Approaches to the Cephalotaxine Skeleton Using an Intramolecular Heck Reaction

Masazumi IKEDA,*[,a] Ken-ichi HIROSE,[a] Serry A. A. EL BIALY,[a] Tatsunori SATO,[a] Takayuki YAKURA,[a] and Said M. M. BAYOMI[b]

Kyoto Pharmaceutical University,[a] Misasagi, Yamashina, Kyoto 607–8414, Japan, and Faculty of Pharmacy, University of Mansoura,[b] Mansoura 35516, Egypt. Received February 9, 1998; accepted March 18, 1998

1-[2-(*o*-Iodophenyl)acetyl]-2-(prop-2-enyl)-2-vinylpyrrolidine (17), upon treatment with palladium(II) acetate [$Pd(OAc)_2$] in the presence of triphenylphosphine and triethylamine in refluxing acetonitrile, gave the monocyclization product 20 as the major product along with a small amount of the tandem cyclization product 21. On the other hand, treatment of the 1-[2-(*o*-iodophenyl)acetyl]-1-azaspiro[4.4]non-8-en-7-one (25) with $Pd(OAc)_2$, 1,3-bis(diphenylphosphino)propane, tributylphosphine, and silver carbonate in boiling *N,N*-dimethylformamide afforded the cyclized product 27 in 51% yield.

Key words intramolecular Heck reaction; *anti*-elimination; cephalotaxine; tandem Heck reaction; Cope rearrangement; intramolecular aldol condensation

Palladium-catalyzed cyclizations of aryl halides to intramolecular alkenes (intramolecular Heck reaction) are now widely used for the construction of a variety of the carbo- and heterocyclic compounds.[1] As part of our studies directed toward the synthesis of optically active cephalotaxine (**1**),[2-4] we envisioned that the ketolactam **2**, which had already been converted into (±)-cephalotaxine by additional three steps by Hanaoka[4c] and us,[4f] would be obtainable in an optically active form using an intramolecular Heck reaction as shown in the retrosynthetic format (Chart 1). One route involves a tandem intramolecular Heck reaction of the diene **4** followed by oxidative cleavage of the resulting methylene derivative **3**, and the other uses an intramolecular Heck reaction of the azaspiro[4.4]nonenone **8** followed by catalytic hydrogenation of the resulting enone **7**. The precursors **4** and **8** themselves would be accessible from D-proline (**6**) through the optically active ester **5**. In order to test the feasibility of the indicated intramolecular Heck reactions, we have carried out preliminary experiments with the readily available racemic compounds **16**, **17**, **24**, and **25**. In this paper we report the results obtained from this model study.[5]

Results and Discussion

We initiated our studies with the intramolecular Heck reaction of the 2-vinylpyrrolidine derivatives **10** and **11**, which were readily prepared from the 2-vinylpyrrolidine **9**.[6] When **10** was treated with palladium(II) acetate [$Pd(OAc)_2$] (3 mol%), triphenylphosphine (Ph_3P) (12 mol%), and triethylamine (Et_3N) (2 eq) in refluxing acetonitrile under an argon atmosphere for 1 h, the lactam **12** was obtained in 84% yield. A closely related reaction has been reported by Tietze and Burkhardt.[7] Similar treatment of **11** gave the lactam **13** in 70% yield. The structures of **12** and **13** were easily characterized by the presence of *exo*-methylene proton signals at δ 5.22 (1H, d, J=2.6 Hz) and 5.58 (1H, d, J=2.6 Hz) for **12** and δ 5.25 (1H, d, J=1.8 Hz) and 5.31 (1H, d, J=1.8 Hz) for **13** in the ^{1}H-NMR spectra.

We then investigated the tandem cyclization of the 2-(prop-2-enyl)-2-vinylpyrrolidine derivatives **16** and **17** which were prepared from the readily available ester **5**[8] as outlined in Chart 2. Thus, **5** was reduced with lithium aluminum hydride in tetrahydrofuran (THF) at 0 °C for 1 h[9] to give the alcohol **14** in 88% yield. Swern oxidation of **14** followed by Wittig olefination of the resulting aldehyde gave the 2-(prop-2-enyl)-2-vinylpyrrolidine **15** in 88% overall yield. Deprotection of **15** and acylation

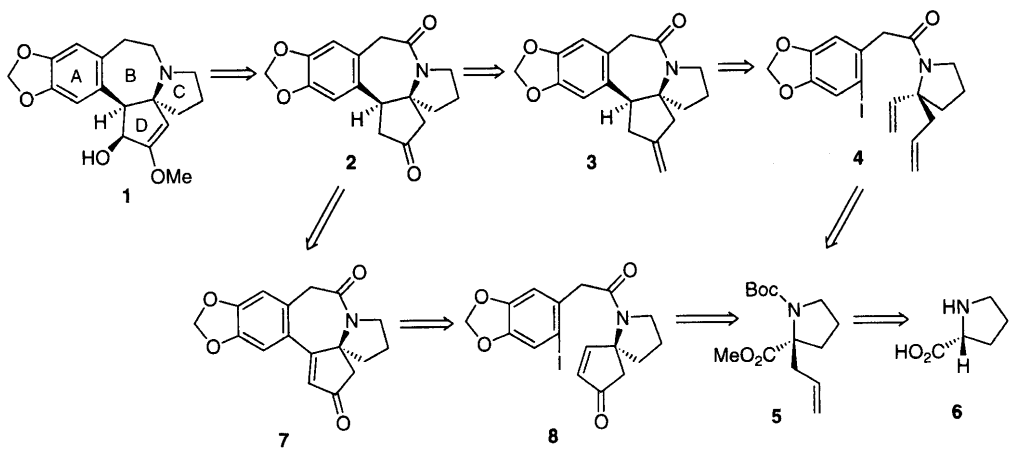


Chart 1

* To whom correspondence should be addressed.

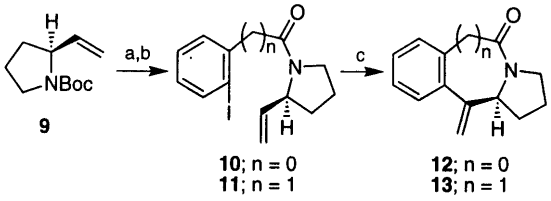
of the resulting amine with *o*-iodobenzoyl chloride or 2-(*o*-iodophenyl)acetyl pivaloyl anhydride gave **16** and **17** in 56 and 94% yields, respectively.

Treatment of **16** with $Pd(OAc)_2$–Ph_3P–Et_3N in refluxing acetonitrile gave **18** in 89% yield. The structure of **18** was based on spectroscopic and chemical evidence. The ^{1}H-NMR spectrum showed the absence of the signals characteristic of the *exo*-methylene protons but the presence of only three olefinic protons at δ 4.97—5.10 (2H, m) and 5.89 (1H, ddt) and the ^{13}C-NMR spectrum revealed the presence of five sp^3 methylene carbons and four olefinic carbons. These data are consistent with structure **18**, which is assumed to be produced *via* a Cope rearrangement of the initially formed **19**. Indeed, when the same reaction was carried out at lower temperature (at 50—60 °C), **19** was isolated in 52% yield along with unchanged **16** (46%). Compound **19** showed the expected *exo*-methylene proton signals at δ 5.08 (1H, s) and 5.63 (1H, s) and signals characteristic of the allylic system. When a solution of **19** in acetonitrile was heated under reflux for 4 h, **19** completely rearranged to **18**.

