Considerable attention has been directed toward the synthesis of cephalotaxine (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). So far, eight total syntheses of (6)-1 including ours have been reported and the synthesis of (2)-1 has recently been achieved by Morig’s and Nagasaka’s groups. As a part of our own efforts to synthesize this alkaloid in an optically active form, we envisioned that the ketolactam 4, which had already been converted into (6)-cephalotaxine using three additional steps by Hanaoka and us, 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 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 (2)-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). As an extension of this reaction, we examined the intramolecular Heck reaction of the optically active azaspiro[4.4]nonene 5, which was prepared as illustrated in Chart 3. The azabicyclic compound 6, prepared from D-proline according to Seebach’s procedure, was hydrolyzed with 10% sulfuric acid followed by protection with di-tert-butyl dicarbonate [(Boc)₂O] and esterification with trimethylsilyldiazomethane (TMSCHN₂) to give the methyl ester 12. Following the same procedure as used in the preliminary work, 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) in 4 steps: 1) Friedel–Crafts alkylation of 15 with ethyl α-methylthioacetate in the presence of tin(IV) chloride, 2) desulfurization of the sulfide 16 with zinc in acetic acid, 3) hydrolysis of the

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A Formal Total Synthesis of (2)-Cephalotaxine

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A formal total synthesis of (2)-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 acetoxyl 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 (2)-cephalotaxine; intramolecular aldol condensation; Pummerer reaction; Friedel–Crafts alkylation; D-proline; intramolecular Heck reaction

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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), tri- butylphosphine, and silver carbonate (Ag₂CO₃) in refluxing N,N-dimethylformamide (DMF) for 3 h, gave the cyclized enone 19 and the reduction product 20 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.

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 in benzene at room temperature for 3 h to give the desired a,b-unsaturated ketone 8 in 43% yield. Catalytic hydrogenation of 8 over platinum(IV) oxide (PtO₂) 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 (NaBH₄) proceeded in a highly stereoselective manner to give the (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)acetyl acid in the presence of dicyclohexylcarbodiimide
(DCC) in dichloromethane (CH₂Cl₂) gave, in 83% yield from 24, the amide 26, which had spectral characteristics identical with those of an authentic racemic sample. Following the synthetic operations developed for the synthesis of racemic cephalotaxine, 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 (K₂CO₃) in CH₃Cl–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. ¹H-NMR spectra were determined with a JEOL JNM-MY 60 (60 MHz) or a Varian XL-300 (300 MHz) spectrometer, using CDCl₃ as a solvent and tetramethylsilane as an internal standard. High resolution MS were determined with a JEOL JMS-SX102A 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-Methoxy-carbonyl-2-(prop-2-enyl)pyrrolidine-1-carboxylate (12) After a mixture of (25S,5S)-2-tert-butyl-5-(prop-2-enyl)-1-aza-3-oxabicyclo[3.3.0]octan-4-one (6) [α]D⁰ = −16.6 (c = 3.62, CHCl₃), lit. [α]D⁰ = −13.1 (c = 1.8, CHCl₃), 2.5 g, 11.25 mmol) and 10% sulfuric acid (100 ml) was stirred for 24 h. Sodium hydroxide (13.5 g), 1,4-dioxiane (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) 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 (MgSO₄), and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 30 : 1) to give 16 (1.70 g, 94%) as an oil. IR (CCl₄) cm⁻¹: 1735. ¹H-NMR (60 MHz) δ: 1.27 (3H, t, J = 7.0 Hz, OCH₂CH₃), 2.13 (3H, s, SCH₂), 4.20 (2H, q, J = 7.0 Hz, OCH₂CH₃), 4.93 (1H, s, CH₂(OH)), 5.98 (2H, s, OCH₂O), 7.23 (2H, s, ArH). Exact MS m/z: 379.9575 (Calcd for C₂₁H₂₂O₈: 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 (25 ml) at 0 °C and (Boc)₂O (12.3 g, 56.3 mmol) was added to the solution. The mixture 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)acetic acid (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 (1.70 g, 40.0 mmol) was stirred for 15 min, water (H₂O) was added. The entire mixture was extracted with CH₂Cl₂, the extract was dried (MgSO₄) and concentrated. The residue was chromatographed on silica gel (AcOEt) to give ethyl (6-iodo-3,4-methylenedioxyphenyl)acetate (609 mg, 50%) as colorless crystals, mp 180—181 °C. IR (KBr) cm⁻¹: 3200—2800, 1700. ¹H-NMR (60 MHz) δ: 4.80 (2H, s, CH₂(OH)), 5.90 (2H, s, OCH₂O), 6.80 (1H, s, ArH), 7.18 (1H, d, J = 5 Hz, ArH). Anal. Calcd for C₁₂H₁₂INO₄: C, 45.07; H, 3.20; N, 4.46. Found: C, 45.05; H, 3.17; N, 4.38.

