	C23	C24	1.49 (1)
C2	C18	1.514 (8)			

TABLE II. Bond Angles of Non-H Atoms with e.s.d.'s in Parentheses

Atom	Atom	Atom	Angle (°)	Atom	Atom	Atom	Angle (°)
C13	S21	C22	97.8 (4)	O9	C10	C6	109.7 (5)
C19	O2	C23	117.5 (5)	O9	C10	C11	128.4 (5)
C6	O7	C8	105.5 (5)	C6	C10	C11	121.8 (5)
C8	O9	C10	106.6 (5)	C10	C11	C12	118.1 (5)
C2	N1	C14	128.2 (5)	C4	C12	C11	120.8 (5)
C2	N1	C15	111.9 (4)	C4	C12	C13	117.5 (5)
C14	N1	C15	119.7 (4)	C11	C12	C13	121.4 (5)
N1	C2	C3	115.6 (4)	S21	C13	C12	116.5 (4)
N1	C2	C17	99.9 (4)	S21	C13	C14	109.2 (4)
N1	C2	C18	111.4 (4)	C12	C13	C14	106.6 (5)
C3	C2	C17	110.8 (5)	O1	C14	N1	122.8 (5)
C3	C2	C18	105.8 (4)	O1	C14	C13	121.5 (5)
C17	C2	C18	113.5 (5)	N1	C14	C13	115.7 (5)
C2	C3	C4	118.6 (4)	N1	C15	C16	104.4 (5)
C2	C3	C20	106.0 (5)	C15	C16	C17	102.8 (5)
C4	C3	C20	112.9 (4)	C2	C17	C16	105.0 (5)
C3	C4	C5	120.0 (5)	C2	C18	C19	108.5 (5)
C3	C4	C12	120.8 (5)	O2	C19	C18	110.6 (5)
C5	C4	C12	119.1 (5)	O2	C19	C20	107.3 (5)
C4	C5	C6	118.6 (5)	C18	C19	C20	105.6 (5)
O7	C6	C5	128.3 (5)	C3	C20	C19	107.6 (5)
O7	C6	C10	110.0 (5)	O2	C23	O3	123.9 (6)
C5	C6	C10	121.6 (5)	O2	C23	C24	111.5 (7)
O7	C8	O9	107.8 (5)	O3	C23	C24	124.6 (7)

TABLE III. Fractional Atomic Coordinates and Equivalent Isotropic Thermal Parameters of Non-H Atoms with e.s.d.'s in Parentheses

Atom	x	y	z	B_{eq}
S(21)	0.9298 (1)	0.0500 (1)	0.1948 (1)	4.25 (6)
O(1)	0.7808 (4)	−0.1091 (3)	0.3232 (4)	4.7 (2)
O(2)	1.0710 (4)	0.4244 (3)	0.6982 (4)	4.2 (2)
O(3)	1.1642 (4)	0.4622 (5)	0.9304 (5)	6.8 (2)
O(7)	0.3467 (4)	0.3152 (4)	0.1946 (4)	5.0 (2)
O(9)	0.4522 (4)	0.1831 (4)	0.0004 (4)	5.0 (2)
N(1)	0.7492 (4)	0.0616 (4)	0.5367 (4)	3.6 (2)
C(2)	0.7631 (5)	0.2067 (4)	0.6482 (5)	3.3 (2)
C(3)	0.7151 (5)	0.3182 (4)	0.5848 (5)	3.1 (2)
C(4)	0.6451 (5)	0.2705 (4)	0.4267 (5)	2.8 (2)
C(5)	0.5211 (5)	0.3169 (5)	0.3957 (6)	3.4 (2)
C(6)	0.4652 (5)	0.2808 (4)	0.2500 (6)	3.1 (2)
C(8)	0.3413 (8)	0.2598 (9)	0.0340 (7)	6.0 (3)
C(10)	0.5284 (5)	0.2022 (5)	0.1345 (5)	3.1 (2)
C(11)	0.6459 (5)	0.1515 (5)	0.1592 (5)	3.3 (2)
C(12)	0.7066 (5)	0.1870 (4)	0.3072 (5)	2.7 (2)
C(13)	0.8322 (6)	0.1252 (5)	0.3453 (6)	4.0 (2)
C(14)	0.7875 (5)	0.0153 (5)	0.4019 (6)	3.4 (2)
C(15)	0.6953 (7)	−0.0373 (6)	0.5971 (6)	4.6 (3)
C(16)	0.6897 (8)	0.0488 (5)	0.7597 (6)	4.7 (3)
C(17)	0.6708 (7)	0.1900 (6)	0.7572 (6)	4.1 (2)
C(18)	0.9078 (6)	0.2547 (5)	0.7199 (6)	4,2 (2)
C(19)	0.9377 (6)	0.4033 (5)	0.7338 (6)	3.5 (2)
C(20)	0.8381 (6)	0.4219 (5)	0.6158 (6)	3.7 (2)
C(22)	0.996 (1)	0.2083 (8)	0.183 (1)	6.5 (4)
C(23)	1.1747 (6)	0.4469 (5)	0.8053 (8)	4.2 (3)
C(24)	1.3051 (8)	0.447 (1)	0.747 (1)	6.3 (4)

$B_{eq} = (8/3)\pi^2 \Sigma_i \Sigma_j U_{ij} a_i^* a_j^* a_i a_j$.

ordinates were refined by the full-matrix least-squares method using anisotropic temperature factors for all the non-hydrogen atoms and isotopic ones for hydrogen atoms. The final refinement converged to $R = 0.06$ and $R_W = 0.08$. The atomic scattering factors were taken from ref. 14. Bond lengths and bond angles are listed in Tables I and II, respectively. Atomic coordinates for non-hydrogen atoms are given in Table III.