Similar treatment of compound **17** gave the monocyclization product **20** (51% yield) and a mixture of the double cyclization product **21** (<20% yield) and an unidentified product. Although the mixture could not be separated by column chromatography, several recrystallizations gave a pure sample of **21**. Confirmation of the structure **21** was made by an X-ray analysis (Fig. 1). The structure of **20** was assigned by comparison of its spectroscopic data with those of **19** (see Experimental). In contrast to compound **19**, compound **20** was found to be stable in refluxing acetonitrile or toluene. The facile rearrangement of **19** to **18** may be attributed to the higher stability of the rearranged product **18** due to its aromatic character.

The failure of the tandem cyclization of **16** and the poor yield of the tandem cyclization product **21** from **17** may be because the (σ-alkyl)palladium intermediates A decomposed by elimination of β-hydrogen faster than the intermediates reacted with another olefinic bond.[10]

We next examined the intramolecular Heck reaction of the 1-azaspiro[4.4]non-8-en-7-ones **24** and **25** which were prepared as illustrated in Chart 4. Swern oxidation of **14** followed by Wacker oxidation[11] of the resulting aldehyde gave the ketoaldehyde **22** in 72% overall yield from **14**. Intramolecular aldol condensation of **22** was effected by



a) CF_3CO_2H, CH_2Cl_2; b) *o*-iodobenzoyl chloride or 2-(*o*-iodophenyl)acetyl pivaloyl anhydride, Et_3N, DMAP, CH_2Cl_2; c) $Pd(OAc)_2$, Ph_3P, Et_3N, MeCN, reflux

Chart 2

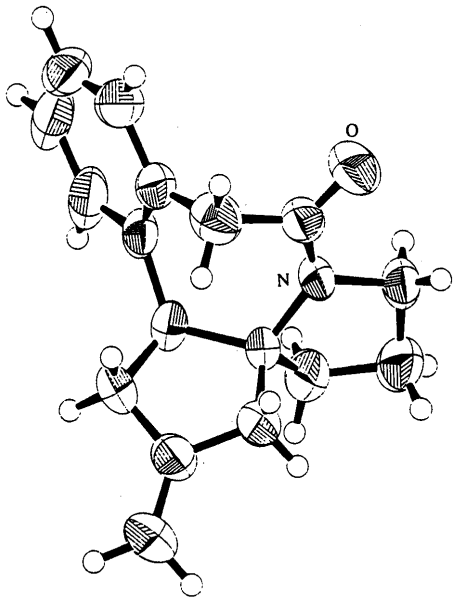
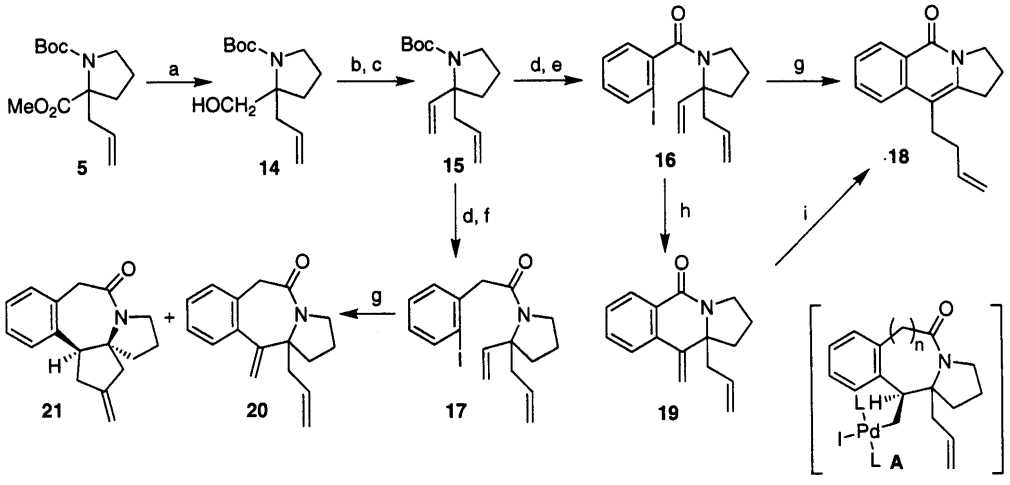
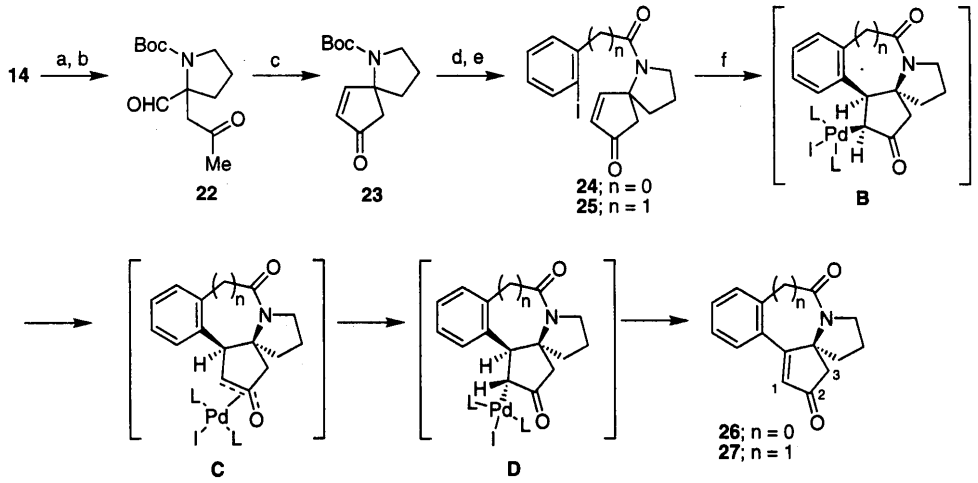


Fig. 1. ORTEP Drawing of **21**



a) $LiAlH_4$, THF, 0 °C; b) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2; c) $Ph_3P^+MeBr^-$, NaH, DMSO; d) CF_3CO_2H, CH_2Cl_2; e) *o*-iodobenzoyl chloride, Et_3N, DMAP, CH_2Cl_2; f) 2-(*o*-iodophenyl)acetyl pivaloyl anhydride, Et_3N, DMAP, CH_2Cl_2; g) $Pd(OAc)_2$, Ph_3P, Et_3N, MeCN, reflux; h) $Pd(OAc)_2$, Ph_3P, Et_3N, MeCN at 50—60 °C; i) MeCN, reflux

Chart 3



a) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2; b) O_2, $PdCl_2$, CuCl, DMF–H_2O, room temp.; c) K_2CO_3, MeOH–H_2O, 70 °C; d) CF_3CO_2H, CH_2Cl_2; e) *o*-iodobenzoyl chloride or 2-(*o*-iodophenyl)acetyl pivaloyl anhydride, Et_3N, DMAP, CH_2Cl_2; f) $Pd(OAc)_2$, POT, Ag_2CO_3, DMF, reflux

Chart 4

treatment with potassium carbonate in aqueous methanol at 70 °C for 40 min to give the enone **23** in 50% yield. Deprotection of **23** with trifluoroacetic acid (TFA) in dichloromethane followed by acylation of the resulting amine with *o*-iodobenzoyl chloride or 2-(*o*-iodophenyl)-acetyl pivaloyl anhydride in the presence of *N*,*N*-dimethylaminopyridine (DMAP) and Et_3N in dichloromethane gave the desired precursors **24** and **25** in 43 and 93% yields, respectively.

