A New Synthetic Method for an Indolizidine Skeleton by C–N Bond Formation *via* a π-Allylpalladium Complex

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Pd(0)-catalyzed intramolecular cyclic reaction *via* a π-allylpalladium complex provided an indolizidine skeleton in satisfactory high and reproducible yields by using allylic compound having an acetoxyl group as a leaving group. These results must be available for syntheses of various functional indolizidine alkaloids.

Key words π-allylpalladium complex; indolizidine; Pd(0); C–N bond formation

In recent years, π-allylpalladium complexes have found wide application in the field of synthetic organic chemistry[1] since the report by Smidt in 1959.[2] Especially, allylic alkylation *via* a π-allylpalladium complex is an important reaction.[3] This reaction is known to involve the processes of oxidative addition of Pd(0) to allylic compounds which have appropriate leaving groups to make a π-allylpalladium complex and subsequent reaction with such nucleophiles as carbon, nitrogen, oxygen to make C–C, C–N, C–O bond formation. Among them, amines have been known to be the most reactive nucleophiles to a π-allylpalladium complex to make both intra- and intermolecular C–N bond formation readily.[4] Several intramolecular C–N bond formations *via* π-allylpalladium complex have been applied to the synthesis of alkaloids such as inandenin-12-one,[5] perhydrohistrionicotoxin.[6,7] We are interested in application of π-allylpalladium complex in the synthesis of alkaloids having nitrogen in the bridge head such as pyrrolizidine and indolizidine. However, little study has been reported on the synthesis of condensed-ring compounds such as pyrrolizidine, indolizidine *via* a π-allylpalladium complex except only a few reports.[5,8,9] In 1989, Trost reported the synthesis of *all*-pumiliotoxin 339B[8] by constructing an indolizidine skeleton *via* intramolecular C–N bond formation of an allyllic compound having epoxide as a leaving group. However, construction of pyrrolizidine and indolizidine skeleton by palladium-catalyzed intramolecular C–N bond formation of allylic compound having other leaving group than epoxide group have not yet been reported. Generally, allylic acetate and allylic carbonate which have each acetoxyl and methoxycarbonyloxyl group as a leaving group, respectively have been well used as allylic compounds up to date in palladium-catalyzed cyclic reaction. In this paper we wish to communicate our results in the application of a π-allylpalladium complex to construct an indolizidine skeleton which has nitrogen at the brige-head using acetoxyl group as a leaving group.

Initially, we selected a pyrrolizidine skeleton as a target for a condensed-ring compound having nitrogen at the bridge-head. Our strategy for the synthesis of the pyrrolizidine skeleton *via* a π-allylpalladium complex involves the synthesis of a key compound **4** from a L-proline derivative, following the palladium-catalyzed cyclic reaction.

One of the reason for using allylacetate **4** having bisallyl group is to raise the reactivity of palladium-catalyzed cyclic reaction and the other is if cyclization occurs to give **5**, vinyl group of the side chain will serve to convert **5** to a biologically active compound.

In initial studies when employing Boc, Cbz, Moz as an amino-protected group, acetyl group was removed at the same time in the process of the elimination of these amino-protective group due to acid conditions in the reaction. Finally, the Aloc (allyloxycarbonyl) group proved to be suitable for an amino-protected groups because it is easily removed under mild neutral conditions by using a Pd(0) reagent. The synthetic procedure of a precursor **4** is shown as follows (Chart 1).

L-Proline methyl ester hydrochloride **1** was protected with the Aloc group by treatment with Aloc-chloride in pyridine–CH_2Cl_2 at 0 °C to afford *N*-Aloc derivative **2**, quantitatively. Grignard reaction of methyl ester **2** using three equivalents of vinyl magnesium bromide in THF at 0 °C, followed by acetylation with acetyl chloride at room temperature afforded bisallylic compound **3** in 67% yield from **2**.

Two kinds of reaction conditions (A, B) were adopted for removal of the Aloc group. Compound **3** reacted with $Pd(Ph_3P)_4$ in the presence of dimedone in THF at room temperature to give amine **4** in 75% yield, and also with