(2*S,3a*S**,14b*S**)-2-Acetoxy-1,2,3,5,6,8,9,14b-octahydro-4*H*-cyclopenta[*a*]-1,3-dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]benzazepin-8-one (21)** A mixture of the sulfide **20** (1.08 g, 2.77 mmol) and Raney nickel (W-2) (*ca.* 10 g) in acetone (20 ml) was refluxed for 1 h. The Raney nickel was removed by filtration and the solvent was evaporated off. The residue was chromatographed on silica gel (hexane–AcOEt, 2:1) to give **21** (0.95 g, quant.), mp 188—189 °C (from EtOH). IR ν_{max}^{KBr} cm^{-1}: 1735, 1650. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.6—2.8 (8H, m), 2.04 (3H, s), 3.0—3.8 (3H, m), 3.28, 3.90 (1H, each, ABq, J = 14 Hz), 4.6—5.2 (1H, m), 5.86 (2H, s), 6.52 (1H, s), 6.73 (1H, s). *Anal.* Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.05; H, 5.94; N, 3.94.

(3a*S,14b*S**)-1,2,3,5,6,8,9,14b-Octahydro-4*H*-cyclopenta[*a*]-1,3-dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]benzazepin-2,8-dione (4)** K_2CO_3 (834 mg, 5.58 mmol) was added to a solution of the acetate **21** (1.20 g, 3.49 mmol) in dichloromethane (6 ml) and methanol (50 ml) and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with dichloromethane (100 ml), washed with brine, dried ($MgSO_4$), and concentrated to give the alcohol (1.04 g), which was used for the next reaction without further purification.

A solution of dimethyl sulfoxide (4.85 ml, 69.0 mmol) in dichloromethane (20 ml) was added to a solution of oxalyl chloride (2.86 ml, 34.5 mmol) in dry dichloromethane (20 ml) at −60 °C over the period of 10 min. A solution of the alcohol (1.04 g, 3.45 mmol) obtained above in dry dichloromethane (30 ml) and dimethyl sulfoxide (5 ml) was added and the whole mixture was stirred at the same temperature for 40 min. Triethylamine (24.2 ml, 172.5 mmol) was then added and the mixture was allowed to warm to room temperature. After 60 min, water (5 ml) was added and the organic layer was separated and washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (AcOEt) to give **4** (0.86 g, 83%), mp 189—190 °C (from AcOEt) (lit.[6c] mp 188—189 °C). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1745, 1635. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.71—1.95 (2H, m, 5-H), 2.07—2.14 (2H, m, 4-H), 2.58 (1H, dd, J = 19.0, 1.5 Hz, one of 3-H), 2.70 (1H, ddd, J = 19.5, 9.8, 2.2 Hz, one of 1-H), 2.86 (1H, dd, J = 19.0, 2.0 Hz, one of 3-H), 2.89 (1H, ddd, J = 19.5, 10.7, 1.5 Hz, one of 1-H), 3.34 (1H, d, J = 14.4 Hz, one of 9-H), 3.38—3.44 (1H, m, one of 6-H), 3.64 (1H, ddd, J = 11.5, 9.5, 2.1 Hz, one of 6-H), 3.70 (1H, d, J = 14.4 Hz, one of 9-H), 3.76 (1H, t, J = 10.3 Hz, 14b-H), 5.94, 5.95 (1H each, ABq, J = 1.4 Hz, 12-H), 6.65 (1H, s, arom. H), 6.80 (arom. H). ^{13}C-NMR ($CDCl_3$) δ: 20.6, 42.0, 44.7, 46.2, 47.0, 48.6 (14b-C), 52.3, 67.6 (3a-C), 101.3 (12-C), 110.7, 111.0, 126.9, 130.5, 147.0, 147.1, 169.1 (8-C), 213.5 (2-C).