Compound **24**, when treated with $Pd(OAc)_2$–Ph_3P–Et_3N in refluxing acetonitrile for 3 h, gave, in addition to a small amount of several unidentified products and the unreacted **24**, the cyclized enone **26** but in only 12% yield. The structure of **26** was determined on the basis of the spectroscopic evidence: the ^{1}H-NMR spectrum revealed a singlet at δ 6.54 due to the 1-H proton and a singlet at δ 2.74 assignable to the methylene protons at 3-position, and the IR spectrum showed the carbonyl groups at 1710 cm^{-1} (an α,β-unsaturated five-membered ketone) and 1655 cm^{-1} (amide and double bonds). In order to improve the yield of **26**, cyclization of **24** was attempted under a variety of conditions, among which the most effective was the use of $Pd(OAc)_2$ and tris(*o*-methylphenyl)phosphine (POT) as a catalyst and silver carbonate (Ag_2CO_3) as a base in *N*,*N*-dimethylformamide (DMF) at reflux,[12] affording **26** in 66% yield.

Similar treatment of **25** with $Pd(OAc)_2$–POT–Ag_2CO_3 in refluxing DMF gave **27** in 35% yield. Use of $Pd(OAc)_2$, 1,3-bis(diphenylphosphino)propane (DPPP), tributylphosphine (Bu_3P), and Ag_2CO_3 in refluxing DMF[13] improved the yield of **27** to 51%. The structure of **27** was assigned by a comparison of the spectroscopic data with those of **26**.

In view of the accepted mechanism of the Heck reaction which involves a *syn*-1,2-addition of a palladated aryl group to the alkene followed by a *syn*-β-elimination of palladium and a hydrogen atom from the resulting σ-Pd-complex, it is interesting to note that significant amounts of **26** and **27** were formed in spite of the fact that its formation formally involves an *anti*-elimination of palladium hydride. Some other examples of such an *anti*-elimination have been reported.[14] One plausible mechanism for the formal *anti*-elimination would involve prior isomerization of the σ-complex B to the isomeric σ-complex D *via* oxy-π-allyl complex C followed by a *syn*-elimination.[14a,b]

An application of this method to the synthesis of optically active cephalotaxine and its analogues is now in progress.

Experimental

Melting points are uncorrected. ^{1}H-NMR spectra were determined with a JEOL JNM-PMX 60 (60 MHz), JEOL JNM-EX 270 (270 MHz), or a Varian XL-300 (300 MHz) spectrometer, using $CDCl_3$ as a solvent and tetramethylsilane as an internal standard. ^{13}C-NMR spectra were recorded on a Varian XL-300 (75 MHz) spectrometer using $CDCl_3$ as a solvent and reported in ppm using solvent resonance as internal standard (77.0 for $CDCl_3$). All ^{13}C-NMR spectra were determined with complete proton decoupling. High resolution MS were determined with a JEOL JMS-SX 102A spectrometer at 20 eV. Optical rotations were measured with a JASCO DIP-360 polarimeter. Column chromatography was performed on Silica gel 60 PF_{254} (Nacalai Tesque, Inc.) under pressure.

(*S*)-1-(*o*-Iodobenzoyl)-2-vinylpyrrolidine (10) TFA (1 ml) was added to a solution of *tert*-butyl (*S*)-2-vinylpyrrolidine-1-carboxylate (**9**)[6] (200 mg, 1.02 mmol) in dichloromethane (1 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 dichloromethane (5 ml). Et_3N (514 mg, 5.08 mmol), DMAP (12 mg, 0.10 mmol), and then a solution of *o*-iodobenzoyl chloride (406 mg, 1.52 mmol) in dichloromethane (5 ml) were added successively, and the whole was stirred at room temperature overnight. After water (3 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 (hexane–AcOEt, 2 : 1) to give **10** (277 mg, 87%) as a 1.5 : 1 oily mixture of two rotamers, $[\alpha]_D^{26}$ −55.8° (c = 0.5, $CHCl_3$). IR (CCl_4) cm^{-1}: 1625. ^{1}H-NMR (300 MHz) for the major rotamer δ: 1.20—1.30 and 1.72—2.21 (total 4H, m), 3.12—3.43 (1H, m, one of 5-H_2), 3.63—3.82 (1H, m, one of 5-H_2), 4.03—4.10 (1H, m, 2-H), 4.73 (1H, d, J = 17.0 Hz, one of CH=C$\underline{H}_2$), 4.93 (1H, d, J = 10.3 Hz, one of CH=C$\underline{H}_2$), 5.57 (1H, ddd, J = 17.0, 10.3, 5.8 Hz, C$\underline{H}$=CH_2), 7.00—7.10 (1H, m, ArH), 7.18 (1H, dd, J = 7.8, 1.7 Hz, ArH), 7.31 (1H, td, J = 7.8, 1.0 Hz, ArH), 7.78 (1H, dd, J = 8.3, 1.0 Hz, ArH). Selected signals for the minor rotamer δ: 4.79—4.86 (1H, m, 2-H), 5.20 (1H, d, J = 10.3 Hz, one of CH=C$\underline{H}_2$), 5.34 (1H, d, J = 17.0 Hz, one of CH=C$\underline{H}_2$), 5.95 (1H, ddd, J = 17.0, 10.3, 5.8 Hz, C$\underline{H}$=CH_2), 7.24 (1H, dd, J = 7.8, 1.7 Hz, ArH), 7.39 (1H, td, J = 7.8, 1.0 Hz, ArH), 7.82 (1H, dd, J = 8.3, 1.0 Hz, ArH). *Anal.* Calcd

for $C_{13}H_{14}INO$: C, 47.73; H, 4.31; N, 4.28. Found: C, 47.65; H, 4.46; N, 4.24.

