A Formal Total Synthesis of (−)-Cephalotaxine

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A formal total synthesis of (−)-cephalotaxine (1) has been achieved. The key step is an intramolecular aldol condensation of the diketone 9, which in turn was obtained in three steps from the azabicyclic compound 6 derived from D-proline according to Seebach's procedure. Treatment of 9 with a catalytic amount of sodium 2-methyl-2-butanolate in benzene at room temperature gave the α,β-unsaturated ketone 8 in 43% yield. Catalytic hydrogenation of 8 followed by reduction of the ketone 22 with sodium borohydride and acetylation of the resulting alcohol 23 gave the acetoxy derivative 24, which, after deprotection, was acylated with (methylthio)acetic acid to give the amide 26. Compound 26 was converted into optically active ketolactam 4 following the synthetic operations developed for the synthesis of the racemic compound.

Key words (−)-cephalotaxine; intramolecular aldol condensation; Pummerer reaction; Friedel–Crafts alkylation; D-proline; intramolecular Heck reaction

Considerable attention has been directed toward the synthesis of cephalotaxine (**1**),[1] the major alkaloid of the *Cephalotaxus* species, because of its unique structural features and antileukemic activity of its ester derivatives, harringtonine (**2**) and homoharringtonine (**3**).[2] So far, eight total syntheses of (±)-**1** including ours have been reported[3] and the synthesis of (−)-**1** has recently been achieved by Mori's[4a] and Nagasaka's groups.[4b] As a part of our own efforts to synthesize this alkaloid in an optically active form,[5] we envisioned that the ketolactam **4**, which had already been converted into (±)-cephalotaxine using three additional steps by Hanaoka[3c] and us,[3f] would be obtainable in an optically active form starting from D-proline as shown in the retrosynthetic format (Chart 1): one involves an intramolecular Heck reaction of the enone **5** and the other utilizes an intramolecular aldol condensation of the diketone **9** as a key step. Here we wish to report a formal total synthesis of (−)-**1**.

Results and Discussion

In a previous paper we described that the racemic enone **10** undergoes an intramolecular Heck reaction to give the tetracyclic cephalotaxine skeleton **11** in good yield (Chart 2).[6] As an extension of this reaction, we examined the intramolecular Heck reaction of the optically active azaspiro[4.4]nonenone **5**, which was prepared as illustrated in Chart 3. The azabicyclic compound **6**, prepared from D-proline according to Seebach's procedure,[7] was hydrolyzed with 10% sulfuric acid followed by protection with di-*tert*-butyl dicarbonate [$(Boc)_2O$] and esterification with trimethylsilyldiazomethane ($TMSCHN_2$) to give the methyl ester **12**. Following the same procedure as used in the preliminary work,[6] the ester **12** was converted into the azaspiroenone **13** in 26% overall yield. The mixed anhydride **18** was prepared from iodo-3,4-methylenedioxybenzene (**15**)[8] in 4 steps: 1) Friedel–Crafts alkylation of **15** with ethyl α-methylthio-α-chloroacetate in the presence of tin(IV) chloride,[9] 2) desulfurization of the sulfide **16** with zinc in acetic acid, 3) hydrolysis of the