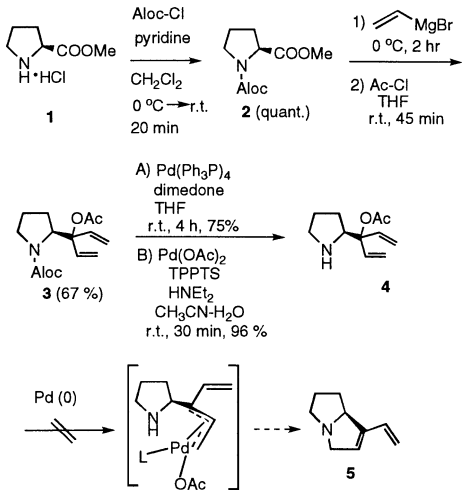

Chart 1

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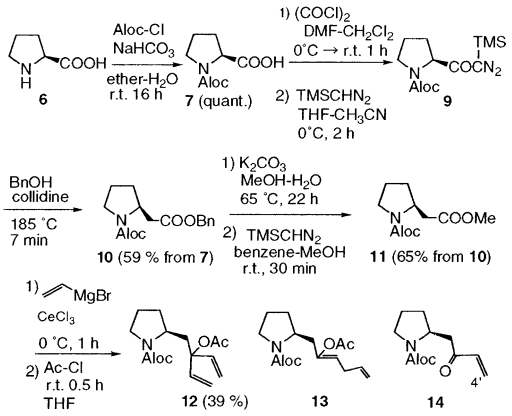

Chart 2

$Pd(OAc)_2$ in the presence of 3,3′,3″-phosphinidynetris(benzenesulfonic acid)trisodium salt (TPPTS), $HNEt_2$ in CH_3CN–H_2O to give amine **4** in 96% yield.

Unfortunately, C–N bond formation to produce **5** did not occur with substrate **4** using Pd(0) in spite of our many efforts varying the catalyst such as $Pd(Ph_3P)_4$, $Pd_2(dba)_3$, varying the base such as NEt_3, NaH, DBU and varying the solvent such as CH_3CN, DMF, THF to give mostly starting material **4** only in all cases. Pd(0) catalyzed cyclic reaction from **3** to **5** directly did not occur using $Pd(Ph_3P)_4$, dimedone in THF even under violent condition at 70 °C.

Then we turned our attention to construction of an indolizidine skeleton. The precursor **12** for Pd(0)-catalyzed cyclic reaction to an indolizidine skeleton was synthesized as described in Chart 2. L-Proline was protected with the Aloc group in a similar way to give **7**, quantitatively. The Arndt–Eistert reaction[10,11] was employed to obtain benzyl *N*-Aloc-pyrrolidine-2-acetate **10**. *N*-Aloc proline **7** was converted to acyl chloride **8** by oxalyl chloride in DMF–CH_2Cl_2 at 0 °C to room temperature, followed by formation of diazoketone **9** using $TMSCHN_2$ in THF–CH_3CN at 0 °C and then the crude substance **9** was heated at 185 °C in collidine in the presence of benzyl alcohol to afford benzyl acetate **10** in 59% yield from **7**. Alkaline hydrolysis of ester **10** by treatment with K_2CO_3 in MeOH–H_2O, followed by esterification with $TMSCHN_2$ in benzene–MeOH at room temperature afforded methyl ester **11** in 65% yield from **10**. Grignard reaction of **11** by using three equivalents of vinyl magnesium bromide in the presence of anhydrous $CeCl_3$[12] in THF at 0 °C, followed by acetylation gave a bisallylic compound **12** as a main product in 39% yield. When Grignard reaction was carried out in the absence of $CeCl_3$, **12** was obtained in 24% yield, accompanied with isomer **13** which resulted from conjugate addition of a second molecule of vinyl group to the initially formed vinyl ketone **14** (Chart 2).

Then, transformation of the indolizidine precursor **12** by Pd(0)-catalyzed cyclic reaction was performed. Attempts for removal of the Aloc group of **12** caused, fortunately, C–N bond formation at the same time as described belows. π-Allylpalladium cyclization of **12** using $Pd(Ph_3P)_4$ in the presence of dimedone in THF at −20 °C to 0 °C afforded successfully indolizidine derivative **15** as a single product in 62% yield. The base **15** was derived to HCl salts by treatment with 0.1 N HCl in 75% yield. The indolizidine **15** will

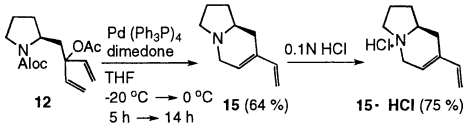

Chart 3

serve as an important precursor to synthesize naturally occurring alkaloids such as the Ipalpidine[13] group (Chart 3). We are now going to transformation of **15** to Ipalpidine by following strategy.

Selective oxidation of vinyl group of side chain, followed by appropriate reduction would produce methyl group, then Heck reaction of phenyl iodide with an inner olefin of the ring would give Ipalpidine.

The reason why the Pd(0)-catalyzed cyclic reaction did not occur in precursor **3** and it occurred successfully in precursor **12** is considered that the strain of the five-membered ring having bridge-head nitrogen is presumed more large than that of six-membered ring.

This cyclic reaction will be utilized for syntheses of various functional indolizidine alkaloids and other condensed-ring compound having nitrogen at the bridge-head. We are now examining the scope and limitations of this reaction. In conclusion, Pd(0)-catalyzed cyclic reaction using allylic compound **12**, having an acetoxyl group as a leaving group provided an indolizidine skeleton in satisfactory high and reproducible yields. These results will serve to build up various indolizidine skeletons and other condensed-ring compounds having nitrogen at the bridge-head such as quinolizidine.