(1*S,3a*S**,14b*S**)-1,2,3,5,6,8,9,14b-Octahydro-1-hydroxy-2,2-dimethoxy-4*H*-cyclopenta[*a*]-1,3-dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]benzazepin-8-one (22)** $PhI(OAc)_2$ (416 mg, 1.29 mmol) and a solution of KOH (197 mg, 3.51 mmol) in absolute methanol (5 ml) were added to a solution of **4** (350 mg, 1.17 mmol) in absolute methanol (25 ml) at 0 °C under a nitrogen atmosphere, and the mixture was stirred at 0 °C for 3 h. Methanol was evaporated off, and the residue was dissolved in dichloromethane (20 ml). The solution was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (AcOEt) to give **22** (331 mg, 78%) as colorless crystals, mp 205—206 °C (from isopropanol)(lit.[6c] mp 210—211 °C). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580, 1625. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.65—1.89 (4H, m, 4-, 5-H), 2.23 (1H, dd, J = 13.7, 1.0 Hz, one of 3-H), 2.30 (1H, br d, J = 13.7 Hz, one of 3-H), 2.33—2.44 (1H, m, OH), 3.08 (1H, d, J = 13.7 Hz, one of 9-H), 3.18—3.35 (1H, m, one of 6-H), 3.30 (3H, s, OMe), 3.35 (3H, s, OMe), 3.45 (1H, d, J = 5.7 Hz, 14b-H), 3.59—3.69 (1H, m, one of 6-H), 4.11 (1H, dd, J = 5.7, 1.2 Hz, 1-H), 4.76 (1H, d, J = 13.7 Hz, one of 9-H), 5.92 (2H, s, 12-H), 6.62 (1H, s, arom. H), 6.78 (1H, s, arom. H). ^{13}C-NMR ($CDCl_3$) δ: 20.4, 42.1, 42.3, 43.8, 47.4, 48.7 (OCH_3), 50.4 (OCH_3), 55.9 (14b-C), 64.4 (1-C), 68.1 (3a-C), 101.1 (12-C), 106.5 (2-C), 110.4, 111.9, 126.2, 130.9, 146.6, 147.1, 170.8 (8-C).

(1*S,3a*S**,14b*S**)-1,2,3,5,6,8,9,14b-Octahydro-1-hydroxy-2,2-dimethoxy-4*H*-cyclopenta[*a*]-1,3-dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]benzazepine (23)** Using a procedure similar to that described for the preparation of **10**, **22** (240 mg, 0.66 mmol) was reduced with Red-Al (70% in toluene, 1.20 ml, 3.98 mmol), and the crude product was chromatographed on alumina (hexane–AcOEt, 2:1) to give **23** (190 mg, 83%) as colorless crystals, mp 150—151 °C (from AcOEt) (lit.[6c] mp 150—151.5 °C). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.60—1.81 (4H, m, 4-, 5-H), 2.03—2.25 (3H, m, 3-H, OH), 2.40 (1H, dd, J = 14.9, 5.9 Hz, 9α-H). 2 42—2.55 (1H, m, 6β- or 8β-H), 2.58—2.71 (1H, m, 8β- or 6β-H), 2.99 (1H, dt, J = 6.8, 12.0 Hz, 8α-H), 3.01—3.12 (1H, m, 6α-H), 3.29 (3H, s, OMe), 3.36 (3H, s, OMe), 3.41 (1H, d, J = 6.3 Hz, 14b-H), 3.91 (1H, ddd, J = 14.4, 12.7, 7.6 Hz, 9β-H), 4.09 (1H, dd, J = 6.3, 1.0 Hz, 1-H), 5.89 (2H, s, 12-H), 6.63 (1H, s, arom. H), 6.68 (1H, s, arom. H).

(±)-Cephalotaxine (1) PTSA monohydrate (33 mg, 0.173 mmol) was added to a solution of **23** (60 mg, 0.173 mmol) in dry THF (6 ml) and the mixture was refluxed for 1.5 h. THF was evaporated off and the residue was dissolved in dichloromethane (30 ml). The solution was washed with saturated $NaHCO_3$ solution, dried (Na_2SO_4), and concentrated. The residue was chromatographed on alumina (hexane–AcOEt, 1 : 1) to give **1** (46 mg, 85%), mp 122—124 °C (from AcOEt) (lit.[6e] mp 122—124 °C). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3625, 1650. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.64—1.80 (3H, m, 7-H, OH), 1.87 (1H, ddd, J=12.1, 7.6, 4.2 Hz, one of 6-H), 2.01 (1H, dt, J=12.1, 9.5 Hz, one of 6-H), 2.35 (1H, dd, J=14.3, 6.8 Hz, 11α-H), 2.53—2.64 (2H, m, 8β-, 10β-H), 2.92 (1H, dt, J=6.8, 12.1 Hz, 10α-H), 3.03—3.11 (1H, m, 8α-H), 3.35 (1H, ddd, J=14.3, 12.1, 7.9 Hz, 11β-H), 3.67 (1H, d, J=9.4 Hz, 4-H), 3.72 (3H, s, OMe), 4.76 (1H, dd, J=9.4, 3.1 Hz, 3-H), 4.92 (1H, s, 1-H), 5.90 (2H, s), 6.64 (1H, s, arom. H), 6.67 (1H, s, arom. H). ^{13}C-NMR ($CDCl_3$) δ: 20.3, 31.6, 43.6, 48.6, 53.9, 57.2 (OCH_3), 58.0 (4-C), 70.6 (5-C), 73.3 (3-C), 97.6 (1-C), 100.9 (14-C), 110.3, 112.6, 128.0, 134.3, 146.1, 146.9, 160.4 (2-C).

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