(*S*)-1-[2-(*o*-Iodophenyl)acetyl]-2-vinylpyrrolidine (11) According to the procedure described for the preparation of **10**, **11** (134 mg, 47%) was obtained from **9** (163 mg, 0.83 mmol) and 2-(*o*-iodophenyl)acetyl pivaloyl anhydride (245 mg, 0.91 mmol) as a 1.6 : 1 oily mixture of two rotamers, $[\alpha]_D^{26}$ −14.1° (*c*=0.3, $CHCl_3$). IR (CCl_4) cm^{-1}: 1640. ^{1}H-NMR (300 MHz) for the major rotamer δ: 1.76—2.14 (4H, m), 3.48—3.64 (2H, m, 5-H_2), 3.66 and 3.78 (2H, ABq, *J*=15.9 Hz, CH_2Ar), 4.44—4.50 (1H, m, 2-H), 5.06—5.23 (2H, m, CH=CH_2), 5.85 (1H, ddd, *J*=16.8, 10.5, 5.4 Hz, CH=CH_2), 6.89—6.97 (1H, m, ArH), 7.24—7.34 (2H, m, ArH), 7.79—7.84 (1H, m, ArH). Selected signals for the minor rotamer δ: 3.75, 3.80 (2H, ABq, *J*=15.9 Hz, CH_2Ar), 4.67—4.73 (1H, m, 2-H), 5.79 (1H, ddd, *J*=16.8, 10.5, 5.4 Hz, CH=CH_2). *Anal.* Calcd for $C_{14}H_{16}INO$: C, 49.28; H, 4.73; N, 4.11. Found: C, 49.38; H, 4.78; N, 4.26.

Intramolecular Heck Reaction of Compound 10. General Procedure Et_3N (58 mg, 0.60 mmol) was added to a solution of **10** (100 mg, 0.30 mmol), $Pd(OAc)_2$ (2 mg, 0.0089 mmol), Ph_3P (9 mg, 0.034 mmol) in acetonitrile (3 ml) and the mixture was refluxed under an argon atmosphere until the starting material disappeared by TLC (1 h). The reaction mixture was filtered through Celite and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 2 : 1) to give (*S*)-1,2,3,5,10,10a-hexahydro-10-methylenepyrrolo[1,2-*b*]isoquinolin-5-one (**12**) (50 mg, 84%), mp 158—159 °C (from AcOEt), $[\alpha]_D^{22}$ +86.7° (*c*=0.15, $CHCl_3$). IR (CCl_4) cm^{-1}: 1665. ^{1}H-NMR (270 MHz) δ: 1.20—2.48 (4H, m), 3.58—4.34 (2H, m, 3-H_2), 4.37—4.46 (1H, m, 10a-H), 5.22 (1H, d, *J*=2.6 Hz, one of C=CH_2), 5.58 (1H, d, *J*=2.6 Hz, one of C=CH_2), 7.38—7.74 (3H, m, ArH), 8.11 (1H, dd, *J*=7.3, 1.7 Hz, ArH). Exact MS *m/z*: 199.0999 (Calcd for $C_{13}H_{13}NO$: 199.0997).

Intramolecular Heck Reaction of Compound 11 According to the general procedure, **11** (76 mg, 0.22 mmol) was treated with $Pd(OAc)_2$ (2 mg, 0.0089 mmol) to give (*S*)-2,3,5,6,11,11a-hexahydro-11-methylene-1*H*-pyrrolo[2,1-*b*][3]benzazepin-5-one (**13**) (30 mg, 70%) as an oil, $[\alpha]_D^{22}$ −185.0° (*c*=1.0, $CHCl_3$). IR (CCl_4) cm^{-1}: 1650. ^{1}H-NMR (270 MHz) δ: 1.74—2.04 (3H, m), 2.29—2.41 (1H, m), 3.27 (1H, dt, *J*=11.9, 8.2 Hz, one of 3-H_2), 3.32 (1H, d, *J*=13.2 Hz, one of 6-H_2), 3.63—3.76 (1H, m, one of 3-H_2), 3.91 (1H, d, *J*=13.2 Hz, one of 6-H_2), 4.69 (1H, dd, *J*=8.8, 7.1 Hz, 11a-H), 5.25 (1H, d, *J*=1.8 Hz, one of C=CH_2), 5.31 (1H, d, *J*=1.8 Hz, one of C=CH_2), 7.22—7.38 (4H, m, ArH). Exact MS *m/z*: 213.1139 (Calcd for $C_{14}H_{15}NO$: 213.1153).

***tert*-Butyl 2-Hydroxymethyl-2-(prop-2-enyl)pyrrolidine-1-carboxylate (14)** A solution of **5**[8] (200 mg, 0.74 mmol) in THF (2 ml) was added to a suspension of $LiAlH_4$ (31 mg, 0.82 mmol) in THF (2 ml) at 0 °C and the mixture was stirred at the same temperature for 1 h. Water was carefully added to decompose excess reagent. The inorganic material was filtered off and washed with hot ethanol. The filtrate was dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 1 : 1) to give **14** (158 mg, 88%), mp 53—55 °C (from hexane). IR (CCl_4) cm^{-1}: 3400, 1670. ^{1}H-NMR (300 MHz) δ: 1.46 (9H, s, *tert*-Bu), 1.66—1.97 (4H, m, 3- and 4-H_2), 2.57 (1H, d of a pair of ABq, *J*=13.8, 8.1 Hz, one of CH_2CH=CH_2), 2.64 (1H, d of a pair of ABq, *J*=13.8, 6.8 Hz, one of CH_2CH=CH_2), 3.31—3.48 (2H, m, 5-H_2), 3.61 (1H, d of a pair of ABq, *J*=11.5, 9.0 Hz, one of CH_2OH), 3.66 (1H, d of a pair of ABq, *J*=11.5, 2.7 Hz, one of CH_2OH), 5.07—5.16 (2H, m, CH=CH_2), 5.40 (1H, dd, *J*=9.0, 2.7 Hz, CH_2OH), 5.81 (1H, dddd, *J*=17.2, 10.2, 8.1, 6.8 Hz, CH=CH_2). *Anal.* Calcd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.44; H, 9.90; N. 5.65.

***tert*-Butyl 2-(Prop-2-enyl)-2-vinylpyrrolidine-1-carboxylate (15)** A solution of dimethyl sulfoxide (DMSO) (2.79 g, 35.7 mmol) in dry dichloromethane (5 ml) was added to a solution of oxalyl chloride (2.13 g, 16.8 mmol) in dry dichloromethane (5 ml) at −78 °C over a period of 10 min and the mixture was stirred for 10 min. Then a solution of **14** (3.59 g, 14.9 mmol) in dichloromethane (8 ml) at −78 °C was added to the mixture which was stirred at the same temperature for 15 min. After addition of Et_3N (7.53 g, 74.4 mmol) to the mixture, it was allowed to warm to room temperature. The mixture was diluted with water (10 ml) and the organic layer was separated and washed with 5% HCl, sat. aq. $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 12 : 1) to give *tert*-butyl 2-formyl-2-(prop-2-enyl)pyrrolidine-1-carboxylate (3.56 g, quant.) as an oil. IR (CCl_4) cm^{-1}: 1730, 1695. ^{1}H-NMR (60 MHz) δ: 1.43 (9H, s, *tert*-Bu), 1.7—2.2 (4H, m, 3- and 4-H_2), 2.4—2.9 (2H, m, CH_2CH=CH_2), 3.3—3.8 (2H, m, 5-H_2), 4.9—5.35 (2H, m, CH=CH_2), 5.4—6.2 (1H, m, CH=CH_2), 9.39 and 9.49 (total 1H, both br s, CHO). This compound was used for the next step without further purification.