Experimental

^{1}H- and ^{13}C-NMR were recorded on Varian VXR-300, XL-400 spectrometers. IR spectra were recorded with a JASCO FT/IR Spectrometer for windows. Mass spectra were obtained on a JEOL-JMX-DX 300 mass spectrometer (low-resolution mass spectrometry) and JEOL-JMS-AX505 HA mass spectrometer (high-resolution mass spectrometry). Routine monitoring of reaction was carried out using Merck 60 GF254 silica gel, glass-supported plates (TLC). Flash column chromatography was done on silica gel 60 PF254 (Merck).

(2*S*)-*N*-Allyloxycarbonyl-L-proline Methyl Ester (2) Pyridine (4.68 ml, 57.8 mmol), allyloxycarbonyl (Aloc) chloride (3.68 ml, 34.7 mmol) were added to a solution of proline methyl ester hydrochloride (3.83 g, 23.1 mmol) in CH_2Cl_2 (96 ml), stirred for 20 min at 0 °C and stirred further for 20 min at room temperature. A reaction mixture was diluted with $CHCl_3$ (100 ml), washed with saturated $NaHCO_3$ solution (40 ml×2), saturated NaCl solution (10 ml×2) and organic layer was dried over Na_2SO_4, concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, *n*-hexane : AcOEt=1 : 1) to give **2** (4.92 g, 100%) as colorless oil. *Rf*=0.90 ($CHCl_3$: MeOH=10 : 1); $[\alpha]_D^{22}$ −54.34° (*c*=0.99, $CHCl_3$); IR ($CHCl_3$) ν_{max} cm^{-1}: 1650 (vinyl), 1690 (–NCOO–), 1740 (–$COOCH_3$); ^{1}H-NMR (400 MHz) δ: 1.90 (2H, m, 4-H_2), 2.00 (1H, m, 3-Ha), 2.20 (1H, m, 3-Hb), 3.48 (1H, m, 5-Ha), 3.57 (1H, m, 5-Hb), 3.69, 3.71 (total 3H, each s, $COOCH_3$), 4.34 (1H, ddd, *J*=15.0, 10.0, 4.0 Hz, 2-H), 4.55 (2H, m, –OCH_2–), 5.14, 5.18 (total 1H, each dd, *J*=11.0, 2.0 Hz, =CH_2-*cis*), 5.23, 5.29 (total 1H, each dd, *J*=18.0, 2.0 Hz, =CH_2-*trans*), 5.88 (1H, m, –CH=); ^{13}C-NMR (100.6 MHz) δ: 23.44, 24.26 (each t, 4-C), 29.83, 30.86 (each t, 3-C), 46.28, 46.79 (each t, 5-C), 52.07, 52.13 (each q, $COO\underline{C}H_3$), 58.74, 59.05 (each d, 2-C), 65.71, 65.87 (each t, –OCH_2), 116.90, 117.21 (each t, =CH_2), 132.73, 132.88 (each d, –CH=), 154.09, 154.64 (each s, NCOO), 173.05, 173.20 (each s, $\underline{C}OOCH_3$); HR-FAB-MS *m*/*z*: 214.1082 $[M+H]^+$, Calcd for $C_{10}H_{16}O_4N$: 214.1079.

(2*S*)-*N*-Allyloxycarbonyl-2-(1-acetyloxy-1-vinyl-2-propenyl) Pyrrolidine (3) Vinyl magnesium bromide solution (1 M, in THF) (4.31 ml, 4.31 mmol) was dropped to a solution of **2** (437 mg, 2.05 mmol) at 0 °C, stirred for 1 h under argon and vinyl magnesium bromide solution (1 M, in THF) (1.00 ml, 1.00 mmol) was further added and stirred 1 h at 0 °C. After