(6-Iodo-3,4-methylenedioxyphenyl)acetic Pivalic Anhydride (18) Pivaloyl chloride (177 mg, 1.47 mmol) and trimethylamine (Et₃N) (148 mg, 1.47 mmol) in CH₂Cl₂ (2 ml) was stirred 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 CH₂Cl₂ (10 ml). 4-(N,N-Dimethylethylamino)pyridine (DMAP) (22 mg, 0.18 mmol), Et₃N (892 mg, 9.15 mmol), and a solution of 18 (1.07 g, 2.73 mmol) in CH₂Cl₂ (10 ml) were added successively at 0 °C, 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.

(5)-[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 CH₂Cl₂ (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 CH₂Cl₂ (10 ml). 4-(N,N-Dimethylethylamino)pyridine (DMAP) (22 mg, 0.18 mmol), Et₃N (892 mg, 9.15 mmol), and a solution of 18 (1.07 g, 2.73 mmol) in CH₂Cl₂ (10 ml) were added successively at 0 °C, 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.
the whole mixture was extracted with AcOEt. The extract was washed with oxygen atmosphere. The mixture was poured into ice cooled 10% HCl and reaction mixture was filtered on celite and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 1 : 1) to give the titled compound (8 ml) and the mixture was refluxed under an argon atmosphere for 3 h. Selected signals for the minor rotamer: δ 1.93 (9H, s, tert-Bu), 2.01—2.10 (2H, m), 2.65—2.70 (1H, m), 2.86 (1H, d, 8.3 Hz), 3.05 (1H, m of 15-H2), 3.19 (1H, d, 7.6 Hz), 3.72 (1H, d, 7.6 Hz). Anal. Calcd for C20H25NO6: C, 63.99; H, 6.71; N, 3.73. Found: C, 63.61; H, 6.54; N, 3.54.

8-Acetoxy-6-(3,4-methylenedioxyphenyl)-1-aza-spiro[4.4]nonane-1-carboxylate (22) A suspension of 8 (580 mg, 1.62 mmol) and a catalytic amount of PtO2 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). [α]D 25: +2.76 (c = 0.8, EtOAc). IR (CHCl3) cm−1: 1680. 1H-NMR (300 MHz) δ 1.93—1.97 (9H, s, tert-Bu), 2.09 (3H, m), 2.34—2.48 (1H, m), 2.55 (1H, d, 17.6 Hz, one of 9-H2), 2.94 (1H, d, 17.6 Hz, one of 9-H2), 3.52 (1H, td, 10.8, 7.0 Hz, one of 2-H), 3.78—3.87 (1H, m, one of 2-H), 6.02 (2H, s, OCH2O), 6.36 (1H, s, H-7), 6.86 (1H, d, 17.6 Hz, one of 9-H2), 7.13 (1H, dd, 8.3, 1.8 Hz, 5'-H). Selected signals for the minor rotamer: δ 1.39 (9H, s, tert-Bu), 6.02 (2H, s, OCH2O), 6.38 (2H, s, H-7). Anal. Calcd for C25H25NO6: C, 62.71; H, 6.89; N, 3.92. Found: C, 66.91; H, 6.51; N, 3.94.