DMSO (5 ml) was added to a flask containing NaH (60% mineral oil dispersion) (303 mg, 7.58 mmol) (washed several times with dry ether), and the mixture was heated with stirring at 65—70 °C until the evolution of hydrogen gas ceased. After cooling of this solution to 0 °C, a solution of methyltriphenylphosphonium bromide (2.71 g, 7.58 mmol) in DMSO (5 ml) was added, and the mixture was stirred at room temperature for 1 h. A solution of the aldehyde (1.21 g, 5.06 mmol) in DMSO (5 ml) was added to the above solution and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with hexane. The extract was dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 10 : 1) to give **15** (1.05 g, 88%) as a 1 : 1 oily mixture of two rotamers. IR (CCl_4) cm^{-1}: 1680. ^{1}H-NMR (300 MHz) δ: 1.44 (9H, s, *tert*-Bu), 1.64—1.85 (3H, m), 1.91—2.08 (1H, m), 2.40 and 2.53 (total 1H, both dd, *J*=13.8, 8.2 Hz, one of CH_2CH=CH_2), 2.81 and 2.94 (total 1H, both dd, *J*=13.8, 6.4 Hz, one of CH_2CH=CH_2), 3.22—3.37 (1H, m, one of 5-H_2), 3.48—3.57 and 3.58—3.68 (total 1H, both m, one of 5-H_2), 4.90—5.14 (4H, m, 2×CH=CH_2), 5.65—5.79 (1H, m, CH_2CH=CH_2), 5.87 and 5.97 (total 1H, both dd, *J*=17.1, 10.5 Hz, CH=CH_2). Exact FAB-MS *m/z*: 238.1819 (Calcd for $C_{14}H_{23}NO_2$+H: 238.1807).

1-(*o*-Iodobenzoyl)-2-(prop-2-enyl)-2-vinylpyrrolidine (16) According to the procedure described for the preparation of **10**, **16** (174 mg, 56%) was obtained from **15** (200 mg, 0.84 mmol) and *o*-iodobenzoyl chloride (338 mg, 1.26 mmol) as an oil. IR (CCl_4) cm^{-1}: 1640. ^{1}H-NMR (300 MHz) δ: 1.69—1.88 (2H, m), 1.90—2.00 (1H, m), 2.02—2.14 (1H, m), 2.55—3.40 (4H, br, 5-H_2 and CH_2CH=CH_2), 5.05—5.45 (3H, br, CH_2CH=CH_2 and one of CH=CH_2), 5.19 (1H, dd, *J*=10.7, 0.8 Hz, one of CH=CH_2), 5.77—6.05 (1H, br, CH_2CH=CH_2), 6.31 (1H, dd, *J*=17.3, 10.7 Hz, CH=CH_2), 7.04 (1H, td, *J*=7.6, 1.8 Hz, ArH), 7.19 (1H, dd, *J*=7.6, 1.8 Hz, ArH), 7.37 (1H, td, *J*=7.6, 1.0 Hz, ArH), 7.81 (1H, dd, *J*=7.6, 1.0 Hz, ArH). *Anal.* Calcd for $C_{16}H_{18}INO$: C, 52.33; H, 4.94; N, 3.81. Found: C, 52.36; H, 5.00; N, 3.74.

1-[2-(*o*-Iodophenyl)acetyl]-2-(prop-2-enyl)-2-vinylpyrrolidine (17) According to the procedure described for the preparation of **10**, **17** (756 mg, 94%) was obtained from **15** (500 mg, 2.11 mmol) and 2-(*o*-iodophenyl)-acetyl pivaloyl anhydride (1.09 g, 3.16 mmol) as a 4 : 1 oily mixture of two rotamers. IR (CCl_4) cm^{-1}: 1655. ^{1}H-NMR (300 MHz) for the major rotamer δ: 1.78—2.06 (4H, m, 3- and 4-H_2), 2.66 (1H, dd, *J*=13.5, 8.1 Hz, one of CH_2CH=CH_2), 3.03 (1H, ddt, *J*=13.5, 6.4, 1.3 Hz, one of CH_2CH=CH_2), 3.47—3.87 (2H, m, 5-H_2), 3.76 (2H, s, CH_2Ar), 5.00—5.20 (4H, m, 2×CH=CH_2), 5.67—5.82 (1H, m, CH_2CH=CH_2), 6.10 (1H, dd, *J*=17.3, 10.7 Hz, CH=CH_2), 6.90—6.97 (1H, m, ArH), 7.25—7.35 (2H, m, ArH), 7.82 (1H, d, *J*=7.8 Hz, ArH). Selected signals for the minor rotamer δ: 1.78—2.39 (4H, m, 3- and 4-H_2), 2.79 (1H, dd, *J*=13.5, 8.1 Hz, one of CH_2CH=CH_2), 2.95 (1H, ddt, *J*=13.5, 6.4, 1.3 Hz, one of CH_2CH=CH_2), 3.77 (2H, s, CH_2Ar). Exact FAB-MS *m/z*: 382.0653 (Calcd for $C_{17}H_{20}INO$+H: 382.0668).

Intramolecular Heck Reaction of Compound 16 According to the general procedure, **16** (496 mg, 1.35 mmol) was treated with $Pd(OAc)_2$ (10 mg, 0.045 mmol) to give 10-(3-butenyl)-1,2,3,5-tetrahydropyrrolo-[1,2-*b*]isoquinolin-5-one (**18**) (289 mg, 89%) as an oil. IR (CCl_4) cm^{-1}: 1650, 1620. ^{1}H-NMR (300 MHz) δ: 2.19 (2H, quintet, *J*=7.3 Hz), 2.28—2.38 (2H, m), 2.74—2.82 (2H, m), 3.11 (2H, t, *J*=7.6 Hz), 4.21 (2H, dd, *J*=7.3, 6.8 Hz), 4.97—5.10 (2H, m, C=CH_2), 5.89 (1H, ddt, *J*=17.0, 10.3, 6.8 Hz, CH_2CH=CH_2), 7.43 (1H, ddd, *J*=8.0, 6.0, 2.1 Hz, ArH), 7.60—7.69 (2H, m, ArH), 8.46 (1H, br d, *J*=8.0 Hz, ArH). ^{13}C-NMR δ: 21.6 (CH_2), 27.4 (CH_2), 30.2 (CH_2), 33.6 (CH_2), 48.3 (CH_2), 109.7 (quaternary C), 115.4 (=CH_2), 122.2, 125.3, 125.4 (quaternary C), 127.8, 131.8, 137.4 (quaternary C), 137.7, 140.6 (quaternary C), 160.9 (C=O). Exact FAB-MS *m/z*: 240.1396 (Calcd for $C_{16}H_{17}NO$+H: 240.1388).