that, acetyl chloride (0.36 ml, 5.13 mmol) was added to the reaction mixture and stirred for 45 min at room temperature. THF was evaporated *in vacuo* and neutralized with saturated NH_4Cl solution, extracted with AcOEt (100 ml×3). The organic layer was washed with saturated NaCl (20 ml×3), dried over Na_2SO_4, concentrated *in vacuo* to afford crude substance (642 mg) as orange oil, which was purified by flash column chromatography (silica gel, *n*-hexane : AcOEt=10 : 1—7 : 1—5 : 1) to afford **3** (383 mg, 67%) as light yellow oil. *Rf*=0.18 (*n*-hexane : AcOEt=5 : 1); $[\alpha]_D^{24}$ −38.8° (*c*=0.98, $CHCl_3$); IR ($CHCl_3$) ν_{max} cm^{-1}: 1735 ($OCOCH_3$), 1690 (NCOO); ^{1}H-NMR (400 MHz, pyridine-d_5, 80.0 °C) δ: 1.63—1.71 (1H, m, 4-Hb), 1.83—1.95 (3H, m, 3-H, 4-Ha), 2.08 (3H, s, $OCOCH_3$), 3.35 (1H, ddd, *J*=11.0, 8.0, 6.0 Hz, 5-Hb), 3.38 (1H, ddd, *J*=11.0, 8.0, 6.0 Hz, 5-Ha), 4.72 (1H, ddt, *J*=13.5, 5.0, 1.5 Hz, –OCHa–), 4.78 (1H, ddt, *J*=13.5, 5.0, 1.5 Hz, –OCHb–), 5.01 (1H, dd, *J*=6.0, 5.0 Hz, 2-H), 5.22 (1H, dq, *J*=10.5, 1.5 Hz, $=CH_2$-*cis*), 5.31 (2H, dd, *J*=11.0, 1.5 Hz, 3′,3″-H_2-*cis*), 5.40 (2H, dq, *J*=17.5, 1.5 Hz, $=CH_2$-*trans*), 5.40 (2H, dq, *J*=17.5, 1.5 Hz, 3′,3″-H_2-*trans*), 6.07 (1H, ddt, *J*=17.5, 10.5, 5.0 Hz, –CH=), 6.32 (1H, dd, *J*=17.5, 11.0 Hz, 2′-H), 6.45 (1H, dd, *J*=17.5, 11.0 Hz, 2″-H); HR-FAB-MS *m/z*: 302.1357 $[M+Na]^+$, Calcd for $C_{15}H_{21}O_4NNa$: 302.1368.

(2*S*)-2-(1-Acetyloxy-1-vinyl-2-propenyl) Pyrrolidine (4) by Method A Tetrakis (triphenylphosphine) palladium (0) $[Pd(Ph_3P)_4]$ (31.7 mg, 0.03 mmol), dimedone (293 mg, 2.09 mmol) were added to a solution of **3** in THF (5.0 ml) at room temperature under argon and stirred for 2 h. $Pd(Ph_3P)_4$ (31.7 mg, 0.03 mmol) was further added and stirred for 1.5 h. $Pd(Ph_3P)_4$ (9.5 mg, 0.008 mmol) was further added and stirred for 30 min. The reaction mixture was concentrated *in vacuo*, diluted with ether (30 ml) and filtered. The filtrate was extracted with citric acid (20 ml×4), the water layer was adjusted to pH=10 with $NaHCO_3$ and extracted by ether (100 ml×4). Ether layer was dried over Na_2SO_4, concentrated *in vacuo* to afford the residue (56.9 mg) as light yellow oil, which was purified by preparative TLC (silica gel, $CHCl_3$: MeOH=10 : 1) to give **4** (40.1 mg, 75%) as orange oil. *Rf*=0.15 (benzene : acetone=10 : 1); $[\alpha]_D^{24}$ −62.3° (*c*=1.39, $CHCl_3$); IR ($CHCl_3$) ν_{max} cm^{-1}: 1735 ($OCOCH_3$); ^{1}H-NMR (400 MHz) δ: 1.70 (1H, m, 4-Ha), 1.90 (1H, m, 4-Hb), 2.00 (2H, m, 3-H_2), 2.10 (3H, s, $OCOCH_3$), 3.35 (1H, dt, *J*=11.0, 8.0 Hz, 5-Ha), 3.56 (1H, ddd, *J*=11.0, 8.0, 5.0 Hz, 5-Hb), 4.19 (1H, dd, *J*=9.0, 6.0 Hz, 2-H), 5.19, 5.22 (total 2H, each dd, *J*=11.0, 2.0 Hz, 3′,3″-H_2-*cis*), 5.46, 5.49 (total 2H, each dd, *J*=17.0, 2.0 Hz, 3′,3″-H_2-*trans*), 5.93, 5.95 (total 2H, each dd, *J*=17.0, 11.0 Hz, 2′,2″-H), 6.78 (1H, s, NH); ^{13}C-NMR (100.6 MHz) δ: 23.10 (q, $OCO\underline{C}H_3$), 24.27 (t, 4-C), 28.30 (t, 3-C), 49.69 (t, 5-C), 67.42 (d, 2-C), 78.83 (s, 1′-C), 115.33 (t, 3′-C), 116.09 (t, 3″-C), 137.29 (d, 2′-C), 140.15 (d, 2″-C), 172.57 (s, $O\underline{C}OCH_3$); HR-FAB-MS *m/z*: 218.1153 $[M+Na]^+$, Calcd for $C_{11}H_{17}O_2NNa$: 218.1157.