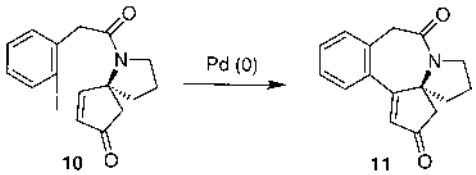

Chart 2

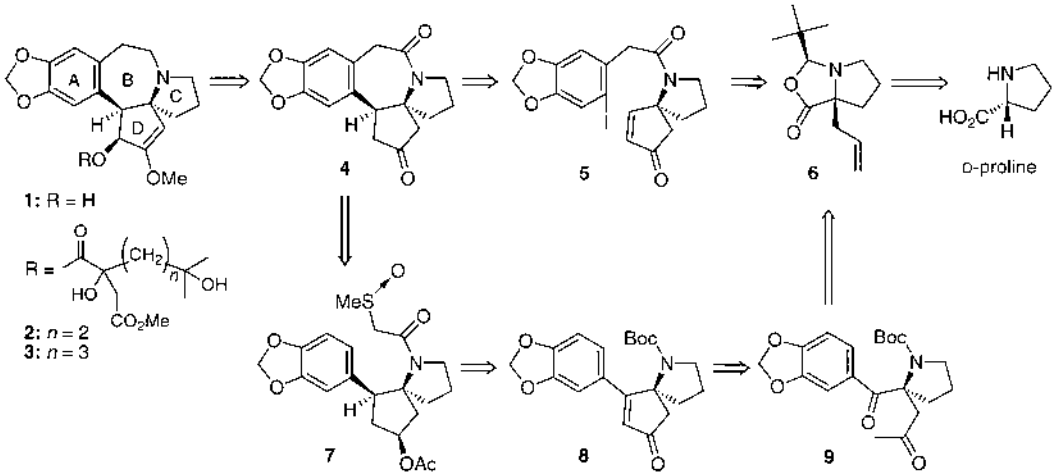

Chart 1

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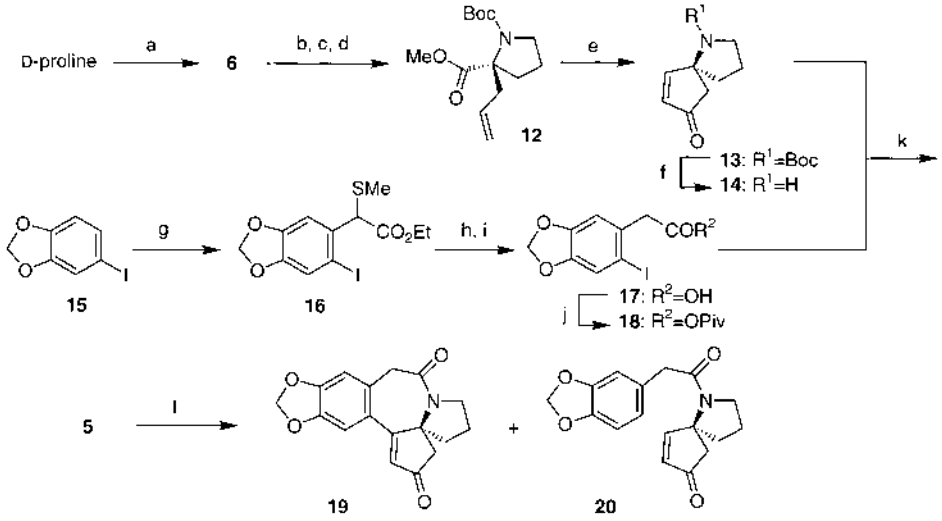
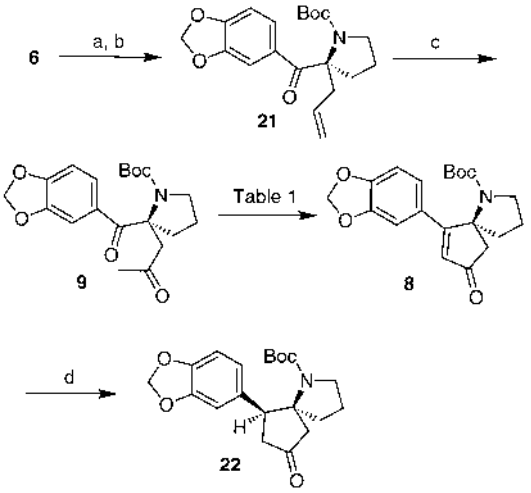


a) ref. 7; b) 10% H_2SO_4; c) $(Boc)_2O$, NaOH, 1,4-dioxane; d) $TMSCHN_2$, MeOH; e) ref. 6; f) CF_3CO_2H, CH_2Cl_2; g) ethyl α-methylthio-α-chloroacetate, $SnCl_4$, CH_2Cl_2; h) Zn, AcOH; i) LiOH, THF–H_2O; j) pivaloyl chloride, Et_3N, Et_2O; k) Et_3N, DMAP, CH_2Cl_2; l) $Pd(OAc)_2$, DPPP, Bu_3P, Ag_2CO_3, DMF

Chart 3



a) 3,4-methylenedioxyphenyllithium, THF; b) $(Boc)_2O$, MeCN; c) O_2, $PdCl_2$ (cat.), CuCl, DMF–H_2O; d) H_2, PtO_2, EtOH

Chart 4

ester with lithium hydroxide, and 4) treatment of the resulting carboxylic acid **17** with pivaloyl chloride. Deprotection of **13** with trifluoroacetic acid (TFA), followed by acylation of the resulting amine **14** with the mixed anhydride **18** gave **5** in 73% yield from **13**.

Compound **5**, when treated with palladium(II) acetate [$Pd(OAc)_2$], 1,3-bis(diphenylphosphino)propane (DPPP), tributylphosphine, and silver carbonate (Ag_2CO_3) in refluxing *N*,*N*-dimethylformamide (DMF) for 3 h,[6,10] gave the cyclized enone **19** and the reduction product **20**[11] but in only 7 and 4% yields, respectively. The structure of **19** was confirmed by a comparison of the spectroscopic data with those of **11**. Although the reason why **5** gave a low yield of **19** is not clear, we discontinued further pursuance of this route.

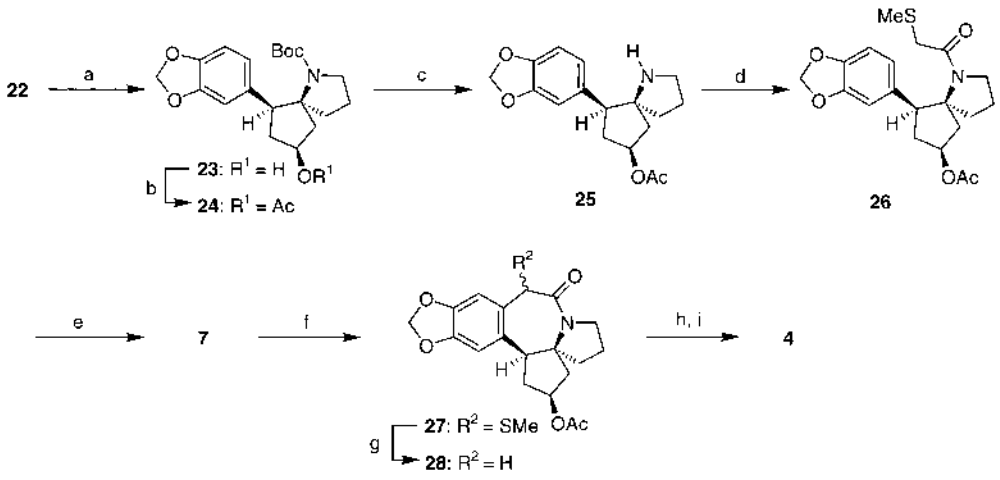
We then investigated a second route which involves an intramolecular aldol condensation of the diketone **9**, which was prepared as shown in Chart 4. Thus, the compound **6** was treated with 3,4-methylenedioxyphenyllithium in tetrahydrofuran (THF) to give the oily aminoketone which was protected with *tert*-butyloxycarbonyl (Boc) group to afford the *N*-Boc derivative **21** in 85% overall yield from **6**. Wacker oxidation of **21** gave the diketone **9** as an oil in 67% yield.