When the same reaction was carried out at 50—60 °C for 30 min, **16** (160 mg, 0.44 mmol) gave 1,2,3,5,10,10a-hexahydro-10-methylene-10a-(prop-2-enyl)pyrrolo[1,2-*b*]isoquinolin-5-one (**19**) (54 mg, 52%) along with the starting material **16** (74 mg, 46%). Compound **19** was an oil. IR (CCl_4) cm^{-1}: 1645. ^{1}H-NMR (300 MHz) δ: 2.04—2.13 (3H, m), 2.23—2.37 (3H, m), 3.70—3.84 (2H, m), 4.88—4.97 (1H, m, one of CH=CH_2), 4.97—5.03 (1H, m, one of CH=CH_2), 5.08 (1H, s, one of C=CH_2), 5.53 (1H, dddd, *J*=17.0, 10.2, 7.8, 6.9 Hz, CH_2CH=CH_2), 5.63 (1H, s, one of C=CH_2), 7.42 (1H, td, *J*=7.4, 1.7 Hz, ArH), 7.49 (1H, td, *J*=7.4, 1.5 Hz, ArH), 7.52—7.57 (1H, m, ArH), 8.07—8.11 (1H, m, ArH). ^{13}C-NMR δ: 20.7 (CH_2), 34.4 (CH_2), 42.0 (CH_2), 44.9 (CH_2),

67.6 (10a-C), 111.9 (=CH_2), 118.7 (=CH_2), 124.1, 127.5, 128.5 (quaternary C), 128.7, 132.0, 132.8, 135.5 (quaternary C), 144.8 (5a-C), 162.0 (C=O). Exact MS *m/z*: 239.1316 (Calcd for $C_{16}H_{17}NO$: 239.1310).

Thermal Isomerization of 19 to 18 A solution of **19** (54 mg, 0.23 mmol) in acetonitrile (5 ml) was refluxed for 4 h. The mixture was concentrated and the residue was chromatographed on silica gel (hexane–AcOEt, 2 : 1) to give **18** (50 mg, 93%) as an oil.

Intramolecular Heck Reaction of Compound 17 According to the general procedure, **17** (756 mg, 1.98 mmol) was treated with $Pd(OAc)_2$ (13 mg, 0.058 mmol) and the crude products were chromatographed on silica gel (hexane–AcOEt, 5 : 1). The first fraction gave hexahydro-1*H*-pyrrolo[2,1-*b*][3]benzazepin-5-one (**20**) (256 mg, 51%) as an oil. IR (CCl_4) cm^{-1}: 1640. ^{1}H-NMR (270 MHz) δ: 1.84—2.16 (4H, m), 2.58 (1H, dd, J=14.2, 8.3 Hz, one of $CH_2CH=CH_2$), 2.82 (1H, dd, J=14.2, 6.6 Hz, one of $CH_2CH=CH_2$), 3.27 (1H, d, J=13.5 Hz, one of 6-H_2), 3.46—3.65 (2H, m, 3-H_2), 3.97 (1H, d, J=13.5 Hz, one of 6-H_2), 5.12—5.22 (2H, m, $CH_2CH=CH_2$), 5.27 (1H, s, one of $C=CH_2$), 5.43 (1H, s, one of $C=CH_2$), 5.99 (1H, dddd, J=17.8, 9.6, 8.3, 6.6 Hz, $CH_2CH=CH_2$), 7.14—7.27 (4H, m, ArH). Exact MS *m/z*: 253.1463 (Calcd for $C_{17}H_{19}NO$: 253.1467). The second fraction gave a mixture (102 mg, <20%) of compound **21** and an unidentified compound, which was recrystallized several times from hexane–AcOEt to give (3a*S**,13b*S**)-1,2,3,5,6,8,9,13b-octahydro-2-methylene-4*H*-cyclopenta[*a*]pyrrolo[2,1-*b*][3]benzazepin-8-one (**21**) as a pure sample, mp 107—108 °C. IR ($CHCl_3$) cm^{-1}: 1625. ^{1}H-NMR (300 MHz) δ: 1.72—1.97 (3H, m, one of 4- and 5-H_2), 2.02—2.14 (1H, m, one of 4-H_2), 2.50 (1H, d, J=15.4 Hz, one of 3-H_2), 2.55—2.90 (2H, m, 1-H_2), 2.82 (1H, br d, J=15.4 Hz, one of 3-H_2), 3.20—3.32 (1H, m, one of 6-H_2), 3.39 (1H, d, J=13.5 Hz, one of 9-H_2), 3.59—3.81 (2H, m, one of 6-H_2 and 13b-H), 4.02 (1H, d, J=13.5 Hz, one of 9-H_2), 4.92 (2H, s, =CH_2), 7.07—7.31 (4H, m, ArH). *Anal.* Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.57; H, 7.55; N, 5.31.

Crystal Structure Determination of Compound 21[15] A single crystal of **21** was obtained by recrystallization from hexane–AcOEt. Crystal data of **21**: $C_{17}H_{19}NO$, Mr=253.34, colorless prismatic, space group $P2_1/c$, a=7.974(5) Å, b=23.050(4) Å, c=7.452(5) Å, V=1369(1) Å^3, Z=4, $D_{calcd.}$=1.229 g cm^{-3}, μ(Cu$K\alpha$)=5.90 cm^{-1}. The R (R_w) value of **21** was 0.082 (0.117). The data were collected on a Rigaku AFC7R diffractometer at 23±1 °C using graphite monochromated Cu$K\alpha$ (λ=1.54178 Å) radiation. The structure was solved by direct methods (MITHRIL84[16]). The non-hydrogen atoms were refined anisotropically. Hydrogen atoms included but not refined. Neutral atom scattering factors were taken from Cromer and Weber.[17] All calculations were performed using the teXsan[18] crystallographic software package of Molecular Structure Corporation.

***tert*-Butyl 2-Formyl-2-acetonylpyrrolidine-1-carboxylate (22)** A suspension of $PdCl_2$ (296 mg, 1.67 mmol) and CuCl (871 mg, 8.36 mmol) in DMF (6 ml)–H_2O (2 ml) was stirred under an oxygen atmosphere at room temperature for 1 h. A solution of *tert*-butyl 2-formyl-2-(prop-2-enyl)pyrrolidine-1-carboxylate (2.0 g, 8.4 mmol) in DMF (4 ml) was added to the suspension and the mixture was stirred overnight at room temperature under an oxygen atmosphere. The mixture was poured into ice-cooled 10% HCl and extracted with dichloromethane. The extract was washed with sat. aq. $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 5 : 1) to give **22** (1.53 g, 72%) as an oil. IR (CCl_4) cm^{-1}: 1735, 1700, 1685. ^{1}H-NMR (60 MHz) δ: 1.43 (9H, s, *tert*-Bu), 1.75—2.2 (4H, m, 3- and 4-H_2), 2.23 (3H, s, CH_3CO), 2.8—3.2 (2H, m, CH_3COCH_2), 3.35—3.75 (2H, m, 5-H_2), 9.2—9.4 (1H, br, CHO). This compound was used for the next step without further purification.