(2*S*)-2-(1-Acetyloxy-1-vinyl-2-propenyl) Pyrrolidine (4) by Method B $HNEt_2$ (0.49 ml, 4.69 mmol), $Pd(OAc)_2$ (9.6 mg, 0.04 mmol), TPPTS (48.5 mg, 0.09 mmol) were added to a solution of **3** (595 mg, 2.13 mmol) in CH_3CN : H_2O=10 : 1 (0.6 ml) under argon at room temperature and stirred for 30 min. The reaction mixture was evaporated *in vacuo*, diluted by $CHCl_3$ (200 ml), washed with saturated NaCl (10 ml×2). Water layer was extracted with $CHCl_3$ (200 ml). Combined $CHCl_3$ solution was dried over Na_2SO_4, evaporated *in vacuo* to afford **4** (400 mg, 96%) as light yellow oil, which was used next reaction without purification. Compound **4** was identified to **4** obtained by above procedure by comparison of ^{1}H-NMR, *Rf*=0.23 benzene : acetone=10 : 1.

(2*S*)-*N*-Allyloxycarbonyl-L-proline (7) A solution of allyloxycarbonyl chloride (Aloc-Cl) (3.57 ml, 33.7 mmol) in ether (40 ml) was dropped to a solution of L-proline (5.97 g, 51.8 mmol), $NaHCO_3$ (11.3 g, 135 mmol) in H_2O (118 ml) under argon, and stirred for 1.5 h at room temperature. Then, a solution of $NaHCO_3$ (5.66 g, 67.4 mmol) in H_2O (59 ml) and Aloc-Cl (3.57 ml, 33.7 mmol) in ether (40 ml) were added again and stirred for 16 h. The reaction mixture was diluted with ether (160 ml) and partitioned to aqueous and organic layers. Aqueous layer was acidified with concentrated HCl, extracted with AcOEt (200 ml×3). AcOEt layer was washed with saturated NaCl solution (40 ml×2), dried over Na_2SO_4, evaporated *in vacuo* to afford **7** as colorless oil, quantitatively. *Rf*=0.63 (*t*-BuOH : AcOH : H_2O=4 : 1 : 5); $[\alpha]_D^{22}$ −95.58° (*c*=0.95, $CHCl_3$); IR ($CHCl_3$) ν_{max} cm^{-1}: 1750 (–COOH), 1690 (–NCOO–), 1600 (vinyl), ^{1}H-NMR (400 MHz) δ: 1.85—2.30 (4H, m, 3, 4-H_2), 3.47 (1H, m, 5-Ha), 3.57 (1H, m, 5-Hb), 4.36, 4.40 (total 1H, each dd, *J*=8.0, 4.0 Hz, 2-H), 4.58, 4.62 (total 2H, each d, *J*=5.0 Hz, –OCH_2), 5.16, 5.22 (total 1H, each dd, *J*=10.5, 1.5 Hz, $=CH_2$-*cis*), 5.31 (1H, dd, *J*=18.0, 1.5 Hz, $=CH_2$-*trans*), 5.84—5.98 (1H, m, –CH=), 8.04 (1H, br, –COOH); ^{13}C-NMR (100.6 MHz) δ: 23.41, 24.27 (each t, 4-C), 29.26, 30.88 (each t, 3-C), 46.57, 46.85 (each t, 5-C), 58.56, 59.23 (each d, 2-C), 66.02, 66.45 (each t, –OCH_2), 117.22, 117.72 (each t, $=CH_2$), 132.55, 132.62 (each d, –CH=), 154.33, 156.75 (each s, NCOO), 176.04, 177.87 (s, COOH); HR-FAB-MS *m/z*: 200.0920 $[M+H]^+$, Calcd for $C_9H_{14}O_4N$: 200.0923.