8-Acetoxy-6-(3,4-methylenedioxyphenyl)-1-aza-spiro[4.4]nonane-1-carboxylate (22) A solution of 8 (580 mg, 1.62 mmol) and a catalytic amount of PtO2 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). [α]D 25: +2.76 (c = 0.8, EtOAc). IR (CHCl3) cm−1: 1680. 1H-NMR (300 MHz) δ 1.93—1.97 (9H, s, tert-Bu), 2.09 (3H, m), 2.34—2.48 (1H, m), 2.55 (1H, d, 17.6 Hz, one of 9-H2), 2.94 (1H, d, 17.6 Hz, one of 9-H2), 3.52 (1H, td, 10.8, 7.0 Hz, one of 2-H), 3.78—3.87 (1H, m, one of 2-H), 6.02 (2H, s, OCH2O), 6.36 (1H, s, H-7), 6.86 (1H, d, 17.6 Hz, one of 9-H2), 7.13 (1H, dd, 8.3, 1.8 Hz, 5'-H). Selected signals for the minor rotamer: δ 1.39 (9H, s, tert-Bu), 6.02 (2H, s, OCH2O), 6.38 (2H, s, H-7). Anal. Calcd for C25H25NO6: C, 62.71; H, 6.89; N, 3.92. Found: C, 66.91; H, 6.51; N, 3.94.
chromatographed on silica gel (hexane–AcOEt, 5:1) to give 24 (448 mg, 92%) as colorless crystals; mp 110–112 °C (from AcOEt). \[^{1}H\text{NMR}(	ext{CDCl}_{3}); \delta = 3.37 \text{ (s, } 18H, \text{EtO})\text{, IR (CHCl}_{3}); \text{cm}^{-1}; 1170, 1670, 1170, \text{H}^{1}NMR(300 \text{MHz})\text{, Chemical Shifts.}]

A solution of NaIO\(_4\) (811 mg, 5.87 mmol), (methylthio)acetic acid (685 mg, 6.45 mmol), and DCC (1.33 g, 0.56 mmol) was added to a solution of \(\text{NaClO}_2\) (5 mmol) in H\(_2\)O (30 ml) was added dropwise to a solution of \(\text{NaClO}_2\) (30 ml) at 0 °C and the mixture was stirred at room temperature. After 24 h. The mixture was diluted with CH\(_2\)Cl\(_2\) (20 ml) and washed with aq. K\(_2\)CO\(_3\) (84 mg, 0.6 mmol) by aq. K\(_2\)CO\(_3\). The organic layer was separated, washed with brine, dried (Na\(_2\)SO\(_4\)), and concentrated. The residue was dissolved in AcOEt. The mixture was made alkaline (pH 10) by aq. K\(_2\)CO\(_3\). The organic layer was separated, washed with brine, dried (Na\(_2\)SO\(_4\)), and concentrated and the residue was dissolved in AcOEt. The mixture was made alkaline. A solution of dimethyl sulfoxide (DMSO) (539 mg, 5.87 mmol), (methylthio)acetic acid (685 mg, 6.45 mmol), and DCC (1.33 g, 0.56 mmol) was added to a solution of \(\text{NaClO}_2\) (5 mmol) in H\(_2\)O (30 ml) at 0 °C and the mixture was diluted with CH\(_2\)Cl\(_2\) (20 ml), washed with aq. K\(_2\)CO\(_3\) (84 mg, 0.6 mmol) by aq. K\(_2\)CO\(_3\). The organic layer was separated, washed with brine, dried (Na\(_2\)SO\(_4\)), and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 2:1) to give 4\(^{27}\) (95 mg, quant.) as colorless crystals; mp 212–214 °C (from hexane–AcOEt). \[^{1}H\text{NMR}(\text{CDCl}_{3}); \delta = 5.74 \text{ (s, } 14H, \text{CHCl)}\] 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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References and Notes


13) All spectroscopic data were identical with those of racemic authentic samples.\(^{27}\)