Table 1. Intramolecular Aldol Condensation of **9**

Entry	Conditions	Yield (%) of **8**
1	NaH, 2-methyl-2-butanol, benzene, r.t., 3 h	43
2	*tert*-BuOK, benzene, reflux, 8 h	15
3	*tert*-BuOK, *tert*-BuOH, reflux, 5 h	0
4	EtONa, EtOH, reflux, 3 h	0
5	KOH, MeOH–H_2O, reflux 1 h	0

Considerable difficulty was encountered, however, in finding conditions suitable for the base catalyzed aldol condensation of **9**. The results are shown in Table 1. Among the conditions examined, the most effective was the use of a catalytic amount of sodium 2-methyl-2-butanolate[12] in benzene at room temperature for 3 h to give the desired α,β-unsaturated ketone **8** in 43% yield. Catalytic hydrogenation of **8** over platinum(IV) oxide (PtO_2) gave the saturated ketone **22** as a single isomer in 84% yield, whose stereochemistry was assigned based on the assumption that hydrogen would come from the less hindered side of the double bond.

With the requisite spirobicyclic ketone **22** so assembled, we then examined the replacement of the *N*-Boc group into (methylthio)acetyl group. Since all attempts to convert **22** directly into the (methylthio)acetyl derivative were unsuccessful, an alternative procedure was investigated. Reduction of **22** with sodium borohydride ($NaBH_4$) proceeded in a highly stereoselective manner to give the (8*S*)-isomer **23** in quantitative yield as an essentially single isomer, as a result of attack of hydride ion from the less hindered *Re*-face. Acetylation of **23** gave the acetoxy derivative **24**, which was treated with TFA to give the amine **25**. Treatment of **25** with (methylthio)acetic acid in the presence of dicyclohexylcarbodiimide



a) $NaBH_4$, EtOH; b) Ac_2O, pyridine; c) CF_3CO_2H, CH_2Cl_2; d) $MeSCH_2CO_2H$, DCC, CH_2Cl_2; e) $NaIO_4$, MeOH–H_2O; f) TFAA, CH_2Cl_2; g) Ra-Ni, acetone; h) K_2CO_3, CH_2Cl_2–MeOH; i) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2

Chart 5

(DCC) in dichloromethane (CH_2Cl_2) gave, in 83% yield from **24**, the amide **26**, which had spectral characteristics identical with those of an authentic racemic sample.[3f] Following the synthetic operations developed for the synthesis of racemic cephalotaxine,[3f] **26** was converted into the ketolactam **4**. Thus, the Pummerer reaction of the sulfoxide **7** derived from **26**, followed by desulfurization of the resulting cyclized product **27** with Raney nickel, hydrolysis of the acetate **28** with potassium carbonate (K_2CO_3) in CH_2Cl_2–methanol (MeOH), and Swern oxidation of the resulting alcohol gave the optically active ketolactam **4**, which was identical with an authentic sample in the spectroscopic data. The HPLC analysis using a chiral column showed that the optical purity of thus obtained ketolactam **4** was 88% ee. This constitutes the formal total synthesis of (−)-cephalotaxine (**1**).

Experimental

Melting points are uncorrected. ^{1}H-NMR spectra were determined with a JEOL JNM-MY 60 (60 MHz) or a Varian XL-300 (300 MHz) spectrometer, using $CDCl_3$ as a solvent and tetramethylsilane as an internal standard. High resolution MS were determined with a JEOL JMS-SX 102A spectrometer. Optical rotations were measured with a JASCO DIP-360 polarimeter. Column chromatography was performed on Silica gel 60 PF254 (Nacalai Tesque, Inc.) under pressure.

***tert*-Butyl (*S*)-2-Methoxycarbonyl-2-(prop-2-enyl)pyrrolidine-1-carboxylate (12)** After a mixture of (2*S*,5*S*)-2-*tert*-butyl-5-(prop-2-enyl)-1-aza-3-oxabicyclo[3.3.0]octan-4-one (**6**)[7] {$[\alpha]_D^{24}$ −16.6 (*c*=3.62, $CHCl_3$), lit.[7] $[\alpha]_D^{25}$ −13.1 (*c*=1.8, $CHCl_3$), 2.5 g, 11.25 mmol} and 10% sulfuric acid (100 ml) was stirred for 24 h, sodium hydroxide (13.5 g), 1,4-dioxane (100 ml), and $(Boc)_2O$ (12.3 g, 56.3 mmol) were added to the cooled mixture at 0 °C. The resultant mixture was stirred at room temperature for a further 24 h. The reaction mixture was acidified by 10% hydrochloric acid (HCl) and extracted with ethyl acetate (AcOEt), the extract was dried ($MgSO_4$), and concentrated. The residue was dissolved in MeOH (75 ml), $TMSCHN_2$ (2.0 M in hexane, 27.5 ml, 56.3 mmol) was added to this solution at 0 °C. After the reaction was completed, the mixture was concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 20 : 1) to give **12** (2.389 g, 79% from **6**) as an oil, whose spectroscopic data were identical with a racemic authentic sample.[6] $[\alpha]_D^{24}$ −41.3 (*c*=0.94, $CHCl_3$).

***tert*-Butyl (*S*)-7-Oxo-1-azaspiro[4.4]non-8-ene-1-carboxylate (13)** According to the procedure for the preparation for a racemic **13**,[6] **13** was obtained in 26% yield from **12** in 4 steps as colorless crystals, mp 76—77 °C (from hexane). $[\alpha]_D^{24}$ −85.7 (*c*=0.99, $CHCl_3$).