Benzyl (2*S*)-*N*-Allyloxycarbonylpyrrolidine-2-acetate (10) Oxalyl chloride (4.8 ml, 56 mmol), DMF (2 drops) were dropped to a solution of **7** (9.4 g, 47 mmol) in CH_2Cl_2 (78 ml) at 0 °C and stirred for 15 min and stirred further for 1 h at room temperature. A reaction mixture was concentrated *in vacuo* to afford acyl chloride **8**. Trimethylsilyl diazomethane ($TMSCHN_2$) (2 M solution in hexane) (52 ml, 103 mmol) was added to a solution of **8** in CH_3CN (98 ml)–THF (98 ml) at 0 °C under argon and stirred for 2 h. The reaction mixture was evaporated *in vacuo* to afford diazo compound **9**. Compound **9** was dissolved in a solution of benzyl alcohol (20 ml) and 2,4,6-collidine (20 ml) and stirred at 185 °C for 7 min. The reaction mixture was diluted with benzene (500 ml), washed with 10% citric acid (100 ml×5), H_2O (100 ml×2), saturated NaCl (100 ml×2), dried over Na_2SO_4, concentrated *in vacuo* to afford light yellow oil (28 g), which was purified by flash column chromatography (silica gel, benzene : $CHCl_3$: ether=2 : 2 : 1) to afford **10** (8.4 g, 59%) as light green oil. *Rf*=0.45 (benzene : $CHCl_3$: ether=2 : 2 : 1); $[\alpha]_D^{22}$ −38.89° (*c*=0.54, $CHCl_3$); IR ($CHCl_3$) ν_{max} cm^{-1}: 1720 ($COOCH_2Ph$), 1680 (NCOO), 1600 (vinyl), 1500—1470 (arom); ^{1}H-NMR (400 MHz): δ: 1.70—1.80 (1H, m, 3-Ha), 1.81—1.87 (2H, m, 4-H_2), 2.07 (total 1H, ddd, *J*=15.0, 12.0, 8.0 Hz, 3-Hb), 2.40 (1H, dd, *J*=15.0, 9.0 Hz, 1′-Ha), 2.87, 3.02 (total 1H, each dd, *J*=15.0, 3.5 Hz, 1′-Hb), 3.40 (2H, m, *J*=6.0 Hz, 5-H_2), 4.23, 4.25 (total 1H, dm, *J*=8.0 Hz, 2-H), 4.58 (2H, t, *J*=6.0 Hz, –OCH_2), 5.10, 5.13 (total 2H, each d, *J*=12.0 Hz, benzyl–CH_2–), 5.19 (1H, d, *J*=11.0 Hz, $=CH_2$-*cis*), 5.29 (1H, dq, *J*=17.0, 2.0 Hz, $=CH_2$-*trans*), 5.92 (1H, ddt, *J*=17.0, 11.0, 6.0 Hz, –CH=), 7.35 (5H, s, arom); ^{13}C-NMR (100.6 MHz): δ: 22.76, 23.58 (each t, 4-C), 30.58, 31.37 (each t, 3-C), 38.32, 39.32 (each t, 1′-H), 46.37, 46.72 (each t, 5-C), 53.99, 54.55 (each d, 2-C), 65.59, 65.75 (each t, –OCH_2), 66.26 (t, benzyl–CH_2), 117.16, 117.28 (each t, $=CH_2$), 127.22, 127.36, 128.20, 128.54, 128.71 (each d, $COOCH_2\underline{Ph}$), 133.00, 133.17 (each d, –CH=), 135.90 (s, $COOCH_2\underline{Ph}$–1′-C), 154.55 (s, NCOO), 171.10, 171.24 (each s, $\underline{C}OOCH_2Ph$); HR-FAB-MS *m/z*: 304.1551 $[M+H]^+$, Calcd for $C_7H_{22}O_4N$: 304.1549.

Methyl (2*S*)-*N*-Allyloxycarbonylpyrrolidine-2-acetate (11) A solution of **10** (902 mg, 2.98 mmol) in MeOH (36 ml) was dropped to a solution of K_2CO_3 (1.44 g, 10.4 mmol) in H_2O (1.8 ml) and stirred at 65 °C for 4 h. K_2CO_3 (0.41 g, 2.98 mmol) was further added and stirred for 18 h. The reaction mixture was acidified with 10% HCl, diluted with H_2O (30 ml), extracted by AcOEt (100 ml×3). The organic layer was washed with H_2O (30 ml), dried over Na_2SO_4, concentrated *in vacuo* to afford crude carboxylic acid. $TMSCHN_2$ (2 M solution in hexane) (1.93 ml, 3.87 mmol) was dropped to a solution of the carboxylic acid in MeOH (6.0 ml)–benzene (24 ml) and stirred for 30 min at room temperature. The reaction mixture was concentrated *in vacuo* to afford yellow oil (735 mg), which was purified by flash column chromatography (silica gel, benzene : $CHCl_3$: ether=20 : 20 : 1) to afford yellow oil **11** (442 mg, 65% from **10**). *Rf*=0.30 (benzene : $CHCl_3$: ether=2 : 2 : 1); $[\alpha]_D^{22}$ −43.20° (*c*=0.50, $CHCl_3$); IR ($CHCl_3$) ν_{max} cm^{-1}: 1720 (–$COOCH_3$), 1680 (–NCOO–), 1600 (vinyl); ^{1}H-NMR (400 MHz) δ: 1.70—1.80 (1H, m, 3-Ha), 1.80—1.90 (2H, m, 4-H_2), 2.07 (total 1H, ddd, *J*=16.0, 12.0, 8.5 Hz, 3-Hb), 2.34 (1H, dd, *J*=15.0, 8.5 Hz, 1′-Ha), 2.82, 2.96 (total 1H, each dd, *J*=15.0, 3.5 Hz, 1′-Hb), 3.40 (2H, m, 5-H_2), 3.66 (3H, s, $COOCH_3$), 4.19, 4.24 (total 1H, dm, *J*=8.5 Hz, 2-H), 4.58 (2H, t, *J*=5.0 Hz, –OCH_2), 5.19 (1H, dd, *J*=10.0, 1.0 Hz, $=CH_2$-*cis*), 5.29 (1H, dd, *J*=17.0, 1.0 Hz, $=CH_2$-*trans*), 5.93 (1H, ddt, *J*=17.0, 10.0, 5.0 Hz, –CH=); ^{13}C-NMR (100.6 MHz) δ: 22.72, 23.55 (each t, 4-C), 30.58, 31.35 (each t, 3-C), 38.14, 39.05 (each t, 1′-H), 46.37, 46.72 (each t, 5-C), 51.54 (q, 3′-C), 53.96, 54.52 (each d, 2-C), 65.57, 65.75 (each t, –OCH_2), 117.13, 117.28 (each t, $=CH_2$), 133.03, 133.16 (each d, –CH=), 154.55 (s, NCOO), 171.85 (each s, $\underline{C}OOCH_3$); HR-FAB-MS *m/z*: 228.1236 $[M+H]^+$, Calcd for $C_{11}H_{18}O_4N$: 228.1236.