***tert*-Butyl 7-Oxo-1-azaspiro[4.4]non-8-ene-1-carboxylate (23)** A solution of K_2CO_3 (1.93 g, 14.1 mmol) in water (20 ml) was added to a solution of **22** (2.40 g, 9.40 mmol) in methanol (25 ml) and the mixture was stirred at 70 °C for 40 min. Sat. aq. NH_4Cl was added to it and the whole was extracted with dichloromethane. The extract was dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 1 : 1) to give **23** (1.12 g, 50%) as a 2 : 1 mixture of two rotamers, mp 76—77 °C (from hexane). IR (CCl_4) cm^{-1}: 1720, 1690. ^{1}H-NMR (300 MHz) for the major rotamer δ: 1.36 (9H, s, *tert*-Bu), 1.82—2.01 (4H, m, 3- and 4-H_2), 2.37 and 2.77 (1H each, ABq, J=18.1 Hz, 6-H_2), 3.38—3.69 (2H, m, 2-H_2), 6.10 (1H, d, J=5.4 Hz, 8-H), 7.35 (1H, d, J=5.6 Hz, 9-H). Selected signals for the minor rotamer δ: 1.44 (9H, s, *tert*-Bu), 2.33 and 2.95 (1H each, ABq, J=18.0 Hz, 6-H_2), 6.15 (1H, d, J=5.4 Hz, 8-H), 7.44 (1H, d, J=5.5 Hz, 9-H). *Anal.* Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.53; H, 8.10; N, 5.89.

1-(*o*-Iodobenzoyl)-1-azaspiro[4.4]non-8-en-7-one (24) According to the procedure described for the preparation for **10**, **24** (158 mg, 43%) was obtained from **23** (239 mg, 1.01 mmol) and *o*-iodobenzoyl chloride (424 mg, 1.51 mmol), mp 130—131 °C (from AcOEt). IR (CCl_4) cm^{-1}: 1725, 1625. ^{1}H-NMR (300 MHz) δ: 1.88—2.06 (3H, m), 2.10—2.21 (1H, m), 2.42 (1H, d, J=17.6 Hz, one of 6-H_2), 3.23—3.43 (3H, br, 2-H_2 and one of 6-H_2), 6.26 (1H, d, J=5.6 Hz, 8-H), 7.09 (1H, ddd, J=8.0, 7.5, 1.7 Hz, ArH), 7.23 (1H, dd, J=7.6, 1.5 Hz, ArH), 7.40 (1H, td, J=7.5, 1.1 Hz, ArH), 7.62 (1H, br d, J=5.5 Hz, 9-H), 7.82 (1H, dd, J=8.0, 1.1 Hz, ArH). *Anal.* Calcd for $C_{15}H_{14}INO_2$: C, 49.07; H, 3.84; N, 3.81. Found: C, 48.92; H, 3.79; N, 3.66.

1-[2-(*o*-Iodophenyl)acetyl]-1-azaspiro[4.4]non-8-en-7-one (25) According to the procedure described for the preparation of **11**, **25** (595 mg, 93%) was obtained from **23** (400 mg, 1.69 mmol) and 2-(*o*-iodophenyl)-acetyl pivaloyl anhydride (709 mg, 2.53 mmol), mp 145—146 °C (from hexane–AcOEt). IR ($CHCl_3$) cm^{-1}: 1700, 1640. ^{1}H-NMR (300 MHz) δ: 1.80—1.90 (1H, m), 2.00—2.16 (3H, m), 2.33 and 3.06 (1H each, ABq, J=17.4 Hz, 6-H_2), 3.63—3.84 (2H, m, 2-H_2), 3.74 (2H, s, $ArCH_2CO$), 6.12 (1H, d, J=5.6 Hz, 8-H), 6.95 (1H, ddd, J=7.8, 7.2, 2.0 Hz, ArH), 7.26 (1H, dd, J=7.5, 2.0 Hz, ArH), 7.31 (1H, ddd, J=7.5, 7.1, 1.2 Hz, ArH), 7.46 (1H, d, J=5.6 Hz, 9-H), 7.82 (1H, dd, J=8.0, 1.1 Hz, ArH). *Anal.* Calcd for $C_{16}H_{16}INO_2$: C, 50.41; H, 4.23; N, 3.67. Found: C, 50.61; H, 4.30; N, 3.43.

Intramolecular Heck Reaction of Compound 24 According to the general procedure, **24** (158 mg, 0.43 mmol) was treated with $Pd(OAc)_2$ (3 mg, 0.013 mmol) to give 2,3,4,5-tetrahydro-6*H*,8*H*-cyclopenta[*c*]pyrrolo[1,2-*b*]isoquinoline-2,8-dione (**26**) (12 mg, 12%), mp 121—122 °C (from AcOEt). IR (CCl_4) cm^{-1}: 1710, 1655. ^{1}H-NMR (300 MHz) δ: 1.79 (2H, t, J=7.1 Hz), 1.97—2.15 (2H, m), 2.74 (2H, s, 3-H_2), 3.23 (1H, ddd, J=12.5, 9.1, 7.0 Hz, one of 6-H_2), 4.66 (1H, ddd, J=12.5, 8.2, 5.7 Hz, one of 6-H_2), 6.54 (1H, s, 1-H), 7.60—7.76 (3H, m, ArH), 8.27—8.34 (1H, m, ArH). ^{13}C-NMR δ: 22.0 (CH_2), 37.8 (CH_2), 44.8 (CH_2), 50.9 (CH_2), 69.3 (3a-C), 125.7 (1-C), 127.8, 127.9 (quaternary C), 129.6, 130.0 (quaternary C), 132.3, 133.0, 164.6 (8-C or 12b-C), 165.5 (12b-C or 8-C), 202.0 (C=O). Exact FAB-MS *m/z*: 240.1033 (Calcd for $C_{15}H_{13}NO_2$+H: 240.1025). *Anal.* Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.84; H, 5.69; N, 5.68.

The yield of **26** was improved by the following procedure. A mixture of **24** (100 mg, 0.27 mmol), $Pd(OAc)_2$ (12 mg, 0.05 mmol), POT (33 mg, 0.11 mmol), and Ag_2CO_3 (150 mg, 0.55 mmol) in DMF (10 ml) was refluxed under an argon atmosphere until the starting material disappeared by TLC (2 h). The reaction mixture was filtered through Celite and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 1 : 1) to give **26** (43 mg, 66%).

Intramolecular Heck Reaction of Compound 25 Following the procedure described above for the preparation of **26**, treatment of **25** (113 mg, 0.30 mmol) with $Pd(OAc)_2$ (13 mg, 0.058 mmol), POT (36 mg, 0.12 mmol), and Ag_2CO_3 (163 mg, 0.59 mmol) in DMF (10 ml) gave 2,3,5,6,8,9-hexahydro-4*H*-cyclopenta[*a*]pyrrolo[2,1-*b*][3]benzazepine-2,8-dione (**27**) (26 mg, 35%), mp 257—258 °C (from hexane–AcOEt). IR ($CHCl_3$) cm^{-1}: 1700, 1620. ^{1}H-NMR (300 MHz) δ: 1.65—1.74 (2H, m), 1.92—2.11 (2H, m), 2.80 (2H, s, 3-H_2), 3.42 and 3.81 (1H each, ABq, J=13.8 Hz, 9-H_2), 3.42—3.52 (1H, m, one of 6-H_2), 3.67—3.79 (1H, m, one of 6-H_2), 6.15 (1H, s, 1-H), 7.29—7.45 (4H, m, ArH). ^{13}C-NMR δ: 20.8 (CH_2), 40.3 (CH_2), 42.1 (CH_2), 46.2 (CH_2), 50.4 (CH_2), 70.5 (3a-C), 126.3 (1-C), 127.8 (arom. CH), 128.4 (arom. CH), 130.5, 130.6, 133.8 (quaternary C), 132.6 (quaternary C), 167.3 (13b-C), 175.8 (8-C), 202.3 (C=O). *Anal.* Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.71; H, 5.95; N, 5.33.