Ethyl (6-Iodo-3,4-methylenedioxyphenyl)-α-(methylthio)acetate (16) Tin(IV) chloride (313 mg, 4.76 mmol) was added to a solution of **15**[8] (1.18 g, 4.76 mmol) and ethyl α-methylthio-α-chloroacetate (802 mg, 4.76 mmol) in CH_2Cl_2 (25 ml) at 0 °C under a nitrogen atmosphere. After the mixture was stirred for 15 min, water (H_2O) was added. The entire mixture was extracted with CH_2Cl_2, the extract was dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 30 : 1) to give **16** (1.70 g, 94%) as an oil. IR (CCl_4) cm^{-1}: 1735. ^{1}H-NMR (60 MHz) δ: 1.27 (3H, t, *J*=7.0 Hz, $OCH_2C\underline{H}_3$), 2.13 (3H, s, SCH_3), 4.20 (2H, q, *J*=7.0 Hz, $OC\underline{H}_2CH_3$), 4.93 (1H, s, $C\underline{H}SCH_3$), 5.98 (2H, s, OCH_2O), 7.23 (2H, s, ArH). Exact MS *m/z*: 379.9575 (Calcd for $C_{12}H_{13}IO_4S$: 379.9579).

(6-Iodo-3,4-methylenedioxyphenyl)acetic Acid (17) A suspension of **16** (1.39 g, 7.29 mmol) and zinc powder (477 mg, 7.29 mmol) in acetic acid (2 ml) was stirred at reflux for 3 h. The precipitate was filtered off and the filtrate was concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 50 : 1) to give ethyl (6-iodo-3,4-methylenedioxyphenyl)acetate (609 mg, 50%) as colorless crystals, mp 56—57 °C (from hexane). A mixture of thus obtained ester (200 mg, 0.60 mmol) and lithium hydroxide monohydrate (101 mg, 2.40 mmol) in THF–H_2O (1 : 1, 2 ml) was stirred at room temperature overnight. The mixture was acidified with 10% HCl and extracted with diethyl ether (Et_2O). The extract was dried ($MgSO_4$) and concentrated. The residue was recrystallized from AcOEt to give **17** (181 mg, 99%) as colorless crystals, mp 180—181 °C. IR (KBr) cm^{-1}: 3200—2800, 1700. ^{1}H-NMR (60 MHz) δ: 4.80 (2H, s, $C\underline{H}_2CO_2H$), 5.90 (2H, s, OCH_2O), 6.80 (1H, s, ArH), 7.18 (1H, s, ArH). *Anal.* Calcd for $C_9H_7IO_4$: C, 35.32; H, 2.31. Found: C, 35.60; H, 2.40.

(6-Iodo-3,4-methylenedioxyphenyl)acetic Pivalic Anhydride (18) Pivaloyl chloride (177 mg, 1.47 mmol) and triethylamine (Et_3N) (148 mg, 1.47 mmol) was added to a solution of **17** (450 mg, 1.47 mmol) in Et_2O (25 ml) at −78 °C. The mixture was stirred at the same temperature for 45 min and then at 0 °C for 15 min. The precipitate was filtered off and the filtrate was concentrated to give crude **18** (421 mg, 73%). This material was used in the next step without further purification.

(*S*)-1-[2-(6-Iodo-3,4-methylenedioxyphenyl)acetyl]-1-azaspiro[4.4]non-8-en-7-one (5) TFA (2 ml) was added to a solution of **13** (434 mg, 1.83 mmol) in CH_2Cl_2 (2 ml) at 0 °C and the mixture was stirred at the same temperature for 30 min. The solvent was evaporated off and the residue was dissolved in CH_2Cl_2 (10 ml). 4-(*N*,*N*-Dimethylamino)pyridine (DMAP) (22 mg, 0.18 mmol), Et_3N (924 mg, 9.15 mmol), and a solution of **18** (1.07 g, 2.73 mmol) in CH_2Cl_2 (10 ml) were added successively at 0 °C, and the whole was stirred at room temperature overnight. After H_2O (6 ml) had been added to the reaction mixture, the organic layer was separated, washed with 5% HCl, sat. aq. $NaHCO_3$, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (AcOEt) to give **5** (568 mg, 73% from **13**) as colorless crystals, mp 155—156.5 °C (from AcOEt). $[\alpha]_{25}^{D}$ −77.5 (*c*=0.28, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 1710, 1640. ^{1}H-NMR (300 MHz) δ: 1.77—1.90 (1H, m), 2.05—2.16 (3H, m), 2.33, 3.04 (1H each, ABq, *J*=17.3 Hz, 6-H_2), 3.57—3.83 (2H, m, 2-H_2), 3.66 (2H, s, $ArCH_2CO$), 5.94 (2H, s, OCH_2O), 6.13 (1H, d, *J*=5.7 Hz, 8-H), 6.79 (1H, s, ArH), 7.23 (1H, s, ArH), 7.59 (1H, d, *J*=5.6 Hz, 9-H). *Anal.* Calcd for $C_{17}H_{16}INO_4$: C, 48.02; H, 3.79; N, 3.29. Found: C, 48.06; H, 3.94; N, 3.01.