(2*S*)-*N*-Allyloxycarbonyl-2-(2-acetyloxy-2-vinyl-3-butenyl)pyrrolidine (12) Anhydrous $CeCl_3$ (264 mg, 1.1 mmol) prepared by the literature procedure[12] was suspended in THF (0.5 ml) and stirred for 2 h under argon at room temperature, then a solution of **11** (83 mg, 0.365 mmol) in THF (1 ml) was added and stirred for 1 h at room temperature. Vinyl magnesium bromide (0.97 ml, 1 M solution in hexane, 1.1 mmol) was dropped at 0 °C and stirred for 30 min. Acetyl chloride (0.062 ml, 0.88 mmol), dimethylaminopyridine (5 mg) was added at 0 °C, then stirred for 30 min at room temperature. Saturated NH_4Cl (20 ml) was added to quench Grignard reagent completely, extracted with ether (100 ml×2). The organic layer was washed with saturated NaCl (10 ml×3), dried over Na_2SO_4, concentrated *in vacuo*. The resulted residue was purified by flash column chromatography (Silica gel,

hexane : AcOEt = 8 : 1) to afford **12** (42.2 mg, 39.4%) as colorless oil. *Rf* = 0.58 (*n*-hexane : AcOEt = 1 : 1); $[\alpha]_D^{22}$ −14.12° (*c* = 0.85, $CHCl_3$); IR ($CHCl_3$) ν_{max} cm^{-1}: 1740 (–OCOOCH$_3$), 1680 (NCOO), 1640 (vinyl); ^{1}H-NMR (300 MHz) δ: 1.84 (2H, m, 4-H$_2$), 1.92 (2H, m, 3-H$_2$), 1.98 (1H, m, 4-Hb), 2.26 (1H, m, 1′-Ha), 2.67 (2H, t, *J* = 6.5 Hz, 4′-H$_2$), 2.82 (1H, d, *J* = 15.0 Hz, 1′-Hb), 3.40 (2H, br d, *J* = 5.0 Hz, 5-H$_2$), 3.81 (3H, s, –OCOOCH$_3$), 3.99 (1H, br t, *J* = 7.0 Hz, 2-H), 4.57 (total 2H, d, *J* = 5.0 Hz, –OCH$_2$), 4.98 (1H, d, *J* = 10.5 Hz, 6′-H-*cis*), 5.03 (1H, dd, *J* = 17.0, 1.0 Hz, 3′-H), 5.07 (1H, d, *J* = 17.0 Hz, 6′-H-*trans*), 5.19 (1H, dd, *J* = 10.5, 1.0 Hz, =CH$_2$-*cis*), 5.29 (1H, dd, *J* = 17.0, 10.5 Hz, =CH$_2$-*trans*), 5.75 (1H, ddt, *J* = 17.0, 10.5, 5.0 Hz, 5′-H), 5.93 (1H, ddt, *J* = 17.0, 10.5, 6.5 Hz, –CH=); ^{13}C-NMR (75 MHz) δ: 22.77, 23.64 (each t, 4-C), 29.44, 29.67 (each t, 4′-H), 30.03, 30.12 (each t, 3-C), 36.99, 38.09 (each t, 1′-C), 46.36, 46.63 (each t, 5-C), 55.10, 55.15 (q, OCOO<u>C</u>H$_3$), 55.96 (d, 2-C), 65.46, 65.68 (each t, –OCH$_2$), 115.42 (d, 3′-H), 116.85 (t, =CH$_2$), 117.04 (t, 6′-H), 133.14, 133.26 (each d, –CH=), 135.36, 135.40 (each d, 5′-C), 146.69, 146.74 (each s, 2′-C), 153.26 (s, NCOO), 154.57 (s, O<u>C</u>OOCH$_3$); HR-FAB-MS *m*/*z*: 318.1322 $[M+Na]^+$, Calcd for $C_{15}H_{21}O_5NNa$: 318.1317.