The yield of **27** was further improved to 51% by using the following procedure. A mixture of **25** (120 mg, 0.32 mmol), $Pd(OAc)_2$ (71 mg, 0.32 mmol), DPPP (130 mg, 0.32 mmol), Bu_3P (64 mg, 0.32 mmol) and Ag_2CO_3 (174 mg, 0.63 mmol) in DMF (10 ml) was refluxed for 3 h under an argon atmosphere. Work-up as above gave **27** (41 mg, 51%).

Acknowledgement The authors would like to thank Mr. Ken-ichiro Matsubayashi, Susumu Akamatsu, and Kazuya Iwamoto for their technical assistance.

References and Notes

1) *a*) Heck R. F., *Org. React.*, **27**, 345—390 (1982); *b*) Tsuji J., "Organic Synthesis with Palladium Compounds," Springer-Verlag, Wien,

1980; *c*) Grigg R., *J. Heterocycl. Chem.*, **31**, 631—639 (1994); *d*) Daves G. D., Hallberg A., *Chem. Rev.*, **89**, 1433—1445 (1989).
2) For reviews of the *Cephalotaxus* alkaloids, see: Huang L., Xue Z., "The Alkaloids-Chemistry and Pharmacology," Vol. 23, ed. by Brossi A., Academic Press, Orland, 1984, pp. 157—226; Smith C. R., Jr., Mikolajczak K. L., Powell R. G., "Anticancer Agents Based on Natural Product Models," ed. by Cassady J. M., Douros J. D., Academic Press, New York, 1980, pp. 391—416; Miah M. A. J., Hudlicky T., Reed J. W., "The Alkaloids-Chemistry and Biology," Vol. 51, ed. by Cordell G. A., Academic Press, San Diego, 1998, pp. 199—269.
3) For the synthesis of optically active cephalotaxine, see: *a*) Isono N., Mori M., *J. Org. Chem.*, **60**, 115—119 (1995); *b*) Nagasaka T., Sato H., Saeki S., *Tetrahedron: Asymmetry*, **8**, 191—194 (1997).
4) For other total syntheses of (±)-cephalotaxine, see: *a*) Weinreb S. M., Auerbach J., *J. Am. Chem. Soc.*, **97**, 2503—2506 (1975); *b*) Semmelhack M. F., Chong B. P., Stauffer R. D., Rogerson T. D., Chong A., Jones L. D., *ibid.*, **97**, 2507—2516 (1975); *c*) Yasuda S., Yamada T., Hanaoka M., *Tetrahedron Lett.*, **27**, 2023—2026 (1986); *d*) Kuehne M. E., Bornmann W. G., Parsons W. H., Spitzer T. D., Blount. J. F., Zubieta J., *J. Org. Chem.*, **53**, 3439—3449 (1988); *e*) Burkholder T. P., Fuchs P. L., *J. Am. Chem. Soc.*, **112**, 9601—9613 (1990); *f*) Ikeda M., Okano M., Kosaka K., Kido M., Ishibashi H., *Chem. Pharm. Bull.*, **41**, 276—281 (1993); *g*) Lin X. D., Kavash R. W., Mariano P. S., *J. Org. Chem.*, **61**, 7335—7347 (1996); *h*) Tietze L. F., Schirok H., *Angew. Chem., Int. Ed. Engl.*, **36**, 1124—1125 (1997).
5) Parts of this work have appeared as preliminary communications: Ikeda M., Akamatsu S., Kugo Y., Sato T., *Heterocycles*, **42**, 155—158 (1996); Ikeda M., Matsubayashi K., Imoto T., Kitao K., Ishibashi H., Sato T., *ibid.*, **38**, 1237—1240 (1994).
6) Takeuchi Y., Yamada A., Suzuki T., Koizumi T., *Tetrahedron*, **52**, 225—232 (1996).
7) Tietze L. F., Burkhardt O., *Synthesis*, **1994**, 1331—1336.
8) Confalone P. N., Huie E. M., Ko S. S., Cole G. M., *J. Org. Chem.*, **53**, 482—487 (1988).
9) Reduction of **5** with LiI and $NaBH_4$ in ether under reflux for 24 h or with diisobutylaluminum hydride in dichloromethane at room temperature for 24 h gave **14** in 64 and 60% yields, respectively.
10) Abelman M. M., Overman L. E., *J. Am. Chem. Soc.*, **110**, 2328—2329 (1988).
11) Tsuji J., *Synthesis*, **1984**, 369—384.
12) Harayama T., Akiyama T., Kawano K., *Chem. Pharm. Bull.*, **44**, 1634—1636 (1996).
13) Harayama T., Akiyama T., Nakano Y., *Chem. Pharm. Bull.*, **45**, 1723—1725 (1997).
14) For Pd-catalyzed aryl-enone cyclizations, see: *a*) Ishibashi H., Ito K., Hirano T., Tabuchi M., Ikeda M., *Tetrahedron*, **49**, 4173—4182 (1993); *b*) Friestad G. K., Branchaud B. P., *Tetrahedron Lett.*, **36**, 7047—7050 (1995); *c*) Comins D. L., Joseph S. P., Zhang Y.-M., *ibid.*, **37**, 793—796 (1996); *d*) Yoneda R., Kimura T., Kinomoto J., Harusawa S., Kurihara T., *J. Heterocycl. Chem.*, **33**, 1909—1913 (1996); *e*) Gibson S. E., Guillo N., Tozer M. J., *Chem. Commun.*, **1997**, 637—638; *f*) Friestad G. K., Branchaud B. P., *Tetrahedron Lett.*, **34**, 5933—5936 (1997). For other examples of the formal *anti*-elimination, see: Dieck H. A., Heck R. F., *J. Organomet. Chem.*, **93**, 259—263 (1975); Amos P. C., Whiting D. A., *J. Chem. Soc., Chem. Commun.*, **1987**, 510—511; Grigg R., Sridharan V., Stevenson P., Sukirthalingam S., Worakun T., *Tetrahedron*, **46**, 4003—4018 (1990); McIntosh M. C., Weinreb S. M., *J. Org. Chem.*, **58**, 4823—4832 (1993); Grigg R., Fretwell P., Meerholtz C., Sridharan V., *Tetrahedron*, **50**, 359—370 (1994).
15) The authors have deposited the atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from The Director, Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.
16) MITHRIL84: Gilmore C. J. (1984). An integrated direct methods computer program. Univ. of Glasgow, Scotland.
17) Cromer D. T., Waber J. T., "International Tables for X-ray Crystallography," Vol. 4, The Kynoch Press, Birmingham, 1974, Table 2.2 A.
18) teXan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 and 1992).