Intramolecular Heck Reaction of Compound 5 Ag_2CO_3 (32 mg, 0.48

mmol) was added to a solution of **5** (100 mg, 0.24 mmol), $Pd(OAc)_2$ (54 mg, 0.24 mmol), Bu_3P (49 mg, 0.24 mmol), DPPP (99 mg, 0.24 mmol) in DMF (8 ml) and the mixture was refluxed under an argon atmosphere for 3 h. The reaction mixture was filtered on celite and concentrated. The residue was chromatographed on silica gel (AcOEt) to give a mixture of (*S*)-2,3,5,6,8,9-hexahydro-4*H*-cyclopenta[*a*]-1,3-dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]benzazepine-2,8-dione (**19**) and (*S*)-1-[2-(3,4-methylenedioxyphenyl)acetyl]-1-azaspiro[4.4]non-8-en-7-one (**20**). This mixture was separated by a preparative HPLC using a YMC ODS-AQ300 column (20×250 mm) which was eluted with a linear gradient of acetonitrile (30—70%, 30 min) in 0.09% aq. TFA at a flow rate of 5.0 ml/min. The first fraction gave **19** (5 mg, 7%) as an oil. IR (CCl_4) cm^{-1}: 1710, 1630. ^{1}H-NMR (300 MHz) δ: 1.55—1.80 (2H, m), 1.92—2.11 (2H, m), 2.77 (2H, s, 3-H_2), 3.28, 3.71 (1H each, ABq, J=14.0 Hz, 9-H_2), 3.38—3.53 (1H, m, one of 6-H_2), 3.62—3.83 (1H, m, one of 6-H_2), 6.01, 6.02 (1H each, ABq, J=1.4 Hz, OCH_2O), 6.10 (1H, s, 1-H), 6.79 (1H, s, ArH), 6.82 (1H, s, ArH). Exact MS *m/z*: 297.1005 (Calcd for $C_{17}H_{15}NO_4$: 297.1001). The second fraction gave **20** (3 mg, 4%) as an oil. IR (CCl_4) cm^{-1}: 1710, 1640. ^{1}H-NMR (300 MHz) δ: 1.73—1.86 (1H, m), 1.91—2.09 (3H, m), 2.30, 3.00 (1H each, ABq, J=17.3 Hz, 6-H_2), 3.51—3.62 (1H, m, one of 2-H_2), 3.54 (2H, s, $ArCH_2CO$), 3.64—3.72 (1H, m, one of 2-H_2), 5.94 (2H, s, OCH_2O), 6.14 (1H, d, J=5.6 Hz, 8-H), 6.64—6.69 (1H, m, ArH), 6.75 (2H, d, J=7.9 Hz, ArH), 7.40 (1H, d, J=5.6 Hz, 9-H). Exact MS *m/z*: 299.1157 (Calcd for $C_{17}H_{17}NO_4$: 299.1171).

(*R*)-2-(3,4-Methylenedioxybenzoyl)-2-(prop-2-enyl)pyrrolidine Butyllithium (1.6 M in hexane, 5.6 ml, 8.96 mmol) was added to a solution of 4-bromo-1,2-(methylenedioxy)benzene (1.7 g, 8.96 mmol) in THF (10 ml) at −78 °C under a nitrogen atmosphere and the mixture was stirred at the same temperature for 10 min. A solution of **6** (1.0 g, 1.02 mmol) in THF (10 ml) was added successively at −78 °C, and the whole mixture was stirred at room temperature for 3 h. After sat. aq. NH_4Cl (10 ml) had been added to the reaction mixture, the mixture was extracted with AcOEt. The extract was separated, dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 1 : 1) to give the titled compound (1.05 g, 90%) as an oil. $[\alpha]_D^{24}$ +80.6 (c=1.13, EtOH). IR (CCl_4) cm^{-1}: 1625. ^{1}H-NMR (300 MHz) δ: 1.66—1.82 (1H, m), 1.89 (1H, ddd, J=15.1, 12.2, 7.6 Hz), 2.08 (1H, ddd, J=12.7, 8.3, 5.1 Hz), 2.33 (1H, dd, J=12.7, 8.0 Hz), 2.60, 2.73 (2H, AB of ABX system, J_{AB}=13.8 Hz, J_{AX}=J_{BX}=7.1 Hz, C$\underline{H}_2$CH=), 2.86 (1H, ddd, J=9.9, 7.9, 6.9 Hz, one of 5-H_2), 3.02 (1H, ddd, J=9.9, 6.8, 4.6 Hz, one of 5-H_2), 3.33—3.47 (1H, br, NH), 4.92 (1H, br d, J=17 Hz, one of =CH_2), 4.99 (1H, br d, J=10 Hz, one of =CH_2), 5.69 (1H, ddd, J=17.1, 10.2, 7.1 Hz, C$\underline{H}$=CH_2), 6.05 (2H, s, OCH_2O), 6.85 (1H, d, J=8.1 Hz, 6′-H), 7.53 (1H, d, J=1.5 Hz, 2′-H), 7.68 (1H, dd, J=8.3, 1.8 Hz, 5′-H). *Anal.* Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.74; H, 6.92; N, 3.67.