(8a*S*)-6,7-Dehydro-7-vinylindolizidine (15) Pd(Ph$_3$P)$_4$ (13.5 mg, 11.7 μmol), dimedone (65.6 mg, 0.47 mmol) were added to a solution of **12** (38 mg, 0.13 mmol) in THF (1.4 ml) at −20 °C under argon and stirred for 4 h. Pd(Ph$_3$P)$_4$ (13.5 mg, 11.7 μmol) was further added and stirred for 1 h. After that the mixture was stirred at 0 °C for 14 h. The reaction mixture was concentrated *in vacuo*, diluted with ether (20 ml), filtered through celite pad, concentrated *in vacuo* to give crude substance, which was purified by flash column chromatography (Silica gel, benzene : hexane = 10 : 1–$CHCl_3$: MeOH = 50 : 1—30 : 1) to afford **15** (12.3 mg, 63.7%) as red oil. *Rf* = 0.18 ($CHCl_3$: MeOH = 10 : 1); $[\alpha]_D^{23}$ +20.00° (*c* = 0.06, $CHCl_3$); ^{1}H-NMR (400 MHz) δ: 1.54 (2H, m, 1-H$_2$), 1.88 (2H, m, 2-H$_2$), 2.02 (1H, m, 8-Ha), 2.16 (1H, m, 3-Ha), 2.22 (1H, m, 8a-H), 2.48 (1H, dt, *J* = 16.0, 3.0 Hz, 8-Hb), 2.86 (1H, d, *J* = 17.0 Hz, 5-Ha), 3.22 (1H, td, *J* = 9.0, 2.0 Hz, 3-Hb), 3.61 (1H, ddd, *J* = 17.0, 5.0, 2.0 Hz, 5-Hb), 4.96 (1H, d, *J* = 10.0 Hz, 2′-H-*cis*), 5.11 (1H, d, *J* = 17.0 Hz, 2′-H-*trans*), 5.72 (1H, td, *J* = 2.0, 1.0 Hz, 6-H), 6.42 (1H, dd, *J* = 17.0, 10.0 Hz, 1′-H) ^{13}C-NMR (100.6 MHz) δ: 21.43 (t, 2-C), 30.80 (t, 1-C), 31.02 (t, 8-C), 52.57 (t, 5-C), 54.17 (t, 3-C), 59.83 (d, 8a-C), 110.92 (t, 2′-C), 126.47 (d, 6-C), 135.00 (s, 7-C), 138.60 (d, 1′-C); HR-EI-MS *m*/*z*: 149.1205 $[M]^+$, Calcd for $C_{10}H_{15}N$: 149.1204.

(8a*S*)-6,7-Dehydro-7-vinylindolizidine HCl salt (**15**·HCl). Compound **15** (13.3 mg) was dissolved in AcOEt (10 ml) and extracted with 0.1 N HCl (2 ml×2), the HCl layer was concentrated *in vacuo* to afford colorless powder (12.4 mg, 75%). $[\alpha]_D^{23}$ +43.75° (*c* = 0.16, $CHCl_3$); ^{1}H-NMR (400 MHz) δ: 2.10 (1H, m, 2-Ha), 2.24 (2H, m, 1-H), 2.40 (1H, m, 2-Hb), 2.74 (1H, m, 8-Ha), 2.80 (1H, m, 3-Ha), 2.90 (1H, m, 8-Hb), 3.14 (1H, m, 8a-H), 3.42, 3.44, 3.57 (total 1H, each d, *J* = 15.5 Hz, 5-Ha), 3.97 (1H, m, 3-Hb), 4.16 (1H, d, *J* = 15.5 Hz, 5-Hb), 5.16 (1H, d, *J* = 10.5 Hz, 2′-H-*cis*), 5.24 (1H, d, *J* = 17.5 Hz, 2′-H-*trans*), 5.67 (1H, br s, 6-H), 6.40 (1H, dd, *J* = 17.5, 10.5 Hz, 1′-H), 12.5 (1H, br s, HCl); ^{13}C-NMR (100.6 MHz) δ: 20.46, 20.63 (each t, 2-C), 27.36 (t, 8-C), 28.59 (t, 1-C), 50.30 (t, 5-C), 52.91 (t, 3-C), 62.65 (d, 8a-C), 114.67, 114.69 (each t, 2′-C), 117.82 (d, 6-C), 135.94 (s, 7-C), 136.35 (d, 1′-C), HR-FAB-MS *m*/*z*: 150.1290 $[M-HCl+H]^+$, Calcd for $C_{10}H_{16}N$: 150.1283.

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