***tert*-Butyl (*R*)-2-(3,4-Methylenedioxybenzoyl)-2-(prop-2-enyl)pyrrolidine-1-carboxylate (21)** A solution of $(Boc)_2O$ (1.32 g, 6.0 mmol) in acetonitrile (5 ml) was added to a stirred solution of (*R*)-2-(3,4-methylenedioxybenzoyl)-2-(prop-2-enyl)pyrrolidine (1.42 g, 5.5 mmol) in acetonitrile (25 ml) at 0 °C and the mixture was stirred at room temperature for 30 h. The reaction mixture was concentrated and the residue was dissolved in Et_2O, washed with 5% HCl and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 5 : 1) to give **21** (1.86 g, 94%) as a 5 : 1 oily mixture of two rotamers. $[\alpha]_D^{24}$ −12.4 (c=1.35, EtOH). IR (CCl_4) cm^{-1}: 1695, 1690. ^{1}H-NMR (300 MHz) for the major rotamer δ: 1.14 (9H, s, *tert*-Bu), 1.96—2.20 (3H, m), 2.24—2.46 (1H, m), 2.79, 2.87 (2H, AB of ABX system, J_{AB}=14.1 Hz, J_{AX}=7.8 Hz, J_{BX}=7.1 Hz, C$\underline{H}_2$CH=), 3.62—3.83 (2H, m, 5-H_2), 5.08—5.15 (2H, m, =CH_2), 5.90 (1H, ddt, J=17.3, 9.8, 7.5 Hz, C$\underline{H}$=CH_2), 6.02, 6.03 (1H each, ABq, J=1.3 Hz, OCH_2O), 6.81 (1H, d, J=8.3 Hz, 6′-H), 7.35 (1H, d, J=1.7 Hz, 2′-H), 7.43 (1H, dd, J=8.3, 1.8 Hz, 5′-H). Selected signals for the minor rotamer δ: 1.31 (9H, s, *tert*-Bu), 3.06 (1H, A of ABX system, J_{AB}=14.0 Hz, J_{AX}=7.0 Hz, one of C$\underline{H}_2$CH=), 3.54—3.62 (2H, m, one of 5-H_2), 5.15—5.19 (1H, m, one of =CH_2), 6.00 (2H, s, OCH_2O), 6.59 (1H, d, J=8.3 Hz, 6′-H), 7.30 (1H, d, J=1.7 Hz, 2′-H), 7.38 (1H, dd, J=8.3, 1.8 Hz, 5′-H). *Anal.* Calcd for $C_{20}H_{25}NO_5$: C, 66.84; H, 7.01; N, 3.90. Found: C, 66.74; H, 6.92; N, 3.67.

***tert*-Butyl (*S*)-2-Acetonyl-2-(3,4-methylenedioxybenzoyl)pyrrolidine-1-carboxylate (9)** Oxygen was bubbled into a stirred suspension of palladium(II) chloride (33 mg, 0.19 mmol), and copper(I) chloride (98 mg, 0.94 mmol) in DMF (10 ml) and H_2O (2 ml) at room temperature for 1 h. A solution of **21** (339 mg, 0.94 mmol) in DMF (4 ml) was added to the suspension and the mixture was sttired at the same temperature overnight under an oxygen atmosphere. The mixture was poured into ice cooled 10% HCl and the whole mixture was extracted with AcOEt. The extract was washed with sat. aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 5 : 1) to give a 2 : 1 mixture of the two rotamers of **9** (237 mg, 67%) as colorless crystals; mp 78—79 °C (from Et_2O). $[\alpha]_D^{23}$ +5.90 (c=2.0, EtOH). IR (CCl_4) cm^{-1}: 1700, 1695. ^{1}H-NMR (300 MHz) for the major rotamer δ: 1.15 (9H, s, *tert*-Bu), 2.01—2.20 (2H, m), 2.24—2.41 (1H, m), 2.36 (3H, s, $COCH_3$), 2.44 (1H, d, J=14.4 Hz, one of C$\underline{H}_2COCH_3$), 3.03 (1H, ddd, J=13.3, 6.5, 2.8 Hz), 3.27 (1H, d, J=14.2 Hz, one of C$\underline{H}_2COCH_3$), 3.71 (2H, dd, J=8.8, 5.9 Hz, 5-H_2), 6.02, 6.04 (1H each, ABq, J=1.3 Hz, OCH_2O), 6.81 (1H, d, J=8.3 Hz, 6′-H), 7.37 (1H, d, J=1.7 Hz, 2′-H), 7.45 (1H, dd, J=8.3, 1.8 Hz, 5′-H). Selected signals for the minor rotamer δ: 1.31 (9H, s, *tert*-Bu), 2.34 (3H, s, $COCH_3$), 2.66 (1H, d, J=14.5 Hz, one of C$\underline{H}_2COCH_3$), 2.89 (1H, ddd, J=13.0, 6.0, 4.2 Hz), 3.33 (1H, d, J=14.4 Hz, one of C$\underline{H}_2COCH_3$), 3.64 (2H, d, J=7.6, 6.8 Hz, 5-H_2), 6.01 (2H, s, OCH_2O), 6.78 (1H, d, J=8.3 Hz, 6′-H), 7.32 (1H, d, J=1.7 Hz, 2′-H), 7.41 (1H, dd, J=8.3, 1.8 Hz, 5′-H). *Anal.* Calcd for $C_{20}H_{25}NO_6$: C, 63.99; H, 6.71; N, 3.73. Found: C, 63.61; H, 6.86; N, 3.54.

***tert*-Butyl (*S*)-6-(3,4-Methylenedioxyphenyl)-8-oxo-1-azaspiro[4.4]-non-6-ene-1-carboxylate (8)** A catalytic amount of 2-methyl-2-butanol was added to a suspension of sodium hydride (60% dispersion in oil, 38 mg, 0.95 mmol) in benzene (2 ml) under a nitrogen atmosphere and the mixture was refluxed for 10 min. A solution of **9** (280 mg, 0.75 mmol) in benzene (1 ml) was added to the mixture and the solution was stirred at room temperature for 3 h. After the reaction mixture was concentrated, H_2O was added to the residue. The mixture was extracted with Et_2O and the extract was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 4 : 1) to give a 3 : 1 mixture of the two rotamers of **8** (114 mg, 43%) as colorless crystals; mp 155—157 °C (from hexane–AcOEt). $[\alpha]_D^{23}$ +2.75 (c=0.8, EtOH). IR ($CHCl_3$) cm^{-1}: 1680. ^{1}H-NMR (300 MHz) for the major rotamer δ: 1.19 (9H, s, *tert*-Bu), 1.75—2.09 (3H, m), 2.34—2.48 (1H, m), 2.55 (1H, d, J=17.6 Hz, one of 9-H_2), 2.94 (1H, d, J=17.6 Hz, one of 9-H_2), 3.52 (1H, td, J=10.8, 7.0 Hz, one of 2-H_2), 3.78—3.87 (1H, m, one of 2-H_2), 6.04 (2H, s, OCH_2O), 6.36 (1H, s, 7-H), 6.86 (1H, d, J=8.2 Hz, 6′-H), 7.05 (1H, d, J=1.7 Hz, 2′-H), 7.13 (1H, dd, J=8.3, 1.8 Hz, 5′-H). Selected signals for the minor rotamer δ: 1.39 (9H, s, *tert*-Bu), 6.02 (2H, s, OCH_2O), 6.38 (2H, s, 7-H). *Anal.* Calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 66.91; H, 6.51; N, 3.94.

***tert*-Butyl (5*S*,6*S*)-6-(3,4-Methylenedioxyphenyl)-8-oxo-1-azaspiro-[4.4]nonane-1-carboxylate (22)** A suspension of **8** (580 mg, 1.62 mmol) and a catalytic amount of PtO_2 in ethanol (3 ml) was vigorously stirred under a hydrogen atmosphere at room temperature overnight. The catalyst was removed by filtration on celite and the filtrate was concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 5 : 1) to give **22** (491 mg, 84%) as colorless crystals; mp 107—109 °C (from hexane–AcOEt). $[\alpha]_D^{23}$ +1.40 (c=1.07, EtOH). IR (CCl_4) cm^{-1}: 1745, 1690. ^{1}H-NMR (300 MHz) δ: 1.47 (9H, s, *tert*-Bu), 1.45—1.60 (1H, m), 1.69—1.76 (1H, br), 2.06—2.25 (2H, m), 2.51 (1H, d, J=18.5 Hz, one of 9-H_2), 2.54 (1H, dd, J=18.4, 9.5 Hz, one of 7-H_2), 2.70 (1H, ddd, J=10.9, 8.2, 4.3 Hz, one of 2-H_2), 2.95 (1H, d, J=18.3 Hz, one of 9-H_2), 3.13 (1H, br dd, J=18.5, 12 Hz, one of 7-H_2), 3.29 (1H, dt, J=10.7, 7.8 Hz, one of 2-H_2), 3.39 (1H, dd, J=12.2, 9.6 Hz, 6-H), 5.94, 5.98 (1H each, ABq, J=1.4 Hz, OCH_2O), 6.74 (2H, s, ArH), 6.81 (1H, s, ArH). Exact MS *m/z*: 359.1737 (Calcd for $C_{20}H_{25}NO_5$: 359.1731).

***tert*-Butyl (5*S*,6*S*,8*S*)-8-Hydroxy-6-(3,4-methylenedioxyphenyl)-1-azaspiro[4.4]nonane-1-carboxylate (23)** $NaBH_4$ (56 mg, 1.67 mmol) was added portionwise to a solution of **22** (200 mg, 0.56 mmol) in ethanol (25 ml) and the mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated to 3 ml, then diluted with H_2O (10 ml), and extracted with AcOEt. The extract was dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 1 : 3) to give **23** (200 mg, quant.) as an oil. IR ($CHCl_3$) cm^{-1}: 3600—3200, 1680. ^{1}H-NMR (300 MHz) δ: 1.14—1.32 (1H, m), 1.38—1.54 (1H, m), 1.48 (9H, s, *tert*-Bu), 1.94—2.12 (2H, m), 2.38—2.48 (4H, m), 2.74 (1H, ddd, J=11.0, 8.8, 3.2 Hz, one of 9-H_2), 2.86 (1H, t, J=10.6 Hz, one of 6-H), 3.28 (1H, dt, J=11.0, 8.5 Hz, one of 2-H_2), 4.34 (1H, d of quint, J=11.2, 7.0 Hz, 8-H), 4.80 (1H, d, J=11.2 Hz, OH), 5.92, 5.95 (1H each, ABq, J=1.5 Hz, OCH_2O), 6.71 (2H, s, ArH), 6.81 (1H, s, ArH). *Anal.* Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.64; H, 7.75; N, 3.90.

***tert*-Butyl (5*S*,6*S*,8*S*)-8-Acetoxy-6-(3,4-methylenedioxyphenyl)-1-azaspiro[4.4]nonane-1-carboxylate (24)** A mixture of **23** (434 mg, 1.2 mmol) and acetic anhydride (247 mg, 2.42 mmol) in pyridine (4 ml) was stirred at room temperature overnight. The reaction mixture was concentrated and the residue was dissolved in AcOEt. The mixture was washed with sat. aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. The residue was chro-

matographed on silica gel (hexane–AcOEt, 5 : 1) to give **24** (448 mg, 92%) as colorless crystals; mp 110—112 °C (from AcOEt). $[\alpha]_D^{22}$ +33.7 (c=1.8, EtOH). IR ($CHCl_3$) cm^{-1}: 1730, 1670. ^{1}H-NMR (300 MHz) δ: 1.20—1.45 (1H, m), 1.34 (9H, s, *tert*-Bu), 1.47—1.80 (3H, m), 1.95—2.45 (2H, m), 2.08 (3H, s, $COCH_3$), 2.73—2.90 (2H, m), 2.90—3.12 (2H, m), 3.30—3.45 (1H, m), 5.05 (1H, quint, J=7.0 Hz, 8-H), 5.91 (2H, s, OCH_2O), 6.69 (1H, d, J=7.6 Hz, ArH), 6.75 (1H, d, J=7.6 Hz, ArH), 6.93 (1H, s, ArH). *Anal.* Calcd for $C_{22}H_{29}NO_6$: C, 65.49; H, 7.24 ; N, 3.47. Found: C, 65.47; H, 7.28; N, 3.37.

(5*S*,6*S*,8*S*)-8-Acetoxy-6-(3,4-methylenedioxyphenyl)-1-[(methylthio)-acetyl]-1-azaspiro[4.4]nonane (26) TFA (3 ml) was added dropwise to a solution of **24** (1.82 g, 4.51 mmol) in CH_2Cl_2 (30 ml) at 0 °C and the mixture was stirred at the same temperature for 1 h. The reaction mixture was concentrated and the residue was dissolved in AcOEt. The mixture was made alkaline (pH 10) by aq. K_2CO_3. The organic layer was separated, washed with brine, dried (Na_2SO_4), and concentrated to give (5*S*,6*S*,8*S*)-8-acetoxy-6-(3,4-methylenedioxyphenyl)-1-azaspiro[4.4]nonane (**25**) (1.36 g, quant.) which was used for the next step without purification. A mixture of **25** (1.78 g, 5.87 mmol), (methylthio)acetic acid (685 mg, 6.45 mmol), and DCC (1.33 g, 6.45 mmol) in CH_2Cl_2 (30 ml) was stirred at room temperature overnight. The precipitated dicyclohexylurea was filtered off and the filtrate was concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 2 : 1) to give **26**[13] (1.90 g, 83% from **24**) as colorless crystals; mp 123—124 °C (from hexane–Et_2O). $[\alpha]_D^{20}$ +36.4 (c=1.4, $CHCl_3$).

(5*S*,6*S*,8*S*)-8-Acetoxy-6-(3,4-methylenedioxyphenyl)-1-[(methylsulfinyl)acetyl]-1-azaspiro[4.4]nonane (7) A solution of $NaIO_4$ (811 mg, 3.45 mmol) in H_2O (30 ml) was added dropwise to a solution of **26** (1.35 g, 3.45 mmol) in MeOH (30 ml) at 0 °C and the mixture was stirred at room temperature overnight. The precipitated inorganic material was filtered off and the filtrate was concentrated. H_2O (30 ml) was added to the residue and the mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (AcOEt–MeOH, 10 : 1) to give **7**[13] (1.38 g, 98%) as colorless crystals, which was directly used for the next step.

(2*S*,3a*S*,13b*S*)-2-Acetoxy-9-methylthio-1,2,3,5,6,8,9,13b-octahydro-4*H*-cyclopenta[*a*]-1,3-dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]benzazepin-8-one (27) Trifluoroacetic anhydride (TFAA) (0.1 ml, 0.32 mmol) was added dropwise to a solution of **7** (130 mg, 0.32 mmol) in CH_2Cl_2 (5 ml) at 0 °C under a nitrogen atmosphere and the mixture was stirred at room temperature for 24 h. The mixture was diluted with CH_2Cl_2 (20 ml) and washed with sat. aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 2 : 1) to give **27**[13] (108 mg, 85%) as colorless crystals; mp 222—224 °C (from EtOH).

(2*S*,3a*S*,13b*S*)-2-Acetoxy-1,2,3,5,6,8,9,13b-octahydro-4*H*-cyclopenta[*a*]-1,3-dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]benzazepin-8-one (28) A mixture of **27** (108 mg, 0.28 mmol) and Raney nickel (W-2) (1 g) in acetone (15 ml) was refluxed for 1 h. The Raney nickel was filtered off and the filtrate was concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 2 : 1) to **28**[13] (95 mg, quant.) as colorless crystals; mp 190—191 °C (from Et_2O). $[\alpha]_D^{23}$ +0.05 (c=1.4, EtOH).

(3a*S*,13b*S*)-1,2,3,5,6,8,9,13b-Octahydro-4*H*-cyclopenta[*a*]-1,3-dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]benzazepine-2,8-dione (4) K_2CO_3 (84 mg, 0.56 mmol) was added to a solution of **28** (120 mg, 0.35 mmol) in CH_2Cl_2 (1 ml) and MeOH (5 ml) and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with CH_2Cl_2 (10 ml), washed with brine, dried ($MgSO_4$), and concentrated to give (2*S*,3a*S*,13b*S*)-2-hydroxy-1,2,3,5,6,8,9,13b-octahydro-4*H*-cyclopenta[*a*]-1,3-dioxolo[4,5-*h*]pyrrolo-[2,1-*b*][3]benzazepin-8-one which was used for the next reaction without further purification. A solution of dimethyl sulfoxide (DMSO) (539 mg, 6.9 mmol) in CH_2Cl_2 (2 ml) was added to a solution of oxalyl chloride (438 mg, 3.45 mmol) in CH_2Cl_2 (2 ml) at −60 °C over 10 min under a nitrogen atmosphere. A solution of the alcohol (104 mg, 0.345 mmol) obtained above in CH_2Cl_2 (3 ml) was added and the whole mixture was stirred at the same temperature for 40 min. Et_3N (1.7 g, 17.3 mmol) was added and the mixture was allowed to warm to room temperature. After 60 min, H_2O (5 ml) was added. The organic layer was separated, washed with sat. aq. $NaHCO_3$, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 2 : 1) to give **4**[13] (95 mg, quant.) as colorless crystals; mp 212—214 °C (from hexane–AcOEt). $[\alpha]_D^{27}$ +57.4 (c=1.4, $CHCl_3$). The optical yield was determined to be 88% ee by HPLC using a column packed with CHIRALPAK AD (DAICEL) (hexane–2-propanol, 8 : 2).

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